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Effects of saxagliptin on postmenopausal osteoporosis in rats: an investigation into its anti-inflammatory and anti-osteoporotic properties

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ABSTRACT
Background: Saxagliptin (SAXA) is one of the dipeptidyl peptidase-4 inhibitors (DPP-4i), awidely used drug class in the management of type 2 diabetes mellitus (T2DM).Through modulating cytokine production, DPP-4i appear to exhibit anti-inflammatory benefits. Worldwide, up to one-third of women over 50 suffer from postmenopausal osteoporosis (OP), which is abone condition that makes affected bones susceptible to fractures. In postmenopausal OP, estrogen deficiency enhances the inflammatory cytokine production, promoting bone resorption. The central focus of this study was to explore the possible impacts of SAXA on bone remodeling and inflammation in a rat model of OP, and to compare these effects with those of calcitonin (CT).
Materials and methods: For the induction of OP, the two ovaries of female Sprague-Dawley rats were removed. Two weeks post-ovariectomy (OVX), rats of the CT group, the SAXA group, and the SAXA-CT combination therapy group started to receive CT (5 U/kg/d, 5 days/week, by S.C. injections), SAXA (2 mg/kg/d, by oral gavage), and combination therapy, respectively, from the 15th day post-OVX and lasted for 4 weeks. Then, all rats were euthanized. Serum Procollagen type I N propeptide (PINP) as a marker of bone formation, carboxy-terminal telopeptide of type I collagen (CTX-I) as a marker of bone resorption, and tumor necrosis factor-α (TNF-α) were assayed, with histological examination of femoral bone sections.
Results: OVX caused a notable deterioration in bone histopathology, a substantial decrease in serum PINP, a substantial increase in serum CTX-I, and a marked elevation of serum TNF-α levels relative to the sham group. All these findings were significantly reversed by CT, SAXA, and combination therapy, with the latter group showing the most significant results.
Conclusion: SAXA suppressed TNF-α, leading to anti-osteoporotic and anti-inflammatory effects that ameliorated OVX-induced OP.

Keywords: Osteoporosis, bone remodelling, DPP-4 inhibitor, saxagliptin, calcitonin, PINP, CTX, TNF-α.

1. INTRODUCTION

OP is the most common worldwide bone condition, characterized by diminished BMD, which makes the impacted bones vulnerable to fractures (Song et al., 2022). OP affects an estimated 200 million people globally, with most of them being elderly adults ≥ 60 years old(Noh et al., 2020). Typically, OP presents no detectable symptoms unless it progresses to a fracture, primarily affecting the spine and hips (Mu et al., 2021). The diagnosis of OP is primarily established by assessing bone mineral density (BMD) by non-invasive dual-energy X-ray absorptiometry (DEXA) (Tu et al., 2018). OP is typically categorized as primary or secondary. The primary condition results from an abrupt decline in sex hormones and age-related physiological degenerative processes. Postmenopausal and senile OP are the most common forms in humans. Secondary OP, constituting approximately 10% of overall cases, may be precipitated by illnesses or drugs (Mu et al., 2021).
Despite its apparent static nature, bone tissue undergoes continuous cycles of modeling and remodeling (Allen & Burr, 2014). Bone remodeling involves a well-controlled sequence of simultaneous resorption and formation at a given location. It regenerates aged and damaged bone to maintain skeletal integrity (Föger-Samwald et al.,

2020). Typically, bone resorption slightly exceeds bone formation. In conditions such as postmenopausal OP, resorption significantly outweighs formation, resulting in bone loss and weakened bone microarchitecture (Allen & Burr, 2014; Rochefort & Benhamou, 2013). Disorders of the bones, including OP, rheumatoid arthritis, osteomyelitis, and metastatic cancer, can develop when there is an imbalance in the process of bone anabolism and catabolism (Schiellerup et al., 2019).

