World Journal of Sport Sciences 4 (2): 185-191, 2011
ISSN 2078-4724

Effects of Exhaustive Aerobic Exercise on Matrix Metaloproteases Activity in Athletes and Non-Athletes

[1]Amirsasan Ramin, [2]Mirshafiei Abbas, [3]Gaeini Abbas Ali, [3]Ravaasi Ali Asghar, [4]Letafatkar Amir, [5]Saadat Farshid and [6]Biorani Hussein

[1]Department of Sport Physiology, University of Tabriz, Iran
[2]Department of Immunology, Tehran Medical University, Iran
[3]Department of Sport Physiology, University of Tehran, Iran
[4]Department of Sport Medicine and Hygiene, University of Tehran, Iran
[5]Department of Immunology, Guilan Medical University, Iran
[6]Department of Statistics, University of Tabriz, Iran

Abstract: Matrix metaloproteases (MMPS) belong to a main group of proteases which have roll in extracellular matrix degradation. Their activities such as wounds healing and angiogenesis are very important in physiological conditions, but they are transient and under the control of endogenous blockers. The aim of this research was to investigate effects of one exhaustive endurance exercise session on MMP2 and MMP9 activities (the most complex and the most abundant enzymes) in male well trained and untrained peoples. 11 elite male endurance runners with age 22.27±3.87; Vo2max 60.68±6.19 and 10 untrained male subject with age 23±4.04; Vo2max 37.90±5.90 participated voluntarily in this research. Blood samples were collected from two groups in three phase which they include: basal levels (20 minutes before exercise), 20 and 24 hour after end of exercise. Then the variables were measured by means of gelatin zymography technique and collected data were analyzed with ANOVA and post-hoc and independent T student tests. The result showed that blood MMP2 and MMP9 levels increased following of one exhaustive aerobic activity session ($P<0.001$). It should be noted that despite of significant decrease of MMP2 and MMP9 levels after 24 hour ($P<0.001$), but their levels were higher than basal levels ($P<0.001$). In all phases of measurements, changes of MMP2 and MMP9 activities in non-athletes were similar to those in athletes but none of these changes were significant. Moreover, athletes MMP2 and MMP9 activities in pre-exercise, 20 and 24 hour after exercise were significantly higher than non-athletes ($P<0.001$). With increasing MMPS activities inflammatory responses to physical and mechanical stimuli (one session of exhaustive exercise) has been started in both of subjects (well trained and untrained) which continued up to 34 hours after exercise. In seems that, the rate of mentioned inflammatory indices responses is dependent on the duration and intensity of the exercise.

Key words: MMP2 and MMP9 % Exhaustive Aerobic Activity

INTRODUCTION

Matrix metalloproteinases (MMPs) are a family of nine or more highly homologous Zn++- endopeptidases that collectively cleave most if not all of the constituents of the extracellular matrix. MMPs in the circulation are thought to modulate the activation of growth factors, cytokines [1] and angiogenesis, facilitating physiological adaptations to exercise training [2, 3]. The MMP families of enzymes contribute to both normal and pathological tissue remodeling [4 -6]. Each MMP targets a specific substrate, thus, the appropriate MMP must be released in a time- and location-specific manner to orchestrate membrane remodeling and adaptation [7, 8].

Of the MMPs that have been characterized thus far, MMP1 (Collagenase 1), MMP2 (Gelatinase A), MMP3 (Stromelysin 1) and MMP9 (Gelatinase B) play critical roles in cleaving muscle-specific proteins and assisting in extracellular matrix formation, remodeling and regeneration in skeletal and cardiac muscle, as well as the surrounding vasculature [4, 9].

Corresponding Author: Ramin Amirsasan, Department of Sport Physiology,University of Tabriz, Azadi St, Tabriz -Iran.
Tel: +09357365993, E-mail: Amirsasanramin@gmail.com.

Certain stimuli, particularly those that induce high levels of mechanical stress such as eccentric or high-impact exercise activate the local production of MMPs in skeletal muscle. It is generally accepted that MMPs function in skeletal muscle to process extracellular matrix (ECM) proteins, assisting in matrix degradation and repair, while those released into the circulation facilitate angiogenesis [10-15]. MMPs in the circulation are also thought to modulate the activation of growth factors and cytokines through degradation of their precursors, binding proteins and inhibitors [2, 10, 16].

