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Effect of pioglitazone on serum FGF23 levels among patients with diabetic kidney disease: a randomized controlled trial

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Abstract

Aim Elevated fibroblast growth factor-23 (FGF23) is an established marker of cardiovascular disease among patients with type 2 diabetes (T2DM) and chronic kidney disease (CKD). Recently, circulating FGF23 positively correlated with insulin resistance level among patients with CKD. Pioglitazone improves insulin sensitivity and it may have potential for treating CKD-related FGF23 overactivity.

Methods A randomized, open-label, controlled trial was performed among patients with T2DM and CKD. Eligible participants were randomly assigned to either oral 15 mg/day of pioglitazone ($N=22$) or control group ($N=24$) for 16 weeks. Serum FGF23 and homeostatic Model Assessment of Insulin Resistance (HOMA-IR) were measured.

Results Forty-six patients completed the trial. After 16 weeks of treatment, significant decreases in serum intact FGF23 level (median change − 49.01 (IQR, − 103.51 to − 24.53) vs. 1.07 (IQR, − 22.4–39.53) pg/mL, $P=0.01$) and HOMA-IR (mean change − 1.41 (95% CI, − 2.24 to − 0.57) vs. − 0.05 (95% CI, − 1.00–0.89), $P=0.031$) were observed in the pioglitazone group compared with the control group. HemoglobinA1C also significantly decreased in the pioglitazone group compared with the control group. No difference was found in the changes of serum phosphorus, calcium and serum intact parathyroid hormone between the two groups. Changes of FGF23 were positively associated with changes of HOMA-IR ($R=0.47$) and insulin levels ($R=0.47$). No serious adverse event was reported during the study.

Conclusion This study confirmed that pioglitazone effectively reduced serum FGF23 levels and related to improved insulin sensitivity among patients with T2DM and CKD.

Clinical trial registration TCTR20210316009.

Keywords Fibroblast growth factor-23 · Insulin resistance · HOMA-IR · Pioglitazone · Type 2 diabetes

Background

Elevated serum fibroblast growth factor-23 (FGF23) levels are the earliest findings in chronic kidney disease (CKD) with mineral bone metabolism disorders and its levels contribute to high rates of left ventricular hypertrophy, cardiovascular disease and adverse outcomes among patients with CKD [1, 2]. Existing literature showed increased concentrations of FGF23 were associated with abnormal carbohydrates metabolism and higher levels of inflammatory markers among patients with CKD [3, 4]. Insulin resistance related to higher FGF23 levels in CKD stages 3–5 [5] and was possibly associated with disturbed FGF23 among patients with CKD [6]. In vitro and animal models indicated insulin signaling suppressed FGF23 production [7]. The data have stimulated interest in developing insulin sensitivity strategies to reduce FGF23 levels in CKD.

Thiazolidinediones (TZDs), synthetic exogenous agonists of the nuclear peroxisome, and proliferator-activated, receptor-gamma (PPARγ) increased insulin sensitivity and inhibited adipose inflammatory response [8]. Besides its glycemic lowering effect, TZDs has several pleiotropic effects,

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such as increased insulin sensitivity and anti-inflammatory effect [9]. The effects of TZDs may decrease serum FGF23 levels among patients with T2DM and CKD but this effect has been less well studied yielding inconsistent results. We conducted an open labeled, placebo-controlled, randomized study to test the hypothesis that 16-week pioglitazone treatment with dietary phosphate restriction achieved through outpatient dietary counseling would decrease FGF23 levels and insulin resistance among patients with T2DM and CKD stages 3–4.

Methods

Study design

The study comprised a 16-week randomized, open labeled, controlled study conducted among patients with T2DM and CKD stages 3–4 at Phramongkutklao Hospital, Bangkok, Thailand between July 15, 2020, and December 31, 2020. The study was approved by the Ethics Committee of the Institute Review Board at the Royal Thai Army Medical Department (R064h/63) and all patients gave written informed consent. The authors confirmed that all ongoing and related trials for this intervention were registered. Treatment protocols of patients were randomized using computer generated randomization procedure in blocks of four.

