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Protective Effect of Coenzyme Q10 on Diabetic Bone Loss by Targeting Oxidative Stress, and TLR4/NFκB Pathway

Efecto Protector de la Coenzima Q10 Sobre la Pérdida Ósea Diabética Mediante la Modulación del Estrés Oxidativo y la Vía TLR4/NFκB

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SUMMARY: Diabetic osteoporosis is a major complication of Type 1 Diabetes Mellitus (T1DM), driven by hyperglycemia, oxidative stress, inflammation, and apoptosis of osteogenic cells. This study investigated the protective role of coenzyme Q10 (CoQ10) on bone loss in a rat model of T1DM. Forty male Wistar rats were divided into four groups: control, CoQ10 alone, untreated diabetic, and diabetic treated with CoQ10 (50 mg/kg/day for 8 weeks). Diabetes was induced by streptozotocin injection. We performed biochemical, histological, and molecular analyses. Results showed that diabetic rats exhibited hyperglycemia, reduced osteocalcin, elevated bone resorption markers (CTX-1, TRACP 5b), and dysregulated regulatory proteins (RUNX2, OPG, RANKL). Histological examination revealed trabecular bone loss and marrow cavity expansion. CoQ10 supplementation significantly enhanced osteogenic activity, suppressed osteoclast function, and restored trabecular architecture. Antioxidant enzyme activities (SOD, CAT, GPx) were markedly improved in CoQ10-treated diabetic rats. Moreover, CoQ10 downregulated the TLR4/NF-κB signaling pathway and decreased proinflammatory cytokines (TNF-α, IL-6, IL-1β). Apoptotic markers (Bax and caspase-3) were reduced, while the anti-apoptotic protein Bcl-2 was elevated, confirming the anti-apoptotic effect of CoQ10. In conclusion, CoQ10 supplementation mitigates diabetes-induced bone loss through antioxidant, anti-inflammatory, and antiapoptotic mechanisms. These findings highlight CoQ10 as a promising adjunctive therapy for preserving bone health in T1DM.

KEY WORDS: Diabetes mellitus; Coenzyme Q10; Osteogenic; Oxidative stress; Inflammation; Apoptosis.

INTRODUCTION

Type 1 diabetes mellitus (T1DM) is a chronic condition characterized by the selective destruction of pancreatic beta cells, resulting in persistent hyperglycemia (American Diabetes Association, 2014). This state is associated with serious long-term vascular complications, including retinopathy, neuropathy, and nephropathy (Thrailkill *et al*., 2005; Motyl & McCabe, 2009; American Diabetes Association, 2014).

While often receiving less attention, skeletal disorders are a recognized complication of diabetes. The connection is well-established and involves a complex pathogenesis that arises from an interplay of mechanical, hormonal, and vascular factors that ultimately lead to an imbalance between bone formation and bone resorption.

Significant distinctions exist between diabetic osteoporosis (DOP) and postmenopausal osteoporosis (PMOP). DOP is primarily driven by the metabolic disturbances of diabetes. Chronic hyperglycemia inhibits osteoblast proliferation and function, stimulates osteoclast differentiation and activity, and reduces osteocalcin expression, while also promoting calcium loss and a subsequent decline in bone mineral density (BMD) (Chandran *et al*., 2018). In contrast, postmenopausal osteoporosis is chiefly caused by elevated bone resorption resulting from estrogen deficiency. This fundamental difference extends to treatment strategies: managing DOP first necessitates stringent glycemic control, after which bone parameters often improve, leading to a relatively shorter treatment course. Conversely, postmenopausal osteoporosis typically requires long-term, continuous management (Starup-Linde & Vestergaard, 2015).

While insulin effectively lowers blood glucose, it can simultaneously suppress bone turnover. Furthermore,

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hormone-based therapies are associated with side effects, including breast cancer, hypoglycemia, headaches, and flu-like symptoms (Sahasrabudhe *et al*., 2017). Conventional osteoporosis treatments, such as bone resorption inhibitors (e.g., bisphosphonates) or bone formation promoters (e.g., raloxifene), are also costly and can cause adverse effects like gastrointestinal irritation (Both *et al*., 2018). Consequently, identifying a safe and effective natural product for the prevention of DOP is a necessary and valuable endeavor.