Insufficient estrogen in the female body reduces osteo-anabolic and anti-osteoclastic actions, leading to ongoing bone deterioration. Furthermore, estrogen normally influences various immune cells, leading to a sustained low-grade pro-inflammatory phenotype when estrogen is deficient (Fischer & Haffner-Luntzer, 2021). T lymphocytes release TNF-α, increasing osteoblast apoptosis and facilitating osteoclastogenesis through B lymphocytes' secretion of receptor activator of nuclear factor kappa-B ligand (RANKL),triggering bone loss in postmenopausal OP (Roggia et al., 2001).

OP medications are classified as either antiresorptive agents (bisphosphonates, denosumab, estrogen agonists/antagonists, estrogens, and CT) or anabolic agents (parathyroid hormone analogues or romosozumab) (Tu et al., 2018). Nevertheless, numerous medications exhibit significant side effects or are inappropriate for prolonged usage. Consequently, it is imperative to formulate more efficacious treatment agents grounded in the novel pathophysiology of OP (Song et al., 2022).

Among the anti-diabetic medications arethe DPP-4i, which encompass SAXA. These drugs affect blood glucose level by increasing the half-lives of incretins, glucose-dependent insulinotropic polypeptide (GIP), glucagon-like peptide-1 (GLP-1). Numerous anti-diabetic medications are linked to diverse risk concerns, such as hypoglycemia, bone fractures, weight gain, cardiovascular problems, renal abnormalities, and additional comorbidities. This led to the development of a novel treatment approach, namely incretin-based therapy, emphasizing DPP-4i (Ramanathan, 2017).

Numerous experimental model studies have revealed that immune cells overexpress GLP-1R mRNA, which affects peripheral T cell proliferation and pro-inflammatory cytokines and chemokines. Incretin hormones and their derivatives can diminish inflammation by affecting lymphocyte proliferation, activation, and emigration patterns, reducing pro-inflammatory cytokines, chemokines, and adhesion molecules, and decreasing macrophage infiltration. GLP-1 has been demonstrated to lower TNF-α levels in human cell cultures, showing anti-inflammatory effects (Radbakhsh et al., 2021).

This study was designed to explore the possible impacts of SAXA on bone remodeling and inflammation in a rat model of OP, and to compare these effects with those of CT.

2. MATERIALS AND METHODS

2.1. Drugs

Saxagliptin powder (Haosen Pharmaceutical Group Co., Ltd, Jiangsu, China), Calcitonin ampoules (Calcitonium® 50 IU/ml, ACDIMA International Trading Company, Cairo, Egypt), Ketamine vials (Ketamax 50® 50 mg/ml, Troikaa Pharmaceuticals Company, Ahmedabad, India), Xylazine vials (Xyla-Jcet® 100mg/ml, ADWIA Company, 5th Settlement, New Cairo, Egypt), and Ketoprofen ampoules (Ketofan® 100mg/2ml, AMRIYA PHARM. IND. Company, Alexandria, Egypt).

2.2. Animals

Forty (40) female Sprague-Dawley rats (3 months old, 250-300 g body weight) were bought from the Medical Experimental Research Center (MERC), Faculty of Medicine at Mansoura University. Rats were maintained under specific pathogen-free conditions, acclimated for 1 week at room temperature (23±2 ℃) and humidity (55±5%) in a 12-h light/dark cycle before the experiments with free access to food and water.

The Local Ethical Committee of the Faculty of Medicine at Mansoura University approved the experimental methodology for this study, which was consistent with the Ethics Committee of Egypt's National Research Center and the Guide for the Care and Use of Laboratory Animals, Eighth Edition (2011)**(Council, 2011)**. All surgical procedures were conducted at the MERC, with all possible measures used to alleviate the animals' pain. All hazardous items and deceased rats were disposed of hygienically following the completion of the tests.