Although investigators have explored the effects of an acute bout of exercise on MMP concentrations in skeletal muscle and plasma, the effects of exercise training on circulating MMP concentrations have not been elucidated [17-20]. Since serum concentrations of MMPs are reported to peak within a relatively short time period following a single bout of exercise, it is possible that post-training serum concentrations of MMPs represent the effects of repeated bouts of exercise that have initiated adaptive responses in skeletal muscle. To this end, it is not known whether different exercise training programs, to include one that incorporates machine-based resistance exercises and one composed of aerobic and bodyweight exercises such as pull-ups, push-ups and sit-ups, promote different MMP responses [5, 21-23]. Such information would be valuable in understanding whether the type of exercise and the specific MMP response plays a role in mediating physiological adaptations to exercise training. Additionally, previous investigations have only focused on one or two MMPs and the effects of exercise on circulating concentrations of the various MMPs have not been elucidated [5, 13, 19, 24].

Related to immune response cells such as granulocytes, monocytes - macrophages, lymphocytes and other inflammatory intermediates such as acute phase proteins and different types of sporting activities Cytokins, much research done and a lot of information are available [19]. Discussion of proteinase Matrix metalloproteinases, particularly as the final ring long chain reaction and cell mediated immune and inflammatory response to various sports activities, is brand new and few studies have been done in this area and the same theory about them does not exist. In continuation of these efforts, the researchers intend to compare the ways of activity of two type of proteinase enzymes MMP9 and MMP2 (most complex proteinase) during a pathologic process in the trained subjects (with long-term adaptation to exercise) and untrained or non-athletic persons (without adaptation to exercise).

This research was conducted at Tehran Medical institution. The main aim of this study was to evaluating the response of some Matrix metalloproteinases (MMP2 and MMP9) reaction to one period of exhaustive aerobic exercise in athletes and non athletes.

MATERIALS AND METHODS

Eleven elite male athletes (endurance runners with VO2max$ 55 ml/kg/min) and 10 non athletes matched evenly for age, were recruited. The protocol used in this study was reviewed and approved by Tehran University's Institutional Review Board prior to participant recruitment and all participants provided written informed consent prior to beginning the study. As assessed by a medical history questionnaire, each participant was free of cardiovascular and neurological diseases, severe musculoskeletal injuries and low back pain. Participants attended having performed no vigorous exercise in the 24 hour prior to testing and with diet standardized for 48 hour proceeding in each test. Participants had all experimental methods explained to them and participated in this experiment after giving their free and voluntary informed consent. All were pre-screened via a health history questionnaire and an examination by a physician. The caliper and YMCA suggested method used for subject's body fat percent measuring. One week prior to the start of the training programs, each subject participated in a Bruce test and a series of exercises designed to assess physical performance (maximal oxygen consumption [VO2 max].

Bruce Test: The Bruce treadmill test protocol was designed in 1963 by Robert. A. Bruce, MD, as non-invasive test to assess patients with suspected heart disease. In a clinical setting, the Bruce treadmill test is sometimes called a stress test or exercise tolerance test.

Today, the Bruce Protocol is also one common method for estimating VO2 max in athletes. VO2 max, or maximal oxygen uptake, is one factor that can determine an athlete's capacity to perform sustained exercise and is linked to aerobic endurance. VO2 max refers to the maximum amount of oxygen that an individual can utilize during intense or maximal exercise. It is measured as "milliliters of oxygen used in one minute per kilogram of body weight" (ml/kg/min).

The Bruce Treadmill Test is an indirect test that estimates VO2 max using a formula rather than using direct measurements that require the collection and measurement of the volume and oxygen concentration of inhaled and exhaled air. This determines how much oxygen the athlete is using.

The Bruce Protocol: The Bruce Protocol is a maximal exercise test whereas the athlete works to complete exhaustion as the treadmill speed and incline is increased every three minutes (See chart). The length of time on the treadmill is the test score and can be used to estimate the VO2 max value. During the test, heart rate, blood pressure and ratings of perceived exertion are often also collected.