Coenzyme Q10 (CoQ10), also referred to as ubiquinone, is a fat-soluble, vitamin-like compound. It is a crucial component of the electron transport chain, where it contributes to the production and regulation of cellular energy (Groneberg *et al*., 2005; Linnane *et al*., 2007). Due to its bioenergetic and potent antioxidant capabilities (Littarru & Tiano, 2007), CoQ10 is widely used in managing numerous conditions, including cardiovascular, metabolic, neurological, and reproductive disorders, as well as cancer (Jolliet *et al*., 1998). It has also been shown to help prevent bone disease by modulating the differentiation of osteoblasts and osteoclasts (Moon *et al*., 2013). Despite this, its efficacy as a therapeutic intervention for diabetic osteoporosis remains poorly understood.

Consequently, this study was designed to investigate the therapeutic potential of CoQ10 and to elucidate its underlying mechanisms in a diabetic rat model with associated bone loss.

MATERIAL AND METHOD

Experimental animals

Our study utilized forty male Wistar rats with an initial body weight of 220 ± 20 g. Throughout the experimental period, the animals were housed individually under controlled environmental conditions, maintaining a constant temperature of 24 °C and a relative humidity of 50 ± 5 %. All rats had ad libitum access to a standard chow diet and distilled water.

Induction of Diabetic Model and CoQ10 Treatment

Following a seven-day acclimatization period, diabetes was induced in rats assigned to the model group via a single intraperitoneal injection of streptozotocin (STZ; Sigma-Aldrich, USA) at a dose of 60 mg/kg, freshly prepared in 0.1 M citrate buffer (pH 4.5), as previously described (Zheng *et al*., 2018). Control animals received an equivalent volume of the citrate buffer vehicle. After 72 hours, blood glucose levels were measured using an ACCU-CHEK Advantage® glucometer (Roche Diagnostics, USA). Rats exhibiting venous blood glucose concentrations ≥16.7 mmol/L were considered diabetic and included in subsequent experiments.

The animals were then randomly allocated into four experimental groups (n = 10 per group) to evaluate the effects of CoQ10 treatment:

- Control group (CON): Non-diabetic rats receiving only the vehicle (cottonseed oil) without STZ induction.
- CoQ10-alone group: Non-diabetic rats receiving oral CoQ10 (50 mg/kg/day) dissolved in cottonseed oil via gavage for eight weeks, serving as a negative control.
- Untreated diabetic group (T1DM): Rats rendered diabetic by STZ injection and subsequently receiving only the vehicle without CoQ10.
- CoQ10-treated diabetic group (T1DM + CoQ10): Diabetic rats treated with CoQ10 at 50 mg/kg/day orally via gavage for eight weeks.

CoQ10 was dissolved in cottonseed oil for administration, while the CON and T1DM groups received cottonseed oil as a vehicle. Body weight and blood glucose levels were monitored weekly throughout the study. The CoQ10 dosage was selected based on the protocol described by Wu *et al*. (2020).

Analysis of Serum Biomarkers of Bone Metabolism and oxidative stress

Upon completion of the 8-week treatment period, all animals were fasted for 12 hours and subsequently euthanized under deep anesthesia induced by isoflurane overdose. Blood samples were collected from the abdominal aorta and centrifuged at 4 °C for 15 min to obtain serum. The serum levels of key bone turnover markers and regulatory proteins were quantified using commercially available enzyme-linked immunosorbent assay (ELISA) kits, following the manufacturers' instructions. The analyzed markers included bone formation and resorption indicators: osteocalcin (OC; cat# abx051840, detection range: 31.2–2000 pg/mL), C-terminal telopeptide of type I collagen (CTX-1; cat# abx155410, detection range: 0.12–10 ng/mL), and tartrate-resistant acid phosphatase 5b (TRACP 5b; cat# abx256068, detection range: 0.156–10 ng/mL). Additionally, serum concentrations of osteoprotegerin (OPG; cat# E-EL-R3005, detection range: 15.63–1000 pg/mL), receptor activator of nuclear factor kappa-B ligand (RANKL; cat# E-EL-R0841, detection range: 15.63–1000 pg/mL), and runt-related transcription factor 2 (RUNX2; cat# MBS760533, detection range: 0.313–20 ng/mL) were determined to evaluate bone regulatory activity.

Furthermore, the serum activity of the antioxidant enzymes superoxide dismutase (SOD; Cat# E-EL-R1424, detection range: 0.16-10 ng/mL), catalase (CAT; Cat# CSB-E13439r, detection range: 93.75-6000 mIU/mL), and glutathione peroxidase (GPx; Cat# E-EL-R2491, detection range: 31.25-2000 pg/mL) was also determined.

