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Comparison of serum levels of relaxin hormone and flexibility of active and inactive women

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Abstract
Introduction. **Changes in the concentration of the relaxin hormone are associated with changes in the structure of joints and the musculoskeletal system.** Aim of Study. **Therefore, this study aimed to compare the serum levels of relaxin and flexibility in active and inactive women.** Material and Methods. **This research was retrospective and included two groups consisting of active women (n = 8) and inactive women (n = 8) with an age range of 20-35 years, who were selected after a public call according to the inclusion and exclusion criteria of the research. Then, blood sampling and upper and lower limb flexibility measurements were performed. After collecting the data, Stata statistical software version 12 was used to analyze the data at a significant level of p < 0.05.** Results. **The research results showed that the serum levels of relaxin in active women were higher than in inactive women; but this mean difference was not statistically significant (p = 0.069 and t = 1.973). Also, the results indicated that only the relationship between relaxin and lower limb flexibility was statistically direct and significant (p = 0.006). Sports history is probably the cause of an increase in serum levels of the relaxin hormone in active young women. Moreover, the research results showed a significant relationship between the serum concentration of relaxin and the flexibility of the lower limb.** Conclusions. **Sports training in active young women increases the relaxin hormone, which may also be associated with increased flexibility, especially in the lower limbs (where it has the greatest effect on the musculoskeletal system).**

KEYWORDS: women, flexibility, joint, inactive, relaxin hormone, sports history.

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Introduction

A decrease in physical activity is associated with atrophy and a decrease in muscle strength; following immobility, the ligament, tendon, and joint capsule structure, especially their collagen composition, changes. Notably, collagen fibers and fibroblasts are out of their organized state and the mechanical properties of ligaments and tendons are changed, which leads to disorders and injuries of connective tissues [4]. Also, tendon disorders are common in athletes, including tendinopathy and incomplete and complete tendon tears. In particular, it has been mentioned that in most sports fields, about 50% of athletes have been dealing with tendon disorders during their sports careers [30]. Tendon disorders are related to age, gender, physical and sports activity type, occupation, and risk factors such as metabolic and cardiovascular diseases. Distinctly, it has been stated that the amount of tension or load on a tendon or a group of tendons is one of the critical factors causing tendon injuries. So, on average, about 30% of all sports injuries are attributed to these disorders [17]. Although rapid structural changes following acute bouts of sports activity can stimulate positive adaptations in tendons, in some circumstances, these changes may play a role in the development of tendon injuries. However, there is still little experimental evidence that the duration or intensity of sports activities can cause tendon disorders or positive adaptations in tendons [29]. Especially previous studies have shown that sports activity is an essential factor in the direction of hormonal stability and balance, and increasing awareness of biochemical and cellular-molecular markers can create a suitable platform for examining tendon response and adaptations, leading to sports activity [13]. One of the markers that have an important effect on the function of the musculoskeletal system is the relaxin hormone. It has been shown that the relaxin hormone, in connection with the estrogen hormone, can change the functioning of body systems. Relaxin plays a vital role in collagen metabolism in different body organs [23]. Also, several studies have shown the potential therapeutic effects of relaxin in treating cardiac, vascular, musculoskeletal and infertility diseases [7]. Also, it has been shown that the relaxin family peptides are structurally related to the insulin hormone and are potent regulators of collagen expression and fibroblast metabolism in various organs [7]. Regarding the effect of relaxin on tendons, findings indicate the control of the length of tendon growth and the reduction of tendon stiffness due to the increase in tendon laxity, which is applied by the effect of relaxin on the activation of collagenase [21]. In addition, the relaxin family peptides have been shown to be important in conducting signals between extracellular/intracellular terminals and to be activated in vertebrates as a neuropeptide in response to stress, perception and neurological diseases [26].