Bruce Treadmill Test Stages:

Stage 1 = 1.7 mph at 10% Grade
Stage 2 = 2.5 mph at 12% Grade
Stage 3 = 3.4 mph at 14% Grade
Stage 4 = 4.2 mph at 16% Grade
Stage 5 = 5.0 mph at 18% Grade
Stage 6 = 5.5 mph at 20% Grade
Stage 7 = 6.0 mph at 22% Grade
Stage 8 = 6.5 mph at 24% Grade
Stage 9 = 7.0 mph at 26% Grade

The Bruce Protocol Formula for Estimating VO2 Max

- For Men VO2 max = 14.8 - (1.379 x T) + (0.451 x T^2) - (0.012 x T^3)
- For Women VO2 max = 4.38 x T - 3.9
- T = Total time on the treadmill measured as a fraction of a minute (ie: A test time of 9 minutes 30 seconds would be written as T=9.5).

Because this is a maximal exercise test, it should not be performed without a physician's approval and without reasonable safety accommodations and supervision.

Blood Sampling: Basal blood draws were collected at baseline, 20 min after and 24 hour after training via venipuncture. Blood samples were also collected during the Bruce using an indwelling venous catheter (pre, 20 min after and 24 hour after Bruce). Serum concentrations of MMPs were corrected for albumin to account for plasma volume shifts.

MMP Multiplexed Analysis: Circulating serum MMP concentrations were analyzed using a commercially available multiplex bead-based antibody sandwich assay (R&D Systems, Inc., Minneapolis, MN) which combined color-coded microparticles (coded for each analyte) with lasers and flow cytometry to quantify analyte concentrations in 15-l of serum. Color-coded microspheres were identified by one laser and streptavidin-phycoerythrin conjugate bound to the biotinylated detection antibodies on the spheres was excited by a second laser which quantified the amount of antigen present in the samples. Median fluorescence intensity from each bead set was calculated and translated to a concentration. The MMP kit was reported to have sensitivities of 4.4 and 25.4pg/ml for MMP-1 and -2 respectively. Samples were run in duplicate and intra- and inter-assay coefficient of variations (CVs) for the MMP panel were <10%. All samples were analyzed on a Luminex 200 System (Luminex Corporation, Austin, TX) using Masterplex QT Software version 2.5 (MiraiBio, Inc., Alameda, CA).

Data Analysis: When the ANOVA revealed a significant F ratio, a sheffe HSD post hoc test was employed to determine statistical differences. There was one ANOVA ran for the exercise induced MMP response and another ANOVA ran for the basal MMP concentrations. Also independent t test was used between group comparisons. Statistical analyses were performed using SPSS (SPSS, v. 15.0; Chicago, IL). All data are presented as mean± SE. An alpha level of P= 0.001 was considered statistically significant for all data. Also Lab works software (UVP company product) were used for evaluation of densitometry.

RESULTS

Mean and standard deviation of athletes and non athlete's demographic data'sare shown in Table 1.

Table 1: Mean and standard deviation of athletes and non athlete's demographic characteristics

	Group	
Variables	Athletes	Non Athletes
Age (years)	22.27±3.870	23±4.03
Weight (Kg)	62.02±3.040	74.14±12.56
Height (Cm)	171.63±4.680	175.30±5.05
BMI (Kg/m2)	21.12±1.810	24.10±3.77
Body Fat (%)	9.72±1.410	19.12±5.61
VO2 max (ML/Kg*min)	60.68±6.190	37.9±5.90
Maximum heart rate in exhaustion phase (beats per min)	203.18±12.66	213±7.45
Time for reaching to exhaustion (Minute + second)	16.64±1.870	10.64±1.49

There arn't significant differences between two groups demographic characteristics

Table 2: Mean changes of MMPs activity in subjects during different measurement phases.

Variables		MMP2 (Ng/ml)		MMP9 (Ng/ml)	
Phases	Subjects	Athletes	Non Athletes	Athletes	Non Athletes
Phase 1					
30 min before activity	M	73977.27	66343.800	74038.45	66411.100
	SD	3267.492	2858.730	3259.190	2862.278
Phase 2					
20 min after activity	M	92900.55*	68400.100	92971.45*	68474.600
	SD	3507.314	3074.503	3509.070	3080.031
Phase 3					
24 hour after activity	M	79172.55*	66712.200	79296.18*	66776.000
	SD	3382.586	2995.052	3532.713	2978.950

C Significant differences ($p < 0.001$)

MMP2 and MMP9 activity in athletes have a significant increase immediately after the exhausting activity and also have significant decrease in the next day. But still compared to basic conditions (30 minutes before activity) is significantly improved. While non-athletes also change the amount of MMP2 and MMP9 activity was similar to athletes and did not show any significant changes