2.3. OP induction by OVX

Rats were randomly allocated into five experimental groups, with eight rats in each group. They were subjected to identical housing circumstances.Rats wereanesthetized under aseptic conditions via intraperitoneal injection of a ketamine (75 mg/kg) and xylazine (10 mg/kg) mixture(Flecknell, 2015), subsequently positioned in a supine orientation on the surgical board. The abdomen was depilated and disinfected with Betadine and alcohol swabs. The abdominal skin was elevated using sterile forceps. A 1 cm midline incision through the skin and muscles was performed with sterile scissors to access the peritoneal cavity. Following the ligation of the blood vessels, the connections between the Fallopian tube and the uterine horn were severed bilaterally, and both ovaries were removed (while not removed in the sham group), after which the skin incisions were repaired with a single suture, as shown in Figure 1. After the surgery, the rats were placed on warmer pads and closely

observed until they had recovered from anaesthesia (Olson & Bruce, 1986; Sankar et al., 2014). Then for three days,rats were given ketoprofen (S.C., 5mg/kg/day) (Roughan & Flecknell, 2001; Spofford et al., 2009).

2.4. Animal groups and Treatments

No specific treatments were administered during the first two weeks following the operation (to allow for the development of OP). Beginning two weeks post-operation (from the 15th day post-operation), the rats started receiving the different treatments for 4 weeks. Negative control group (Sham group) rats underwent abdominal incisions and suturing without concomitant oophorectomy then received normal saline as S.C. injections (0.5 ml/kg/d) and oral gavage (5 ml/kg/d), Positive control group (OVX) rats underwent OVX then received normal saline (as previous group), CT group (OVX + CT) rats underwent OVX then received CT (5 U/kg/d, 5 days/week, by S.C. injections) (C.-Y. Hsiao et al., 2020), SAXA group (OVX + SAXA) rats underwent OVX, then received SAXA (2 mg/kg/d, dissolved in normal saline solution, by oral gavage) (Sbaraglini et al., 2014)and CT-SAXA group (OVX + CT + SAXA) rats underwent OVX, then received a combination treatment of CT and SAXA with the same previous doses.There was a loss of some rats in some groups during the operation and in the first post-operative days (one rat from the OVX group, one rat from the CT group, two rats from the SAXA group, and one rat from the CT-SAXA group).Four weeks following the beginning of the treatment intervention, all rats were euthanized by i.p. injection of ketamine (320mg/kg) /xylazine solution (32mg/kg)(American Veterinary Medical Association, 2020; University of Rochester Medical Center, 2020).

2.5. Biochemical assessment

Blood was obtained from the carotid arteries and permitted to coagulate at ambient temperature for 20-30 min. before centrifugation at 3000 rpm for 10-15 min. at 4°C. The resultant clear serum was meticulously collected and preserved at -80°C until analyzed**(**G. Huang et al., 2025). Enzyme-linked immunosorbent assay (ELISA) testing was done toassess serum PINP (using rat PINP ELISA kit, Wuhan Fine Biotech Co., Ltd., China, Cat. No. ER1265), CTX-I (using rat CTX-I ELISA kit, AFG Bioscience LLC, USA, Cat. No. EK720901), and TNF-α (rat TNF-α ELISA kit, BioLegend, Inc., San Diego, USA, Cat. No. 438204), as the ELISA method described by Crowther (2000)and as per the manufacturer's guidelines.

2.6. Histopathological assessment

The femurswere excised and preserved in 10% neutral buffered formalin (pH 7.4) for 24 hours, followed by decalcification with a 10% EDTA solution(Callis & Sterchi, 1998). Longitudinal sections of 5 µm were prepared and stained with hematoxylin and eosin for histological analysis. Histomorphometric parameters were assessed utilizing ImageJ software (version 1.53c, NIH, USA) by a pathologist who was unaware of the study concept. The femurs were examined in the trabecular bone-dense ‘secondary spongiosa area’ (Elvy Suhana et al., 2011). The histomorphometric parameterswere bone volume /tissue volume (BV/TV, %), trabecular thickness (Tb. Th, µm), trabecular number (Tb. N, 1/mm), and trabecular separation (Tb. Sp, µm)(Parfitt et al., 1987).

2.7. Statistical analysis

The data were analysed with the Statistical Package for the Social Sciences (SPSS) program for Windows (Standard version 24). The Shapiro-Wilk test, the ANOVA test, and the post hoc LSD test were used. A P-value of 5% is statistically significant. The results were classified as'significant' when $P < 0.05$ and 'non-significant when $P > 0.05$.