With sports activity, Olesen et al. [20] showed that in response to 36 km of running and after tissue removal from the Achilles tendon among six subjects of the experimental group and six subjects of the control group, the levels of procollagen type I C-peptide (PICP) and insulin-like growth factor binding protein-1 (IGFBP-1) in the serum and the tendon tissue increased. However, the values of insulin-like growth factor-1 (IGF-1) and carboxyterminal telopeptide of type I collagen (ICTP) did not show a significant change, indicating an increase in the biomarkers that strengthen the Achilles tendon structure. Also, in another study, Skovgaard et al. [25], using isotopic symptoms (fluorothymidine, FLT), investigated the amount of cell proliferation in the Ki-67 factor in the Achilles tendon of rats caused by exercise, and the results showed that the amount of FLT was up to 21%. It was increased in the Achilles tendon after running on a treadmill, which indicated an increase in cell proliferation in the Achilles tendon following short-term sports activity. However, another study [5] examining the breakdown of knee extensor tendon collagen after two bouts of 50 repetitions of eccentric and concentric movements, showed a change in the serum levels of hydroxyproline (HP) and collagen type I even nine days after the exercise. It was not seen. Also, Koskinen et al.'s study [16] showed that a one-hour treadmill running protocol with a positive incline is associated with an increase in tendon degradation biomarkers such as pro-matrix metalloproteinase-9 (pro-MMP9) and pro-matrix metalloproteinase-2 (pro-MMP2).

However, tissue metalloproteinase inhibitory proteins (TIMPs) were also increased. In addition, it has been shown that sports activity can effectively increase estrogen levels [13]. However, the effect of exercise training and exercise history on relaxin levels is unclear [27]. Notably, only two studies investigated the effects of sports activity on relaxin; one study was conducted on postmenopausal women, and the other one was conducted on mice. In particular, Rezvani et al. [22] investigated the effect of exercise training on relaxin in postmenopausal women, and their results showed a decrease in relaxin levels. However, another study showed increased relaxin levels in mice [18]. However, despite performed searches, it seems no other study investigated the effect of exercise or exercise history on relaxin levels, and the few published studies have conflicting results. On the one hand the health of tendons is considered a vital issue for athletes and even ordinary people (those involved in jobs such as carpentry, plumbing installations, building walls, musicians, and surgeons) [12] and on the other hand, the presence of tendon injuries and disorders has been estimated at 50% in most athletes (especially volleyball players) and 30% in runners, yet studies focusing specifically on this issue in female athletes are scarce or lacking [2]. It has not been done, therefore, the present research evaluated this new biomarker related to tendon health in active and inactive women.

Aim of Study

The present study aimed to compare the serum levels of relaxin and flexibility of active and inactive women.

Material and Methods

The current study was a retrospective study using two active and inactive women groups. The statistical population consisted of all active women who were selected according to the research criteria and after a public call in Mashhad city clubs. Then, among them and based on the determined sample size, eight subjects who met the criteria for entering the research were randomly selected. The present study included two groups of active and inactive young women with an age range of 20-35 years, who after a general call in Mashhad city clubs were selected according to the research inclusion criteria (regular exercise during the last three years; lack of experiencing severe stress or an unfortunate accident in the last six months, having a regular menstrual cycle and performing tests in the follicular period). The research exclusion criteria included amenorrhea or having an abnormal menstrual cycle, taking steroid drugs, not participating in the interview day, or refusing to fill out the consent form to participate in the research. Then, the qualified applicants were invited to partake. After getting acquainted with the objectives and steps of the research and filling out the consent forms, the subjects were assigned to active (n = 8) and inactive (n = 8) groups of women. Also, the homogenization criteria of active and inactive women groups in this research were based on normal distribution in demographic data (such as age, height, weight, and body mass index) prior to evaluating independent variables. Also, using statistical tests, the level of homogeneity of the groups in the demographic data expressed was measured and confirmed based on the evaluation of the sameness of variances in the indicators related to the dependent variables. It should be noted that the sample size selection criterion was based on a study that was conducted in this field and considering the conditions of the two-domain test, β-1 equals 0.95, alpha level 0.05, and effect size = 4.5. The number of six subjects was sufficient for each group, which was considered to be eight subjects in each group so as to increase the power of the test and prevent the dropout of subjects. Also, in all stages of the research, the principles of the Declaration of Helsinki and ethics in the research were observed (code 99-10-10-18063).