Study population

Eligible participants were aged 18 years or older, had an estimated GFR of 15–59 ml/min per 1.73 m^2 and albuminuria (urinary albumin-to-creatinine ratio, > 30, with albumin measured in milligrams and creatinine in grams) with normal serum phosphate levels, diagnosed T2DM with stable glycemic treatment with glycosylated hemoglobinA1C between 6 and 8% at least 12 weeks before starting the study. Exclusion criteria comprised glomerulonephritis, polycystic kidney disease, acute kidney injury, malignancy, severe heart, lung or liver disease, chronic infection, limited life expectancy within 12 months or history of treatment with pioglitazone or insulin within 12 weeks. In the absence of preliminary data on the 16-week effects of pioglitazone on serum FGF23 levels, we based the sample size calculation on the estimated effects of phosphate-restricted diet plus lanthanum carbonate compared with control. Assuming a conservative SD of the change in FGF23 from baseline to end of study, we estimated that 20 participants treated with pioglitazone and 20 treated with placebo would provide 80% power at an α of 5% to detect a between-group difference in change in FGF23 of 30% [10].

Interventions

Eligible patients were randomly assigned to two groups. One group consisted of 22 patients treated with pioglitazone 15 mg/day orally; the other group consisted of 24 patients treated with placebo orally. All patients were instructed to adhere to a disease-based diet and the dietitian used the food records to counsel participants to follow a phosphate diet tailored to their randomization group. This was followed by a 16-week intervention period with every 8-week data collection.

Initial screening included medical history, physical examination and routine blood tests. Every eight weeks, all patients were monitored regarding body weight, body mass index (BMI), blood pressure, symptoms and signs suggestive of adverse effects and compliance with the medication and dietary intake. Baseline and follow-up dietary phosphate intake was assessed with three-day food records that were analyzed using the standard national food database program (Inmucal, Version 3.2). The subjects were given pills and compliance was assessed by pill count on follow-up visits. Adverse events that were or were not considered to be related to pioglitazone treatment were monitored every eight weeks.

Outcomes

The primary endpoints were absolute changes in serum FGF23 levels from baseline. Serum level of intact FGF23 was determined using a two-site (NH2-terminal/C-terminal) enzyme-linked immunosorbent assay (Human FGF23 kit, R&D Systems, Minneapolis, MN, USA). Other outcomes included changes in fasting plasma glucose, fasting plasma insulin, insulin resistance, hemoglobinA1C, serum phosphate, calcium, parathyroid hormone (PTH) and 25-hydroxy-vitamin D level. Insulin resistance was estimated using a homeostatic Model Assessment of Insulin Resistance (HOMA-IR) which was calculated as fasting glucose (mmol/L) × fasting insulin (μU/mL)/22.5 [11].

Statistical analyses

Data were summarized in frequencies or percentages for categorical variables and as means ± SD for continuous variables. The chi-square test or Fisher's exact test was used to compare differences between the groups for categorical variables. The independent *t* test or Mann–Whitney *U* test was used to compare differences between the groups for continuous variables. Changes in continuous measures between baseline and study periods were tested by means of the paired *t* test or median of Wilcoxon Signed Rank test.

Nonparametric methods were used for nonnormally distributed values. Pearson's correlation coefficient between changes of FGF23 and different studied variables was calculated. Analysis was performed using SPSS Software, Version 15.0. All statistical tests were two sided, and $P < 0.05$ was considered to represent a statistically significant difference.

Results

A total of 96 patients in the outpatient clinic were screened for eligibility, of whom 46 (47.9%) underwent randomization (Fig. 1). Patients with T2DM, mean age 69.33 ± 7.81 years and mean GFR 44.12 ± 12.15 mL/min/1.73 m^2 were eligible according to the entry criteria. The estimated dietary phosphate intake at baseline was 512.08 ± 138.20 mg/day in the pioglitazone group and 459.29 ± 211.59 mg/day in the placebo group. Baseline characteristics were similar among groups except the proportion of men was significantly higher in the placebo group (Table 1). No difference was also found in baseline comorbid diseases, antihypertensive and hypoglycemic medications. Patients were adherent with the study drugs, defined as > 80% pill consumption throughout the study as estimated from pill counts.

