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The role of the Activin–Inhibin–Follistatin system in regulating bone metabolism in postmenopausal women affected by osteoporosis.

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Abstract :

Background: Postmenopausal osteoporosis (PMOP) is a common type of osteoporosis that occurs when a lack of estrogen after menopause leads to a rapid loss of bone. The amount of bones that are reabsorbed reaches the maximum within 2 to 3 years after menopause. The activin-follistatin-inhibin (AFI) hormonal pathway influences bone metabolism. It has been discovered that ACT stimulates the pituitary gland to secrete the hormone FSH, while the INH and FST hormones inhibit the FSH secretion. **Methodology:** 90 women with and without (control group) osteoporosis participated in the study. A blood sample was collected; serum was utilized for the estimation of a range of biochemical tests by using Sandwich-ELISA. **Results:** The findings indicated that the average follistatin level for women with osteoporosis (21.17 ± 24.17) was higher than the control group (10.14 ± 10.39). The results of the current study revealed significant differences (P = 0.00027) in the inhibin rate among the studied groups. At the same time, the ACTIVIN rate was higher in women with osteoporosis (191.33 ± 101.14) than in the group of women without osteoporosis (134.85 ± 40.28), with significant differences at the probability level (P = 0.002). **Conclusion:** The study data indicate major changes in the AFI system in postmenopausal osteoporosis.

Keywords: Postmenopausal osteoporosis, activin, Inhibin, Follistatin.

دور أكتيفين-إنهبين-فوليستاتين في تنظيم عملية التمثيل الغذائي للعظام لدى النساء بعد انقطاع الطمث المصابات بهشاشة العظام

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مستخلص:

الخلفية: هشاشة العظام بعد انقطاع الطمث (PMOP) هي نوع شائع من هشاشة العظام، يحدث عندما يؤدي نقص هرمون الإستروجين بعد انقطاع الطمث إلى فقدان سريع للعظام. تصل كمية العظام التي يُعاد امتصاصها إلى أقصى حد لها في غضون سنتين إلى ثلاث سنوات بعد انقطاع الطمث. يؤثر المسار الهرموني أكتيفاتين-فوليستاتين-إينهبين (AFI) على استقلاب العظام. وقد اكتُشف أن هرمون أكتيفاتين-فوليستاتين-إينهبين يُحفز الغدة النخامية على إفراز هرمون FSH، بينما يُثبط هرمونا INH و FST إفراز FSH. **طرق العمل:** شاركت في الدراسة 90 امرأة مصابة بهشاشة العظام وغير مصابات بها (مجموعة ضابطة). جمعت عينة دم، واستُخدم مصل الدم لتقدير مجموعة من الاختبارات الكيميائية الحيوية باستخدام اختبار ساندويتش-إليزا. **النتائج:** أشارت النتائج إلى أن متوسط مستوى فوليستاتين لدى النساء المصابات بهشاشة العظام (24.17 ± 21.17) كان أعلى منه لدى المجموعة الضابطة (10.39 ± 10.14). وكشفت النتائج عن فروق ذات دلالة إحصائية (P = 0.00027) في معدل إنهيبين لدى مجموعات المرضى المدروسة. في الوقت نفسه، كان معدل الأكتيفين أعلى لدى النساء المصابات بهشاشة العظام (101.14 ± 191.33) منه لدى النساء غير المصابات بهشاشة العظام (40.28 ± 134.85)، مع فروق ذات دلالة إحصائية على مستوى الاحتمال (P = 0.002).

الكلمات المفتاحية: هشاشة العظام، انقطاع الطمث، أكتيفين، إنهيبين، فوليستاتين .

Introduction

Postmenopausal osteoporosis is a common type of osteoporosis, when a lack of estrogen after menopause leads to a rapid loss of bone. Menopause is the result of a failure of ovarian function, accompanied by a decrease in hormone levels, which increases the risk of many diseases [1]. Menopause is often accompanied by fatigue, sleep disturbance, depression, anxiety, bone and joint pain, hot flashes, and sweating [2]. Long-term lack of hormones leads to the risk of osteoporosis, heart disease, and blood vessel disease [3]. There are a variety of hormones that play an important role in organizing bone metabolism. When females get older, the ovarian reserve function decreases, the exhaustion of the eggs is accelerated, and estrogen levels decrease in the body, and thus the possibility of osteoporosis increases [4, 5].