Personal profile forms and medical records were used to measure demographic indexes. Also, the Kaiser Physical Activity Assessment Questionnaire (KPAS) evaluated participants' physical activity level. The questionnaire assesses the habits and patterns of physical activity, especially in women, and includes four parts: activities related to housework and family care, job activities, active lifestyle habits, and participation in sports activities. It served to evaluate women aged 20 to 60 years, and its internal validity is also acceptable according to the studies conducted (α = 0.83). According to this questionnaire, women who had little physical activity in their normal and daily life and were non-athletes, i.e., did not have 3 to 5 years of regular sports experience, and in the last two months leading to the implementation of the present research, had participated in sports more than one session a week, were considered as the group of inactive women. Those who were active in a sport at the provincial and national level were considered the group of active women (participation in sports) [28].

Then, the subjects were asked to attend the medical diagnosis laboratory for blood sampling. For this purpose, they were asked to refrain from eating food, energizing substances, and drinking juices, tea, or coffee for at least 12 hours. Also, 48 hours before taking blood samples, the subjects were asked to refrain from vigorous physical and sports activities. Ten cc of blood was taken from the antecubital vein after the subjects entered the laboratory. To evaluate the concentration of serum relaxin, blood was drawn during the fasting state (centrifuge at a speed of 3000 rpm; duration 7 minutes; temperature 5 °C) and to measure the desired variables until the evaluation of all blood samples, in the conditions, they were stored in a freezer at –70 °C [24]. The serum concentration of relaxin was measured after transfer to the laboratory using the ELISA method and Crystal D, China kit. The sensitivity range of the kit was from 6 to 400 (pg/ml), the internal precision (CV) and the external precision were less than 8% and less than 10% respectively, with a wavelength of 450 nm. In addition, the subjects' body composition was measured with a body composition analysis device (Tanita BC-418, Japan). In the current research, the range of motion of the upper limbs in the state of arm hyperextension and hip hyperextension using a Saehan metal goniometer (South Korea) was used to evaluate the range of motion of the lower limbs.

Statistical analysis

In this research, to check and confirm the normality of the distribution of demographic data (such as age, height, weight and body mass index) before using the assumed statistical methods and evaluating the independent variables, the Shapiro–Wilk exploratory test was used. According to the results obtained from the test, all the variables were of normal distribution. As a result, to check the level of homogeneity of the groups and compare the averages for the relevant dependent variables, Lyon and Student's t-tests of independent groups were used. The results obtained from Lyon's test to evaluate the sameness of variances in indicators related to dependent variables and anthropometric indicators showed that all dependent variables had relative homogeneity before evaluating the independent variable.

After collecting the data, Stata statistical software version 12 (StataCorp LP, USA) was used to analyze it. Thus, the values of central tendency, mean dispersion and standard deviation were used to estimate the descriptive statistics of the research. In addition, the independent t-test was used to estimate the differences between groups, and the Pearson correlation coefficient test was used to determine the relationship between the variables. Also, SAS statistical software calculated the number of samples required to achieve significant levels, considering β-1 values equal to 0.95 and alpha level 0.05. A significant level of $p < 0.05$ was considered as a decision rule for testing the hypotheses.

Results

Comparing the average anthropometric sizes of active (n = 8) and inactive (n = 8) women using the parametric independent t-statistical test showed that this average difference in body weight variable was not statistically significant (t = 0.108 and p = 0.915). Also, the mean difference in the variable of body mass index was not statistically significant (t = 0.94, t = 0.74 and p = 0.74). This means there was no significant difference between active and inactive women in weight and body mass index ($p > 0.05$) (Table 1).

