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Original Article

Liraglutide in combination with zoledronic acid and calcium carbonate and vitamin D3 for diabetic osteoporosis: efficacy and glycometabolism impact

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Abstract: This study focuses on people with diabetic osteoporosis (DOP), exploring the efficacy of triple therapy with liraglutide (LIR), zoledronic acid (ZOL) and Calcium Carbonate and Vitamin D3 (CCD3) and the impact of this regimen on glycometabolism (GM). Ninety-nine eligible DOP patients visiting our hospital (January 2023-December 2025) were selected and assigned to a control group (n=46; receiving ZOL + CCD3) and a research group (n=53; receiving LIR + ZOL + CCD3) based on their treatment regimen. Between-group comparisons were made regarding of: efficacy, electrolyte metabolism (calcium [Ca], phosphorus [P]); bone metabolism (bone-specific alkaline phosphatase [BALP], secreted frizzled-related protein 5 [SFRP5], β-C-terminal telopeptide of type 1 collagen [β-CTX]), GM (glycosylated hemoglobin [HbA1c], fasting plasma glucose [FPG], fasting insulin [FINS]), glycemic variability (mean/largest amplitude of glycemic excursion [MAGE/LAGE], coefficient of variation [CV]), hepatorenal function (alanine aminotransferase [ALT], serum creatinine [SCr]), inflammatory cytokines (interleukin [IL]-6, IL-8, tumor necrosis factor-α [TNF-α]) and adverse drug reactions (ADRs; flatulence, nausea, fatigue, abdominal pain and fever). The analysis results showed that compared with controls, the total effective rate of the research group was increased, Ca, BALP and SFRP5 were elevated and the post-medication P, β-CTX, GM indices, glycemic variability parameters and inflammatory markers were decreased ($P<0.05$). No significant changes in hepatorenal function were observed within (pre- vs. post-treatment) or between groups. The total ADR rate was equivalent across the groups. It is suggested that concomitant administration of LIR, ZOL and CCD3 can significantly improve curative efficacy and ameliorate GM in DOP patients without compromising hepatorenal function.

Keywords: Liraglutide, zoledronic acid, calcium carbonate and vitamin D3, diabetic osteoporosis, therapeutic efficacy, glycometabolism

Introduction

Diabetes mellitus (DM) and osteoporosis (OP), two prevalent chronic metabolic conditions, occur predominantly in the elderly [1]. Nowadays, diabetic osteoporosis (DOP) poses a growing risk, which is closely related to population aging and DM-related metabolic disorders [2]. Essentially, it is a common complication of DM, pathologically manifested as a decrease in bone mineral density (BMD) and the deterioration of trabecular microstructure, accompanied by a high risk of fragility fractures [3]. The pathogenesis of DOP is complex and is known to involve calcium (Ca)-phosphorus (P) imbalances, skeletal metabolism abnormalities, glycometabolism (GM) disorders and low-grade chronic inflammation, all of which can disrupt bone homeostasis to varying degrees [4, 5]. Treating DOP is challenging due to the coexistence of DM and OP [6]. Although traditional anti-OP agents can inhibit bone resorption, they are ineffective in alleviating the impairment of bone formation specific to diabetic conditions [7]. Additionally, while playing a glucose control role, some hypoglycemic agents (e.g., thiazolidinedione) may promote bone loss by interfering with bone metabolism, resulting in a conflict

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between hypoglycemic effects and bone protection [8]. It is therefore pressing to optimize DOP treatment.

Zoledronic acid (ZOL), a nitrogen-containing bisphosphonate, can effectively suppress bone resorption by inhibiting farnesyl pyrophosphate synthase activity in osteoclasts. It also demonstrates high efficacy in increasing the BMD of patients' lumbar vertebrae, femoral neck (FN) and femoral trochanter (FT), as well as preventing fractures [9]. When applied to type 2 diabetes patients with DOP, this drug shows a clinical outcome equivalent to Denosumab in terms of 5-year cumulative fracture incidence, mortality and post-hip fracture mortality [10]. As a Ca supplement, calcium carbonate and vitamin D3 (CCD3) contains abundant vitamins and trace elements, exerting a positive effect on improving bone metabolism and BMD in OP-affected individuals [11]. Its concomitant administration with ZOL can further improve bone health in OP patients without increasing the risk of adverse drug reactions (ADRs) [12]. Liraglutide (LIR) is a glucagon-like peptide-1 receptor (GLP-1R) agonist and a novel antidiabetic drug. Its application to DOP may work by activating the Wingless/Integrated (Wnt) signaling and the phosphorylated AMP-activated protein kinase/Peroxisome proliferator-activated receptor gamma coactivator 1-alpha (p-AMPK/PGC1α) axis to promote osteoblast proliferation, as well as by ameliorating osteopenia through anti-inflammatory, anti-oxidative and autophagy-regulating pathways to suppress osteoclast activation [13]. LIR has been indicated to effectively enhance the osteogenesis of human alveolar bone marrow mesenchymal stem cells in diabetic patients on insulin therapy and positively impact osseointegration and new bone formation in diabetic rats [14].

