The Effects of Pioglitazone on Respiratory Function Test in Patients with Asthma and Type 2 Diabetes Mellitus- A before –after Study

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Abstract

Objective: Pioglitazone is one of the oral medications of type 2 diabetes (T2DM). The purpose of this study was to evaluate the effect of pioglitazone on asthma and diabetes treatment outcomes among patients with concurrent asthma and T2DM.

Materials and Methods: We conducted a quasi-experimental study on 11 patients with concurrent asthma and T2DM in Yazd Afshar Hospital and Yazd diabetic research center 2014-2017. The inclusion criteria were patients between 20-60 years old, at least one year with concurrent asthma and T2DM (documented with spirometer, bronchodilator test), ejection fraction more than 50%. Patients who were smoker, on oral corticosteroids, phenobarbital, methotrexate, rifampin, phenytoin and gemfibrozil were excluded. Laboratory tests (FBS, HbA1c, 2hpp, leptin), spirometer test, exhaled nitric oxide were done before and after 10 weeks of pioglitazone medication. All patients were visited every two weeks. The before and after pioglitazone treatment differences were checked by paired t-test and Wilcoxon Rank sum test.

Results: The mean (± SD) age of participants was 55.81 (±7.66). The median of differences of leptin (p-value: 0.885), FEV1 to FVC (*P*-value: 0.185), FEV1 (p-value: 0.386), NO (*P*-value: 0.574), FVC percent (*P*-value: 0.477), FEV1 percent (*P*-value: 0.515) did not differ before and after pioglitazone treatment.

Conclusion: Our finding suggested that pioglitazone may not be effective in the treatment and improvement of respiratory function in T2DM with concurrent asthma.

Keywords: Bronchial asthma, Thiazolidinedione, Diabetes mellitus-type II

Introduction

Diabetes is a metabolic and inflammatory disorder that affects millions of people. The incidence of diabetes is increasing. The association between diabetes and impaired lung function has been frequently observed (1-2). Diabetic patients are at increased risk of pulmonary disease, such as asthma, chronic obstructive

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pulmonary disease (COPD) and lung fibrosis due to collagen and elastin changes, as well as microangiopathy. Lung is one of the target organs for microangiopathy changes. Biochemical changes in lung connective tissue, especially collagen and elastin due to non-enzymatic glycosylation of proteins are caused by chronic hyperglycemia. Collagen, elastin and microangiopathy changes cause thickened of the epithelial base membrane and decrease of carbon monoxide diffusion capacity (DLCO) (3-4). Another hypothesis considers the activation of the inflammatory system as a link between diabetes and pulmonary dysfunction, which is involved in the pathogenesis of both diseases. The peroxisome proliferator-activated receptor gamma (PPAR-γ) family of nuclear receptor transcription factors regulates metabolism, inflammation and immunity (5-8). Asthmatic patient's treatment such as oral steroids leads to worsening glycemic control in patients with diabetes (9), any intervention that controls blood glucose and asthma in these patients is considered. Pharmacological agents that activate PPAR-γ such as pioglitazone induced insulin sensitivity and reduction of inflammatory markers (10). The purpose of this study was to evaluate the effect of pioglitazone on asthma and diabetes treatment outcomes among patients with concurrent asthma and T2DM.

Materials and Methods

Subjects

This study was a quasi-experimental with before-after design. More than 4,500 cases of pulmonary disease were investigated at Yazd Afshar hospital and Yazd diabetic research center from 2014-2017. About 373 patients were suffered from concurrent asthma and diabetes. The inclusion criteria were; patients between 20-60 years old, patients with T2DM, at least one year suffer from asthma (spirometry diagnosis or bronchodilator test), ejection fraction more than 50%, HbA1c between 7-9, under insulin or oral medication treatment, treated with inhaled corticosteroid at least three months with or without long-acting inhaled bronchodilator, pulmonary radiography do not show any other lung diseases.

Patients with hypersensitivity to pioglitazone, receiving oral corticosteroids, phenobarbital, methotrexate, rifampin, phenytoin, gemfibrozil, current or ex-smoker, respiratory infections within a month before the start of the study, past history of pulmonary diseases besides asthma, more than 2+ edema, heart failure, documented osteopenia or osteoporosis (T-score <-2.5 in patients older than 50 and Z-score< -2.5 in patients younger than 50) in bone mineral density test (BMD), diabetes retinopathy and nephropathy were excluded. It should be noted that the intervention period of study was done in the summer.