Also, the results of comparing the average upper limb flexibility of active (n = 8) and inactive (n = 8) women using independent t parametric statistical test indicated that this average difference in upper limb flexibility variable is not statistically significant (t = 1.53 and p = 0.147). Also, the mean difference in the lower limb flexibility variable was not statistically significant (t = 1.74 and p = 0.103) (Table 1).

The independent t parametric statistical test used to compare the average relaxin concentration in active (n = 8) and inactive women (n = 8) showed that this average difference in the relaxin variable is not statistically significant (t = 1.973 and p = 0.069). This means that the relaxin level in active women was higher than in inactive women; this average difference was not statistically significant ($p > 0.05$) (Figure 1). However, Cohen's d values about the effect size were equal to 0.987, which indicated a very high effect size in this regard.

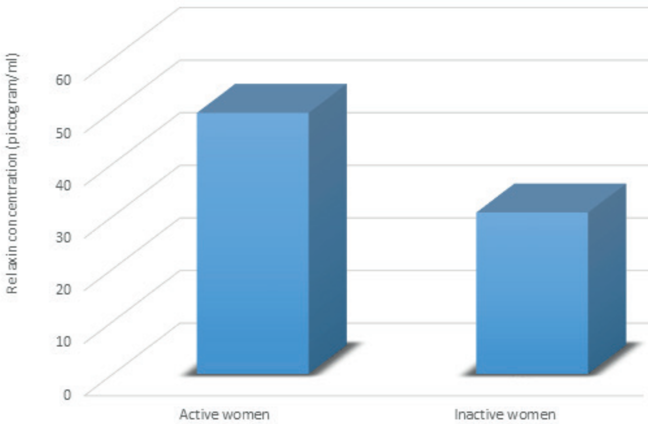

Figure 1. The serum concentration of relaxin in active and inactive women

Table 1. Between-group comparison of anthropometric measures (weight and body mass index) and flexibility of active and inactive women (n = 16)

Index	Groups	Post-test (M ± SD)	Intergroup t value	Significant level
Height	active women	169.75 ± 5.14	–0.108	0.915
	inactive women	170 ± 3.66		
Weight (kg)	active women	77.35 ± 5.6	–0.176	0.268
	inactive women	77.95 ± 8.17		
Body mass index (kg/m²)	active women	26.89 ± 2.2	–0.74	0.942
	inactive women	26.99 ± 2.39		
Upper limb flexibility (degree)	active women	73.57 ± 3.88	1.534	0.147
	inactive women	56.4 ± 5.34		
Lower limb flexibility (degree)	active women	69.12 ± 7.8	1.746	0.103
	inactive women	62.52 ± 9.7		

Note: M – mean, SD – standard deviation of the target group
Significance level accepted at $p < 0.05$.

Table 2. Correlation between relaxin concentration and anthropometric indices and flexibility in active and inactive women

Variable*		Age	Height	Weight	Body mass index	Upper limb flexibility	Lower limb flexibility
Relaxin	r	–0.301	0.161	0.155	0.239	0.135	0.556
	p	0.257	0.55	0.665	0.273	0.617	0.006*

In the table, r indicates the correlation coefficient and p indicates the significant values.
* the accepted significance level $p < 0.05$

The results of correlation measurement of relaxin concentration and anthropometric indices and average flexibility of active and inactive women, using Pearson's correlation coefficient statistical test, showed that only the relationship between relaxin and the average flexibility of the lower limbs is directly statistical and it was significant ($p = 0.006$). This means that relaxin has a direct relationship with the flexibility of the lower limbs, and with its increase, the flexibility of the lower limbs increases ($p < 0.05$). However, the relationship between relaxin levels and other variables was not statistically significant ($p > 0.05$) (Table 2).