Comparison of serum FGF23 levels, HOMA-IR and other parameters between groups

At the end of the 8 and 16 weeks, the median changes of FGF23 level significantly decreased in the pioglitazone group (− 23.09 pg/mL with IQR − 102.61 to − 3.77 and − 49.01 pg/mL with IQR − 103.51 to − 24.53, respectively). A significance difference was observed between the pioglitazone and placebo groups regarding median change difference of FGF23 at 8 weeks [− 23.09, IQR − 102.61 to − 3.77 vs. 20.49, IQR − 20.49 to 49.45, $P = 0.024$] and 16 weeks [− 49.01, IQR − 103.51 to − 24.53 vs. 1.07, IQR − 22.40 to 39.53, $P < 0.001$] (Fig. 2).

Changes of HOMA-IR [− 1.41, IQR − 2.24 to − 0.57 vs. − 0.05, IQR − 1.00 to 0.89, $P = 0.031$ in Fig. 3], hemoglobinA1C [− 0.35, IQR − 0.56, − 0.15 vs. − 0.07, IQR − 0.26, 0.12, $P = 0.039$] and fasting insulin level [− 2.93, IQR − 4.3, − 1.56 vs. 0.19, IQR − 2.19, 2.57, $P = 0.024$] were significantly lower in the pioglitazone group compared with the placebo group at 16 weeks in spite of the absence of significant differences in fasting plasma glucose between the two groups ($P = 0.539$) (Table 2). Blood pressure, renal function, serum calcium, phosphate, 25 hydroxyvitamin D and intact parathyroid hormone did not significantly change in either group throughout the study (Table 2).

Correlations of FGF23 decrement with related parameters

We analyzed the correlations of FGF23 decrement with related parameters among the studied patients. Using Pearson's correlation coefficient, significant correlation with change of FGF23 included HOMA-IR and fasting insulin level. No statistically significant correlations were noted between FGF23 concentration and any of the studied parameters including age, GFR, serum calcium, phosphate, uric acid, intact-PTH, hemoglobinA1C or dietary phosphate intake (Table 3). These results suggested serum FGF23 decrement correlated with the changes in insulin resistance index.

Additionally, during the 24-week study period, no serious adverse event related or unrelated to pioglitazone was reported including drug-induced hepatotoxicity, severe hypoglycemia and congestive heart failure. One patient in the pioglitazone group developed nonserious edema and continued treatment at the end of study.

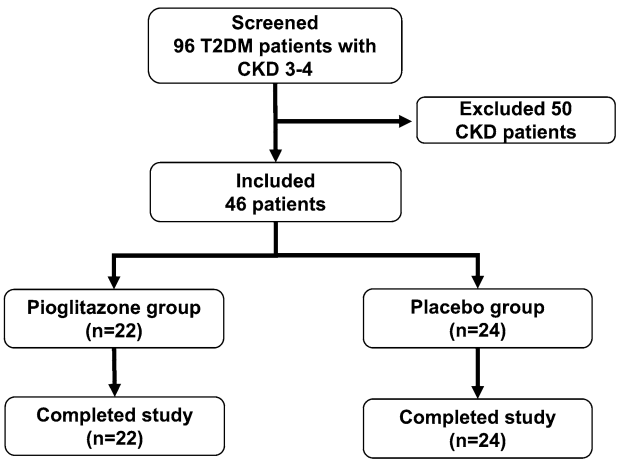

Fig. 1 Flow chart of enrolled patients

Discussion

To best of our knowledge, this constitutes the first randomized, controlled trial to evaluate the effects of pioglitazone on serum FGF23 among patients with T2DM and CKD. After 16-week TZDs treatment, patients had lower serum FGF23 levels and insulin resistance activity. Our study confirmed that serum FGF23 decrement correlated with the changes of insulin resistance index and plasma insulin levels. We did not observe any difference in the phosphate control effects between the two groups. Taken together, these results serve as "proof of concept" that pioglitazone improved phosphaturic hormone related to insulin sensitivity response among patients with T2DM and CKD.