Thirty-five patients fulfilled the inclusion criteria without any exclusion but after physicians (RA and FAM) examination only 15 patients were eligible (Figure 1). Two subjects who were randomized withdrew from the study for personal reasons (sever weight gain and their nutritionist advise but there were no documented data about their weight gain or nutritionist consultation), while intervention was discontinued in 2 subjects due to pioglitazone adverse events (macular edema).

Study protocol

The duration of treatment was 10 weeks. Patients received daily 30 mg of pioglitazone. Pioglitazone were manufactured by Zahravi.Co (GLITOZ 30 MG TAB).During this period, patients were visited every two weeks for examination and possible reports of complications. All of patients were visited in Yazd diabetes research center by an endocrinologist (RA) and lung specialist (FAM).

Anthropometric parameters, fasting plasma glucose (FPG), HbA1c, leptin, spirometry and nitric acid test were measured before and after the intervention. Blood chemistry tests such as FPG was analyzed using an auto analyzer BA-400(Bio systems, European), and

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commercially available kits were used according to the manufacturer's instructions. The determination of leptin levels was performed by enzyme-linked immunosorbent assay (Leptin Human ELIZA, RD191001100). The normal range of leptin with the above assessment method is 1-50 ng/ml. HbA1c was measured by high-performance liquid chromatography on a Diamat Analyser (Bio-Rad, München, Germany).

Weight was measured without shoes and wearing only light clothing using an electronic weighing scale (Glamor, BF-1041-A) and recorded to the nearest 100 g. Height was measured once at baseline without shoes with the subject stretching to the maximum height and the head positioned in the plane using a portable stadiometer and was recorded to the nearest 0.1 cm. weight measurement before and after intervention was measured between 9-11 a.m. Body mass index (BMI) was calculated (kg/m2) using weight and height values.

Statistical analysis

SPSS version 20 software was used for statistical analysis. Results were expressed as mean ± standard deviation (SD). The Wilcoxon Rank sum test was used to compare the continuous variables and the paired t-test was used. P-value of less than 0.05 was considered to be statistically significant.

Ethical considerations

The proposal for this thesis research was presented to the ethics committee of Shahid Sadoughi University of medical sciences and approved by the Internal Medicine Department. The Ethics Committee approved the study with the number 17/ 102110 on August 17, 2014. The patients were informed about the objective of the study and each participant provided written consent prior to the study .Trial registration: IRCT2016050827785N1**.**

Results

Fifteen patients were recruited and received pioglitazone. After 10 weeks of study protocols, 11 patients (5 male and 6 female) completed the study. Mean (± SD) age of patients was 55.81(±7.66) years. Figure 1 shows the flow diagram of patient selection process. The mean (± SD) weight of patients at the beginning of study was 80.45 (±3.48) and after pioglitazone treatment was 82.18 (±3.06) which was clinically significant (p-value: 0.053). The Changes in metabolic indices at baseline and 10 weeks after pioglitazone medication are shown in Table 1.

The results showed that pioglitazone may not be effective in the treatment and improvement of respiratory function in T2DM with concurrent asthma and there were no significant changes in any of the indicators (table 2).

Correlation between pulmonary function with anthropometric and metabolic indices are shown in Table 3. The results indicated that, there was a negative relationship between FEV% (r= -0.736, *P*-value: 0.015) and FEV (r= -0.678, *P*-value: 0.031) with age and BMI respectively at the end of the study. Also, there was a positive correlation between FVC% (*P*-value: 0.004, r = 0.821) and age (table3).

Discussion

The present study aimed to investigate the effect of pioglitazone on asthma treatment in diabetic patients. Included patients were on asthma conventional treatment for at least three months. Treatment responsiveness included improvement of FEV1 and FEV1%, and decreased exhaled NO and leptin levels.

In our study, FEV1 and FEV1% increased after treatment for 10 weeks (70 cc and 1.3%), but it was not statistically significant. Exhaled NO also decreased after 10 weeks of treatment (4PPB). Also, leptin decreased about 0.5 ng / ml, which was not statistically significant.

Hashimoto and Nakahara case report about a 71-year-old man who was not on bronchodilator treatment. The pulmonary function tests showed improvement 4 weeks after the start of pioglitazone treatment (FVC

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increased from 2.33 to 3.02l and FEV1 from 1.46 to 2.03). Hashimoto and Nakahara explained the suppress of macrophages activation, reduction of nitric oxide and inflammatory cytokines, such as tumor necrosis factor-α, interleukin-1ß, and interleukin-6 as the causes of improvement (11). In our study patients were treated with inhaled corticosteroid and they did not show any significant changes in FEV1 and exhaled NO. However, improvements in FEV1 and reduction of NO occurred after 10 weeks of treatment.

