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The Efficacy of Adding Pioglitazone to Insulin Therapy in Type 2 Diabetes: A Systematic Review and Meta-analysis

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ABSTRACT

Background: The significant increase of type 2 diabetes and its complications in individuals requires developing new approaches to control this disease. The present study aimed to evaluate the efficacy of pioglitazone and insulin combination therapy, compared to insulin therapy in patients with type 2 diabetes.

Methods: Medline, Cochrane Library, and Embase were searched for Randomized Controlled Trials (RCTs) comparing pioglitazone in combination with any insulin-containing regimen and the same insulin regimen alone in patients with type 2 diabetes. Hand searching was conducted in journals, congresses, and RCT registration databases related to diabetes. There were no restrictions on the language and publication year of articles. RCTs were evaluated based on the inclusion and exclusion criteria; the quality of studies was evaluated using the Jadad and the Cochrane collaboration's tools. After evaluating and extracting the data, the common results of the selected papers were entered in RevMan. Furthermore, in the cases that studies were homogeneous, meta-analysis was performed; in the cases that studies were heterogeneous, the findings were reported in a qualitative form.

Results: From the first found essays, 12 were elected for studying, including a total of 3208 patients with type 2 diabetes. The trial duration was between 12 weeks and 34.5 months. The study results presented a reduction in HbA1c and insulin dose in the combination therapy with pioglitazone arm. In our meta-analysis, the mean reduction in HbA1c was equal to 0.64%, i.e., significant [95% Confidence Interval (CI): -0.86 to -0.41, P<0.00001].

Conclusion: This systematic review indicated that in patients with type 2 diabetes, the addition of pioglitazone to the insulin regimen, compared to the insulin regimens, reduced HbA1c.

Keywords: Pioglitazone; Insulin; Type 2 diabetes; HbA1c; Efficacy; Systematic review; Meta-analysis

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1. Introduction

Type 2 diabetes is a prevalent condition in individuals with obesity, especially in those with limited physical activities. They are usually resistant to insulin; consequently, to maintaining a healthy blood glucose level, they require higher levels of insulin. Pancreatic beta cells are initially able to increase the production to compensate for insulin resistance. Therefore, blood glucose levels are controlled by such a process. However, in numerous patients, the function of pancreatic beta cells function would gradually decrease, leading to hyperglycemia and clinical diabetes [1]. Diabetes is among the major causes of blindness, renal failure, heart attacks, stroke, and restricted limb amputation. The number of individuals with diabetes has increased from 108 million in 1980 to 422 million in 2014. The global prevalence of diabetes among adults aged over 18 years has increased from 4.7% in 1980 to 8.8% in 2014. In 2012, about 1.5 million and 2.2 million deaths were directly attributed to diabetes and high blood glucose levels, respectively. Approximately 43% of these 3.7 million deaths occur before the age of 70 years [2]. Type 2 diabetes is responsible for 9% of all deaths worldwide [3]. Of all diabetes cases, about 90% to 95% is related to type 2 diabetes [4].

Numerous patients with type 2 diabetes require insulin during their illness course, either as monotherapy or in combination with blood glucose-lowering agents. However, this measure may not always be sufficient to maintain adequate blood glucose control; as a result, additional treatment approaches may be needed [5-7]. Thiazolidinediones are a group of oral anti-diabetic agents, which reduce insulin resistance in the liver and muscle [8]. Pioglitazone is a member of this group, i.e., available for combination therapy in patients with undesirable blood glucose control following insulin therapy [9]. Since 2008, using pioglitazone adjunct to insulin has been authorized in patients with type 2 diabetes insufficiently controlled by insulin and in patients who have been declared to be inappropriate due to inappropriate use or intolerance to metformin. The addition of pioglitazone to insulin for treating type 2 diabetes can help to control blood glucose levels induced by insulin resistance deficiency and insulin deficiency [10]. Pioglitazone improves the insulin resistance of peripheral tissues by increasing insulin-dependent glucose uptake and decreasing liver glucose level [11]. Randomized Controlled Trials (RCTs) revealed that pioglitazone presented significant advances in controlling blood glucose and lipid profiles in patients with type 2 diabetes under insulin treatment [12]. Pioglitazone mono-therapy has not been suggested to increase the risk of hypoglycemic complications. This is because it does not increase insulin secretion, and while combined with insulin, its effects may be due to the mechanism of reducing insulin resistance [13].

Edema and weight gain are the adverse effects associated with using pioglitazone, regardless of treatment background; however, the sole use of pioglitazone is associated with a low risk of hypoglycemia [14]. The current study aimed to evaluate the clinical efficacy and safety of adding pioglitazone to insulin, compared to solely using insulin in patients with type 2 diabetes.

2. Methods

We considered RCTs, i.e., cross-linked or parallel of pioglitazone adjunct to any insulin regimen in patients of any age and gender with type 2 diabetes. Pioglitazone combined with any insulin regimen was compared to the same insulin regimen given as monotherapy. As outcome measures, we considered HbA1c, the frequency of hypoglycemia (especially if severe), glycaemic excursions (including post-prandial hyperglycemia), the total daily dose of insulin, weight change, changes in cardiovascular risk factors, and other adverse events that have led to reducing the consumed insulin.

To collect a complete list of evidence related to the subject matter of the research, the most significant databases were systematically searched until December 27, 2016. The search was conducted at PubMed, Cochrane library, and EMBASE databases. For each database, its appropriate search strategy was used (Appendix 1). Manual searches were also conducted in the journals, related sites, and databases of randomized clinical trials for diabetes-related trials, such as Clinical Trials, Trial register, Controlled trials, and Iranian Registry of Clinical Trials.

After removing duplicated articles, two authors independently reviewed the titles and abstracts in the research of texts based on the defined inclusion criteria. Disputes were resolved through discussions between the two authors. If there was a controversy, a third researcher was involved with the discussion. The quality of clinical trials, i.e., included in the study was independently evaluated by two authors. The quality of clinical trials was independently evaluated by two researchers using Jadad's checklists and Cochrane collaboration's tools for assessing the risk of bias.After assessing the

quality of the studies, the data extraction form was designed based on the previous review studies on the subject; subsequently, the information of the final papers was extracted. The Cochrane Extraction Form was also used in this review.

Two authors separately extracted data from the selected studies. The extracted information included the characteristics of the study (the design & duration of the study), the characteristics of the participants (the age, gender, & number of patients), interventions (daily dose of pioglitazone plus insulin & solely use of insulin), and measured outcomes (blood glucose, HbA1c, & insulin dose). After completing the data extraction forms, the conflicts were discussed and finalized between the two authors. Eventually, the effects of safety and efficacy were analyzed. The main efficacy outcome variable was altering the level of HbA1c. The secondary effects of efficacy were insulin dose and Fasting Blood Glucose (FBG). To reach an overall result of the desired outcome, the change in HbA1c, conducting a meta-analysis was necessary.

3. Results

In total, 7618 related articles were identified (Figure 1). After removing duplicates, there were 6096 articles, i.e., independently reviewed concerning title, abstract, and full text by two authors to prevent any potential prejudices. Accordingly, 35 articles were eligible for a full-text study; only studies completed the phase in which pioglitazone plus insulin was used in comparison with insulin intake. Of which, 12 papers entered the final stage of the study, and the rest of the studies were excluded due to lacking the defined criteria. The characteristics of the reported studies are presented in Table 1.