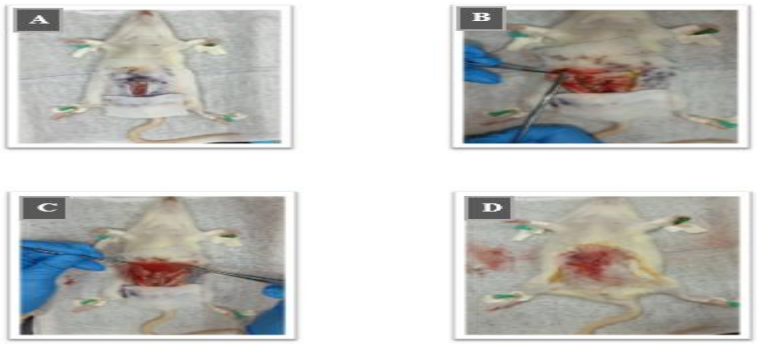

Figure 1:Representative intraoperative steps of OVX: (**A**) **midline cut through the skin and muscles, (B) ligation of blood vessels, (C) cutting the connection between the Fallopian tube and the uterine horn with removal of ovaries at both sides, and (D) suturing muscles and skin wounds.**

3. RESULTS

3.1. Effects of CT and SAXA on serum PINP

As shown in Figure 2A, OVXinduced a significant ($P \leq 0.001$) decrease in serum PINP relative to the negative control group. Administration of CT to rats with OVX-induced OP significantly ($P = 0.003$) increased serum PINP relative to the OVX group, but non-significantly ($P = 0.993$) increased serum PINP relative to the SAXA-treated OVX group. Administration of SAXA to rats with OVX-induced OP significantly ($P = 0.005$) increased serum PINP relative to the OVX group. Concurrent administration of SAXA with CT to rats with OVX-induced OP significantly increased serum PINP relative to the OVX group ($P \leq 0.001$), CT-treated OVX group ($P \leq 0.001$), and SAXA-treated OVX group ($P \leq 0.001$).

3.2. Effects of CT and SAXA on serum CTX-1

As shown in Figure 2B, OVXinduced a significant ($P \leq 0.001$) increase in serum CTX-I relative to the negative control group. Administration of CT to rats with OVX-induced OP significantly ($P \leq 0.001$) decreased serum CTX-I relative to the OVXgroup, but non-significantly ($P = 0.147$) decreased serum CTX-I relative to the SAXA-treated OVX group. Administration of SAXA to rats with OVX-induced OP significantly ($P \leq 0.001$) decreased serum CTX-I relative to the OVX group. Concurrent administration of SAXA with CT to rats with OVX-induced OP significantly decreased serum CTX-I relative to the OVX group ($P \leq 0.001$), the CT-treated OVX group ($P = 0.001$), and the SAXA-treated OVX group ($P \leq 0.001$).

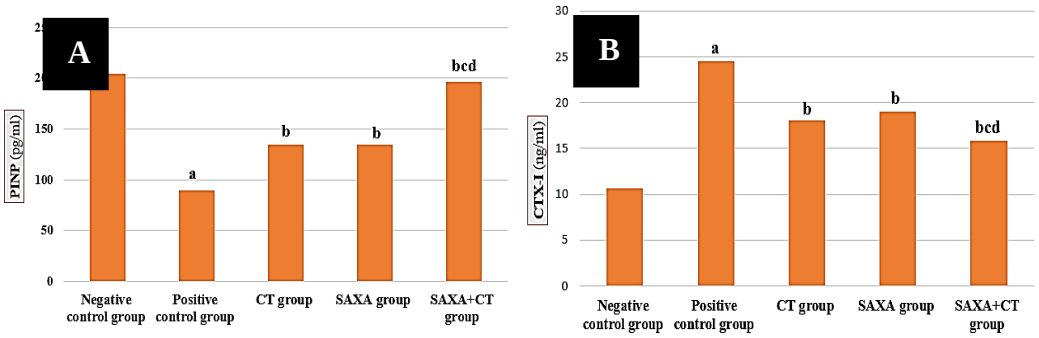

Figure 2:Effects of CT and SAXA on serum PINP (A) and CTX-1 (B): 'a' significance*in relation to* the negative control group, 'b' Significance *in relation to* the OVX group, 'c' Significance *in relation to* the CT group, and 'd' Significance *in relation to* the SAXA group.