It should be noted that patients were not evaluated using asthma control questionnaires before and after the onset of pioglitazone which can be considered as a limitation of this study. Also, the patients were evaluated according to clinical evidences of treatment response. Patients with mild asthma may have some benefit for pioglitazone alone treatment (Of course, if the ethics committee permits this intervention without initiating asthma treatment).

A randomized, placebo-controlled, double-blinded, crossover trial of pioglitazone for severe asthma was published in 2017 by Kaler et al. among 59 subjects screened for the study, 34 patients met the inclusion criteria and 16 subjects underwent randomization. Only 12 subjects completed the study. Two subjects who were randomized withdrew from the study for personal reasons, while intervention was discontinued in 2 subjects due to pioglitazone adverse events.

In this similar study, patients received daily 30 mg of pioglitazone. Pioglitazone, 30 mg daily, was administered for the initial 2 weeks of the first treatment phase, followed by 45 mg daily for an additional 14 weeks. This was followed by a 4 weeks washout period. According to Juniper AQLQ score, no difference was observed in comparison with placebo (12).

Table 1. Metabolic index at baseline and 10 weeks after pioglitazone medication

Variables	Baseline Mean (± SE)	Week 10 Mean (± SE)	*P*-value	Power
BMI (kg/m²)	30.55 (± 1.13)	31.27 (± 1.00)	0.038	65.1
FBS (mg/dl)	150.30 (± 9.13)	120.30 (± 14.22)	0.051	71.07
HbA1c (%)	8.11 (± 0.53)	7.47 (± 0.37)	0.288	32.3
Leptin (ng/ml)	35.53 (± 3.38)	35.08 (± 4.86)	0.885	6

Table 2. Changes in respiratory function at the beginning of the study and 10 weeks after pioglitazone medication

Variables	Baseline (Mean ± SE)	Week 10 (Mean ± SE)	*P*-value
NO (ppb)	26.21 (± 6.61)	22.99 (± 7.72)	0.574
FVC (liters)	2.51 (± 0.26)	2.46 (± 0.12)	0.269
FVC %	77.00 (± 6.94)	78.60 (± 4.39)	0.477
FEV1 (liters)	2.10 (± 0.25)	2.17 (± 0.15)	0.386
FEV1 %	80.00 (± 8.30)	81.30 (± 4.74)	0.515
FEV1/FVC%	81.96 (± 3.60)	84.75 (± 2.85)	0.185

Nitric Oxide
FEV1- Forced expiratory volume in one second
FVC- Forced vital capacity
FEV1/FVC%- amount of air exhaled in the first second divided by all of the air exhaled during a maximal exhalation

Table 3. Correlation between pulmonary function with anthropometric and metabolic indexes (n= 11)

Variables	FVC		FVC%		FEV		FEV%		FEV/FVC%		NO	
	(r)	*P*	(r)	*P*	(r)	*P*	(r)	*P*	(r)	*P*	(r)	*P*
Age (year)	-0.499	0.142	0.821	0.004	-0.603	0.065	-0.736	0.015	-0.516	0.127	-0.478	0.137
Weight (kg)	-0.113	0.755	-0.447	0.195	-0.283	0.428	0.565	0.089	-0.569	0.086	-0.133	0.697
BMI (kg/m)	-0.368	0.296	-0.215	0.550	-0.678	0.031	-0.433	0.212	0.223	0.564	0.038	0.912
HbA1C (%)	0.216	0.576	-0.143	0.714	0.088	0.822	0.204	0.599	-0.206	0.595	0.008	0.912
FBS (mg/dl)	0.476	0.195	0.159	0.684	0.188	0.628	0.214	0.580	-0.319	0.369	0.476	0.476
Leptin (ng/ml)	0.290	0.449	0.290	0.270	-0.119	0.760	0.257	0.505	0.030	0.938	-0.013	0.972