Discussion

During sports activities and coordinated musculoskeletal movements, tendons play a central role in transferring force from muscle to bone [29]. The term overuse injury refers to sports activity medium to long-term effects on tendons. Collagen erosion or breakdown (36 hours) occurs earlier than collagen synthesis (up to 72 hours), especially in high-intensity exercises. Also, it is possible that ensuing stress and lack of adequate recovery will lead to erosion or analysis of the tendon matrix and, as a result, tendon damage. As stated, intense sports activity combined with insufficient recovery leads to the creation of inflammatory factors that may change the collagen synthesis-degradation cycle and cause tendon injuries [29]. Relaxin, as a peptide hormone, plays an essential role in biological processes related to tendons, and together with the estrogen hormone and growth factors such as transforming growth factor-beta, it initiates important processes in tissues. Also, an increase in the concentration of relaxin may be associated with laxity in the joint as well as tearing of the ligaments [8]. In addition, relaxin plays a vital role in musculoskeletal diseases [7]. With relaxin's important role in the musculoskeletal structure of body tissues and the fact that the effect of exercise or sports history on this hormone is not known, this study aims to compare the serum levels of relaxin and flexibility of active and inactive women.

Regarding the role of sports activity and inactivity on tendon health, studies on both sides of this spectrum showed that on the one hand, people with low physical activity have excessive tendon thickness and tendinopathy, and on the other hand exercising for at least 36 hours leads to tendon breakdown exceeding its synthesis [14]. The comparison of the two groups of inactive and active women showed that the serum concentration of the relaxin hormone was higher in active women than in inactive women (38%), and this difference was not statistically significant. However, the values of Cohen's d in relation to the effect size were equal to 0.987, which indicated a very high effect size and the lack of significance was probably due to the low number of subjects. In particular, it can probably be said that exercise is associated with an increase in relaxin hormone concentration in active women. In other words, sports history is probably the reason for the increase in the relaxin hormone [9]. Also, the research results showed a significant relationship between the concentration of relaxin serum and lower limb flexibility. This means that the history of sports training in active women increases the relaxin hormone. According to studies, this hormone is also associated with increased flexibility, especially in the lower limbs (where it has the most significant effect on the musculoskeletal structure).

Relaxin has seven polypeptides that are structurally similar to the insulin hormone, including relaxin type 1, relaxin type 2, relaxin type 3, insulin-like peptide type 3, insulin-like peptide type 4, insulin-like peptide type 5, and insulin-like peptide type 6 [3]. Relaxin type 1 and relaxin type 2 are potent regulators of metabolism and collagen expression in fibroblasts, which are expressed from the corpus luteum, decidua, endometrium, and prostate tissue, and relaxin type 3 is expressed in the brain. By binding to polypeptide receptors, relaxin performs its actions through the ligand-receptor system [15]. In the meantime, relaxin is an osteoclast activating factor in bone resorption on the one hand, and on the other hand relaxin type 2 has its effect on bone tissue by regulating the metabolism and proliferation of human osteoblasts [10]. Also, relaxin along with estrogen helps to reduce inflammation by increasing anti-inflammatory cytokine 10 (IL-10) and is effective in improving arthritic diseases [11]. Regarding ligaments, the relaxin hormone changes the mechanical properties of the ligament due to its collagen lytic effect (collagen breakdown), which is done by matrix metalloproteinases, collagenases, and plasminogen activators. For example, one study stated that female athletes with high relaxin serum levels had an increased risk of anterior cruciate ligament rupture compared to female athletes with lower relaxin levels [8]. Regarding the effect of relaxin on muscles, studies indicate that relaxin improves wound tissue, muscle repair and satellite cell activity by using articular cartilage stiffness by inducing collagenase-1, matrix metalloproteinases type 1 and 3, which is associated with a decrease in collagen content and expression of fibrocartilage cells [19].