Histological Analysis

Tibiae were harvested and carefully dissected to remove all soft tissues. The bones were fixed in 2 % PLP fixative at 4 °C and subsequently processed for histological evaluation. Following fixation, the samples were decalcified in a 14 % EDTA-glycerol solution for 5–7 days at 4 °C. Once decalcified, the specimens were dehydrated, embedded in paraffin, and sectioned at a thickness of 5 μm using a rotary microtome. The resulting sections were stained with hematoxylin and eosin (H&E) and examined under a light microscope for morphological assessment.

Quantification of TLR4/NF-κB signaling, Apoptotic, and Anti-apoptotic Markers by ELISA

To evaluate key signaling pathways and apoptotic regulators, homogenates were prepared from 100 mg of proximal tibial cortical bone using dry ice, a region selected for its high osteocyte concentration. The homogenates were centrifuged at 1000 × g for 10 min at 4 °C, and the resulting supernatant was analyzed using commercially available ELISA kits according to the manufacturers' protocols. Specifically, the concentrations of high mobility group protein B1 (HMGB1; cat# ER0291, range: 31.25–2000 pg/mL), Toll-like receptor 4 (TLR4; cat# MBS705488, range: 0.625–40 ng/mL), its downstream adaptor protein MyD88 (cat# MBS2703631, range: 78–5000 pg/mL), and the transcription factor NF-kB (cat# RK08775, range: 0.16–10 ng/mL) were quantified to assess TLR4/NF-κB pathway activity. In addition, inflammatory cytokines including TNF-α (cat# MBS175904, range: 15.6–1000 pg/mL), IL-6 (cat# ERA31RB, range: 30–10,000 pg/mL), and IL-1b (cat# BMS630, range: 31.3–2000 pg/mL) were measured. The apoptotic cascade was evaluated by determining the levels of caspase-3 (cat# CSB-E08857r, range: 0.312–20 ng/mL), the pro-apoptotic protein Bax (cat# CSB-EL002573RA, range: 62.5–4000 pg/mL), and the anti-apoptotic protein Bcl-2 (cat# CSB-E08854r, range: 0.312–20 ng/mL).

Statistical analysis

All data were analyzed using GraphPad Prism software version 8.0 (GraphPad Software, USA) and are presented as the mean ± standard deviation. For the comparison of parametric variables across groups, a one-way analysis of variance (ANOVA) was performed, which was followed by Tukey's post-hoc test for multiple comparisons. A probability value of less than 0.05 ($p < 0.05$) was considered to indicate statistical significance.

RESULTS

CoQ10 Attenuates Hyperglycemia and Modulates Bone Remodeling in a Type 1 Diabetic Model

As illustrated in Figure 1, rats in the T1DM group exhibited a significant elevation in blood glucose levels ($p < 0.05$), accompanied by a reduction in the bone formation marker osteocalcin and a marked increase in bone resorption markers, including CTX-1 and TRACP 5b. Additionally, regulatory proteins involved in bone cell differentiation showed notable changes: RUNX2 (associated with osteoblast differentiation) was significantly increased, while both OPG and RANKL were elevated, indicating enhanced osteoclast activity compared to the control group.

In contrast, the T1DM + CoQ10 treatment group demonstrated a marked reduction in blood glucose levels and favorable modulation of bone metabolism markers. CoQ10 administration enhanced osteogenic activity, reduced bone turnover, and suppressed osteoclast function relative to the untreated T1DM group.

Histological examination using H&E staining of tibial sections revealed a pronounced decline in bone trabeculae and expansion of bone marrow cavities in the T1DM group (Fig. 2E, F), compared to the control (Fig. 2A, B) and CoQ10-only treated groups (Fig. 2C, D), both of which displayed normal histological architecture. Notably, diabetic rats treated with CoQ10 for 8 weeks showed substantial improvement in the histological structure of bone trabeculae and bone marrow (Fig. 2G, H), indicating a protective and restorative effect of CoQ10 on bone integrity under diabetic conditions.

Antioxidant Effect of CoQ10 in a Rat Model of High Glucose Levels

To assess oxidative stress in a diabetic milieu, we measured the serum levels of key antioxidant enzymes: superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPx). Our findings revealed a significant decline in the levels of these enzymes in the T1DM group compared to the control animals. However, the combined intake of CoQ10 in diabetic rats markedly elevated antioxidant activity, as shown in Figures 3A–C. These results reinforce the established antioxidant potential of CoQ10, as demonstrated in our study.