This study analyzes how the triple therapy with LIR, ZOL and CCD3 affects treatment efficacy and GM in DOP patients. Given insufficient evidence regarding the combined treatment strategy, this study may help fill the relevant gaps and may provide patients with better treatment options.

Information and methods

Case selection

Inclusion criteria: meeting the diagnostic criteria for DOP [15]; age: 30-75; no prior treatment for DOP; no OP-related treatment within 3 months; no mental illness and normal communication; and complete clinical data. Exclusion criteria: known allergies to the study drugs; diabetic ketoacidosis occurring in recent 30 days; serious infection, or hematological/immune system diseases; malignant tumor; ankylosing spondylitis, lumbar disc herniation, or other diseases that affect bone metabolism; serious cardio-cerebrovascular diseases or severe organ functional diseases; OP caused by hyperthyroidism; recent administration of hormone drugs or Ca-lowering drugs; or other conditions associated with generalized pain.

Following the aforementioned selection criteria, we consecutively enrolled 99 DOP patients (January 2023-December 2025) treated at our center. Based on the medication strategies, patients were divided into a control group (n=46; treated with ZOL plus CCD3) and a research group (n=53; treated with LIR + ZOL + CCD3). The groups were clinically comparable (P>0.05) with balanced baseline characteristics. The study protocol received approval from the Shenzhen Traditional Chinese Medicine Hospital Ethics Committee. This study is a retrospective analysis, with the overall effective rate of the two groups as the primary endpoint for sample size calculation in post-hoc analysis. Under the condition of α=0.05 (two-tailed), the effect size corresponding to the two groups' efficacy rates (71.74% vs. 88.68%) was 0.446. The power of the current sample size (46 cases in the control group and 53 cases in the research group) approximated 83%, meeting the conventional requirement of 80%.

Intervening methods

In the control group, 4 mg of ZOL for injection was dissolved in 100 mL of normal saline and administered intravenously over ≥15 minutes, once every 3 weeks. CCD3 Tablets (specifications: 600 mg of calcium and 125 IU of vitamin D3 per tablet) were taken orally, 1 tablet/time, twice a day.

In addition to the treatment in the control group, LIR injection (specification: 3 mL:18 mg, pre-filled) was administered subcutaneously, with an initial dose of 0.6 mg once daily; after 7 days, the dose could be increased to 1.2 mg, depending on the patient's blood glucose level. A 12-month treatment cycle was implemented in both groups.

Data collection and outcome measures

Therapeutic efficacy. Efficacy was evaluated as follows: (1) Markedly effective: clinical symptoms (soreness, weakness and cramps of the waist and knees, lumbago and back pain and lower limb flaccidity) were significantly improved, blood glucose normalized, with a ≥20% increase in serum bone-specific alkaline phosphatase (BALP) and secreted frizzled-related protein 5 (SFRP5) as well as a ≥20% decrease in β-C-terminal telopeptide of type 1 collagen (β-CTX) from baseline; (2) Effective: A 20% reduction in the blood sugar level, alongside relieved clinical symptoms, a ≥10% but <20% rise in serum BALP and SFRP5 and a ≥10% but <20% decrease in β-CTX. (3) Ineffective: Barely changed or even worsened clinical symptoms post-treatment, despite some improvement in blood glucose, with a <10% change or an opposite trend of the above bone metabolism indicators. Overall effectiveness rate = (significant effectiveness cases + effectiveness cases)/ total number of cases.

Electrolyte metabolism. Fasting venous blood (5Ml) was drawn from each participant before and after treatment. After centrifugation, the serum was separated for Ca and P quantification using an automatic biochemical analyzer.

Bone metabolism. BALP, SFRP5 and β-CTX, all bone metabolism-associated indices, were examined using an automatic electrochemiluminescence immunoassay system with commercial kits.

