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Effect of Pioglitazone on Inflammatory and oxidative markers in patient with diabetic nephropathy

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A B S T R A C T

Clinical and economic importance of diabetic nephropathy has gained a lot of interest for finding methods for prevention or decelerating its progress in recent years. According to the importance of the issue and the fact that most of data are from western populations, we aimed to evaluate effect of Pioglitazone on oxidative and inflammatory markers in these patients. In this clinical trial, 57 patients with diabetes mellitus from kidney disease and endocrinology clinics of Tabriz Imam Reza hospital, who fulfilled the inclusion criteria, were randomly assigned to receive either Glibenclamide and placebo or Glibenclamide and Pioglitazone. Serum level of markers for inflammatory, oxidative, real function and glucose control (MDA, TAO, CR, BUN, Hs-CRP, Ferritin, FBS and HbA_1c) were measured and compared before and after 6 months later. The mean age of the patients were 56.32±10.43 years in patients receiving Glibenclamide and 57.74±9.82 in patients receiving Glibenclamide and Pioglitazone. Levels of FBS, Hs-CRP and HbA_1c in patients receiving Glibenclamide and levels of FBS, MDA, BUN and HbA_1c in patients receiving Glibenclamide and Pioglitazone were reduced. Changes in level of inflammatory, oxidative, real function and glucose control were not different between two groups. In patients with diabetes mellitus, 6 months use of Glibenclamide or Glibenclamide and Pioglitazone result in sufficient glucose control. Adding Pioglitazone to Glibenclamide regimen did not affect inflammatory, oxidative, real function and glucose control markers.

Introduction

Recently, the prevalence of diabetes mellitus (DM) has increased in the world. Seemingly, the increase will continue in the future. Diabetic nephropathy(DN) is a chronic

progressive disorder demonstrated through microalbuminuria, overt albuminuria, increased blood pressure, and an irreversible reduction in renal performance, which lead to either renal failure(RF) or end stage renal disease(ESRD)(1-3).

DN is among the most common complications of DM. It has turned into a significant prevalent health condition in the past years due to the increase in conditions leading to ESRD. Due to the clinical and economic importance of DN in the past years, a great deal of attention has been paid to the methods of preventing or slowing the progress of this disease(4-6).

Recent therapeutic strategies have indicated that satisfactory control of BS, blood pressure, and RAA system can lead to a decrease in the development of DN. However, these measures cannot fully inhibit the development of this disease. Hence, it is necessary to develop new therapeutic methods to inhibit the progress of DN (7).

One of the new methods that seems to fairly contribute to the development and progress of DN is oxidative and inflammatory damage. Oxidative damage occurs the production of free radicals of oxygen surpasses the antioxidant capacity of body to remove the free radicals. Therefore, any condition that leads to the production of free radicals or reduces the antioxidant capacity of the body to remove free radicals can cause the development and progress of oxidative damage. There is a close relationship between oxidative damage and inflammation as development of each of which can intensify the other. Oxidative damage caused to human body can activate the NF-kB nuclear factor, which is a transcription factor associated with Redox. This also activates chemokines and inflammatory cytokines. Moreover, activation of the oxidative system also leads to the migration and activation of leukocytes which consequently leads to intensification of inflammation (2).

Recently a new mechanism has been discovered. According to this finding, oxidative damage leads to the production of end products of glycosylation and oxidative lipids. That is to say, free radicals react with the fatty acids of cell walls and cause peroxidation of lipids, arachidonic acid, and other fatty acids. As a result MDA is produced, which is a persistent end product of fat peroxidation (4).

Inflammation and oxidation pathways are important for DN because it is a chronic disease with a high risk of cardiovascular incidents. Evidence suggests that oxidative and inflammatory damages play an important role in the development of atherosclerosis as the most important risk factor of cardiovascular incidents (3).

Patients with DNII and CKD are useful for studying the effect of treatments causing a reduction in the oxidative and inflammatory stress put on the development of renal diseases and cardiovascular incidents.

Thiazolidinediones are a group of BS reducing medicine causing a decrease in resistance to insulin. These medicines are used as adjunctive drugs for the treatment of DM. This group of medicines act by invoking a nuclear receptor named PPARY, which is present in most tissues. In addition to their contribution to the control of BS, these medicines positively influence the metabolic syndrome outbreak and risk factors of cardiovascular incidents. A number of studies on humans have revealed that this group of medicines leads to a

reduction in proteinuria in patients with DN (6).

Most of the existing findings apply only to western societies. Hence, due to the significance of this issue and the need for further investigations, it was decided to study the effect of Pioglitazone on proteinuria and inflammatory/oxidative indicators.

Materials and Methods

In this critical trial, patients with DMII visiting the clinics of the Imam Reza Center for Education and Treatment and meeting the inclusion criteria were included in the study with their informed consent. The patients were randomly divided into two groups: experiment group and control group. This clinical trial is registered under IRCT2013102115105N1 with the Iranian Registry of Clinical Trials.

Inclusion criteria for this study included the following: diabetic nephropathy with DMII; GFR $\geq$ 30; and aged over 18 and below 65 years. Exclusion criteria included the following: DMI; GFR $\leq$ 30; progressive asthma; advanced cardiac failure; advanced hepatic disease (cirrhotic patients); generalized edema; and BMI > 40.