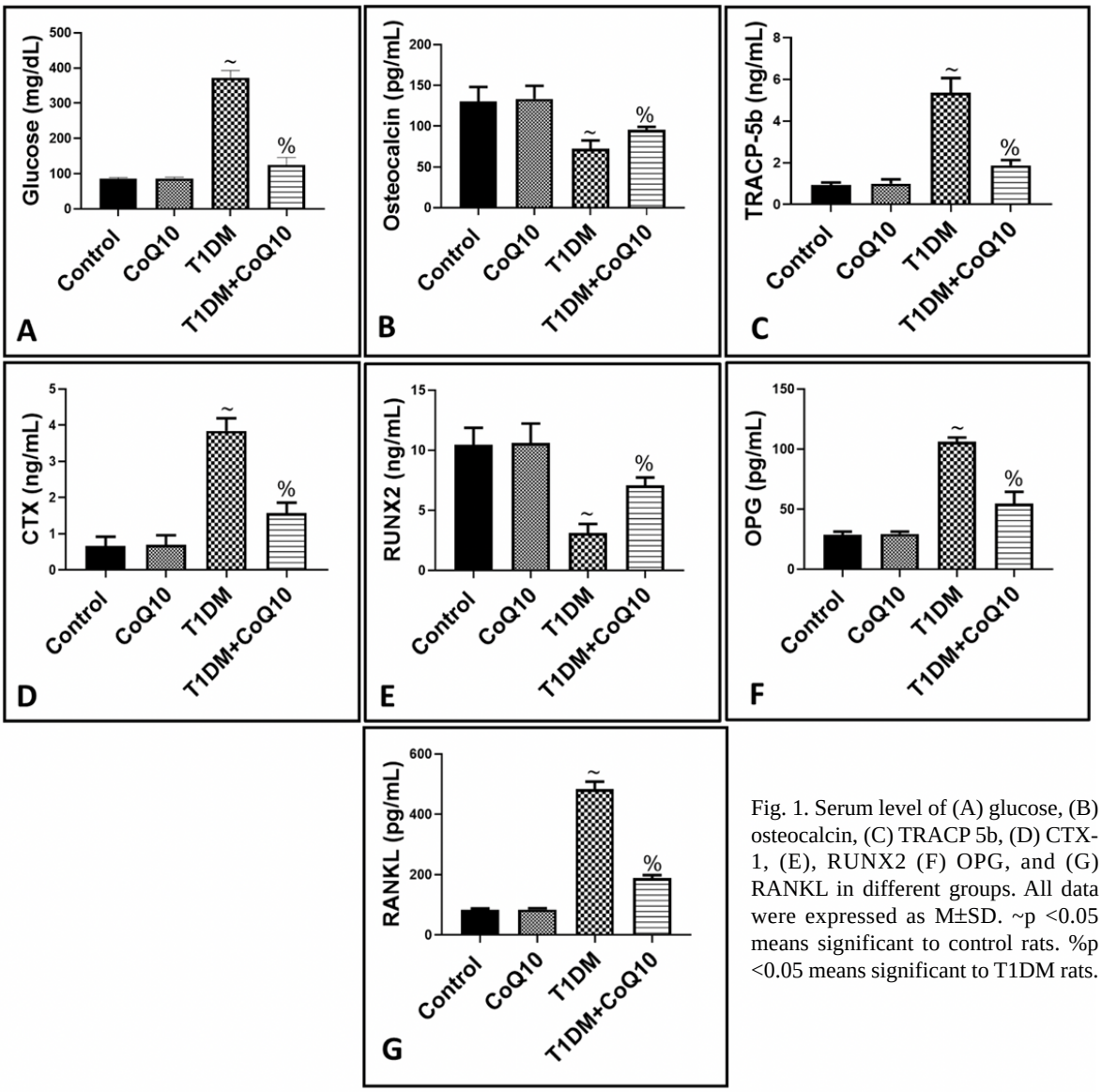

Fig. 1. Serum level of (A) glucose, (B) osteocalcin, (C) TRACP 5b, (D) CTX-1, (E), RUNX2 (F) OPG, and (G) RANKL in different groups. All data were expressed as M±SD. ~p <0.05 means significant to control rats. %p <0.05 means significant to T1DM rats.

