of NVF (11.2% vs. 8.9%, p=0.577) between groups **(Figure 1d)**. The interval between NVF and PKP was similar between groups (8.5 ± 3.8 VS. 7.9 ± 3.4 months, *p*=0.14, **Table 1**).

The gender differences

Female patients in Group II had significantly better improvement in VAS score (4.0±0.9 vs. 4.6±1.1, *p*=0.004, **Figure 2a**), ODI (40.8±2.8 VS. 45.5±3.6, *p*<0.001, **Figure 2b**) and BMD (0.51±0.07 vs. 0.56±0.12, *p*=0.032, **Figure 2c**) while there was no significant difference in the prevalence of NVF between groups **(Figure 2d)**.

Male patients in Group II also had significantly better improvement in VAS score (3.9±0.7 VS. 4.5±0.9 *p*=0.039, **Figure 3a**), ODI (40.7±2.5 VS. 45.9±4.8, *p*<0.001, **Figure 3b**) and BMD T score (0.49±0.07 VS. 0.56±0.11, *p*=0.037, **Figure 3c**) and while there was no significant difference in the prevalence of NVF between two groups **(Figure 3d)**.

Direct comparison demonstrated that female and male patients had similar improvement of VAS score, ODI and BMD and similar prevalence of NVF **(Figures 4 & 5)**.

Table 1. Demographic data.

	Group I (n=152) **T2DM**	**Group II (n=158)** **Non-T2DM**	***p* value**
Age (years)	67.2 ± 7.6	66.8± 8.2	0.66
M/F	46/106	48/110	1
Hip BMD (T score)	-3.2±0.5	-3.3±0.6	0.11
BMI (kg/m2)	25.3 ± 3.1	24.9 ± 3.4	0.28
Fracture location (n)			
Thoracic	12(7.9%)	11(7%)	
Thoracolumbar	99(65.1%)	102(64.6%)	
Lumbar	41(27%)	45(28.4%)	
Operation time (min)	35.3±8.6	34.3±8.2	0.30
Bone cement volume (ml)	4.5± 0.7	4.6± 0.8	0.24
Postoperative refracture interval(months)	8.5 ± 3.8	7.9 ± 3.4	0.14
HbAlc (%)	8.7 ± 2.8	8.1 ± 3.2	0.08

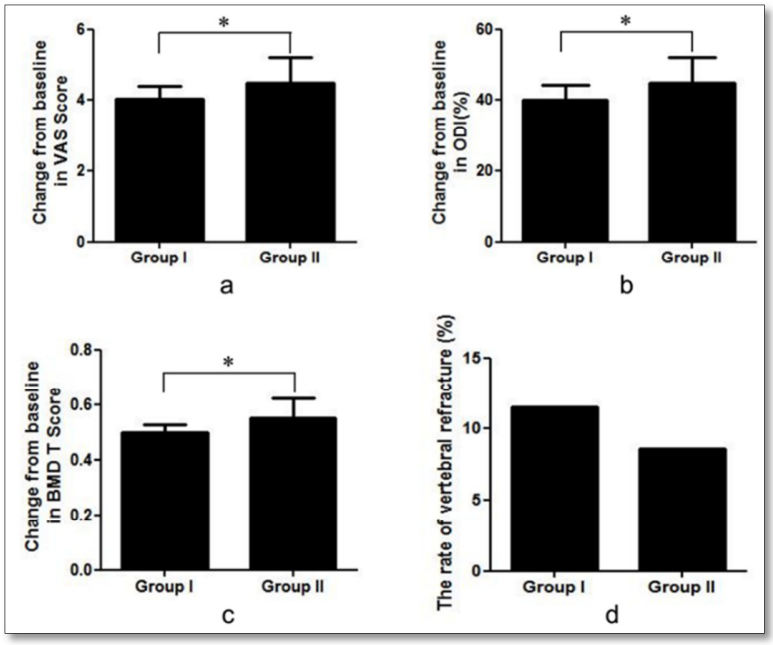

Figure 1. Improvement of clinical outcomes and BMD and the prevalence of NVF. a and b. Improvement of VAS score and ODI were significantly better in group II. c. Patients in group II had better improvement of BMD T scores. d. There was no significant difference in terms of NVF between groups. *(* indicates p<0.05)*