Activin (ACT), inhibin (INH), and follistatin (FST) were initially isolated in the mid-1980s from humans, pigs, rats, and other mammals as a stimulating hormone organization (FSH) [6]. It has been discovered that ACT stimulates the pituitary gland to secrete the hormone FSH, while the INH and FST hormones inhibit the FSH secretion. The FSH hormone is essential for sexual growth and reproduction, as it sends signals to the ovaries of females to produce estrogen and control ovulation and menstruation cycles, while signals are sent to the testes in males to produce testosterone and regulate the formation of sperm [7, 8]. Thus, the ACTIVIN-FOLLISTIN-Inhibin (AFI) axis is an important glandular hormonal system for animal reproductive functions [9]. Despite the secretion of ACT, FST, and INH at their highest levels by pituitary cells and reproductive glands to regulate reproduction, subsequent studies have shown that these proteins from the AFI axis are also manufactured by many non-reproductive tissues and organize many additional biological activities [10]. Activins are diodes that consist of subunits βA or βB either in the form of heterosexuals (βaβb) or symmetricals (αβαβ or βBβB), while the fold of activin's subunits Aβ or βB with a subunit α leads to the formation of inhibins (αβα or αββ) [11]. The activins (A, B) and the inhibins (A, B) belong to the family of the beta-transformed growth fac-

tor (TGF-β) and are highly expressed in the pituitary gland, the gonads, the placenta, and the corpus luteum [12]. Activins enhance the secretion of the stimulating hormone (FSH) of the pituitary gland, while the inhibins have an opposite effect as organizers of negative feedback to secrete the hormone [13]. Thus, both have a role in organizing the menstrual cycle. At the same time, they have paracrine (exterior) effects associated with the development of ovarian follicles and steroid formation, which are two important processes for reproductive function (genital). In particular, during the formation of follicles in natural sessions, the Inhibin A is mainly secreted from dominant follicles, along with the estrogen E2 and progesterone of the corpus luteum [14]. Follistatins are sugary proteins that neutralize many biological effects. Specifically, follistatin (FST) is mainly secreted from the liver, pituitary gland, and ovaries, and it is the main inhibitor of Activin A [15]. Follistins reflect the topical effects of activins, especially on the secretion of the hormone FSH in the pituitary glands, and stimulate the luteinization process [12]. It should be noted that during pregnancy, the chorionic fetal unit is the main source of activin A in the serum [16], while inhibins and follistatins are also expressed greatly by the placenta and fetal membranes [17]. The study aimed to evaluate the level of activin, inhibin, and follistatin in women with postmenopausal osteoporosis due to the role of these hormones in the menstrual cycle, which may have affected the bone.

Methods

Study design

During the period from July 2024 to February 2025, 90 participants were included in the study, of whom 30 were control women, and 60 women had been diagnosed with postmenopausal osteoporosis by the specialist after measuring BMD and T-SCOR by using a bone density unit (DXA), and their ages ranged from 50 to 80 years. The samples were collected from women who were recruited from various locations to Azadi Hospital and from special clinics in Kirkuk Governorate. Each patient completed a customized questionnaire.

Sample collection

(3 ml) Blood samples drawn via venipuncture were collected for ev-

ery postmenopausal woman with and without osteoporosis by medical syringes, and the samples were placed in gel tubes and left for a minimum of 15 minutes at room temperature. Then it was separated by the centrifuge for a period of 5 min at 4000 rpm, and then the serum was isolated in sterile and labeled PLAN Tube plastic tubes and kept at a temperature of 20°C in preparation for conducting biochemical and hormonal tests.

Biochemical test

Sandwich-ELISA assessed the concentration of activin, inhibin, and follistatin, which were measured by using the prepared kit from SUNLONG-China, according to the manufacturer's instructions. The analytical sensitivities of the assays were 0.1 pg/mL for activin, 1 pg/mL for inhibin, and 0.6 ng/mL for follistatin."

Statistical analysis

A statistical analysis was conducted for all study samples and all immune and physiological tests using SPSS version 27.0, the T-test for the average calculation, and standard deviation (SD).

Results and discussions

1- Follistatin levels in females with osteoporosis:

The results of the current study showed the presence of significant differences (P = 0.009) at the level of follistatin in the studied groups, where the rate in women with osteoporosis (24.17 ± 21.17) was higher than in the control women's group (10.39 ± 10.14), as shown in Table (1).