Downregulatory Effect of TLR4/NF-kB Signaling in the Tibia of Diabetic Rats

As shown in Figures 3D–J, the T1DM group exhibited a significant elevation in the protein levels of the TLR4/NF-κB signaling pathway components HMGB1, TLR4, MyD88, and NF-κB in tibial supernatants, as measured by ELISA. This upregulation was accompanied by a marked increase in the expression of proinflammatory cytokines TNF-α, IL-6, and IL-1b compared to control rats. Notably, administration of CoQ10 at a dose of 50 mg/kg/day for eight weeks significantly ($p < 0.05$) reduced the levels of all these inflammatory markers in diabetic rats. These findings suggest that CoQ10 may exert its protective effects in diabetic osteoporosis, at least in part, through the downregulation of the TLR4/NF-kB inflammatory signaling pathway.

Antiapoptotic Effect of CoQ10 in a Diabetic Model of Bone Loss

As shown in Figures 3K–M, ELISA analysis of tibial supernatants from Group III (diabetic rats) revealed a significant increase in the protein levels of proapoptotic markers Bax and caspase-3, along with a marked decrease in the antiapoptotic protein Bcl-2. In contrast, Group IV rats, which received CoQ10 supplementation, exhibited the opposite pattern: elevated levels of Bcl-2 and reduced expression of Bax and caspase-3. These findings confirm the anti-apoptotic effect of CoQ10 on osteogenic cells in the diabetic model, likely as a downstream consequence of its previously demonstrated antioxidant and anti-inflammatory properties.