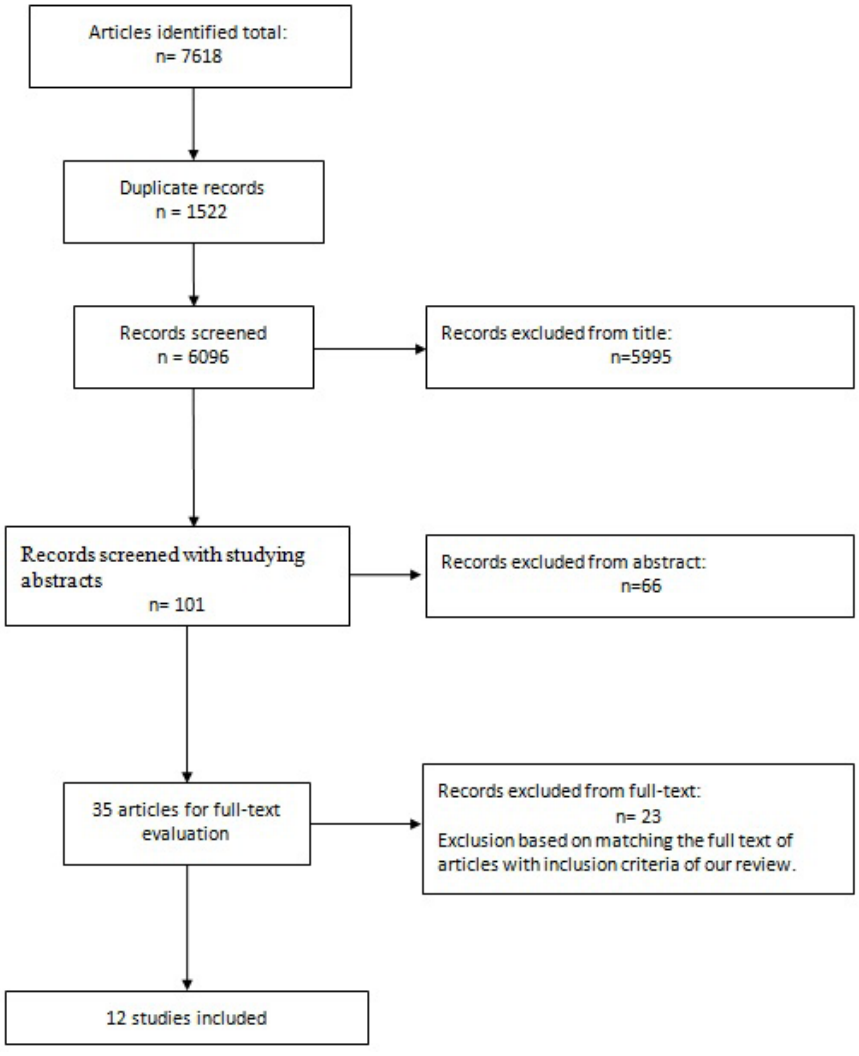

Figure 1. Collection of the studies for the systematic review

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Table 1. Characteristics of the included studies

Study (Published Year)	Disease Status	Age of Patients, y	Sample Size	Duration of Study	Control	Intervention Arm: Pioglitazone, mg/d	Concomitant Medications	Type of Design	Outcomes
Rosenstock et al. (2002) [16]	HbA1c > or = 8.0% and C-peptide > 0.7 microg/l	35-75	566	16 wks	Placebo and insulin	15 30	Stable insulin regimens for > or = 30 days	Multicenter, double-blind, placebo-controlled trial	HbA1c, hypoglycemia, weight, lipid profile, & adverse events
Raz et al. (2005) [20]	HbA1c=7.4%–14.7%	56 (mean)	281	18 wks	Insulin BIAsp 70/30, Glibenclamide (5-15 mg/d)	30	Insulin BIAsp 70/30 or Glibenclamide (5-15 mg/d) were taken orally once daily	Multinational, multicenter, randomized, open-label, parallel-group trial	HbA1c, blood glucose profiles, blood lipid levels, plasminogen activator inhibitor levels, adverse events, & hypoglycemia frequency
Asnani et al. (2006) [24]	HbA1c> 7.5%	35-75 years	20	4 mos	Placebo and insulin	30	Insulin, statins, ACE inhibitors	Randomized double-blind placebo-controlled trial	Flow-Mediated Dilatation (FMD) Nitroglycerine-Induced Dilatation (NID), fat profile, & HbA1c
Scheen et al. (2006) [19]	-	-	1760	34.5 mos	Placebo and insulin	30	Insulin	-	Death, non-lethal myocardial infarction, acute coronary syndrome, heart intercourse, stroke, leg amputation, hypoglycemia, HbA1c, adverse events

Yasunari et al. (2010) [26]	Mudaliar et al. (2010) [30]	Fernandez et al. (2008) [23]	Berhanu et al. (2007) [18]	Shah et al. (2007) [28]	**Study (Published Year)**
HbA1c>7.0%	HbA1c values between 7.5 and 10%	HbA1c>8.0%	HbA1c>8.0%	-	**Disease Status**
56.6 (mean)	58 (mean)	46 (mean)	18-75	-	**Age of Patients, y**
48	25	30	222	25	**Sample Size**
48 wks	12-16 wks	36 wks	20 wks	16 wks	**Duration of Study**
Placebo	Placebo	Placebo, Ramipril 10 mg	Placebo and insulin	Placebo and insulin	**Control**
15-30	45	45	45	30-45	**Intervention Arm: Pioglitazone, mg/d**
Glucose-lowering drugs & other medications	Insulin	Insulin, metformin, sulfonylureas, and/or meglitinides	Insulin, metformin	Insulin	**Concomitant Medications**
Prospective, randomized controlled trial	Randomized, double-blind placebo-controlled trial	Randomized, double-blind placebo-controlled trial	Multicenter, double-blind study	Randomized, double-blind placebo-controlled trial	**Type of Design**
Annual changes in intima-media thickness, HbA1c, and the daily dose of insulin	Changes in body fluids, changes in plasma volume, changes in blood glucose, changes in blood pressure, and also changes in HbA1c	Vascular analysis, HbA1c, adverse events, weight change, hypoglycemia	Alternations in insulin dose, HbA1c, hypoglycemia, weight changes, adverse events, C peptide, lipid profile	The distribution of body fat, subcutaneous adipose tissue, visceral fat tissue, weight change, HbA1c	**Outcomes**

Study (Published Year)	Disease Status	Age of Patients, y	Sample Size	Duration of Study	Control	Intervention Arm: Pioglitazone, mg/d	Concomitant Medications	Type of Design	Outcomes
Henriksen et al. (2011) [31]	HbA1c> or = 7.0%	60.5 (mean)	409	26 wks	Placebo, balaglitazone	45	Insulin	Multicenter, randomized, double-blind placebo-controlled trial	Altered HbA1c, changes in blood glucose, alter in body structure and minerals destiny in the bone
Galle et al. (2012) [25]	HbA1c 7.6±0.9%	69.2 (mean)	36	36 wks	Placebo	30	Insulin	Prospective, randomized, double-blind parallel multicenter	Alternations in the daily dose of insulin, HbA1c, altered blood glucose levels, C peptide, lipid profile, adverse events
Mattoo et al. (2005) [40]	HbA1c> or =7.5%	58.8 (mean)	289	6 mos	Placebo and insulin	30	Using insulin (with or without OAMs) for 3 months before entering the trial	Randomized, double-blind, prospective, multicenter, placebo-controlled, parallel-group study	HbA1c, hypoglycemia, weight, lipid profile, adverse events

wks: Weeks; mos: Months.

The quality of the included studies was independently ranked by two authors. Based on Jadad's criteria for evaluating quality, 5 studies were dedicated 5 points, three were scored 3, and four were ranked 2. The results of the quality of the methodology of the studies were summarized using the Cochrane tool for assessing the risk of bias (Figure 2 & Figure 3).

Safety of using pioglitazone

Hypoglycemia

Although monotherapy with pioglitazone has a slow course of action, adding it to insulin often develops immediate effects in reducing blood glucose levels. Hypoglycemia usually occurs in the first week or several weeks after the commencement of combined therapy [15]. In Rosenstock's study, hypoglycemia was reported in 15% of patients receiving 30mg pioglitazone combined with insulin [16]. The results of the meta-analysis on hypoglycemic alters are presented in Figure 4, indicating a significant change in the combined treatment group with pioglitazone plus insulin. Besides, nothing has been indicated regarding the sole use of insulin.