Table(1): mean level of Follistatin in the osteoporosis women compared with control

variable	Patient group	Control group
Follistatin ng/mL Mean ± SD	**24.1721.17 ±**	**10.39±10.14**
P value	**0.009**	

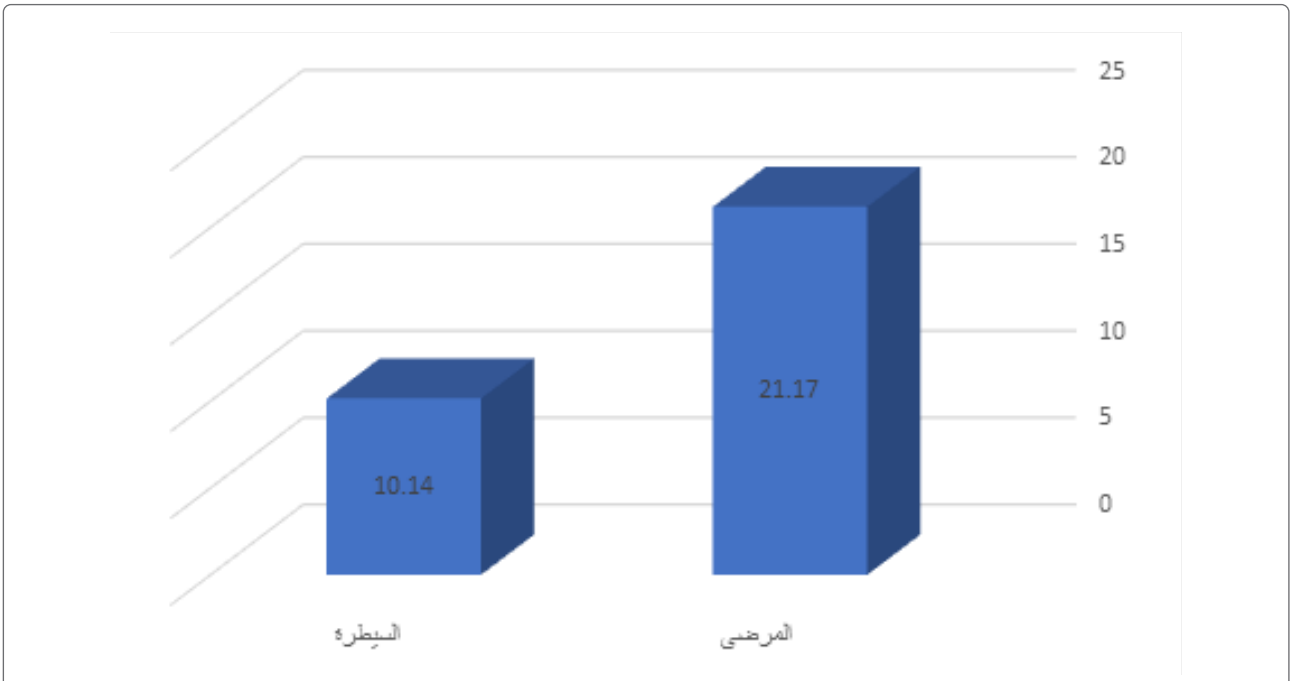

Figure 1. A comparison of FST (Follistatin) levels between the patient group and the control group

The study, conducted in Iraq by WAHEED and others [18], showed that the levels of follistatin were higher in women with osteoporosis and also agreed with the study conducted by Al-Kafaji et al. [19], which showed high levels of follistatin in women with osteoporosis compared to healthy women, and this indicates a possible relationship between the high level of follistatin and the development of osteoporosis in Iraqi women.

The high levels of follistatin were associated with a decrease in mineral density in the bone and osteoporosis, as some studies indicate that follistatin may play a role in reshaping the bones by inhibiting the effects of Activin A, which is a protein involved in bone growth and development (Bowser et al.) [20]. Jürimäe et al. [21] also showed the association of follistatin in serum with mineral values in the bones in the slim teenage girls with increased physical activity. Follistatin was an independent indicator of mineral density in the bones of the cotton spine, which mostly consists of spongy bones.

Follistatin stimulates the composition of bone cells and increases the bone mass and its density, and excessive expression of follistatin leads to

an increase in bone mass (Chan et al.) [22]. A recent study found that women with osteoporosis after menopause have higher levels of follistatin in their blood compared to healthy women before menopause, and these high levels are linked to lower bone density. Also, high levels of follistatin in women with osteoporosis after menopause are associated with bone mineral loss. This indicates that follistatin may be associated with osteoporosis in women after menopause[23].