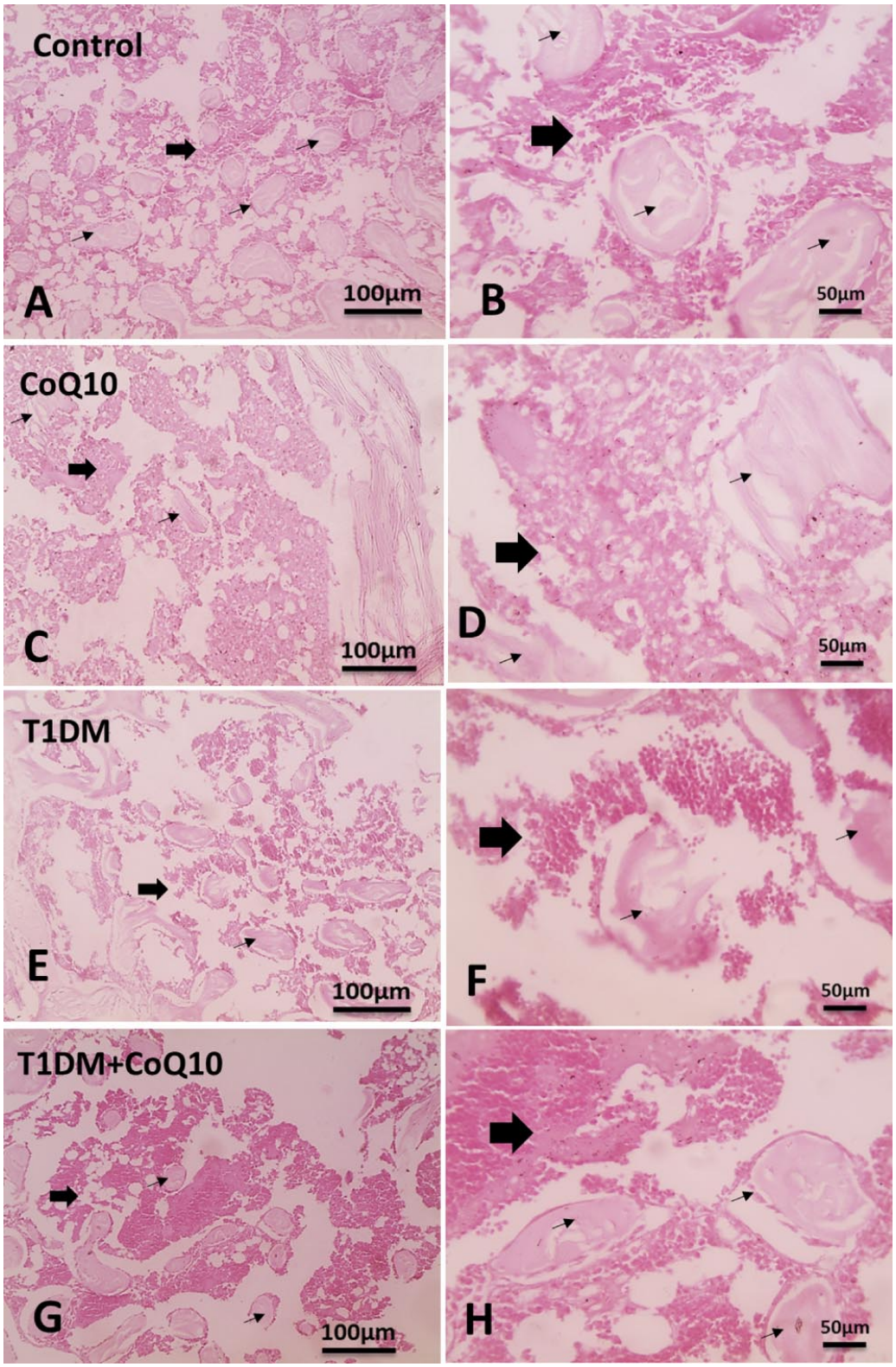

Fig. 2. The T1DM group (E, F) exhibited a significant loss of tibial bone trabeculae, increased spacing between them (thin arrows), and a reduction in bone marrow (thick arrows) compared to the control and CoQ10-only groups (A-D). These negative effects on bone structure were reversed in the T1DM group treated with CoQ10 (G, H). H&E staining. Magnifications: x100, scale bar = 100 µm; x200, scale bar = 50 µm.