3.3. Effects of CT and SAXA on serum TNF-α

As shown in Figure 3, OVXinduced a significant ($P \leq 0.001$) increase in serum TNF-α relative to the negative control group. Administration of CT to rats with OVX-induced OP significantly ($P \leq 0.001$) decreased serum TNF-α relative to theOVXgroup, and non-significantly ($P = 0.258$) decreased serum TNF-α relative to SAXA-treated OVX group. Administration of SAXA to rats with OVX-induced OP significantly ($P \leq 0.001$) decreased serum TNF-α relative to the OVX group. Concurrent administration of SAXA with CT to rats with OVX-induced OP significantly decreased serum TNF-α relative to the OVX group ($P \leq 0.001$), the CT-treated OVX group ($P \leq 0.001$), and the SAXA-treated OVX group ($P \leq 0.001$).

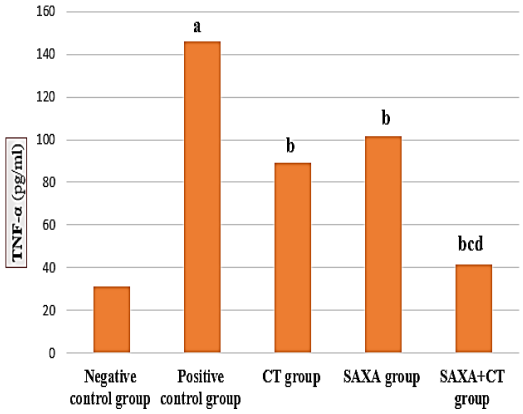

Figure 3:Effects of CT and SAXA on serum TNF-α: 'a' significance in relation to the negative control group, 'b' Significance in relation to the OVX group, 'c' Significance in relation to the CT group, and 'd' Significance in relation to the SAXA group.

3.4. Effects of CT and SAXA on histomorphometric parameters of the Femur

As shown in Figures 4 and 5, OVX (in the OVX group) induced a significant decrease in femur BV/TV ($P \leq 0.001$), Tb. Th($P \leq 0.001$) and Tb. N($P \leq 0.001$) with a significant increase in Tb. Sp ($P \leq 0.001$), relative to the negative control group. CT significantly increased femur BV/TV($P \leq 0.001$), Tb. Th ($P = 0.007$), Tb. N ($P \leq 0.001$) with a significant decrease in Tb. Sp ($P \leq 0.001$), relative to theOVXgroup. SAXA significantly increased femur BV/TV($P \leq 0.001$), Tb. Th ($P = 0.021$) and Tb. N ($P \leq 0.001$) with a significant decrease in Tb. Sp ($P \leq 0.001$), relative to theOVX group. The combination therapy of SAXA and CT significantly increased femur BV/TV($P \leq 0.001$), Tb. Th ($P \leq 0.001$) and Tb. N($P \leq 0.001$) with a significant decrease in Tb. Sp ($P \leq 0.001$), relative to theOVXgroup.