GM. We determined glycosylated hemoglobin (HbA1c), fasting plasma glucose (FPG) and fasting insulin (FINS) levels before and after treatment using the glucose oxidase method.

Glycemic variability. With the 72-hour continuous glucose monitoring system, we monitored patients' blood glucose alterations twice to assess glycemic variability, with the first detection starting from 9:00 am on the day after admission and the second before the end of treatment, each over a 72-hour period. The mean (MAGE) and largest amplitude of glycemic excursions (LAGE), as well as the coefficient of variation (CV), were recorded.

Hepatorenal function. Using an automatic biochemical analyzer, we measured pre- and post-treatment alanine aminotransferase (ALT) and serum creatinine (SCr) for both cohorts.

Inflammatory cytokines (ICKs). Enzyme-linked immunosorbent assays (ELISAs) were performed before and after treatment to examine serum interleukin (IL)-6/8 and tumor necrosis factor-α (TNF-α) concentrations. The kits were ordered from Shanghai Zhongqiao Xinzhou Biological Technology Co., Ltd. (EKH207-P, EKH208-P, EKH002-P).

ADRs. Flatulence, nausea, fatigue, abdominal pain and fever were the ADRs observed during the treatment course, with their occurrences and the overall incidence computed.

Among these endpoints, therapeutic efficacy and ADRs are primary, while electrolyte metabolism, bone metabolism, GM glycemic variability, hepatorenal function and ICKs are secondary.

Statistical methods

All statistical analyses were performed using SPSS 20. Continuous variables were first assessed for normality using the Shapiro-Wilk test. Continuous variables with a normal distribution were expressed as mean ± standard deviation (SD) and between-group comparisons were conducted using independent-sample t-tests and within-group comparisons using paired t-tests. Continuous variables not conforming to a normal distribution were expressed as the median (interquartile range) [M (Q1, Q3)] and the Mann-Whitney U test was used for between-group comparisons. Categorical data, expressed as the number and percentage (n/%), were compared using χ^2 test. A two-sided *P*-value of <0.05 was considered statistically significant.

Results

Baseline data observation and comparison

Patients' baseline data, including sex, age, body mass index (BMI), OP course, DM and DM classification, showed no significant differences between the two groups (P>0.05; **Table 1**).

Efficacy observation and comparison

Following the treatment, the total effective rate was evidently higher in the research group than

Table 1. Comparison of baseline characteristics between groups

Variable	Control group (n=46)	Research group (n=53)	χ^2/t/Z	P
Sex			0.367	0.545
Male	21 (45.65)	21 (39.62)		
Female	25 (54.35)	32 (60.38)		
Age (years)	60.76±7.17	61.81±6.38	0.771	0.443
Body mass index (kg/m^2)	22.98±2.05	22.81±2.46	0.370	0.712
Osteoporosis course (years)	2.00 (2.00, 3.00)	2.00 (2.00, 3.00)	-0.939	0.348
Diabetes course (years)	6.52±2.35	6.26±2.00	0.595	0.553
Diabetes classification			0.325	0.569
I	6 (13.04)	5 (9.43)		
II	40 (86.96)	48 (90.57)		

Table 2. Comparison of treatment efficacy between groups

Variable	Control group (n=46)	Research group (n=53)	χ^2	P
Significant effectiveness	17 (36.96)	25 (47.17)		
Effectiveness	16 (34.78)	22 (41.51)		
Ineffectiveness	13 (28.26)	6 (11.32)		
Overall effectiveness	33 (71.74)	47 (88.68)	4.557	0.033

in the control group (88.68% vs. 71.74%, P=0.033). Specifically, 25 patients (47.17%) in the research group showed marked effectiveness, 22 (41.51%) showed effectiveness and 6 (11.32%) showed ineffectiveness. The number of cases of significant effectiveness, effectiveness and non-effectiveness in the control group was 17 (36.96%), 16 (34.78%) and 13 (28.26%), respectively (**Table 2**).

Observations of electrolyte metabolism

Baseline serum Ca and P levels were comparable between groups (P>0.05). The treatment induced a marked rise in Ca in both cohorts, reaching (2.80±0.40) mmol/L in the research group, which was significantly higher than the (2.40±0.42) mmol/L in the control group (P< 0.001); meanwhile, a decline in P was noted, with the level being even lower in the research group (1.08±0.39 mmol/L) versus the control group (1.26±0.27 mmol/L; t=2.630, P=0.010; **Table 3**).