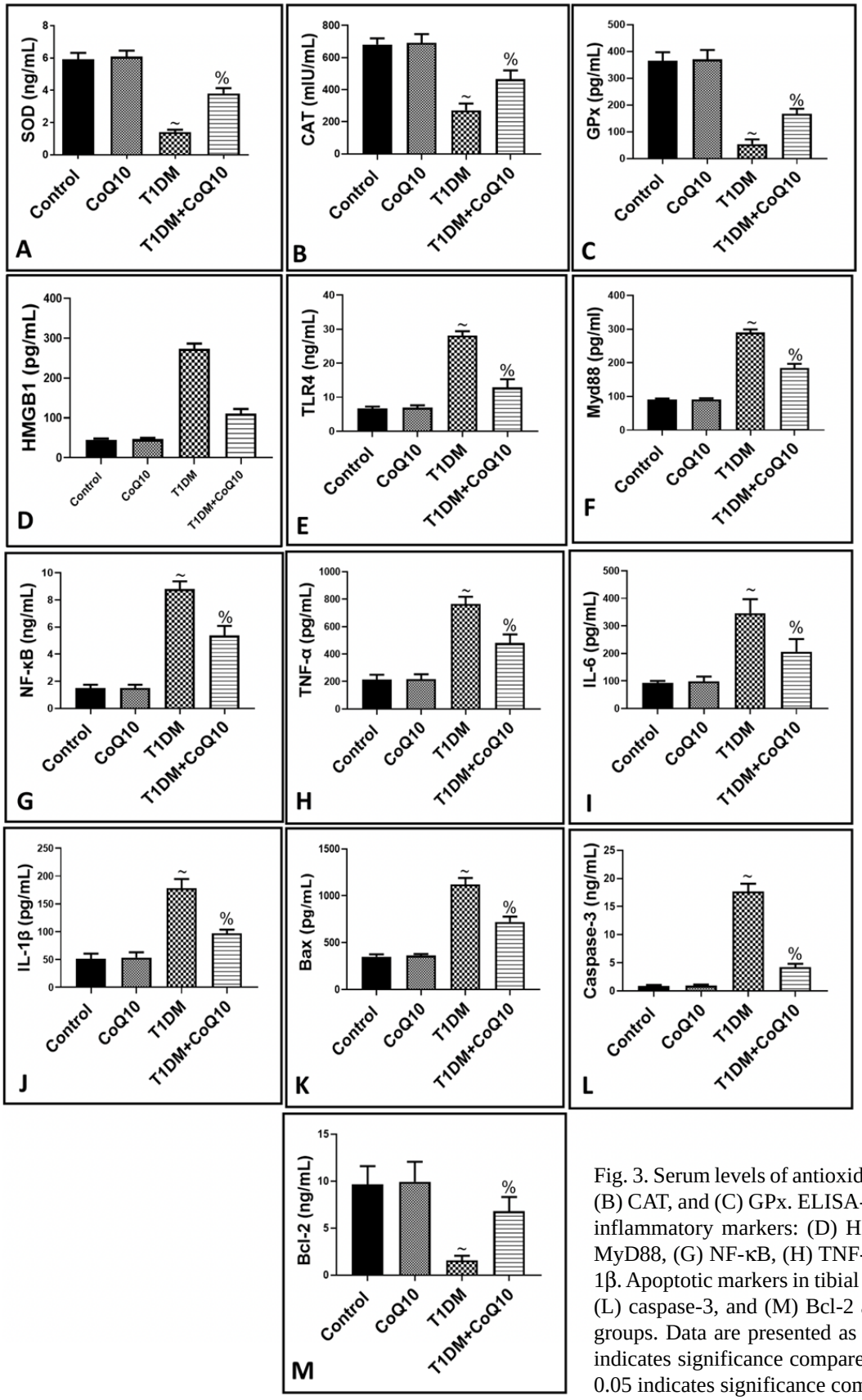

Fig. 3. Serum levels of antioxidant enzymes: (A) SOD, (B) CAT, and (C) GPx. ELISA-based quantification of inflammatory markers: (D) HMGB1, (E) TLR4, (F) MyD88, (G) NF-κB, (H) TNF-α, (I) IL- 6 and (J) IL-1β. Apoptotic markers in tibial homogenates: (K) Bax, (L) caspase-3, and (M) Bcl-2 across all experimental groups. Data are presented as mean ± SD. ~$p < 0.05$ indicates significance compared to control rats; %$p < 0.05$ indicates significance compared to T1DM rats.

DISCUSSION

Skeletal fragility in diabetic bone disease, characterized by reduced bone mineral density and an elevated risk of fracture, is primarily attributed to chronic hyperglycemia (Schwartz, 2013). Elevated glucose levels directly impair osteoblast function by disrupting differentiation, inhibiting mineralization, and inducing apoptosis. This dysfunction is a key contributor to the weakened bone state observed in diabetic osteopenia (Roy, 2013).

Moreover, sustained hyperglycemia alters the bone marrow microenvironment by suppressing osteoblast proliferation while simultaneously promoting osteoclast differentiation. The resulting increase in bone-resorbing osteoclasts is now recognized as a central pathological mechanism in the progression to diabetic osteoporosis (Schwartz, 2017).

Our findings demonstrated that CoQ10 coadministration in diabetic rats significantly increased the bone formation marker osteocalcin and reduced bone resorption markers CTX-1 and TRACP 5b. This was accompanied by enhanced osteogenesis, evidenced by upregulation of the osteoblast differentiation regulator RUNX2 and downregulation of osteoclast differentiation mediators OPG and RANKL. Histological analysis further supported these results, showing preservation of bone trabeculae in CoQ10-treated rats compared to the T1DM group.

These outcomes align with the study by Wu *et al*. (2020), which reported the protective effects of CoQ10 against bone loss in an orchiectomized mouse model, including increased expression of osteocalcin (OCN) and reduced mRNA levels of OPG. The beneficial impact of CoQ10 on cellular preservation may be attributed to its hypoglycemic properties, which inhibit osteoclast differentiation, as well as its capacity to enhance antioxidant enzyme activity. This antioxidant effect, which mitigates reactive oxygen species (ROS) known to impair osteoblast stimulation, was also confirmed in our study. Wu *et al*. (2020), similarly documented the upregulation of antioxidant gene expression, including total antioxidant capacity, CAT, SOD1, SOD2, and GSR.

HMGB1, a significant pro-inflammatory cytokine involved in diabetes and related complications like retinopathy, is produced by bone cells such as osteoblasts and osteoclasts (Feng *et al*., 2022). It regulates bone remodeling by binding to receptors like RAGE and TLR4 (Davis *et al*., 2019). Overexpression of HMGB1 can disrupt normal bone growth and repair by exacerbating inflammation. Furthermore, research indicates that dying osteoblasts release HMGB1, which in turn stimulates bone loss by promoting osteoclast formation and creating a localized inflammatory environment (Davis *et al*., 2019).

The specific impact of HMGB1 on bone depends on the receptor and signaling pathway involved. Early osteoclast differentiation requires HMGB1 signaling through TLR4, while later stages depend on its interaction with RAGE (Zhao *et al*., 2025). By activating both RAGE and TLR4 on bone-resorbing cells, HMGB1 directly drives osteoclast formation. The HMGB1-TLR4 pathway is particularly critical in osteoporosis, as its activation can trigger NF-kB signaling, suppress bone-forming osteoblasts, and stimulate osteoclasts, collectively disrupting bone metabolism and increasing disease risk (Singh *et al*., 2015). The results of our study support previous findings, showing that in the T1DM group, there was a marked elevation in the protein levels of HMGB1, TLR4, MyD88, NF-κB, TNF-α, IL-6, and IL-1β compared to the control group. Interestingly, administration of CoQ10 in the diabetic rat model significantly downregulated diabetes-related inflammation in tibial bone tissue by attenuating TLR4 signaling activation.