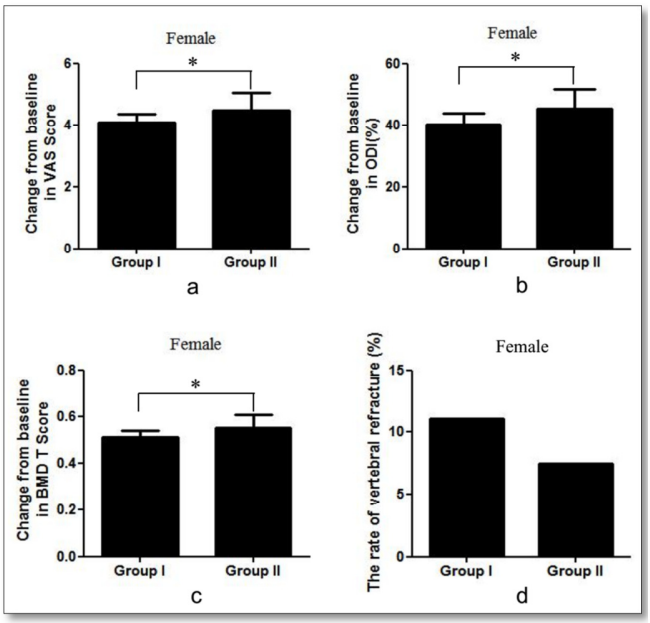

Figure 2. Improvement of clinical outcomes and BMD and the prevalence of NVF in the female. The female patients in Group II had significantly better improvement in VAS score (a), ODI (b) and BMD (c) while there was no significant difference in the prevalence of NVF between groups (d). *(* indicates p<0.05)*

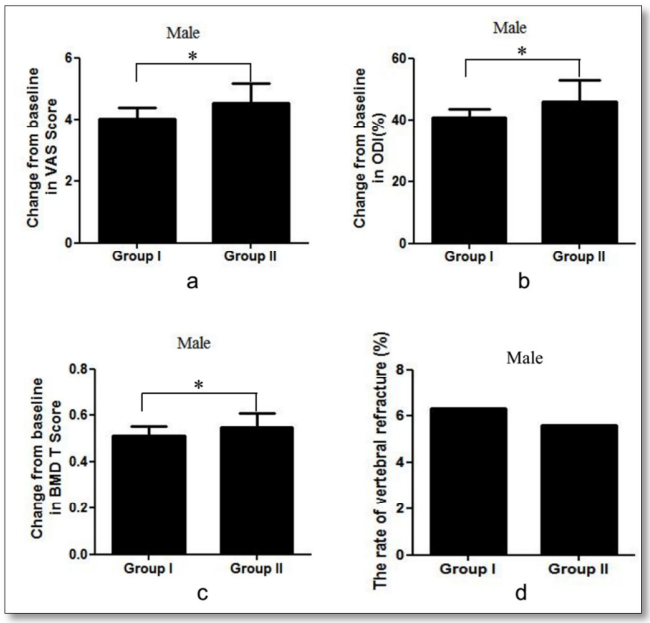

Figure 3. Improvement of clinical outcomes and BMD and the prevalence of NVF in the male. The male patients in Group II had significantly better improvement in VAS score (a), ODI (b) and BMD (c) while there was no significant difference in the prevalence of NVF between groups (d). *(* indicates p<0.05)*