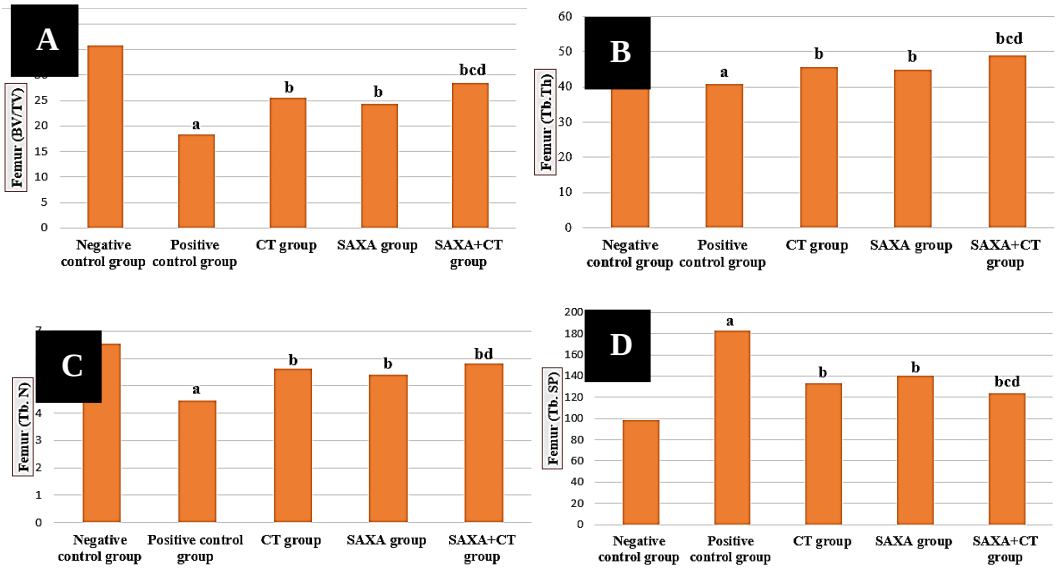

Figure 4: Effects of CT and SAXA on femur BV/TV (A), Tb. Th (B), Tb. N (C), and Tb. Sp (D): 'a' significancein relation to the negative control group, 'b' Significance in relation to the OVX group, 'c' Significance in relation to the CT group, and 'd' Significance in relation to the SAXA group.

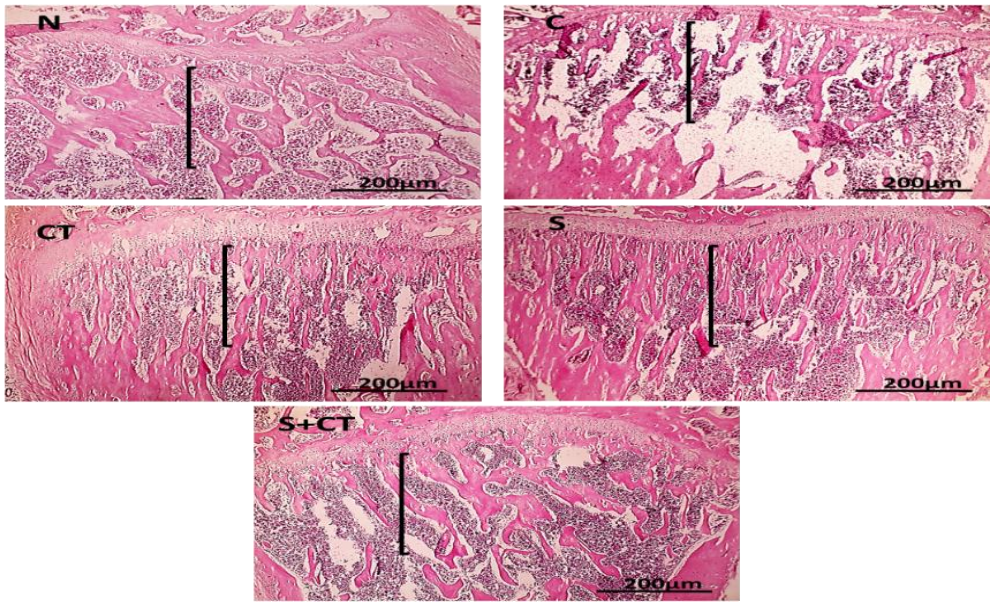

Figure 5:Effects of CT and SAXA on histomorphometric parameters of the femur: Microscopic pictures of H. & E.-stained sections of the femur showing a marked reduction in Tb. Th and Tb. N with increased Tb. Sp at the metaphyseal region ([) in the OVX group (C) when compared to the metaphyseal region in femur sections from the negative control group (N). These parameters are reversed in the treated groups: CT-treated (CT), SAXA-treated (S), and SAXA+CT-treated (S+CT). Magnification x:40 bar 200

4. DISCUSSION

The bilateral OVX model is widely used in preclinical research to study postmenopausal OP. This model is critical for understanding the biology of OP and creating effective treatments that reduce or halt OP progression (Jhong et al., 2022).