This observation aligns with the work of Abu-Elfotuh *et al*. (2022), who demonstrated the neuroprotective role of Coenzyme Q10 in an experimental model of Parkinson's disease. Their study showed that CoQ10 downregulated neuroinflammation by reducing the protein levels of TLR4, NF-kB, and inflammatory cytokines in brain tissue compared to the manganese-induced Parkinson group.

The downregulatory effect of CoQ10 on the TLR4/NF-kB signaling pathway can be attributed to its antioxidant properties. CoQ10 reduces reactive oxygen species (ROS), which are known activators of TLR4 signaling. By lowering oxidative stress, CoQ10 indirectly suppresses TLR4 activation.

It has been reported that AGEs can induce apoptosis of osteoblasts through interaction with their receptor (RAGE) (Liu *et al*., 2016). Consistent with this, our study demonstrated that in T1DM there is a significant elevation in the protein levels of caspase-3 and Bax in tibial supernatant, accompanied by a reduction in the anti-apoptotic protein Bcl-2. In contrast, treatment with CoQ10 in T1DM resulted in a marked decrease in apoptotic markers along with an increase in anti-apoptotic levels, thereby confirming the protective role of CoQ10 in maintaining osteogenic cell health.

CONCLUSION

CoQ10 supplementation showed strong protective effects against diabetes-related bone deterioration in T1DM rats. It lowered blood sugar, improved bone formation, and preserved trabecular structure while boosting antioxidant defenses. By suppressing inflammatory signaling and reducing cell death markers, CoQ10 supported osteogenic cell survival. Overall, these results highlight CoQ10 as a potential supportive therapy for maintaining bone health under diabetic conditions.

Ethical Approval. This study received approval from the Ethics Committee of Umm Al-Qura University, Makkah, Saudi Arabia (Approval No: HAPO-02-K-012-2025-12-3103).

ALBARAKATI, A. J. A. Efecto protector de la coenzima Q10 sobre la pérdida ósea diabética mediante la modulación del estrés oxidativo y la vía TLR4/NFκB. *Int. J. Morphol., 44(3)*:738-746, 2026.

RESUMEN: La osteoporosis diabética es una complicación importante de la diabetes mellitus tipo 1 (DM1), causada por la hiperglucemia, el estrés oxidativo, la inflamación y la apoptosis de las células osteogénicas. Este estudio investigó el papel protector de la coenzima Q10 (CoQ10) sobre la pérdida ósea en un modelo de rata con DM1. Cuarenta ratas Wistar macho se dividieron en cuatro grupos: control, CoQ10 sola, diabéticas no tratadas y diabéticas tratadas con CoQ10 (50 mg/kg/día durante 8 semanas). La diabetes se indujo mediante inyección de estreptozotocina. Se realizaron análisis bioquímicos, histológicos y moleculares. Los resultados mostraron que las ratas diabéticas presentaban hiperglucemia, osteocalcina reducida, marcadores de resorción ósea elevados (CTX 1, TRACP 5b) y proteínas reguladoras desreguladas (RUNX2, OPG, RANKL). El examen histológico reveló pérdida de hueso trabecular y expansión de la cavidad medular. La suplementación con CoQ10 mejoró significativamente la actividad osteogénica, suprimió la función de los osteoclastos y restauró la arquitectura trabecular. Las actividades de las enzimas antioxidantes (SOD, CAT, GPx) mejoraron notablemente en las ratas diabéticas tratadas con CoQ10. Además, la CoQ10 reguló negativamente la vía de señalización TLR4/NF κB y disminuyó las citocinas proinflamatorias (TNF α, IL 6, IL 1β). Los marcadores apoptóticos (Bax y caspasa-3) se redujeron, mientras que la proteína antiapoptótica Bcl-2 aumentó, lo que confirma el efecto antiapoptótico de la CoQ10. En conclusión, la suplementación con CoQ10 atenúa la pérdida ósea inducida por la diabetes mediante mecanismos antioxidantes, antiinflamatorios y antiapoptóticos. Estos hallazgos destacan la CoQ10 como una terapia complementaria prometedora para preservar la salud ósea en la diabetes mellitus tipo 1.

PALABRAS CLAVE: Diabetes mellitus; Coenzima Q10; Osteogénesis; Estrés oxidativo; Inflamación; Apoptosis.

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