Edema and Congestive Heart Failure (CHF)

Edema is frequently observed in patients who respond to thiazolidinedione. Moreover, the overall incidence of edema in combination therapy ranges between 10% and 20% [17]. According to the published reports, thiazolidinedione has led to fluid retention in 2% to 5% of patients under monotherapy; this amount is higher in patients receiving coincident insulin therapy, increasing about 5% to 15% [16]. Thiazolidinedione-induced edema usually occurs in the lower extremities as well as the face. Edema can also occur only in one ankle [18].

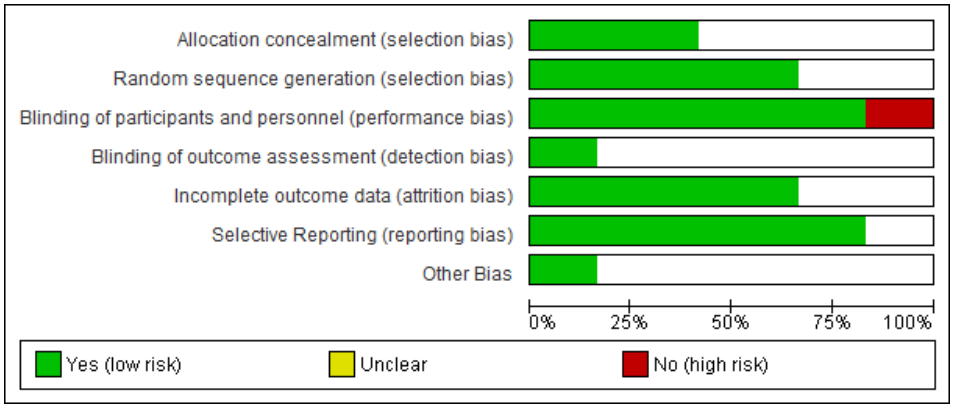

Figure 2. Risk of bias based on Cochrane criteria

Weight gain can also be attributed to water retention or increased body fat. Edema or fluid retention can lead to congestive heart failure. Furthermore, these studies reported no episodes of cardiac insufficiency.

Of the included articles, 3 studies have examined cardiovascular side effects [16, 18, 19]. According to Berhanu [18], in the monotherapy group with insulin, there was a higher incidence of cardiac complications (10.7% vs. 5.5%). In this study, in the mono-therapy group with insulin, one patient manifested myocardial infarction and cardiac hypertrophy. Moreover, in the group receiving pioglitazone plus insulin, one patient presented coronary artery disease; no death was observed. In Raz's study, two cases of myocardial infarction were reported in the insulin mono-therapy group, i.e., irrelevant to the treatment process [20]. In Rosenstock's study, cardiovascular adverse effects were measured as 7.9% in patients receiving insulin adjunct to pioglitazone and 7.0% in patients receiving insulin mono-therapy, i.e., no significant differences in this regard. Congestive heart failure was observed in two patients receiving 15mg/day pioglitazone and in two patients receiving 30mg/day pioglitazone. All cases were found in patients with a history of cardiovascular disease, none of which was attributed to the treatment process [16].

Weight gain

Weight gain occurs during the first weeks of treatment and tends to stabilize consequently. In some cases, weight gain has continued for 2-3 years. Weight gain was also observed in patients receiving the combination of thiazolidinedione and insulin [16]; the same was strongly associated with decreased HbA1c levels (r=0.8844; P=0.002).

The reason that thiazolidinedione causes weight gain may be associated with increased body fluid intake due to edema. However, other causes, including increased fat accumulation and redistribution, may also contribute to weight gain in this respect [18].

Liver damage

The addition of pioglitazone to insulin did not significantly alter the association between treatment and pioglitazone and liver injury in patients with type 2 diabetes. In a multicenter study among patients receiving 15 mg of pioglitazone plus insulin, no Alanine Aminotransferase (ALT) levels were more than triple than normal levels [16]. Compared with troglitazone, pioglitazone presents no potential liver toxicity in patients with type 2 diabetes, including those treated with insulin [15].

An RCT was conducted in 171 centers in the United States among 2097 patients with type 2 diabetes treated with pioglitazone or glibenclamide. Of them, 1051 patients received pioglitazone 15-45mg/day and 411 patients completed the treatment course. The study reported no damage to liver cells in the research subjects [21].

Bone fracture

A meta-analysis study [22] highlighted that the risk of fracture in women with type 2 diabetes receiving thiazolidinedione, including those in pioglitazone, was twice as high, compared to the rest of the study participants (OR 2.23, 95%CI 1.65-3.01; P<0.001). Using thiazolidinedione was also significantly associated with bone mineral density in the lumbar spine and leg.

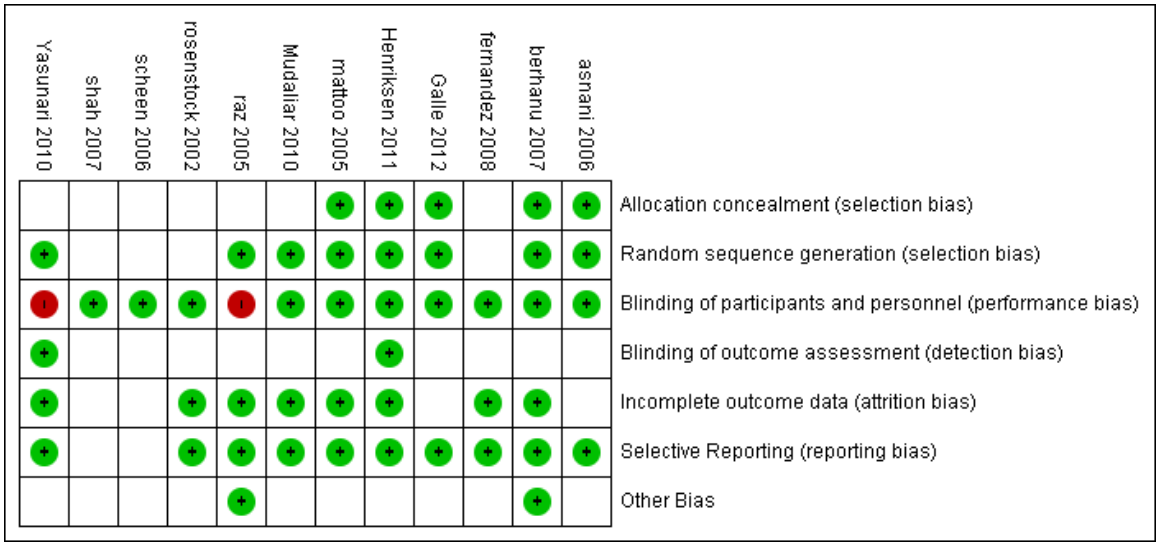

Figure 3. Specification of the risk of bias in the included studies

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Efficacy of using pioglitazone

Changes in glycosylated hemoglobin (HbA1c) levels

Changes in HbA1c levels in the groups receiving pioglitazone-insulin and insulin-placebo were measured (Table 2). In the group receiving pioglitazone and insulin, a decrease of 0.5%-2.1% in HbA1c levels was observed in studies using the higher dose of pioglitazone with the greater effects on the reduction of HbA1c. The meta-analysis data also revealed that adding pioglitazone to insulin is more effective than solely using insulin in patients with type 2 diabetes. Furthermore, the difference in the mean value of the total of 12 studies was equal to -0.64; this score was in favor of combination therapy using pioglitazone plus insulin (Figure 5).

Additionally, the CIs for this value was calculated (-0.41 & -0.86), attributing its significance to the absence of the zero number. This issue can be deduced from the magnitude of the Z statistic, i.e., equal to 5.62 at P<0.00001).