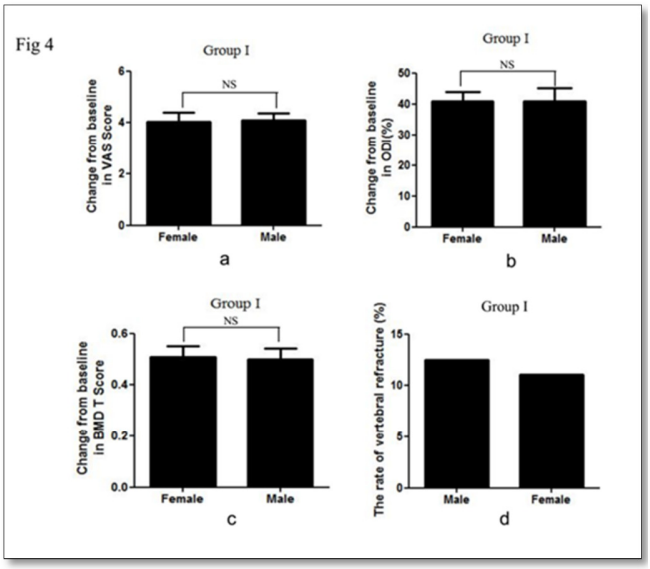

Figure 4. Improvement of clinical outcomes and BMD and the prevalence of NVF in group I. In group I, female and male patients had similar improvement of VAS score (a), ODI (b) and BMD (c) and prevalence of NVF(d).

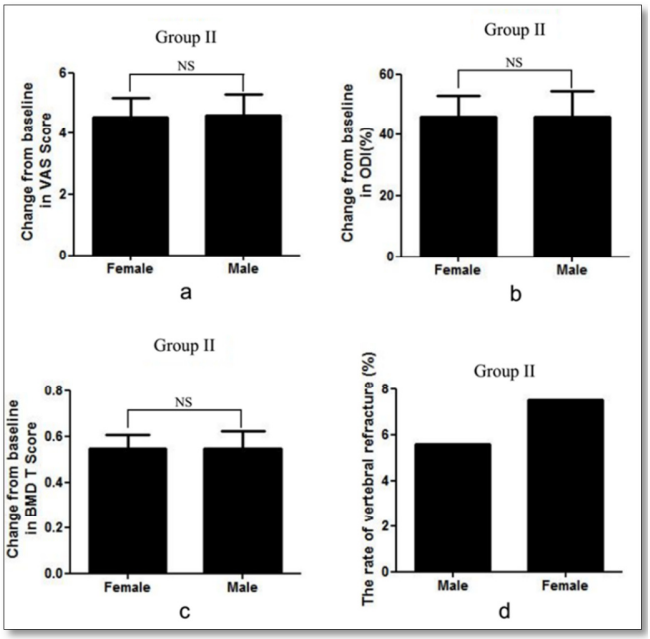

Figure 5. Improvement of clinical outcomes and BMD and the prevalence of NVF in group II. In group II, female and male patients had similar improvement of VAS score (a), ODI (b) and BMD (c) and prevalence of NVF(d).

Adverse events

The common complications of zoledronic acid in the study included fever and muscle soreness, relieved by symptomatic treatment. There were no other severe complications.

DISCUSSION

Combination of PKP and zoledronic acid could significantly improve the clinical outcomes. Huang et al included 60 patients diagnosed with primary OVCF and treated with PKP and found that patients who received zoledronic acid had significantly lower back pain VAS score than patients in the control group [14]. Zhang [13] also observed similar advantages of zoledronic acid in patients after PKP. In the present study, both groups had significantly lower VAS score and ODI at the final follow-up. Patients without T2DM had statistically better clinical outcomes but the difference was minimal and might not have clinical significance, indicating T2DM patients could also expect good clinical outcomes.

According to a meta-analysis [15], the prevalence of NVF after vertebral argumentation was 16.4% but few studies had reported the prevalence of NVF in T2DM patients after PKP although numerous literatures had demonstrated that T2DM patients had higher risk of vertebral fracture. In the present study, the prevalence of NVF in T2DM patients after PKP was11.2%, while it was 8.9%in patients without T2DM, indicating that T2DM patients might not have higher risk of NVF after PKP.

Anti-osteoporosis treatment could reduce the risk of NVF after PKP and Zhang [13] demonstrated that zoledronic acid could reduce the prevalence of NVF to zero. In contrast, the prevalence of NVF after PKP remained high despite anti-osteoporosis treatment with zoledronic acid in the present study. Further analysis demonstrated that the mean interval between NVF and PKP was 8.5 months and 7.9 months respectively and the underlying explanation might be that the time to onset of anti-fracture efficacy of zoledronic acid was still not short enough to prevent NVF. In Boonen's [4] study, 46.3% of the NVF occurred within 3 months in patients after PKP and 80.2% of the NVF occurred within 12 months. In another report, Boonen [16] demonstrated that patients with zoledronic acid had lower risk of vertebral fracture at 12 months and subsequent time-points but had similar risk of vertebral fracture at 6 months compared with patients with placebo. Thus, the spine surgeons should be aware that drugs with shorter time to onset of anti-fracture efficacy were warranted for patients after PKP because they had high risk of NVF shortly after PKP.