This study induced OP in rats via bilateral OVX. Thereafter, serum levels of PINP, CTX-I, and TNF-α were assessed, and histological analysis was performed on femoral bone sections.

The necropsy verified the success of the OVX, as no ovarian tissue was found, and the uterine horns had markedly atrophied.

Our study showed that OVX caused a substantial decrease in serum PINP, which means that bone formation was inhibited, and a substantial increase in serum CTX-I, which means that bone resorption was exacerbated. Histological analysis similarly demonstrated a substantial decrease in BV/TV, Tb. N, and Tb. Th, accompanied by a significant increase in Tb. Sp, indicating a deteriorating trabecular bone architecture.The histological findings of the OVX group are consistent with the previous report of Estaiet al. (2011). Also, the changes in serum PINP and CTX-I levels align with previous findings of Tao et al. (2022).

The groups treated with CT, SAXA, and combination therapy reversed all the serum and pathological findings of the OVX group, with the group that received combination therapy having the most favourable results overall.

The findings of the CT group are consistent with those ofWashimi et al. (2007),Kuo et al. (2012) and C. Y. Hsiao et al. (2020). CT is recognized mainly as an anti-resorptive agent. It attaches to its receptors (CTR) located on the surface of osteoclasts, causing removal of the ruffled border, cell retraction, and reduction of cell motility, ultimately inhibiting bone resorption (Chambers et al., 1984). Canonical wingless-int (Wnt) signaling is essential in numerous biological processes, including cellular proliferation, tissue regeneration, and various systemic consequences (Shi et al., 2016). Wnt signaling constitutes a primary anabolic pathway for bone formation (Baron & Hesse, 2012).CT promotes bone formation by enhancing the osteoclast expression of Wnt10b, a Wnt ligand recognized as a bone formation-stimulating factor generated from osteoclasts, termed ‘clastokine’ (C. Y. Hsiao et al., 2020).

The findings of the SAXA group agree withCusick et al. (2013) and Glorie et al. (2014), who noted that diabetic rats given sitagliptin (DPP-4i) had far lower serum CTX-I levels than animals given a placebo. Also, Glorie et al. (2014)reported thatsitagliptinimproved the reduction in Tb. N and the increase in Tb. Sp, improving trabecular bone structure indiabetic rats.Also, these findings are consistent withL. Huang et al. (2024),who reported an increase in BMD with DPP-4i, with a significantly reduced likelihood of OP.

The gut-bone axis connects the GIT to the bones and is governed by intestinal hormones,GIP, GLP-1, and peptide YY, triggered by food intake, resulting in less bone resorption. DPP4i can affect the gut-bone axis by lengthening GIP and GLP-1 half-lives (Schiellerup et al., 2019).The receptors of these hormones are widely distributed in the body(Baggio & Drucker, 2007; Drucker, 2006). There is growing evidence that these enteric hormones regulate bone turnover and metabolism physiologically. GLP-1 directly stimulates osteoblast proliferation and differentiation, increasing bone anabolism(Kainuma et al., 2016; Yamada et al., 2008). The GIP receptor has been identified in osteoblasts, with a role in inhibiting apoptosis (Bollag et al., 2001; Tsukiyama et al., 2006). GIP receptors have been identified on osteoclasts, inhibiting bone resorption(Zhong et al., 2007).

Moving beyond this point, both heightened bone catabolism and diminished bone anabolism can be triggered by hyperglycemia; hence, SAXA provides an additional indirect route by mitigating the harmful effects of hyperglycemia on bone remodeling, thereby enhancing bone health (Napoli et al., 2017; Starup-Linde et al., 2014).

In contrast to SAXA’s results, Sbaraglini et al. (2014)reported that orally administered saxagliptin adversely affects rat femoral micro-architecture.

Moreover, the combination therapy utilizing SAXA and CT yielded the most substantial enhancement, approaching normalization, of bone histology. Additionally, the most advantageous alterations in biochemical markers were observed. This can show a synergistic link between the two medications, whereby each may boost the other's efficacy to provide enhanced bone protection.