In osteoporosis patients, elevated follistatin levels are generally associated with increased bone mass and density. Follistatin, primarily known for its role in muscle growth, also influences bone metabolism by inhibiting myostatin and activin signaling pathways. These pathways are involved in regulating bone formation and resorption. By suppressing myostatin, follistatin promotes bone formation by stimulating osteoblastogenesis (the development of bone-forming cells) and increasing bone mass. Additionally, follistatin can indirectly affect bone health by influencing muscle mass, as muscle contraction and hypertrophy (muscle growth) are associated with increased follistatin (Han et al.)[24].

2- Inhibin levels in women with osteoporosis

The results of the current study showed the presence of significant differences (P = 0.00027) in the inhibin rate in the studied groups, where the rate in women with osteoporosis (230.9 ± 286.02) was higher than the control group (70.85 ± 130.6), as shown in Table (2).

Table (2): mean level of Inhibin in the osteoporosis women compared with control

Variable	Patient group	Control group
Inhibin pg/ml Mean ± SD	**286.02 ± 230.9**	**130.65 ± 70.8**
P value	**0.00027**	

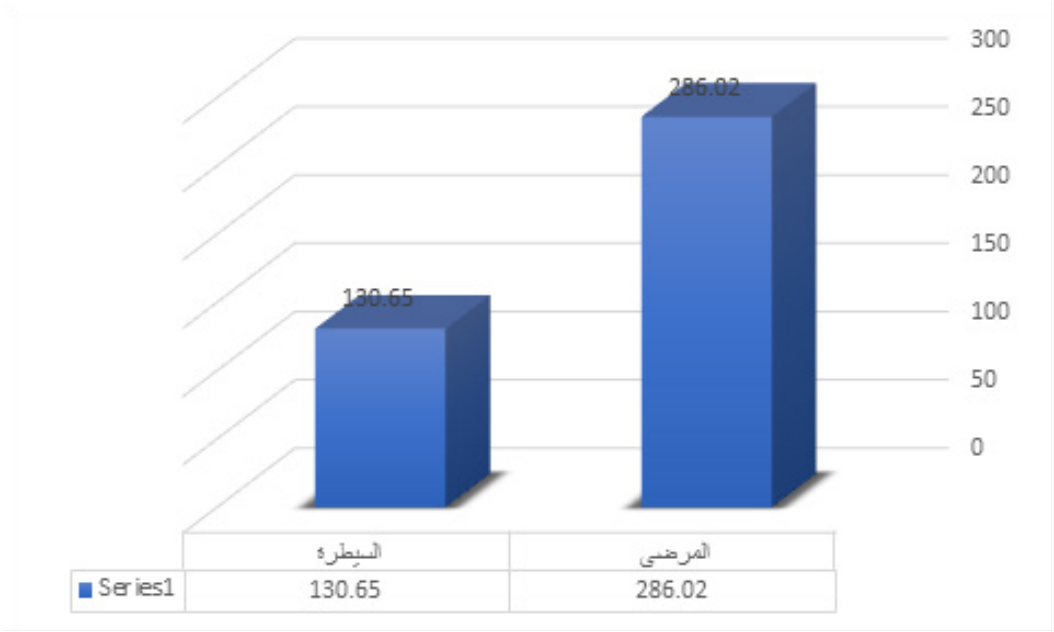

Figure 2. A comparison of INHA levels between the patient group and the control group

Studies have indicated that the levels of Inhibin B were lower in women after menopause with osteoporosis compared to women with natural bone density, indicating that Inhibin B may play a role in the development of osteoporosis during menopause. Studies also indicate that the decrease in inhibin B and the high activin A, B, AB, and follistatin are linked to a decrease in the density of minerals in the bones of the lumbar spine and osteoporosis MA et al.,[25]. Our results did not agree with the study of Wen et al. [26], which showed a decrease in INHB content in women who suffer from osteoporosis of menopause, which was associated with the presence of osteoporosis.

Karim et al. [27] also mentioned that the INHB level has a positive relationship with the level of mineral density in the bone, indicating that INHB may be associated with the presence of osteoporosis. A study conducted by Anastasilakis et al. [23] confirmed that INHB is an independent risk of osteoporosis after menopause in women and can be considered a diagnostic vital sign of the disease. Inhibin A and Inhibin B levels in the serum are also linked to the signs of bone formation and bone absorption in women in the pre-menopause period. In a study by Perien et al. [28], they emphasized the

positive effect of inhibin A on bone formation and strength, indicating its potential treatment role in preventing bone loss associated with osteoporosis.