Changes in bone metabolism across groups

No marked inter-group differences were found in pre-treatment BALP, SFRP5 and β-CTX contents (P>0.05). BALP and SFRP5 increased in both groups, with a greater increase in the research group compared with the control group (BALP: 65.09±9.00 IU/L vs. 57.13±6.36 IU/L; SFRP5: 114.74±11.70 pg/mL vs. 94.00±8.62 pg/mL; both P< 0.001); β-CTX was decreased and to a lower level in the research group (0.47±0.14 ng/mL vs. 0.69± 0.24 ng/mL; P<0.001; **Table 4**).

Observations of GM across groups

No significant between-group differences were found in baseline HbA1c, FPG, or FINS (P>0.05). However, post-treatment levels were significantly reduced in both groups, with lower values in the research group than in the control group (P<0.01; **Figure 1**).

Glycemic variability comparison

The pre-treatment glycemic variability parameters, including MAGE, LAGE and CV, were comparable between groups (P>0.05). All these indices were lowered drastically post-treatment in both groups, particularly in the research group (P<0.05; **Table 5**).

Hepatorenal function observation

Hepatorenal function indicators, ALT and Scr, were comparable between groups before treatment (P>0.05). After treatment, the two markers showed no significant changes (P>0.05), with comparable post-treatment levels between the two groups (P>0.05; **Table 6**).

Table 3. Comparison of electrolyte metabolism markers between groups

Variable	Control group (n=46)	Research group (n=53)	t	P
Ca (mmol/L; pre-treatment)	2.04±0.47	2.07±0.34	0.367	0.714
Ca (mmol/L; post-treatment)	2.40±0.42	2.80±0.40	4.849	<0.001
P (mmol/L; pre-treatment)	1.46±0.43	1.53±0.45	0.788	0.433
P (mmol/L; post-treatment)	1.26±0.27	1.08±0.39	2.630	0.010

Note: Ca, calcium; P, phosphorus.

Table 4. Comparison of bone metabolism markers between groups

Variable	Control group (n=46)	Research group (n=53)	t	P
BALP (IU/L; pre-treatment)	27.96±4.86	28.49±4.79	0.545	0.587
BALP (IU/L; post-treatment)	57.13±6.36	65.09±9.00	5.009	<0.001
SFRP5 (pg/mL; pre-treatment)	66.22±6.95	65.87±7.87	0.233	0.816
SFRP5 (pg/mL; post-treatment)	94.00±8.62	114.74±11.70	9.910	<0.001
β-CTX (ng/mL; pre-treatment)	0.79±0.28	0.74±0.21	1.013	0.314
β-CTX (ng/mL; post-treatment)	0.69±0.24	0.47±0.14	5.658	<0.001

Note: BALP, bone-specific alkaline phosphatase; SFRP5, secreted frizzled-related protein 5; β-CTX, β-C-terminal telopeptide of type 1 collagen.

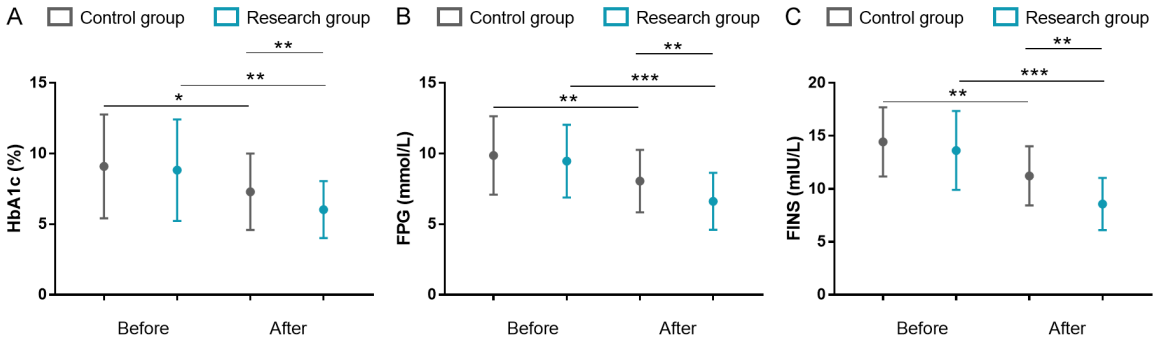

Figure 1. Comparison of glycemic metabolism related markers between groups. A. HbA1c levels. B. FPG levels. C. FINS levels. Note: HbA1c, glycosylated hemoglobin; FPG, fasting plasma glucose; FINS, fasting insulin; *P<0.05, **P<0.01, ***P<0.001.