Table 1 Baseline characteristics and parameters between two groups

Parameters	Pioglitazone ($N=22$)	Placebo ($N=24$)	P value
Age (years)	66.59 ± 8.35	71.83 ± 6.47	0.021
Male (N, %)	16 (72.7)	16 (66.67)	0.655
Comorbidities (n, %)			
- Hypertension	22 (100)	23 (95.8)	0.333
- Ischemic heart disease	0 (0)	3 (12.5)	0.086
- Cerebrovascular disease	3 (13.6)	3 (12.5)	0.909
Current medications (N, %)			
- Angiotensin receptor blockers	10 (45.5)	6 (25)	0.146
- Angiotensin converting enzyme inhibitors	5 (22.7)	7 (29.2)	0.619
- Loop diuretics	1 (4.5)	1 (4.2)	0.950
- Statins	21 (95.5)	24 (100)	0.291
- Vitamin D2	11 (50)	9 (37.5)	0.393
- Metformin	11 (50)	8 (33.3)	0.252
- Sulfonylureas	0 (0)	2 (8.3)	0.166
- Sodium–glucose co-transporter 2 inhibitors	0 (0)	2 (8.3)	0.166
- Dipeptidyl peptidase-4 inhibitor inhibitors	1 (4.5)	5 (20.8)	0.101
- Calcium carbonate	0 (0)	4 (16.7)	0.045
Body mass index (kg/m^2)	26.14 ± 3.74	25.51 ± 2.72	0.517
Systolic blood pressure (mmHg)	138.86 ± 15.54	140.46 ± 19.76	0.764
Diastolic blood pressure (mmHg)	77.73 ± 12.80	77.54 ± 12.56	0.961
Glomerular filtration rate (mL/min/1.73 m^2)	45.42 ± 13.78	42.93 ± 10.60	0.493
Serum creatinine (mg/dL)	1.59 ± 0.48	1.54 ± 0.42	0.722
Fasting plasma glucose (mg/dL)	133.77 ± 26.80	126.13 ± 34.42	0.408
HemoglobinA1C (%)	6.73 ± 0.56	6.68 ± 1.00	0.825
Insulin level (mIU/L)	13.4 ± 5.95	10.81 ± 5.42	0.130
HOMA-IR	4.48 ± 2.34	3.43 ± 2.05	0.113
Serum FGF23 (pg/mL)	252.93 ± 191.97	161.24 ± 145.69	0.073
Serum phosphate (mg/dL)	3.23 ± 0.51	3.26 ± 0.42	0.857
Serum calcium (mg/dL)	9.43 ± 0.43	9.38 ± 0.35	0.695
Serum albumin (g/dL)	4.41 ± 0.34	4.31 ± 0.25	0.293
Serum 25 hydroxyvitamin D (ng/mL)	39.61 ± 14.63	37.62 ± 11.44	0.609
Serum intact parathyroid hormone (pg/mL)	52.94 ± 30.94	67.85 ± 27.60	0.091
Serum uric acid (mg/dL)	7.24 ± 0.90	6.76 ± 1.68	0.236
Dietary phosphate intake (mg/day)	512.08 ± 138.20	459.29 ± 211.59	0.344

Data are number with percentage or mean ± SD

FGF23 is a hormonal regulator of circulating phosphate metabolism. Recently, fibroblast growth factors, a subfamily of endocrine polypeptides, related to carbohydrate metabolism and insulin resistance among patients with CKD and patients after renal transplantation [4]. Data from patients with CKD demonstrated that increased concentrations of FGF23 among patients with CKD were associated with the metabolism of carbohydrates and insulin resistance while serum phosphate levels remained normal [5]. One study confirmed that insulin signaling suppressed FGF23 production in vitro as well as in mice and humans [7]. This suggested a potential link between insulin and FGF23 action. Moreover, elevated FGF23 directly stimulated hepatic production of inflammatory cytokines, including C-reactive protein in the 5/6 nephrectomy rat model of CKD [12] and higher FGF23 levels were associated with higher levels of inflammatory markers significantly related to severe inflammation among patients with CKD [3]. Further, TZD is known to have multiple pleiotropic effects by lowering diabetic dyslipidemia, circulating levels of inflammatory cytokines and prothrombotic factors [13, 14]. Hypothetically, it may reduce FGF23 through one of these activities. Overall, this was consistent with our findings in that pioglitazone resulted in reduced FGF23 concentrations among patients with CKD, while no significant changes in phosphate intake, serum phosphate, calcium, 25 hydroxyvitamin D and intact parathyroid hormone were observed.