Changes in Fasting Plasma Glucose (FPG)

Almost all studies declared a reduction in FPG, compared to a decrease in HbA1c. As per Raz et al. [20], a further decrease in FPG (compared to HbA1c) was observed using biphasic insulin aspart 30/70 twice-daily injection. The connection between HbA1c and FPG is useful when attempting to select the appropriate insulin for use in combination with a thiazolidinedione.

Changes in insulin dose

Although there exist some exceptions to insulin dose protocol plans, numerous studies have reported that the addition of pioglitazone to insulin has led to a decrease in insulin dose with better control of blood glucose levels, compared to the study onset data. The decrease in insulin dose from 4.5 to 6.9 daily was observed when pioglitazone was prescribed respectively at 30mg/day and 7.3-13 units/day; i.e., when pioglitazone 45 mg/day was used, compared to the baseline data. However, in multiple studies, the decrease in insulin dose was not the primary goal of the investigation, and it has only been consumed to prevent hypoglycemia.

With the addition of pioglitazone, a special treatment with insulin glargine has been reported as basal insulin [23] or insulin with the rapid effect [24]. However, numerous studies disregarded completely explaining the type of consumed insulin. Besides, various studies have used different treatment approaches. Ratz et al. [20] detected a decrease in FPG, compared to HbA1c, using an aspartame Insulin Biphasic (IB) 70/30 injection twice daily. At the end of this trial, the mean dose of IB equaled 0.5units/kg weight of the body in the group receiving pioglitazone with insulin. This amount was 0.7units/kg weight of the body in the group receiving only insulin (without oral medication).

Changes in body weight

Of the included studies, 9 cases reported weight changes. In most studies, patients in the pioglitazone plus insulin group gained more weight, compared to the

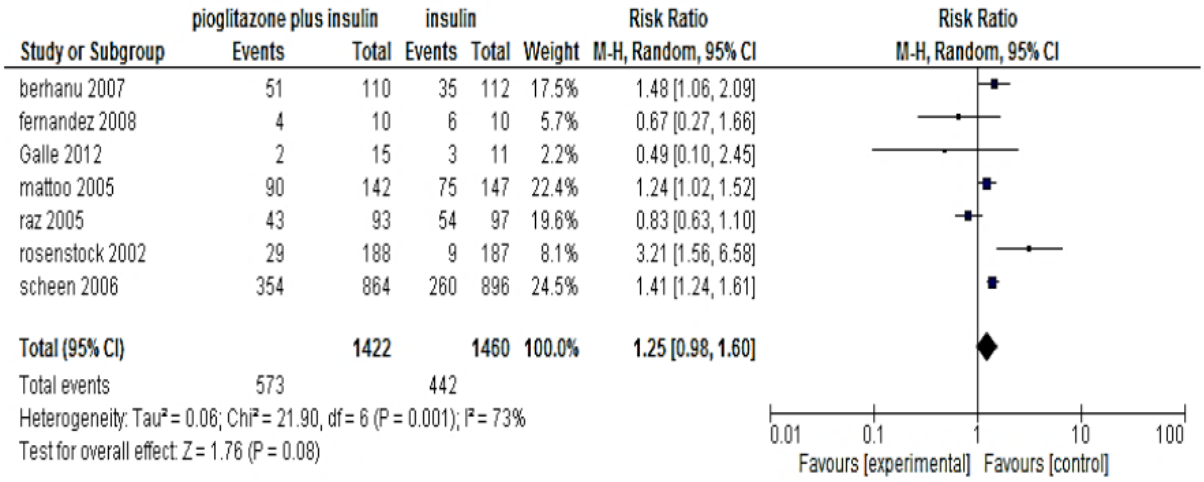

Figure 4. The results of a meta-analysis on the hypoglycemia changes

insulin group. Moreover, the mean intergroup variation at the end of the study was computed as 2.9 kg.

Changes in lipid profile

Of all reviewed studies, 6 [16, 18, 20, 23, 25] reported changes in serum triglycerides. Of the 6 studies, only 3 [16, 18, 25] signified a significant decrease in serum triglyceride levels in the group receiving pioglitazone and insulin, compared to the insulin arm.

Of the included studies, 5 [16, 18, 20, 24, 25] reported changes in the total cholesterol serum. No study detected a significant change in the total cholesterol serum in the pioglitazone and insulin groups, compared to the insulin group. Of the total studies, 6 [16, 18, 20, 23, 25, 26] reported the results of changes in High-Density Lipoprotein (HDL) cholesterol levels, reflecting a significant increase in HDL cholesterol levels in all of these studies.

Generally, pioglitazone adjunct to insulin significantly increased HDL levels and reduced the levels of triglycerides and Free Fatty Acids (FFAs) [18, 26]. Of the total studies, 6 articles [16, 18, 20, 23, 25, 26]reported alternations in serum Low-Density Lipoprotein (LDL) cholesterol; none of the studies documented a significant change in serum LDL cholesterol levels in pioglitazone plus insulin recipients, compared to the insulin group. Smaller particles of LDL, compared to larger ones, have been associated with a higher risk of cardiovascular disease [27]. Pioglitazone alters the concentration of LDL particles from small to large and increases the mean size of LDL particles [18].

4. Discussion

The present systematic review explored the effects of 12 RCTs on the addition of pioglitazone to any insulin regimen, compared to insulin regimen alone in patients with type 2 diabetes. Moreover, the included articles were analyzed based on Cochrane and Jadad's criteria. Then, according to the extracted form, based on the clinical trials, the data were extracted and analyzed by two researchers. Due to unmatched studies, meta-analysis, data integration, and qualitative analysis were applied. From these papers, two studies [19, 28] were available in abstract form.

This systematic review also revealed that the addition of pioglitazone to insulin in patients with type 2 diabetes reduced HbA1c level by an average of 0.64%, compared with the insulin alone regimen (95%CI: −0.86, −0.41, P<0.00001). In these studies, insulin dose reduction in the pioglitazone group was also noted. HDL cholesterol levels also significantly increased in the pioglitazone group. In some studies, the serum triglyceride levels of pioglitazone were significantly decreased. Furthermore, other lipid parameters, such as total cholesterol and LDL of serum cholesterol did not significantly change between the two groups. The actual meaning of these alternations remains undiscovered, and further studies are required in this regard.

In these studies, weight gain and edema were also noted in the pioglitazone group; most cases were mild to moderate and could be easily treated. In terms of safety, pioglitazone should be initiated with low doses in patients with type 2 diabetes who were previously treated with insulin. It is also recommended to reduce pioglitazone dose in patients who were previously treat-

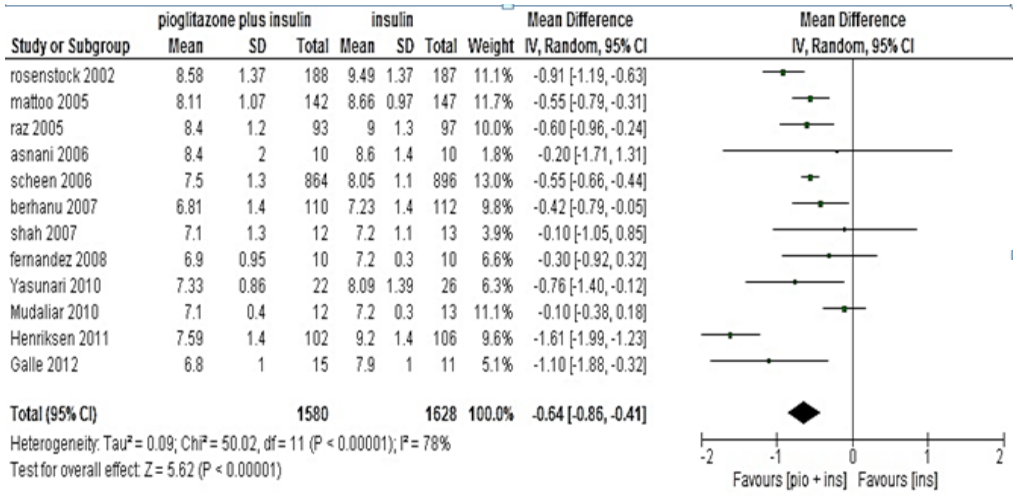

Figure 5. The results of the meta-analysis on HbA1c changes

ed with this medicine and are going to initiate insulin treatment.