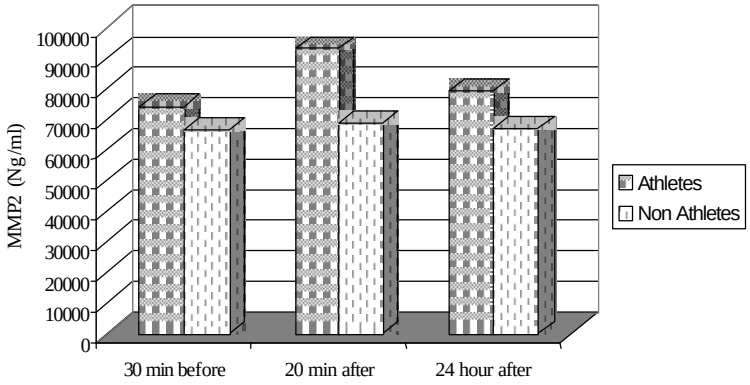

Fig. 1: Mean value of MMP2 in subjects during three different phases

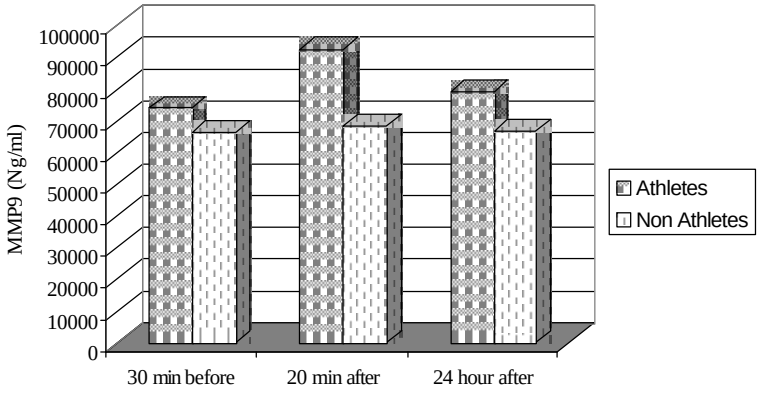

Fig. 2: Mean value of MMP9 in subjects during three different phases

DISCUSSION AND CONCLUSION

In recent years, scientists have a lot of attention to extra cellular catalyze enzymes or Matrix metaloproteases context. In normal body tissues, analysis and synthesis of extracellular matrix components in the balance and to maintain this balance, small amount of metaloproteases expression are in most cells, but But their activity is highly controlled.

With activation and expression of these collagen and gelatin parser enzymes, body tissue and microanatomical structure will be damaged. Research results show that decomposition of extracellular matrix components under physiological conditions Such as embryo development, wound healing and de-vein phenomenon and etc is Important and necessary, but temporary and transient and locally controlled, but such kinds of diseases and pathologic processes of microbial

and chemical stimuli, subsequent physical and mechanical stresses such as heavy types of sports activities, Inflammatory response by activation of histamine or pre-inflammatory cytokines, Such as types of interleukin, alpha and beta tumor necrosis factors, alpha and beta and gamma interferon's and free radicals such as nitric oxide activities started and by stimulating the production of proteinase, hydrogen peroxide and phospholipids and with the aim of breaking the necrotic tissue, leading to inflammatory processes stimulation [2, 25].

Between inflammatory indices mentioned above, proteinase; the final loop, as long chain reaction and cell mediated immune and inflammatory responses to their various sports activities is brand new and few studies have been done in this area and single theory about them does not exist.

In continuation of these efforts, the present study and most sophisticated type of reaction metaloproteases (MMP2 and MMP9) in response to one session of exhausting activity (Bruce protocol) has been compared.

In the present study, MMP2 and MMP9 activity in athletes have a significant increase immediately after the exhausting activity and also have significant decrease in the next day. But still compared to basic conditions (30 minutes before activity) is significantly improved. While non-athletes also change the amount of MMP2 and MMP9 activity was similar to athletes and did not show any significant changes.

Also, Comparison of activity of MMP2 and MMP9 in two groups showed that in all three phases (base state or 30 minutes before activity, 20 minutes and one day after the activity) the activity of mentioned matrix metaloproteases in athletes was significantly higher than non-athlete.

According to some research results, the rate of emergence of MMP2 (protein levels and MMP2 mRNA) have significant increasing in the plantar muscles of 6 months age mice and after two weeks of high intensity exercise in trained mice. While in the group that their legs had been closed for two weeks, similar results were observed with exercise group. Also, slow twitch and fast (Iib) twitch fibers cross section of plantar muscles of immobile mice showed increase and decrease respectively [2].