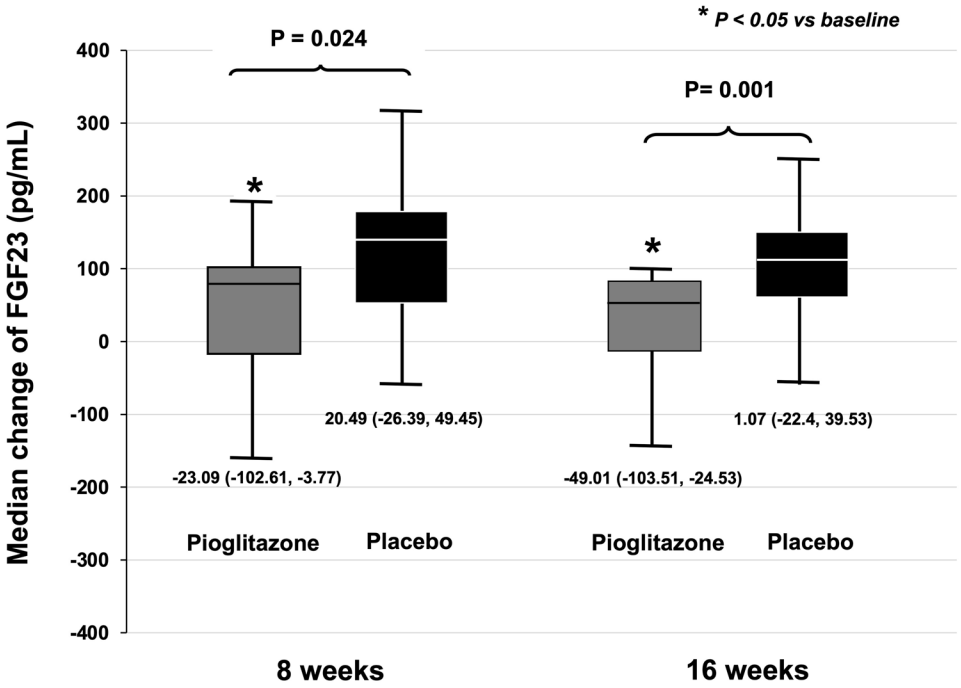

Fig. 2 Baseline and final serum FGF23 levels according to treatment groups

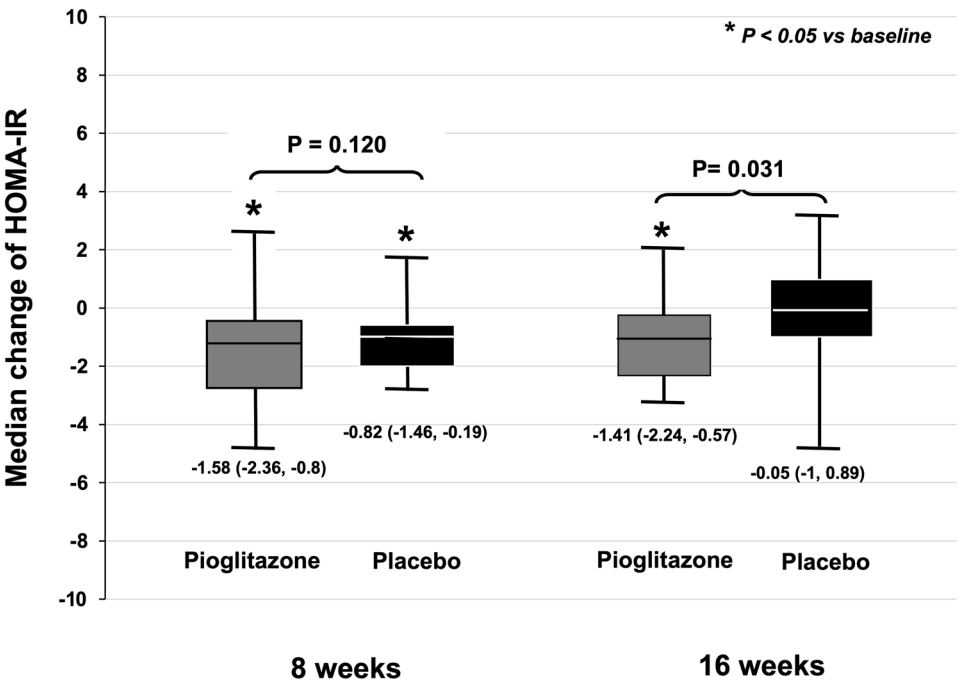

Fig. 3 Baseline and final HOMA-IR according to treatment groups

Besides a key FGF23 role in the pathogenesis of phosphate and vitamin D metabolism in CKD, FGF23 may also be involved in glucose metabolism and its potential contribution to greater adiposity and metabolic syndrome [15, 16]. Elevated FGF23 levels among patients with T2DM were reported in clinical studies [17–19]. Maladaptive responses to FGF23 may lead to harmful effects and development of diabetes [20]. We observed a positive correlation of changes of HOMA-IR index and fasting plasma insulin concentration with FGF23 decrement after treatment among patients with T2DM and CKD. These findings suggested that hyperinsulinemia and insulin resistance might be responsible for increased FGF23 levels in T2DM and CKD. In another study, FGF23 showed significant predictors

Table 2 Comparison of the changes of glycemic, calcium, phosphate, parathyroid hormone and FGF23 before and after treatment between two groups

Mean changes	Pioglitazone ($N=22$)	Placebo ($N=24$)	P value
Mean fasting plasma glucose (mg/dL)			
Baseline	133.77 ± 26.8	126.13 ± 34.42	0.408
Week 16	122.27 ± 24.58	120.43 ± 27.92	0.816
Change from baseline with 95% CI	−11.50 (−23.33, 0.33)	−6.96 (−16.63, 2.72)	0.539
Mean hemoglobinA1C (%)			
Baseline	6.73 ± 0.56	6.68 ± 1	0.825
Week 16	6.37 ± 0.5	6.62 ± 1.03	0.308
Change from baseline with 95% CI	−0.35 (−0.56, −0.15)*	−0.07 (−0.26, 0.12)	0.039
Mean insulin level (mIU/L)			
Baseline	13.4 ± 5.95	10.81 ± 5.42	0.130
Week 16	10.47 ± 5.42	10.97 ± 6.95	0.791
Change from baseline with 95% CI	−2.93 (−4.3, −1.56)*	0.19 (−2.19, 2.57)	0.024
Median HOMA-IR			
Baseline	4.05 (2.7, 5.5)	2.97 (1.8, 3.73)	0.059