This study assessed systemic inflammation by measuring serum TNF-α levels. OVX resulted in a notable elevation of serum TNF-α levels, in relation to the sham group, indicating the exacerbated inflammatory condition linked to estrogen deficiency. The findings of the OVX group align with Orsal et al. (2013) and Seif (2014). This might be accounted for by the generation of free radicals by bone marrow, causing T-cell activation with production of several pro-inflammatory cytokines, especially TNF-α (Grassi et al., 2007).

Treatment of OVX rats with CT, SAXA, and the combination therapy led to a substantialdecline in serum TNF-α levels in relation to the OVX group, with the most substantial reduction in TNF-α levels occurring in the group of combination therapy.

This study is, to our knowledge, the first experimental animal investigation examining the influence of CT on the serum inflammatory cytokine TNF-α, while several prior studies have only partially examined CT's anti-inflammatory properties, asBobalik et al. (1974)and Abdullahi et al. (1977), whoreported CT's potential anti-

inflammatory effects in rodent models of adjuvant arthritis. CT may mitigate soft tissue inflammation in adjuvant arthritis via a mechanism distinct from its effect on bone. Rat adjuvant arthritis is an immunological response to an antigen in mineral oil; thus, Ca modulation may alter the immune process (Abdullahi et al., 1977; Bobalik et al., 1974; Braun et al., 1970).

In earlier studies of different inflammatory disorders, SAXA has demonstrated the ability to decrease serum TNF-α levels. DPP4 promotes the mitogen-activated protein kinase (MAPK) signaling pathway, thereby eliciting an inflammatory response in T2DM. Wronkowitz et al. (2014) found that this effect can be alleviated via inhibition of DPP4 production. Additionally, SAXA can also altermacrophages'function, halting inflammation (Yang et al., 2018). Also, it may inhibit the nuclear factor-kappa B (NF-κB) signalling pathway (Zhou et al., 2019).

SAXA and CT administered together showed the greatest decline in TNF-α levels. To date, studies have not explored CT with DPP4i like SAXA; however, it has been studied with other anti-osteoporotic drugs. Our data suggest this combination may improve OP management synergistically.

While numerous prior studies have examined CT in conjunction with antiresorptive medications, there exists an absence of evidence regarding its efficacy when combined with any DPP-4i, such as SAXA. The combination of SAXA and CT enhanced bone pathology and inhibited inflammatory mediators. This indicates that SAXA-CT may function synergistically and could have translational significance for postmenopausal OP therapy.

While the current study sheds light on the potential anti-inflammatory and anti-osteoporotic benefits of SAXA alone and in conjunction with CT in OP therapy, certain limitations should be acknowledged. A prolonged treatment period is required to assess long-term skeletal repercussions. Future investigations involving prolonged treatment periods and comprehensive evaluations of bone turnover are essential to clarify the effects of CT, SAXA, and their combination in OVX-induced OP.

In conclusion, in this OVX-induced osteoporotic rat model, SAXA treatment dramatically reduced bone tissue histological deterioration, which was coupled with a notable reduction in serum TNF-α levels, indicating an anti-inflammatory action. This research revealsthe therapeutic promise of the DPP-4i SAXA, which is commonly used for diabetes management, as a novel modulator of bone anabolism and catabolism, most likely through the inhibition of inflammation-bone interactions. SAXA can successfully mitigate OP by lowering TNF-α levels, hence influencing the inflammatory aspect of OP. This emphasizes the potential dual advantages of DPP-4i, which exceed their established anti-hyperglycemic effects and encompass a favorable impact on bone health, underscoring the prospective dual benefit of SAXA in diabetic osteoporotic patients. The combination of SAXA and CT resulted in significantly improved therapy outcomes, including a superior decrease in bone pathology and higher suppression of inflammatory mediators. These findings show the synergistic efficacy of the SAXA-CT combination and the potential for translational implications for the treatment of postmenopausal OP. Further studies are warranted to validate the anti-osteoporotic and anti-inflammatory effects of SAXA in OP.

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