Despite evidence for increased risk of fracture in T2DM patients, little was known about the skeletal effects of anti-osteoporosis treatments in T2DM patients. As mentioned above, zoledronic acid had been proven effective and had good compliance but there were no studies focusing on the anti-osteoporotic treatment response of zoledronic acid in T2DM patients after PKP. The present study found that with the anti-osteoporosis treatment with zoledronic acid, although patients without T2DM had statistically better improvement of hip BMD, the difference was minimal and didn't have clinical significance. This indicated that the

presence of T2DM did not alter the anti-osteoporotic treatment response. Noticeably, despite BMD was one of the foremost determinants of bone strength and fracture risk, BMD might underestimate the fracture risk in T2DM patients. Cortical BMD was a major determinant of bone strength but BMD measured by DEXA could not distinguish cortical and trabecular cortical BMD. In fact, T2DM patients might have higher BMD but lower cortical BMD and high cortical porosity [17]. And it was demonstrated that T2DM patients experience fracture at a relatively high BMD [18]. For example, for a similar hip fracture risk, the BMD T-score in diabetic females and males was 0.59 and 0.38 higher than those in non-diabetic subjects [18]. What's more, T2DM was an independent predictor of fracture, probably because of increased risk of falls [19].

Few studies had addressed gender difference of zoledronic acid. According to a recent meta-analysis, only four studies had investigated the effect of zoledronic acid in male patients [20], but the evidence available might be quite weak. Boonen [21] included 1199 men with primary or hypogonadism-associated osteoporosis. Compared with men receiving placebo, the prevalence of new morphometric vertebral fracture and moderate-to-severe vertebral fracture was lower in men who received zoledronic acid. However, in terms of clinical vertebral or nonvertebral fractures, the difference between zoledronic acid and placebo was not significant. In another study, Boonen [22] directly compare the outcomes between men and women and found that although the improvement of BMD was comparable with women, zoledronic acid did not decrease the clinical fracture compared with men who received placebo. Orwoll's [23] study only evaluated BMD and bone turnover markers and the control group received alendronate rather than placebo and Kachnic [24] included male patients with advanced, non-metastatic prostate cancer receiving luteinizing hormone-releasing hormone agonist and radiotherapy, both of which might had not been designed well enough to elucidate the efficacy of zoledronic acid in male. Thus, there was limited evidence indicated its advantages in reducing clinical fracture in male. In the present study, we found that zoledronic acid could effectively improve BMD in male patients with and without T2DM and the improvement in BMD was comparable to female. The prevalence of NVF was also similar between male and female patients. Since zoledronic acid had been proven effective in female, the present study indicated zoledronic acid might be effective in male patients in terms of increasing BMD and preventing NVF.

As to safety, zoledronic had been proven safe. Acute phase response was common and the prevalence could reach up to 42.4%, including fever, musculoskeletal (pain and joint swelling), gastrointestinal (abdominal pain, vomiting, diarrhea), eye inflammation and general (including fatigue, nasopharyngitis, edema) [25]. In the present study, patients received infusion of 750 ml saline and 0.3g ibuprofen orally before zoledronic acid to prevent acute phase response. The adverse events observed in the present study included fever and muscle soreness and there were no severe adverse events. But the long-term safety of zoledronic acid in T2DM patients remained unknown in the present study as well as the literature available.

The present study had several limitations. First, this study was retrospectively designed and the sample size was small and had the potential of selection bias. Second, the study did not investigate the effect of zoledronic acid on bone turnover in T2DM patients. Third, the mean follow-up time was less than 2 years and the long-term efficacy of zoledronic acid in T2DM patients still remained unknown.

CONCLUSION

In this study, we firstly indicated that combination of PKP and zoledronic acid could effectively relieve pain and increase BMD in diabetic patients with OVCF and the risk of NVF was comparable with that in patients without diabetes. Prospective randomized controlled trials should be designed to further explore this largely unknown topic.

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