Regarding the effect of relaxin on tendons, the findings indicate the control of tendon growth length and the reduction of tendon stiffness due to the increase in tendon laxity, which is applied by the effect of relaxin on the activation of collagenase [21] and it has been shown that relaxin can also play an essential role in collagen catabolism of symphysis pubis in mice [23]. Therefore, the increase in the flexibility of the lower limbs in active women is likely due to the catabolism role of this hormone in the lower limbs. The present study showed a significant relationship between relaxin levels and the flexibility of the lower limbs in young women. However, it seems likely to witness a two-sided effect in connection with increasing changes in relaxin and flexibility levels in women. Regarding the effect of training on relaxin levels, the results of the present research conflict with the results of the study by Rezvani et al. [22]. Relaxin can help menopausal women to avoid menopausal complications. However, contrary to them and in agreement with the present research results, Mir et al. [18] investigated the effect of different exercise intensities on serum levels of relaxin in ovariectomized rats. They concluded that after ovariectomy, the levels of this hormone decrease, but intense sports activities are associated with an increase in the concentration of this hormone. The present study findings regarding the effect of exercise on relaxin levels indicated that the concentration of the relaxin hormone in active women is higher than that of inactive young women. In other words, exercise training caused increased changes in relaxin concentration, which was associated with greater flexibility of the lower limbs. Comparing the research conditions between the two above-mentioned studies, it seems that the second study has more generalizability than the first one in terms of controlling the conditions and the nature of the research, which was of the experimental research type. The intensity of the sports activity is an important factor in changes in the relaxin hormone. Regarding physical inactivity and its relationship with tendon analysis, Corrigan et al. [6] showed that in 30 subjects with low physical activity compared to 23 individuals with high physical activity, physical inactivity is associated with an increase in tendon thickness. Also, people with low physical activity reported more severe tendinopathy than the other group. The results of this research were in line with the results of the current research, both of these studies showed that low level of physical activity is a risk factor related to tendon health. Confirming the results of this research, Abate et al. [1] stated that a lack of physical activity is associated with an increase in tendinopathy. On the other hand, Kaux et al. [14] showed in a review article that cases such as overuse syndrome, especially in endurance sports, cause injuries in people who regularly participate in sports activities. Also, these effects have been confirmed by Tardioli et al. [29]. The results of this research regarding increased flexibility values, especially in the lower limbs, were in line with the present research results. However, due to the small number of studies conducted on the history of exercise training and relaxin, caution should be used in generalizing the research results, and it seems that more studies should be conducted on the effect of exercise training and relaxin to determine the correlation. Among the limitations of the current research we can point out the lack of long-term study of the subjects and the effect of sports training on inactive women as a result of the outburst of the COVID-19 pandemic and consequently the lack of up-to-date training record. It was investigated and addressed. In addition, as mentioned, the low number of subjects affected by the mentioned conditions was another limitation of the present research.

As a result, the present research findings showed that the serum levels of the relaxin hormone were higher in active women than in inactive women (38%). In other words, the history of sports training is probably at the cause of the increase in the relaxin hormone. Also, the research results showed a significant relationship between relaxin serum concentration and lower limb flexibility. This means that sports training in young women increases the relaxin hormone and according to studies, the increase of this hormone is also associated with an increase in flexibility, especially in the lower limbs (where it has the greatest effect on the musculoskeletal structure).

Conclusions

Therefore, considering the positive effects of relaxin on different tissues of the body and the reduction of this hormone by reducing physical activity and the effect of this hormone in reducing injuries in active people, it is possible to increase the concentration of relaxin by performing sports activities. Finally, due to the importance of relaxin in the process of rebuilding and healing damaged ligaments/tendons and muscles, it is suggested that sports activity be used as a suitable treatment method (at least three days a week). Therefore, regular physical activity (at least three days a week) may be considered a non-pharmacological strategy to support the prevention and rehabilitation of musculoskeletal injuries by promoting relaxin-mediated tissue repair.

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Conflict of Interest

The authors have no conflicts of interest to report.

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