Week 16	2.8 (1.72, 3.91)	2.24 (1.77, 3.84)	0.982
Change from baseline with 95% CI	−1.41 (−2.24, −0.57)*	−0.05 (−1, 0.89)	0.031
Median serum FGF23 (pg/mL)			
Baseline	207.69 (93.33, 386.77)	116.86 (46.19, 242.43)	0.062
Week 16	139.75 (55.5, 239.05)	108.8 (51.49, 258.85)	0.777
Change from baseline with 95% CI	−49.01 (−103.51, −24.53)	1.07 (−22.40, 39.53)	0.001
Mean serum phosphate (mg/dL)			
Baseline	3.23 ± 0.51	3.26 ± 0.42	0.857
Week 16	3.47 ± 0.38	3.38 ± 0.26	0.365
Change from baseline with 95% CI	0.24 (0.06, 0.42)*	0.11 (−0.07, 0.29)	0.307
Mean serum calcium (mg/dL)			
Baseline	9.43 ± 0.43	9.38 ± 0.35	0.695
Week 16	9.62 ± 0.41	9.55 ± 0.49	0.597
Change from baseline with 95% CI	0.19 (0.07, 0.32)*	0.17 (0.02, 0.32)*	0.791
Mean serum 25 hydroxyvitamin D (ng/mL)			
Baseline	39.61 ± 14.63	37.62 ± 11.44	0.609
Week 16	38.7 ± 14.02	40.45 ± 13.8	0.675
Change from baseline with 95% CI	−0.91 (−4.18, 2.36)	2.7 (−-0.7, 6.1)	0.120
Median serum intact parathyroid hormone (pg/mL)			
Baseline	41.05 (29.4, 68)	64.85 (45.15, 82.9)	0.029
Week 16	35.2 (33.1, 55.8)	59.5 (52.2, 88.5)	0.008
Change from baseline with 95% CI	−1.95 (−5, 1.6)	1.7 (−8, 11.1)	0.547

Data are number with mean with SD, mean with 95% CI and median with interquartile range. Week 16 value compared with baseline

*$P<0.05$

of insulin resistance among patients with CKD [6]. However, in contrast with these results, some studies found that FGF23 showed negative correlation with HOMA-IR and insulin concentration in obese adolescents without CKD [21, 22]. These differences were in a study population with and without CKD and further studies are necessary to determine the participation of other signals involved in regulating insulin and FGF23 relationship [23]. Further studies are needed to prove our understanding on the above mentioned mechanism.