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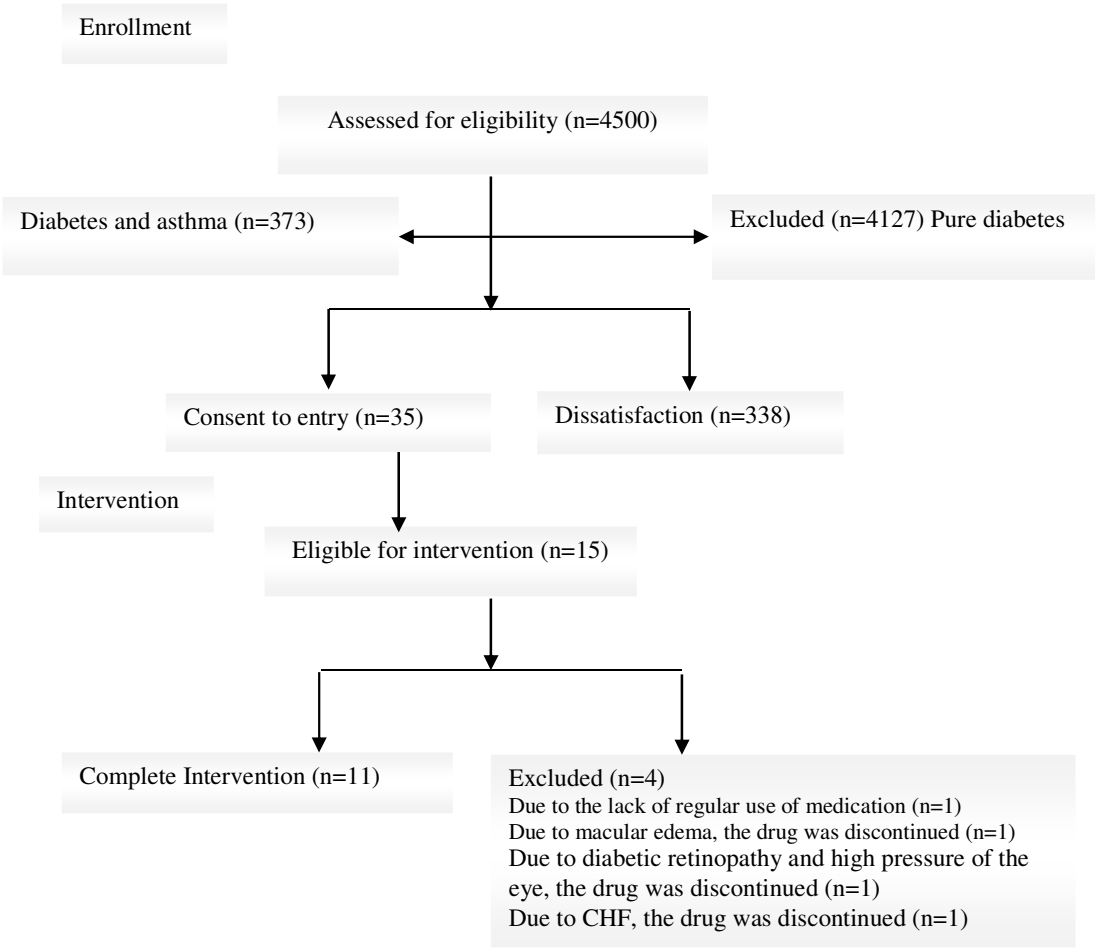

Figure 1. Flow diagram of patients selection process

The results of this study are similar to ours; however, given the short course of treatment (10 week), as well as the small sample size and low power, we cannot definitely evaluate the effect of pioglitazone on asthma.

In present study, we observed the side effects of pioglitazone in three patients, including macular edema, increase in the pressure of the eye and increase in the edema of the limbs. In the study of Kaler et al, two cases of complications including pedal edema and presumptive angioedema occurred. It seems, in both studies, due to the small sample size, creating the adverse events was remarkable

Our study similar to the study by Kaler et al, suggested that pioglitazone is not safe for use in asthmatic patients and dangerous side effects can lead to discontinuation of drug (side effects in Kaler study approximately 0.4% and in our study was 13.3%).

Another research conducted by Dixon et al, on the treatment of poorly controlled obese asthmatics by pioglitazone. Twenty-three participants were randomized to treatment, 19 patients completed the study. The outcome measure was the change in airway methacholine reactivity and exhaled nitric oxide were as treatment outcome and measured at 12 weeks after intervention and compared with baseline. There was no difference in exhaled NO, asthma control or lung function between treatment groups over 12 weeks trial. Participants assigned to pioglitazone suffered from weight gain (13).

There were some obvious limitation in our study; it was more accurate if the HbA1c was

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measured three weeks after intervention. The limited number of studied patients is the other limitation. Also the pioglitazone as the intervention was not in full dose.

In our study, BMI after 10 weeks of treatment increased from 30.5 to 31.27 kg/m (p-value 0.038). The results of the present study showed that, patients with higher BMI had lower FEV1 showed a slight effect of pioglitazone in improvement of the Asthma in obese patients (*P*-value 0.031).

Conclusions

Pioglitazone in asthmatic patients with diabetes does not lead to significant improvement in FEV1, exhaled NO and leptin. The serious side effect of pioglitazone for diabetic patients is weight gain which should be considered.

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Conflict of Interest

The authors declare that they have no competing interests.

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