When menopause occurs, and even before the estrogen levels of the serum, the selective decrease in INHB levels may cause a topical increase in the activity of the bone marrow activin and the activity of BMP. The increased activity of activin and BMP activity, as well as slight increases in FSH, strengthens the polarization of bone cells and the differentiated cells of the bone, leading to an increase in the bone turnover rate and their later loss (Welt et al.) [13].

In women after menopause, and in conjunction with the loss of stabilized estrogen and FSH height, the levels of the overall inhibin decreased significantly, which leads to an additional increase in the activity of activin/BMP and an increase in the differentiation of marrow cells. Increased activity of activin and BMP activity may enhance bone reshaping, whose levels have increased significantly as a result of estrogen loss (Gilmer et al.) [29]. Although bone loss and osteoporosis, ultimately after the loss of the genital glands, were previously attributed to the lack of estrogen only, these data indicate that the contributions of derivative endocrine inhibitors may also play an important role in organizing bone turnover throughout the reproductive life period (Nicks et al.) [30].

Inhibins A and B are gonadal peptide members of the transforming growth factor-beta superfamily that serve as negative feedback regulators of pituitary follicle-stimulating hormone (FSH). Accumulating evidence suggests that bone turnover and bone loss increase in women before menopause and the decrease in serum estradiol levels. Increased FSH levels have been correlated with some of these perimenopausal changes, whereas decreased inhibins strongly correlate with increases in bone formation and resorption across the menopause transition, and predict lumbar bone mass in perimenopausal women, likely resulting from the direct inhibin suppression of osteoblast and osteoclast development. Interestingly, continuous exposure of mice to inhibin A in vivo is anabolic and protective against gonadectomy-induced bone loss(Gaddy et al.) [31].

3- Activin levels in women with osteoporosis

The results of the current study showed that the ACTIVIN rate was higher in women with osteoporosis (101.14 ± 191.33) than in the control group (40.28 ± 134.85), with a significant difference at the probability level (P = .002), as shown in Table (3).

Table(3): mean level of Activin in the osteoporosis women compared with control

variable	Patient group	Control group
Activin pg/ml Mean ± SD	**191.33 ± 101.14**	**134.85± 40.28**
P value	**0.002**	

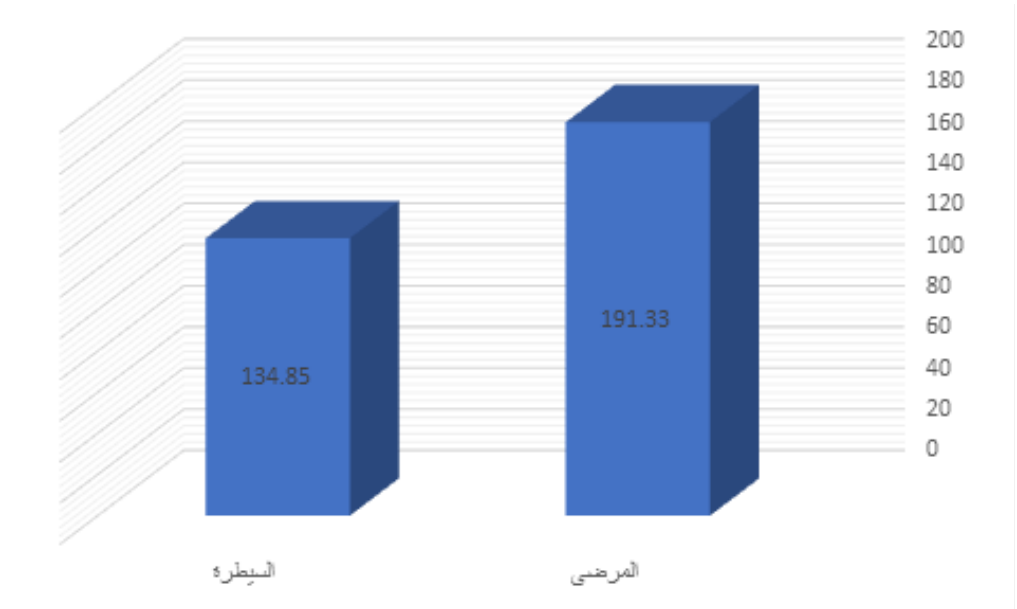

Figure3. A comparison of ACTV (Activin) levels between the patient group and the control group

ACV-A is one of the growth factors and is a member of the beta-transformed growth factor (TGF-β), a protein that plays a role in bone density, where studies indicate its ability to change the density of minerals in the

bone, and also has a major role in inflammation [32]. Some research indicates that activin-A may inhibit the bone cells (Pierce and Perien [33]), while other studies have shown its ability to stimulate bone formation directly. The high levels of activin-A in women after menopause are associated with a decrease in bone mineral density (MILS et al.) [34].