This comprehensive review of studies performed on pioglitazone effects provided different results in subjects with diabetes, pre-diabetes, and insulin resistance. Pioglitazone has been successful in reducing adverse cardiovascular events, such as non-fatal heart attacks, and Major Adverse Cardiac Events (MACEs); however, its use is associated with an elevated risk of heart failure. Using this medicine has also been associated with an increased risk of bone fractures and edema (water retention), as well as weight gain.

A total of 9 studies, conducted on >120000 participants from 1966 to 2016 were reviewed in this study. We aimed to investigate the adverse cardiovascular outcomes and other side effects of this medicine. Participants included those with insulin-resistant, pre-diabetic, and type 2 diabetes; consuming pioglitazone by insulin-resistant or pre-diabetic patients reduced the incidence of type 2 diabetes in them. In all studies, at the follow-up period, i.e., at least one year, the complications of pioglitazone were studied; some of the examined participants presented a history of cardiovascular disease (stroke or heart attack) at the time of the study. Pioglitazone was associated with a 23% reduction in serious cardiovascular complications, like MACE among insulin-resistant or pre-diabetic patients. The reduction in MACE was less pronounced in individuals with type 2 diabetes; thus, it reduced the risk of cardiovascular death by 17% in this population. Pioglitazone provided a slight or even no effect (in many cases) on the risk of heart attack and stroke in subjects with type 2 diabetes. Besides, it seems that pioglitazone increases the risk of heart failure.

Except for cardiovascular outcomes, previous studies highlighted that pioglitazone may be associated with bladder cancer; however, no significant effect of this medicine on the risk of bladder cancer was detected in this meta-analysis.

Regarding the rate of progression of the disease to type 2 diabetes in the analysis of the 9 studies, only two investigations found a reduction in the rate of type 2 diabetes among insulin-resistant and pre-diabetes patients using pioglitazone. Generally, pioglitazone may generate some benefits in reducing the risk of cardiovascular disease; however, it can increase other risks, such as heart failure, edema, and overweight.

A meta-analysis study on the risk of cardiovascular complications associated with receiving pioglitazone by Lincoff et al. In 2007 included 19 trials on 16930 patients; subsequently, they suggested that pioglitazone reduced mortality risk, myocardial infarction, or stroke in the study participants [29].

A meta-analysis study on 3 RCTs revealed a 2.1 chance ratio for the risk of congestive heart failure in consuming thiazolidinedione, compared to placebo (95%CI: 1.08-4.08; P=0.03) [25]. Another meta-analysis study reflected that in patients receiving thiazolidinedione, the relative risk for congestive heart failure increased to 1.72 (95%CI: 1.21-2.42; P=0.002) [13].

Insulin can lead to water retention in the body by activating the epithelial sodium channels in the collecting tubes [30]. Therefore, thiazolidinedione-induced

Table 2. Changes in glycosylated hemoglobin in the included studies

Study	Mean±SD			Δ HbA1c	Mean±SD			Δ HbA1c
	Insulin+Pioglitazone				Insulin			
	N	Baseline	Study Completion		N	Baseline	Study Completion	
Rosenstock [16]	188	9.84	8.58±1.37	-1.26	187	9.75	9.49±1.37	-0.26
Raz [20]	93	9.6±1.3	8.4±1.2	-1.2	97	9.5±1.3	9.0±1.3	-0.5
Asnani [24]	10	10.0±2.3	8.4±2.0	-1.60	10	8.7±2.3	8.6±1.4	-0.1
Scheen [19]	864	8.4	7.47±1.3	-0.93	896	8.5	8.05±1.1	-0.45
Shah [28]	12	7.6	7.1±1.3	-0.50	13	7.8	7.2±1.1	-0.6
Berhanu [18]	110	8.4±0.13	6.81±1.4	-1.60	112	8.6±0.13	7.23±1.4	-1.37
Fernandez [23]	10	9.0±0.7	6.9±0.95	-2.1	10	9.2±0.4	7.2±0.3	-2.0
Yasunari [26]	22	8.59±1.28	7.33±0.86	-1.26	26	8.64±1.23	8.09±1.39	-0.55
Mudaliar [30]	12	7.6±0.3	7.1±0.4	-0.5	13	7.8±0.3	7.2±0.3	-0.6
Henriksen [31]	102	8.7±1.4	7.59±1.4	-1.11	106	8.5±1.3	9.2±1.4	+0.7
Galle [25]	15	7.4±0.9	6.8±1.0	-0.60	11	7.7±0.9	7.9±1.0	+0.2
Mattoo [40]	142	8.85±0.11	8.11±1.07	-0.74	147	8.79±0.10	8.66±0.97	-0.13

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edema in combination with insulin is higher than when these agents are used solely [16, 18, 30, 31].

Congestive Heart Failure (CHF) occurs in approximately 1% of patients receiving pioglitazone [16, 32]. The US Food and Drug Administration has also confirmed that congestive heart failure occurs in 1.1% of patients treated with insulin and pioglitazone. However, this condition has not occurred in patients solely receiving insulin [33].

Some studies reported that pulmonary edema also occurs following treatment with a thiazolidinedione [34, 35]. Older age, the duration of diabetes, and the high dose of insulin (82, 140, & 740 units/day) seem to be among the risk factors for pulmonary edema [15].

Treatment with thiazolidinedione often increases body fat. Weight gain is mainly observed in patients with obesity, i.e., associated with the efficacy of the medicine in reducing blood glucose levels. Weight gain is commonly associated with insulin therapy, especially in patients with type 2 diabetes [36]. A large body of literature indicated that thiazolidinedione elevates the amount of subcutaneous fat, while visceral fat remains unchanged [37-39]. Weight gain in patients treated with BIAsp 30 and pioglitazone (8% of patients) was higher than that in patients treated with BIAsp 30 solely (3%), or glibenclamide adjunct to pioglitazone (2%) [20].

The main study gap concerned the long-term safety evidence. The studies included in this systematic review, both short-term and in the number of cases for assessing the long-term undesirable effects, were few.

The relatively short-term nature of studies prevented us to evaluate whether the benefits of reducing blood glucose, anti-hyperlipidemia, and glitazones could reduce the risk of microvascular and macroscopic complications of diabetes or not.

In addition, significant heterogeneity was identified for numerous outcomes and explanations and may be as follows: First, the included trials considered different input and output criteria and design studies. Second, determining different clinical parameters in the test can potentially impact the outcomes.

A non-interventional study may also reflect the effectiveness of intervention even at best in an RCT. However, the limitations of this analysis for chronic diseases, like type 2 diabetes, remain about 6 months shorter than the study period.

5. Conclusion

This systematic review indicated that the addition of pioglitazone to insulin regimen in patients with type 2 diabetes, compared to insulin consumption, increased the HbA1c mean value to 0.64%. It also reduced insulin in patients receiving inadequate treatment to 15%-20%.

Ethical Considerations

Compliance with ethical guidelines

This study was approved by the Ethics Committee of Tehran University of Medical Sciences.

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Authors contributions

Conceptualization and supervision: Majid Davari, Elahe Khorasani, Parisa Saiyarsarai; Methodology: Majid Davari, Rahim Sarvari Shojaei, Hamidreza Zakeri; Writing – original draft: Rahim Sarvari Shojaei, Elahe Khorasani, Parisa Saiyarsarai; Writing – review & editing: Majid Davari, Ali Akbari Sari.