Results of some studies showed that MMP2 activity in laboratory mice quadriceps and soleus muscle have significant increase, followed by a session running on the slope and in the portion of the muscles that have lower injury intensity, MMP2 have little change. In examining the above Beta-glucuronidases was important indicator of muscular damage. In this study, the rate of change MMPs have been attributed to severely of Myofibrils injury damaged [5, 25, 26].

Ali Carmeli and Myrmas and colleagues [27-31] showed that the emergence rate of MMP3 and MMP9 in fast twitch fibers of mice quadriceps, Solealus and gastrocnemius muscles and the activity of these indexes in sinovial fluid liquid of ankle and feet will remain unchanged, While the high-intensity activity increased the rate of MMP2 emergence (protein levels and mRNA) in mice, but had no effect on MMP9 [27-31]. Also, the amount of TNF- á of pre-inflammatory cytokines and stimulating the emergence of MMPs showed a significant increase in the hours after exercise. As reported in the two above studies, the emergence and activity of MMPs correlated with intensity of Endurance activity and type of muscle fibers and physical activities with medium intensity can not increase the MMPs activity. Physical activity that leads to skeletal muscle injury is increased stimulation to MMPs emergence [3, 32].

Also, research that studied the matrix metaloproteases after physical activity, are very low. Rate of rise of MMP9 in muscle Vastus Medius subsequent training showed significant increase [13,33,34]. Also MMP2 activity in some studies after exercise implementation has remained unchanged and the MMP2/ TIMP-2 (Collection of MMP2 and inhibitor of its tissue proprietary) complex and muscle damage index (CK) significantly increased [35]. But, in some research, MMP2 activity has been shown increase following Bruce Protocol [30]. Based on the results of some studies, despite the increase in CK activity after the impact activity, MMP9 levels did not change but, But the synthesis of collagen type IV decreased temporarily after both types of contact and non contact activities [17].

The only study that has been shown reduced MMP9 activity following the 12-week endurance training, related to research of Niessener and colleagues [2, 3, 5] that was performed On 32 subjects with coronary heart disease. In this study, the amount of IL-8 decreased and IL-6 and CRP remained unchanged. But in implementation of this study, subjects simultaneously used from Stalin's anti-inflammatory drug [21].

So results of this study all is well in line with limited research that the years 2001 to 2007 in relation to inflammatory markers, particularly proteinase reaction to sports activities have been done [2, 3, 5, 13, 15, 18, 20, 29, 30].

The results of this study showed that even 24 hours after activity as exhaustive Bruce protocole, inflammation and the resulting inflammatory response indicators that MMP2 and MMP9 was still not returned to normal and inflammatory response in non athletes, similar but weaker than athletes in two stages after the work based on previous findings can be attributed to less time and intensity of exhaustive activity implementation. As can be seen in Table one, the average time to reach in exhaustion in athlete's 16.64±1.87 minutes and 10.64±1.49 minutes in non-athletes.

In previous studies, emphasis has been the emergence of MMPs activity and intensity endurance activities, the severity of muscle fiber type and Myofibrils damage is directly related and moderate exercise can lead to significant change in MMPs [3, 5, 32]. But the important point is that in the variety of sporting activities in the type of intensity and duration, the basis of the inflammatory response starting based on inflammatory cytokines such as IL-1, IL-6,IL-8, TNF- " and ... and ells in the body to deal with pressures, to achieve consistency in their effort to start [2, 14, 21, 32]. High levels of MMP2 and MMP9 activity in athletes in the base state can be argued, based on a questionnaire completed by all subjects and large company experience training athletes in the national and continent, from one side of probability adjustment from endurance training a few years Angiogenesis Phenomena and tissues turn over and on the other side, tolerance of joint and muscle damage in various parts of the body and inflammation resulting from this damages for their remodeling cause such differences. Previous studies as well as reported high levels of MMPs activity in athletes of various sports disciplines such as baseball, tennis, squash, softball, weightlifting [36] and track and field and also, their role in tissues angiogenesis [8, 11, 24] and turn over and joints& tissues repair [9, 36, 37] were reported.