The study by Anastasilakis et al. [35] indicated that the levels of activin are often high in osteoporosis patients, especially those who suffer from low bone mass. The high levels of activin A are associated with age and are negatively related to the intensity of minerals in the bones of the cotton spine. A study conducted by Leto et al. [36] also showed that activin is the main cause of bone metastasis, a type of malignant tumor that results in bone tumor invasion. Therefore, it can be considered a target for a more specialized therapeutic approach in the treatment of skeletal metastasis, and it may also be useful as an additional, vital chemical indicator of metastatic bone diseases. The role of Activin A in the metabolism of bone was multi-faceted. While the high levels of activin A in women after menopause are linked to a decrease in the density of minerals in the bone, indicating a reinforcement effect (Anastasilakis et al.) [35]. Other studies also indicate that Activin A may enhance the differentiation of bone cells and prevent the formation of osteoclasts of bone, indicating the properties of bone construction. Therapeutic interventions, such as teriparatide, may contribute to their bone-forming effects by regulating the levels of activin. These results shed light on the complexity of the role of Activin A in bone health and the need to conduct more research to clarify its potential as a treatment target for osteoporosis (Lodberg et al.) [37].

4-Correlation Analysis among ACTV, FST, and INHA Levels

The results revealed a significant positive correlation between ACTV and FST ($P = 0.000$; $r = 0.527$), as well as between ACTV and INHA ($P = 0.022$; $r = 0.296$). A strong positive correlation was also observed between FST and INHA ($P = 0.000$; $r = 0.661$), as shown in Figure 4

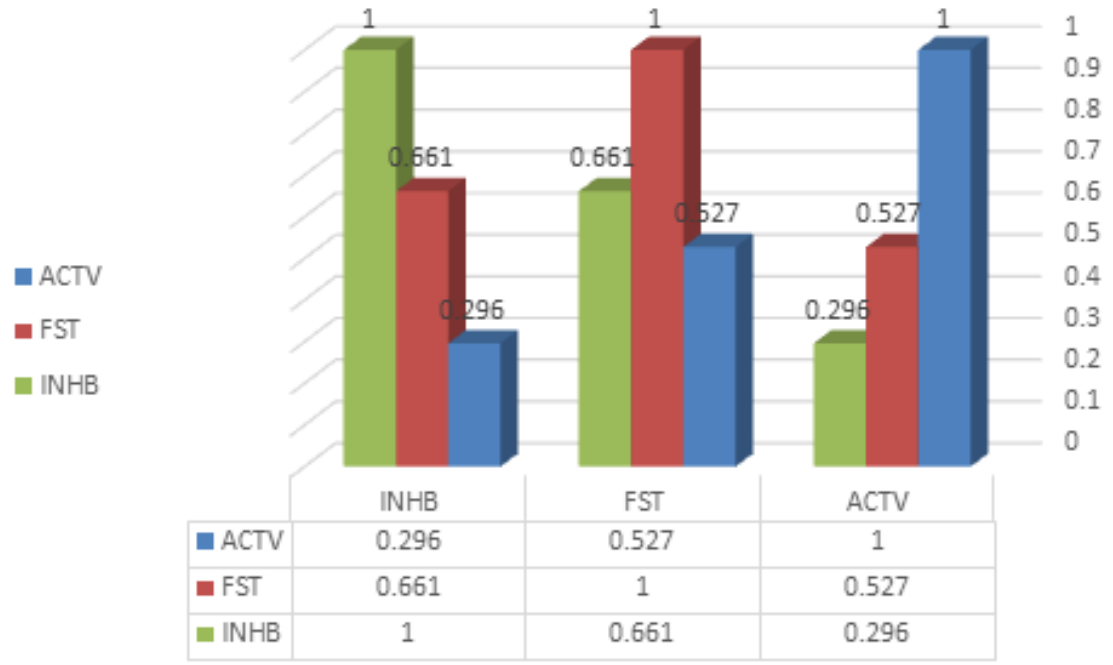

Figure 4. Illustration of the correlations among the studied biomarkers (ACTV, FST, and INHA)

Conclusion:

An increase in AFI hormones may be an indicator of hormonal changes that may lead to osteoporosis, although further studies are needed to confirm this. We suggested that further studies are needed to directly evaluate the relationship between hormones and bone density.

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