Conflict of interest

The authors declared no conflict of interest.

References

[1] DeFronzo RA. Pharmacologic therapy for type 2 diabetes mellitus. Ann Intern Med. 1999; 131(4):281-303. [DOI:10.7326/0003-4819-131-4-199908170-00008] [PMID]

[2] World Health Organization (WHO). Global report on diabetes. [Internet]. 2016 [Updated 2016 April 21]. Available from: https://www.who.int/publications/i/item/9789241565257

[3] World Health Organization (WHO). Definition, diagnosis and classification of diabetes mellitus and its complications: Report of a WHO consultation. Part 1, Diagnosis and classification of diabetes mellitus. [Internet]. 1999 [Updated 1999]. Available from: https://apps.who.int/iris/handle/10665/66040

[4] Lankarani M, Zahedi F. [Primary prevention of type 2 diabetes mellitus (Persian)]. Iran J Diabetes Metab. 2002; 1(2):87-106. https://ijdld.tums.ac.ir/article-1-480-en.html

[5] Horton ES. Defining the role of basal and prandial insulin for optimal glycemic control. J Am Coll Cardiol. 2009; 53(5 Suppl):S21-7. [DOI:10.1016/j.jacc.2008.11.008] [PMID]

[6] German Diabetes Association, Matthaei S, Bierwirth R, Fritsche A, Gallwitz B, Häring HU, et al. Medical antihyperglycaemic treatment of type 2 diabetes mellitus: Update of the evidence-based guideline of the German Diabetes Association. Exp Clin Endocrinol Diabetes. 2009; 117(9):522-57. [DOI:10.1055/s-0029-1239559] [PMID]

[7] Rodbard HW, Jellinger PS, Davidson JA, Einhorn D, Garber AJ, Grunberger G, et al. Statement by an American Association of Clinical Endocrinologists/American College of Endocrinology consensus panel on type 2 diabetes mellitus: An algorithm for glycemic control. Endocr Pract. 2009; 15(6):540-59. [DOI:10.4158/EP.15.6.540] [PMID]

[8] Yki-Järvinen H. Thiazolidinediones. N Engl J Med. 2004; 351(11):1106-18. [DOI:10.1056/NEJMra041001] [PMID]

[9] Huang A, Raskin P. Thiazolidinediones and insulin: Rationale for use and role of combination therapy in type 2 diabetes. Treat Endocrinol. 2005; 4(4):205-20. [DOI:10.2165/00024677-200504040-00002] [PMID]

[10] UK Prospective Diabetes Study (UKPDS) Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). Lancet. 1998; 352(9131):837-53. [DOI:10.1016/S0140-6736(98)07019-6] [PMID]

[11] Saltiel AR, Olefsky JM. Thiazolidinediones in the treatment of insulin resistance and type II diabetes. Diabetes. 1996; 45(12):1661-9. [DOI:10.2337/diabetes.45.12.1661] [PMID]

[12] Davidson JA, Perez A, Zhang J, The Pioglitazone 343 Study Group. Addition of pioglitazone to stable insulin therapy in patients with poorly controlled type 2 diabetes: Results of a double-blind, multicentre, randomized study. Diabetes Obes Metab. 2006; 8(2):164-74. [DOI:10.1111/j.1463-1326.2005.00499.x] [PMID]

[13] Lago RM, Singh PP, Nesto RW. Congestive heart failure and cardiovascular death in patients with prediabetes and type 2 diabetes given thiazolidinediones: A meta-analysis of randomised clinical trials. Lancet. 2007; 370(9593):1129-36. [DOI:10.1016/S0140-6736(07)61514-1] [PMID]

[14] Derosa G. Efficacy and tolerability of pioglitazone in patients with Type 2 Diabetes Mellitus: Comparison with other oral antihyperglycaemic agents. Drugs. 2010; 70(15):1945-61. [DOI:10.2165/11538100-000000000-00000] [PMID]

[15] Scheen AJ. Combined thiazolidinedione-insulin therapy: Should we be concerned about safety? Drug Saf. 2004; 27(12):841-56. [DOI:10.2165/00002018-200427120-00002] [PMID]

[16] Rosenstock J, Einhorn D, Hershon K, Glazer NB, Yu S, Pioglitazone 014 Study Group. Efficacy and safety of pioglitazone in type 2 diabetes: A randomised, placebo-controlled study in patients receiving stable insulin therapy. Int J Clin Pract. 2002; 56(4):251-7. [PMID]

[17] Schwartz AV, Sellmeyer DE, Vittinghoff E, Palermo L, Lecka-Czernik B, Feingold KR, et al. Thiazolidinedione use and bone loss in older diabetic adults. J Clin Endocrinol Metab. 2006; 91(9):3349-54. [DOI:10.1210/jc.2005-2226] [PMID] [PMCID]

[18] Berhanu P, Perez A, Yu S. Effect of pioglitazone in combination with insulin therapy on glycaemic control, insulin dose requirement and lipid profile in patients with type 2 diabetes previously poorly controlled with combination therapy. Diabetes Obes Metab. 2007; 9(4):512-20. [DOI:10.1111/j.1463-1326.2006.00633.x] [PMID]

[19] Scheen A, Charbonnel B. Reduced insulin requirements and improved glycemic control with pioglitazone in insulin-treated patients with type 2 diabetes: Results from PROactive. Diabetes. 2006; 55(Suppl 1):A134. https://scholar.google.com/scholar?q=Reduced+

insulin+requirements+and+improved+glycemic+control+with+pioglitazone+in+insulin-treated+patients+with+type+2+diabetes:+results+from+PROactive.&hl=fa&as_sdt=0,5

[20] Raz I, Stranks S, Filipczak R, Joshi P, Lertoft B, Rastam J, et al. Efficacy and safety of biphasic insulin aspart 30 combined with pioglitazone in type 2 diabetes poorly controlled on glibenclamide (glyburide) monotherapy or combination therapy: An 18-week, randomized, open-label study. Clin Ther. 2005; 27(9):1432-43. [DOI:10.1016/j.clinthera.2005.09.001] [PMID]

[21] Tolman KG, Freston JW, Kupfer S, Perez A. Liver safety in patients with type 2 diabetes treated with pioglitazone: Results from a 3-year, randomized, comparator-controlled study in the US. Drug saf. 2009; 32(9):787-800. [DOI:10.2165/11316510-000000000-00000] [PMID]

[22] Loke YK, Singh S, Furberg CD. Long-term use of thiazolidinediones and fractures in type 2 diabetes: A meta-analysis. CMAJ. 2009; 180(1):32-9. [DOI:10.1503/cmaj.080486] [PMID] [PMCID]

[23] Fernandez M, Triplitt C, Wajcberg E, Sriwijilkamol AA, Musi N, Cusi K, et al. Addition of pioglitazone and ramipril to intensive insulin therapy in type 2 diabetic patients improves vascular dysfunction by different mechanisms. Diabetes Care. 2008; 31(1):121-7. [DOI:10.2337/dc07-0711] [PMID]

[24] Asnani S, Kunhiraman B, Jawa A, Akers D, Lumpkin D, Fonseca V. Pioglitazone restores endothelial function in patients with type 2 diabetes treated with insulin. Metab Syndr Relat Disord. 2006; 4(3):179-84. [DOI:10.1089/met.2006.4.179] [PMID]

[25] Galle J, Kleophas W, Dellanna F, Schmid VHR, Forkel C, Dikta G, et al. Comparison of the effects of pioglitazone versus placebo when given in addition to standard insulin treatment in patients with type 2 diabetes mellitus requiring Hemodialysis: Results from the PIOren Study. Nephron Extra. 2012; 2(1):104-14. [DOI:10.1159/000337334] [PMID] [PMCID]