Based on the results of this study concludes that a Bruce exhaustive activity, causing an inflammatory response and significant change in the activity of metaloproteases matrix (MMP2 and MMP9) is that a day after both, the inflammatory activity continues. Therefore, the results of this experiment, should not to ignore the effects of these heavy activities and deleterious effects of activating metaloproteases matrix (MMP2 and MMP9), as the main indicator of inflammatory and destructive extracellular matrix in the incidence of tissue damage, arthritis and various diseases in the long term.

REFERENCES

1. Brown, G.C. and C.E. Cooper, 1994. Nanomolar concentrations of Nitric oxide Rever sibyl inhibit synap to somal Respiration by competing with oxygen at cytochome oxidase. FES Lett., 356: 295-98.
2. Carmeli, E. and T.G. Haimovitch, 2006. the expression of MMP_2 following immobilization and high intensity running in plantaris muscle fiber rats. Scientific World J., 5(6): 542-50.
3. Carmeli, E., M. Moas, L. Shannon and K.P. Scott, 2005. High intensity exercise increases expression of matrix metallo proteinasses in fast skeletal muscle fibers. Exp Physiol., 90(4): 613-19.
4. Cooksle, S., J.B. Hiokiss, S.P. Tickle, E.H. levers, A.J. Docherty and G. Murphy, 1999. Immunoays for detection of human collagenases, stromelysins, $TIMP_S$ and enzyme-inhibitor complexes Matrix, 10: 285-91.
5. Dimitris Stellas, Avraam El Hamidieh and Evangelia Patsavoudi, 2010. Monoclonal antibody 4C5 prevents activation of MMP2 and MMP9 by disrupting their interaction with extracellular HSP90 and inhibits formation of metastatic breast cancer cell deposits. BMC Cell Biol., 11: 51.
6. Duffy, M.J. and K. Mccarthy, 1998. Matrix metalloproteinases in cancer-prognostic Markers and Targets for Therapy. Int. J. Oncol, 12: 1343-48.
7. Ferlito, S., 2000. Physiological, Metabolic, Neuroendocrine and pharmacological regulation of Nitric Oxide in humans. Minerva-Cardioangiol., 48(6): 169-76.
8. Foda, H.D. and Z. Stanley, 2001. Matrix MetalloProteinases in cancer invasion, metastasis and angiogenesis. DDT, 6(9): 10.
9. Gohji, K., N. Fujimoto, T. Hara, A. Fujii and A. Okada, 1998. Serum matrix metallo proteinases-2 and its density in men with prostate cancer as a new predictor of diseases extension. Int. J. Cancer, 79: 69-101.
10. Graham, D.A. and J.W.E. Rush, 2004. Exercise Training tmprores dortic endothelium dependent vasorelaxa and derminants of nitric oxide: bioavailability in spontaneously hypertensive rate, J. Appl. Physiol., 96: 2088-96.
11. Haas, T.L., M. Milkiewiez, S.J. Davis, *et al*., 2000. Matrix metalloporoteinase activity is required for activity-induced angiogenesis in rat skeletal muscle. Am. J. Physiol Heart Circ Physiol., 279(4): 1540-47.