Observations of ICKs

The pre-treatment IL-6, IL-8 and TNF-α levels showed no significant between-group differences (P>0.05). After treatment, significant reductions were observed in all these markers in both cohorts, with more pronounced decreases observed in the research group (P<0.01; **Figure 2**).

Observations of ADRs

The occurrence of ADRs such as flatulence, nausea, fatigue, abdominal pain and fever, the total ADR rate was recorded for both groups. The incidence of ADRs was 9.43% (5/53) in the research group and 6.52% (3/46) in the control group, showing no significant between-group difference (P=0.721; **Table 7**).

Discussion

In this study, we observed that the triple therapy (LIR + ZOL + CCD3) was more effective on DOP, increasing the total effective rate from 71.74% to 88.68%. Davies et al. [16] reported that LIR also exerted an effective weight-loss effect, which complements our findings. Echoing our results, Tan et al. [17] reported enhanced efficacy of the triple therapy in increasing BMD of the lumbar spine L1-4, FN, FT and Ward's triangle. This may be because LIR, by alleviating hyperglycemia-associated pathological changes, not only promotes bone growth

Table 5. Comparison of glycemic variability between groups

Variable	Control group (n=46)	Research group (n=53)	t	P
MAGE (mmol/L; pre-treatment)	7.68±2.49	7.14±2.42	1.093	0.277
MAGE (mmol/L; post-treatment)	4.11±1.76	3.25±1.50	2.625	0.010
LAGE (mmol; pre-treatment)	8.39±2.02	7.94±2.59	0.953	0.343
LAGE (mmol; post-treatment)	6.23±2.50	4.83±1.59	3.368	0.001
CV (pre-treatment)	24.13±5.17	25.43±5.70	0.380	0.704
CV (post-treatment)	17.57±4.19	15.62±3.16	2.634	0.010

Note: MAGE/LAGE, mean/largest amplitude of glycemic excursion; CV, coefficient of variation.

Table 6. Comparison of hepatorenal function between groups

Variable	Control group (n=46)	Research group (n=53)	t	P
ALT (U/L; pre-treatment)	27.63±4.72	26.30±4.65	1.409	0.162
ALT (U/L; post-treatment)	27.76±4.88	27.47±4.16	0.319	0.750
Scr (μmol/L; pre-treatment)	77.98±6.27	77.26±7.99	0.493	0.623
Scr (μmol/L; post-treatment)	79.98±9.14	76.85±7.56	1.865	0.065

Note: ALT, alanine aminotransferase; SCr, serum creatinine.

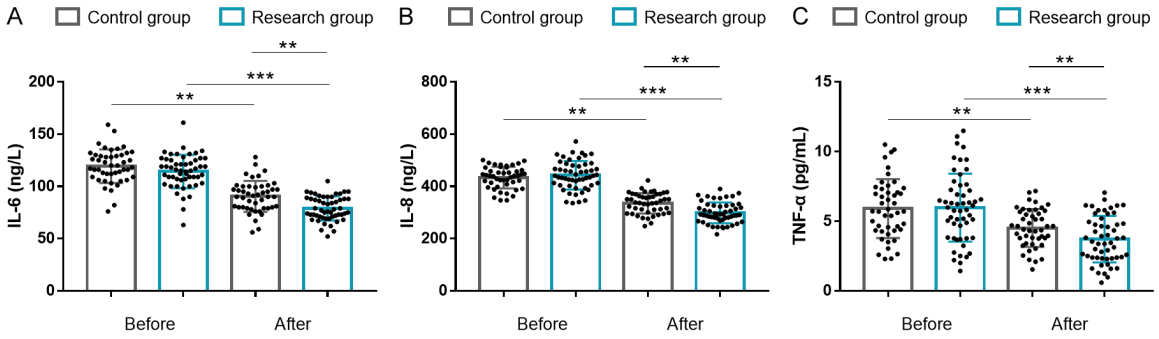

Figure 2. Comparison of inflammatory cytokines between groups. A. IL-6 levels. B. IL-8 levels. C. TNF-α levels. Note: IL-6/8, interleukin-6/8; TNF-α, tumor necrosis factor-α; **P<0.01; ***P<0.001.