[26] Yasunari E, Takeno K, Funayama H, Tomioka S, Tamaki M, Fujitani Y, et al. Efficacy of pioglitazone on glycemic control and carotid intima-media thickness in type 2 diabetes patients with inadequate insulin therapy. J Diabetes Investig. 2011; 2(1):56-62. [DOI:10.1111/j.2040-1124.2010.00064.x] [PMID] [PMCID]

[27] Lamarche B, St-Pierre AC, Ruel IL, Cantin B, Dagenais GR, Després J-P. A prospective, population-based study of low density lipoprotein particle size as a risk factor for ischemic heart disease in men. Can J Cardiol. 2001; 17(8):859-65. [PMID]

[28] Shah PK, Mudaliar S, Aroda V, Wilson J, Chao E, Chang A, et al. 113 weight gain and fat distribution with pioglitazone in patients with type 2 diabetes on insulin therapy. J Investig Med. 2007; 55(1):S95. https://jim.bmj.com/content/55/1/S95.3.citation-tools

[29] Lincoff AM, Wolski K, Nicholls SJ, Nissen SE. Pioglitazone and risk of cardiovascular events in patients with type 2 diabetes mellitus: A meta-analysis of randomized trials. JAMA. 2007; 298(10):1180-8. [DOI:10.1001/jama.298.10.1180] [PMID]

[30] Mudaliar S, Chang AR, Aroda VR, Chao E, Burke P, Baxi S, et al. Effects of intensive insulin therapy alone and with added pioglitazone on renal salt/water balance and fluid compartment shifts in type 2 diabetes. Diabetes Obes Metab. 2010; 12(2):133-8. [DOI:10.1111/j.1463-1326.2009.01126.x] [PMID]

[31] Henriksen K, Byrjalsen I, Qvist P, Beck-Nielsen H, Hansen G, Riis BJ, et al. Efficacy and safety of the PPARγ partial agonist balaglitazone compared with pioglitazone and placebo: A phase III, randomized, parallel-group study in patients with type 2 diabetes on stable insulin therapy. Diabetes Metab Res Rev. 2011; 27(4):392-401. [DOI:10.1002/dmrr.1187] [PMID]

[32] Nissen SE, Nicholls SJ, Wolski K, Nesto R, Kupfer S, Perez A, et al. Comparison of pioglitazone vs glimepiride on progression of coronary atherosclerosis in patients with type 2 diabetes: The PERISCOPE randomized controlled trial. JAMA. 2008; 299(13):1561-73. [DOI:10.1001/jama.299.13.1561] [PMID]

[33] Delea TE, Edelsberg JS, Hagiwara M, Oster G, Phillips LS. Use of thiazolidinediones and risk of heart failure in people with type 2 diabetes: A retrospective cohort study. Diabetes Care. 2003; 26(11):2983-9. [DOI:10.2337/diacare.26.11.2983] [PMID]

[34] Cheng AYY, Fantus IG. Thiazolidinedione-induced congestive heart failure. Ann Pharmacother. 2004; 38(5):817-20. [DOI:10.1345/aph.1D400] [PMID]

[35] Kermani A, Garg A. Thiazolidinedione-associated congestive heart failure and pulmonary edema. Mayo Clin Proc. 2003; 78(9):1088-91. [DOI:10.4065/78.9.1088] [PMID]

[36] Pontiroli AE, Miele L, Morabito A. Increase of body weight during the first year of intensive insulin treatment in type 2 diabetes: Systematic review and meta-analysis. Diabetes Obes Metab. 2011; 13(11):1008-19. [DOI:10.1111/j.1463-1326.2011.01433.x] [PMID]

[37] Larsen TM, Toubro S, Astrup A. PPARgamma agonists in the treatment of type II diabetes: Is increased fatness commensurate with long-term efficacy? Int J Obes Relat Metab Disord. 2003; 27(2):147-61. [DOI:10.1038/sj.ijo.802223] [PMID]

[38] Miyazaki Y, Mahankali A, Matsuda M, Mahankali S, Hardies J, Cusi K, et al. Effect of pioglitazone on abdominal fat distribution and insulin sensitivity in type 2 diabetic patients. J Clin Endocrinol Metab. 2002; 87(6):2784-91. [DOI:10.1210/jcem.87.6.8567] [PMID]

[39] Shadid S, Jensen MD. Effects of pioglitazone versus diet and exercise on metabolic health and fat distribution in upper body obesity. Diabetes Care. 2003; 26(11):3148-52. [DOI:10.2337/diacare.26.11.3148] [PMID]

[40] Mattoo V, Eckland D, Widel M, Duran S, Fajardo C, Strand J, et al. Metabolic effects of pioglitazone in combination with insulin in patients with type 2 diabetes mellitus whose disease is not adequately controlled with insulin therapy: Results of a six-month, randomized, double-blind, prospective, multicenter, parallel-group study. Clin Ther. 2005; 27(5):554-67. https://www.sciencedirect.com/science/article/abs/pii/S0149291805000810

Appendix 1.

	EMBASE	
#1	'non insulin dependent diabetes mellitus'/exp	175339
#2	'non insulin dependent diabetes mellitus'	176552
#3	'diabetes mellitus, noninsulin-dependent':ti,ab,kw OR 'diabetes mellitus, ketosis-resistant':ti,ab,kw OR 'diabetes mellitus, ketosis resistant':ti,ab,kw OR 'ketosis-resistant diabetes mellitus':ti,ab,kw OR 'diabetes mellitus, non insulin dependent':ti,ab,kw OR 'diabetes mellitus, non-insulin-dependent':ti,ab,kw OR 'non-insulin-dependent diabetes mellitus':ti,ab,kw OR 'diabetes mellitus, stable':ti,ab,kw OR 'stable diabetes mellitus':ti,ab,kw OR 'diabetes mellitus, type ii':ti,ab,kw OR 'niddm':ti,ab,kw OR 'diabetes mellitus, noninsulin dependent':ti,ab,kw OR 'diabetes mellitus, maturity-onset':ti,ab,kw OR 'diabetes mellitus, maturity onset':ti,ab,kw OR 'maturity-onset diabetes mellitus':ti,ab,kw OR 'maturity onset diabetes mellitus':ti,ab,kw OR 'mody':ti,ab,kw OR 'diabetes mellitus, slow-onset':ti,ab,kw OR 'diabetes mellitus, slow onset':ti,ab,kw OR 'slow-onset diabetes mellitus':ti,ab,kw OR 'type 2 diabetes mellitus':ti,ab,kw OR 'noninsulin-dependent diabetes mellitus':ti,ab,kw OR 'noninsulin dependent diabetes mellitus':ti,ab,kw OR 'maturity-onset diabetes':ti,ab,kw OR 'diabetes, maturity-onset':ti,ab,kw OR 'maturity onset diabetes':ti,ab,kw OR 'type 2 diabetes':ti,ab,kw OR 'diabetes, type 2':ti,ab,kw OR 'diabetes mellitus, adult-onset':ti,ab,kw OR 'adult-onset diabetes mellitus':ti,ab,kw OR 'diabetes mellitus, adult onset':ti,ab,kw OR 't2dm':ti,ab,kw	147784
#4	#1 OR #2 OR #3	205072
#5	'pioglitazone'/exp	15745
#6	'pioglitazone':ti,ab,kw OR 'pioglitazone hydrochloride':ti,ab,kw OR 'actos':ti,ab,kw OR '5-(4-(2-(5-ethyl-2-pyridyl)ethoxy)benzyl)-2,4-thiazolidinedione':ti,ab,kw OR 'ad 4833':ti,ab,kw OR 'ad-4833':ti,ab,kw OR 'u 72107a':ti,ab,kw OR 'u72,107a':ti,ab,kw OR 'u-72107a':ti,ab,kw	6831
#7	#5 OR #6	16034
#8	'insulin'/exp	260597
#9	'insulin':ti,ab,kw AND 'insulin, regular':ti,ab,kw OR 'regular insulin':ti,ab,kw OR 'soluble insulin':ti,ab,kw OR 'insulin, soluble':ti,ab,kw OR 'insulin a chain':ti,ab,kw OR 'sodium insulin':ti,ab,kw OR 'insulin, sodium':ti,ab,kw OR 'novolin':ti,ab,kw OR 'iletin':ti,ab,kw OR 'insulin b chain':ti,ab,kw OR 'chain, insulin b':ti,ab,kw	2581
#10	#8 OR #9	261401
#11	#4 AND #7 AND #10	3977