12. Harrison, 1998. Disorders of immune system connective tissue and Joints.
13. Heinemier, K.M., S.O.A. Koskinen, J.L. Olesen, H. Langberg and Kjaerm, 2003. Changes in levels of matrix metalloproteinases and their inhibitors in human tendinous tissue after exercise. Scandinavian Congress of Physiol. and Pharmacol., pp: 11-4.
14. Holding, R.A.D., 2005. Cytokine; Hormone interrelationship, Ark international Training Seminar.
15. Koskinen, S.O., W. Wang, A.M. Ahtikoski, *et al*., 2001. Acute exercise induced changes in rat skeletal muscle mRNAs and proteins regulating type IV collagen content. Am. J. Physiol. Regul Integr Comp Physiol., 280(5): R1292-300.
16. Justulin Jr L.A., H.M. Della-Coleta, S.R. Taboga and S.L. Felisbino, 2009. Matrix metalloproteinase (MMP)-2 and MMP-9 activity and localization during ventral prostate atrophy and regrowth. International J. Androl., 33: 1-13.
17. Mackey, A.L., A.E. Donnelly, A. Swanton, *et al*., 2006. The effects of impact and non-impact exercise on circulating markers of collagen remodeling in humans. J. Sports Sci., 24(8): 843-8.
18. Mackey, A.L., A.E. Donnelly, Turpeeniemi-Hujanen and T. Proper, 2004. Skeletal Muscle collagen content in humans after high-orce eccentric contractions. J. Appl. Physiol., 97(1): 197-203.
19. McCarthy, M.M., E. Pick, Y. Kluger, B. Gould-Rothberg, R. Lazova, R.L. Camp, D.L. Rimm and H.M. Kluger, 2008. HSP90 as a marker of progression in melanoma. Ann. Oncol., 19: 590-4.
20. Moses, M., D. Wiederschain, K.R. Loughlin, D. Zurakwski and C.C. Lamb, 1998. Increased incidence of matrix metalloproteinases in urine of cancer patients. Cancer Res., 58: 1395-99.
21. Niessener, A., B. Richter, M. Penka *et al*., 2006. Endurance training reduces circulating inflammatory markers in persons at risk of coronary events: impact plaque stabilization? Atheroscleorosis, 186(1): 160-5.
22. Niessener, A., B. Richter, M. Penka *et al*., 2006. Endurance training reduces circulating inflammatory markers in persons at risk of coronary events: impact plaque stabilization? Atheroscleorosis, 186(1): 160-5.
23. Papadopoulou, S., A. Scorilas and N. Arnogianaki, 2001. Expression of Glatinase a (MMP_2) in Human colon cancer and Normal colon Mucosa. Tumor Biol., 22: 383-9.
24. Ra, H.J. and W.C. Parks, 2007. Control of matrix metalloproteinase catalytic activity. Matrix Biol., 26: 587-96.
25. Rivilis, I., M. Milkiewicz, P. Boyd, *et al*., 2002. Differential involvement of MMP-2 and VEGF during muscle stretch-versus shear stress-induced angiogenesis. Am. J. Physiol. Heart Circ. Physiol., 283(4): 1430-38.
26. Robbins, 2003. Pathologic Basis of Disease, Vol. 1, sixth Edition, Tchehr Co.
27. Saenz, A.J., E. Lee-Lewandrowski, M.J. Wood, *et al*., 2006. Measurement of a plasma stroke biomarker and cardiac troponin T in marathon runners before and after the 2005 Boston marathon. Am. J. Clin Pathol., 126(2): 185-9.
28. Sidera, K., M. Gaitanou, D. Stellas, R. Matsas and E. Patsavoudi, 2008. A critical role for HSP90 in cancer cell invasion involves interaction with the extracellular domain of HER-2. J. Biol. Chem., 283: 2031-41.
29. Sidera, K. and E. Patsavoudi, 2008. Extracellular HSP90: conquering the cell surface. Cell Cycle, 7: 1564-8.
30. Stankovic, S., G. Konjevic, K. Gopcevic, V. Jovic, M. Inic and V. Jurisic, 2010. Activity of MMP-2 and MMP-9 in sera of breast cancer patients. Pathol Res Pract., **15; 206(4): 241-7.**
31. Tayebjee, M.H., G.Y. Lip, A.D. Blann and R.J. Macfadyen, 2005. Effects of age, gender, ethnicity, diurnal variation and exercise on circulating levels of matrix metallo proteinases (MMP)-2 and -9 and their inhibitors, tissue inhibitors of matrix metallo proteinases (TIMP)-1 and -2. Thromb Res., 115(3): 205-10.
32. Tentes, I., B. Asimakopoulos, E. Mourvati, K. Diedrich, S. Al-Hasani and N. Nikolettos, 2007. Matrix metalloproteinase (MMP)-2 and MMP-9 in seminal plasma. J. Assisted Reproduction and Genetics, 24: 278-81.
33. VanDen Boom, R., P.A.J. Brama, *et al*., 2004. The influence of repeated arthrocentesis and exercise on matrix metalloproteinases and tumour necrosis factor " (TNF") activates in normal equine joints. Equine Veterinary J., 36(2): 155-59.
34. Vivian, H. and Hey Ward, 2004. Advanced Fitness Assessment Exercise Precription.
35. Woessner, J.F. and H. Nagase, 2000. Textbook of Matrix metalloproteinases and $TIMP_S$: Oxford University Press, pp: 11-40.
36. Yasunori, O., 2000. Biology of Normal Joint.
37. Zhong, W.D., Z.D. Han, H.C. He, X.C. Bi, Q.S. Dai, G. Zhu, *et al*., 2008. CD147, MMP-1, MMP-2 and MMP-9 protein expression as significant prognostic factors in human prostate cancer. Oncol., 7: 230-36.