After TZDs treatment, our diabetic CKD patients had lower insulin resistance activity. Currently, insulin resistance was a cardiovascular risk factor in a variety of population groups, including the general population and T2DM patients [24]. Improving insulin sensitivity with pioglitazone treatment probably helped to prevent the development of macrovascular complications. A meta-analysis including over 120,100 patients found that adding pioglitazone to standard therapy was associated with risk reduction of major adverse cardiovascular events among

Table 3 Analysis of related parameters with changes in serum FGF23 levels

Parameters	*R*	*P* value
Age (years)	−0.057	0.712
Change of glomerular filtration rate (mL/min/1.73 m^2)	−0.028	0.856
Change of serum calcium (mg/dl)	0.109	0.475
Change of serum phosphate (mg/dl)	−0.133	0.384
Change of intact parathyroid hormone (pg/mL)	0.001	0.996
Change of serum uric acid (mg/dl)	0.091	0.552
Change of hemoglobinA1C (%)	0.226	0.135
Change of fasting plasma glucose (mg/dL)	0.238	0.116
Change of insulin level (mIU/l)	0.473	0.001
Change of HOMA-IR	0.470	0.001
Change of dietary phosphate (mg/day)	−0.036	0.824

patients with insulin resistance and T2DM [25]. However, there are concerns over the side effects of the pioglitazone which include weight gain, edema and heart failure [25]. Recently in analysis from large randomized control trial indicated that lower doses of pioglitazone (15–30 mg/day) and full-dose pioglitazone (45 mg/day) provided similar efficacy for myocardial infarction or recurrent stroke reduction in patients with insulin resistance after stroke, but lower doses of pioglitazone reduced incidence of adverse effects including edema, weight gain and heart failure [26]. The results suggested that low-dose pioglitazone might be benefit on cardiovascular outcomes among CKD patients with T2DM, but further and larger clinical trial is needed to study.

Several limitations were associated with the present study. First, our study comprised a single-center study with a small sample size lacking any blinding of the interventions causing detection and performance bias. Second, the effects of pioglitazone on serum FGF23 levels were observed in our study, but we could not determine the effects of pioglitazone or a short term increase in FGF23 level concerning the clinical endpoints or mortality risk among patients with CKD. Additional research is needed to confirm these results and determine long term clinical outcomes. Third, although FGF23 level significantly decreased in the pioglitazone group, but higher FGF23 level in the pioglitazone group compared to placebo group was found at baseline of study. Finally, we could not evaluate the effects of pioglitazone on inflammation, s-Klotho or other potential mineral and bone biomarkers which is closely associated with treatment outcomes among patients with CKD. The strength of the study stemmed from the comprehensive mineral assessment of the patients' responses to pioglitazone using intact-PTH, serum calcium, phosphate, 25-hydroxy-vitamin D and integrated dietary phosphate intake.

In conclusion, our study constitutes the first to demonstrate the effect of pioglitazone as an add-on to the standard therapy on serum FGF23 and insulin resistance simultaneously in a group of patients with T2DM and CKD. After 16-week pioglitazone treatment, patients showed lower serum FGF23 levels accompanied with a significant improving insulin sensitivity among patients with T2DM and CKD. This may have a therapeutic role in pioglitazone among patients with T2DM and CKD with elevated serum FGF23 levels.

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Availability of data and materials Data supporting this study are available upon request.

Declarations

Conflict of interest The authors declare that they have no competing interests.

Ethics approval The study was approved by the Ethics Committee of the Institute Review Board at the Royal Thai Army Medical Department and was conducted according to the Declaration of Helsinki.

Informed consent Informed consent was obtained from all participants.

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