	Cochrane Library	
#1	MeSH descriptor: [Diabetes Mellitus, Type 2] explode all trees	11513
#2	((((((((((((((((((((((((NIDDM:ti,ab,kw) or Noninsulin-Dependent Diabetes Mellitus:ti,ab,kw) or Type 2 Diabetes Mellitus:ti,ab,kw) or MODY:ti,ab,kw) or Maturity Onset Diabetes Mellitus:ti,ab,kw) or Maturity-Onset Diabetes Mellitus:ti,ab,kw) or Diabetes Mellitus, Type II:ti,ab,kw) or Stable Diabetes Mellitus:ti,ab,kw) or Diabetes Mellitus, Stable:ti,ab,kw) or Slow-Onset Diabetes Mellitus:ti,ab,kw) or Diabetes Mellitus, Slow Onset:ti,ab,kw) or Diabetes Mellitus, Slow-Onset:ti,ab,kw) or Diabetes Mellitus, Noninsulin Dependent:ti,ab,kw) or Non-Insulin-Dependent Diabetes Mellitus:ti,ab,kw) or Diabetes Mellitus, Non-Insulin-Dependent:ti,ab,kw) or Diabetes Mellitus, Non Insulin Dependent:ti,ab,kw) or Diabetes Mellitus, Maturity Onset:ti,ab,kw) or Diabetes Mellitus, Maturity-Onset:ti,ab,kw) or Ketosis-Resistant Diabetes Mellitus:ti,ab,kw) or Diabetes Mellitus, Ketosis Resistant:ti,ab,kw) or Diabetes Mellitus, Ketosis-Resistant:ti,ab,kw) or Diabetes Mellitus, Adult Onset:ti,ab,kw) or Adult-Onset Diabetes Mellitus:ti,ab,kw) or Diabetes Mellitus, Adult-Onset:ti,ab,kw) or Maturity-Onset Diabetes:ti,ab,kw) or Diabetes Mellitus, Noninsulin-Dependent:ti,ab,kw	25507
#3	diabetes near type-2:ti,ab,kw	19724
#4	Type 2 diabetes mellitus	24245
#5	T2DM	2829
#6	“non-insulin dependent”:ti,ab,kw	9887
#7	type-2:ti,ab,kw	21847
#8	“type II”:ti,ab,kw	3220
#9	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8	31876
#10	MeSH descriptor: [Thiazolidinediones] explode all trees	1311
#11	thiazolidinedione*:ti,ab,kw	1664
#12	((Glizone:ti,ab,kw) or Pioz:ti,ab,kw) or ((pioglitazone:ti,ab,kw) or (((((((5- (4- (2- (5-ethyl-2-pyridyl) ethoxy) benzyl) -2,4-thiazolidinedione:ti,ab,kw) or AD-4833:ti,ab,kw) or AD 4833:ti,ab,kw) or Actos:ti,ab,kw) or pioglitazone hydrochloride:ti,ab,kw) or U-72107A:ti,ab,kw) or U72,107A:ti,ab,kw) or U 72107A:ti,ab,kw))	1439
#13	pioglitazone:ti,ab,kw	1425
#14	#10 OR #11 OR #12 OR #13	2353
#15	MeSH descriptor: [Insulin] explode all trees	10011
#16	MeSH descriptor: [Insulins] explode all trees	10585
#17	insulin:ti,ab,kw	35187
#18	((((((((((((Insulin, Regular:ti,ab,kw) or Regular Insulin:ti,ab,kw) or Soluble Insulin:ti,ab,kw) or Chain, Insulin B:ti,ab,kw) or Insulin B Chain:ti,ab,kw) or Iletin:ti,ab,kw) or Novolin:ti,ab,kw) or Insulin, Sodium:ti,ab,kw) or Sodium Insulin:ti,ab,kw) or Insulin A Chain:ti,ab,kw) or Insulin, Soluble:ti,ab,kw) or Insulin:ti,ab,kw)	35271
#19	#15 OR #16 OR #17 OR #18	35329
#20	#9 AND #14 AND #19	1297

	PubMed	
#1	Diabetes Mellitus, Type 2 [MeSH]	106360
#2	diabetes mellitus, type 2/	118094
#3	T2DM	12824
#4	((((((((((((((((((((((((((NIDDM[tiab]) OR Noninsulin-Dependent Diabetes Mellitus[tiab]) OR Type 2 Diabetes Mellitus[tiab]) OR MODY[tiab]) OR Maturity Onset Diabetes Mellitus[tiab]) OR Maturity-Onset Diabetes Mellitus[tiab]) OR Diabetes Mellitus, Type II[tiab]) OR Stable Diabetes Mellitus[tiab]) OR Diabetes Mellitus, Stable[tiab]) OR Slow-Onset Diabetes Mellitus[tiab]) OR Diabetes Mellitus, Slow Onset[tiab]) OR Diabetes Mellitus, Slow-Onset[tiab]) OR Diabetes Mellitus, Noninsulin Dependent[tiab]) OR Non-Insulin-Dependent Diabetes Mellitus[tiab]) OR Diabetes Mellitus, Non-Insulin-Dependent[tiab]) OR Diabetes Mellitus, Non Insulin Dependent[tiab]) OR Diabetes Mellitus, Maturity Onset[tiab]) OR Diabetes Mellitus, Maturity-Onset[tiab]) OR Ketosis-Resistant Diabetes Mellitus[tiab]) OR Diabetes Mellitus, Ketosis Resistant[tiab]) OR Diabetes Mellitus, Ketosis-Resistant[tiab]) OR Diabetes Mellitus, Adult Onset[tiab]) OR Adult-Onset Diabetes Mellitus[tiab]) OR Diabetes Mellitus, Adult-Onset[tiab]) OR Maturity-Onset Diabetes[tiab]) OR Diabetes Mellitus, Noninsulin-Dependent[tiab])	59226
#5	(((#1) OR #2) OR #3) OR #4	130032
#6	“Thiazolidinediones”[Mesh]	10511
#7	pioglitazone	4910
#8	((((Glizone[tiab]) OR Pioz[tiab])) OR ((pioglitazone[tiab]) OR (((((((5-(4-(2-(5-ethyl-2-pyridyl)ethoxy) benzyl)-2,4-thiazolidinedione[tiab]) OR AD-4833[tiab]) OR AD 4833[tiab]) OR Actos[tiab]) OR pioglitazone hydrochloride[tiab]) OR U-72107A[tiab]) OR U72,107A[tiab]) OR U 72107A[tiab]))))	4525
#9	((#6) OR #7) OR #8	11843
#10	“insulin”[Mesh]	171323
#11	“insulins”[Mesh]	176076
#12	insulin	367466
#13	((((((((((((Insulin, Regular[Tiab]) OR Regular Insulin[Tiab]) OR Soluble Insulin[Tiab]) OR Chain, Insulin B[Tiab]) OR Insulin B Chain[Tiab]) OR Iletin[Tiab]) OR Novolin[Tiab]) OR Insulin, Sodium[Tiab]) OR Sodium Insulin[Tiab]) OR Insulin A Chain[Tiab]) OR Insulin, Soluble[Tiab]) OR Insulin[Tiab])	316608
#14	(((#10) OR #11) OR #12) OR #13	368741
#15	((#4) AND #8) AND #13	2344