Table 7. Comparison of adverse reactions between groups

Variable	Control group (n=46)	Research group (n=53)	P
Flatulence	1 (2.17)	0 (0.00)	
Nausea	1 (2.17)	1 (1.89)	
Fatigue	0 (0.00)	1 (1.89)	
Abdominal pain	0 (0.00)	1 (1.89)	
Fever	1 (2.17)	2 (3.77)	
Total	3 (6.52)	5 (9.43)	0.721

but also inhibits bone resorption, thus helping to increase BMD [18]. Furthermore, DOP treatment with LIR combined with ZOL and CCD3 helped correct Ca-P imbalances, which in turn effectively increases serum Ca levels and reduces serum P levels. Then, the triple therapy was found to play a more positive regulatory role in bone metabolism, manifested by significantly increased BALP and SFRP5 and down-regulated β-CTX. This could be linked to the accumulation of ZOL at the sites of high bone turnover, which assists in depositing hydroxyapatite crystals in bones and inhibiting osteoclast-mediated bone resorption, ultimately promoting bone formation [19]. By providing vitamin D supplementation, CCD3 improves Ca-P metabolism, promotes bone formation and thus prevents bone loss [20]. LIR, on the other hand, can alleviate DM-related bone metabolism imbalances by inhibiting the formation of neutrophil extracellular traps (NETs) through the inhibition of SIRT1-mediated neutrophil extracellular trap (NET) formation [21]. Li et al. [22]

reported that LIR, compared with other hypoglycemic agents or placebos, effectively increases Ca and BMD levels and actively regulates bone metabolism in type 2 DM patients, which is consistent with our findings.

In GM and glycemic variability evaluations, LIR + ZOL + CCD3 resulted in better glycemic control and blood glucose stability. This may be attributed to the fact that LIR promotes insulin secretion, inhibits hepatic glucose output and improves insulin sensitivity by binding to GLP-1R in islet β cells, thus enhancing blood glucose control effects and reducing glycemic variability [23]. Meanwhile, the effective glycemic control under the triple therapy helps reduce the influence of hyperglycemia on the balance between osteoblasts and osteoclasts, which also explains the therapy's beneficial effect on bone metabolism balance [24]. We also found that the combined intervention of the three drugs had no significant adverse effect on hepatorenal function, indicating its safety profile. Moreover, LIR in combination with ZOL and CCD3 exerted a more potent anti-inflammatory effect on DOP patients by more significantly reducing IL-6, IL-8 and TNF-α levels. Mechanistically, the anti-inflammatory activity of LIR is related to its inhibition of the TNF-α pathway in macrophages and its promotion of nuclear factor E2-related factor 2 (Nrf2) translocation in the mouse calvarial pre-osteoblastic MC3T3-E1 cell line, thereby exerting anti-inflammatory effects and promoting bone formation [25]. In the study of Zhang et al. [26], LIR reversed advanced glycation end products (AGEs)-induced chondrocyte inflammation and inhibited the secretion of ICKs (IL-6, IL-12 and TNF-α) in chondrocytes, which supports our findings. In terms of safety, we found that both treatment regimens had comparable safety profiles. This may be due to the high safety and tolerance of LIR, which can be effectively metabolized and excreted without imposing an additional physiological burden [27].

This study shows several limitations. First, as a single-center retrospective observational study, it lacks a randomized double-blind design. In the future, a prospective, randomized, double-blind study should be conducted with a placebo control group, in order to further validate the relevant results and enhance the robustness of the findings. Second, no control subgroups were established for LIR or ZOL monotherapy, making it difficult to distinguish the independent effects of each drug from their synergistic interactions and hindering elucidation of the mechanism underlying the additive effect of the triple therapy. Future studies should include multiple single-drug treatment subgroups to further clarify the independent effects and specific mechanisms of each component. Third, there is a lack of in vivo or animal experiments to verify the Wnt/AMPK-related molecular pathways. In the future, relevant evidence from basic transformation experiments should be supplemented to support the hypothesis that LIR regulates bone remodeling through this mechanism.

To summarize, LIR in combination with ZOL and CCD3 can further improve therapeutic outcomes in patients with DOP. It also demonstrates more significant clinical effects in ameliorating electrolyte disturbances, promoting balanced bone metabolism, optimizing glycemic control and blood glucose stability and reducing inflammatory reaction, without increasing the risk of ADRs or compromising hepatorenal function.

Disclosure of conflict of interest

None.

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