In the first visit, in addition to renal function indicators (BUN, Cr), blood samples were taken from the peripheral vein of fasting patients to measure inflammatory indicators studied in this research. The experimental group received 30 mg of Pioglitazone on a daily basis in addition to previous treatments. The control group also received placebo in addition to the previous treatments. A placebo similar in shape and color to Pioglitazone was prepared. The placebo lacked any pharmacological function. After 6 months, MDA inflammatory and oxidative indicators were measured in both groups. A comparison was made between the results of measurements and initial values.

Results were expressed as mean $\pm$ SD (standard deviation) as well as frequency and percentage. First, the normal distribution of variables was examined through Q-Q curves and Shapiro-Wilk tests (based on the number of samples). In order to draw a comparison between the qualitative variables before and after intervention a paired-samples test was conducted.

The 2-related samples non-parametric test was also used for abnormal distribution. Since the only indicators with normal distribution were TAO (P=0.142), BUN (p=0.406) and MDA (p=0.301), in order to study the variations of these variables parametric tests were carried out. Other variables were also examined through non-parametric tests. In the next phase of data analysis, Mann-Whitney U and Wilcoxon tests were used to study the effect of the administered medicine on the variations of inflammatory indicators. The tests were also used to compare the variations of each indicator. In all cases, results were considered to be statistically significant if $P<0.05$.

Results

The total number of patients in Glibenclamide group was 28. However, due to lack of participation or taking the medication regularly only 25 of them finally completed the study. The mean average age of the group was 56.32 ± 10.43 years, ranging from 30 to 69. Regarding the gender, 11 patients (44%) were female and 14 patients (66%) were male.

Glibenclamide & Pioglitazone group consisted of 29 patients some of whom discontinued participating or taking the medication regularly. Consequently, only 23 patients finally completed the study. The mean average age of the group was 57.74 ± 9.82 years, ranging from 34 to 70. In this group, 14 patients (60/9%) were females and 9 patients (39/1%) were male.

Firstly, the initial values of inflammatory and oxidative markers were compared between the two groups which were randomly selected. The initial values of the markers are shown in tables I and II. Data analysis indicated that the initial values of BUN (p = 0.065), MDA (p = 0652), TAO (p = 0.584), FBS (p = 0.332), Hs-CRP (p = 0509), ferritin (p = 0.584), creatinine (p = 0.077) and HbA_1c (p = 0.667) were not significantly different from each other. Furthermore, the mean average weight of the patients (p = 0.645) as well as gender distribution were not statistically different between the two groups (p = 0.754).

The results obtained from comparing the values of inflammatory and oxidative markers in patients receiving Glibenclamide treatment before and after the intervention are shown in table I.

As it can be seen in the table, the values of FBS, Hs-CRP, and HbA_1c in patients under the treatment with Glibenclamide were significantly decreased after the intervention. The values of other markers (MDA, BUN, ferritin, and creatinine) were also decreased; however, such a difference was not statistically significant. In contrast, the value of TAO increased, yet the difference was not statistically significant.
The results of comparing the values of inflammatory and oxidative markers in patients receiving Glibenclamide & Pioglitazone treatment before and after the intervention are presented in table II.

As the table shows, the values of FBS, MDA, BUN and HbA_1c in Pioglitazone & Glibenclamide group were significantly decreased after the intervention. The values of other markers (Hs-CRP, TAO, ferritin, and creatinine) were also decreased, however, not in a statistically significant way. The values of FBS (p = 0.599), Hs-CRP (p = 0.369), MDA (p = 0.124), ferritin (p = 0.642), BUN (p = 0.151) and HbA_1c (p = 0.683), were decreased in the both groups.

However, no significant difference was observed between the two groups regarding such changes. In addition, despite the increase in the value of TAO in Glibenclamide group, the difference was not significant, and overall, there was not any significant difference in the value of TAO between the two groups (p=0.164).

Discussion

Due to the high clinical and economic burden of DN, various studies are trying to find a way to slow the rate of progression of DN. The current study was also conducted with the purpose of investigating the effect of adding Pioglitazone to the medication regimen of patients. The results indicated that despite the decrease in some indicators in both groups, such benefits could not be attributed to addition of Pioglitazone to Glibenclamide. Currently, blood pressure control (8) and using ARB (9, 10) are considered the main pillars of slowing the progression of renal diseases.

Discovering PPAR resulted in production of selected agonists for the treatment of insulin resistance DMII. In addition to BS decreasing characteristic, there is some evidence promising another feature for this drug class in the form of protecting the

kidney from nephropathy progression (11-14).

Furthermore, anti-inflammatory (15) and anti-fibrotic (16) properties have also been identified for receptor PPAR-γ. Inflammation plays a significant and key role in fibrosis and DN (17, 18). Thus, agonists of receptor PPAR-γ may have anti-inflammatory and vasodilatory features, affecting the final outcome of DN.

Some studies on animal samples have also provided evidence for such a beneficial effect (19). According to the results of these studies, activation of receptor PPAR-γ has been helpful for the prevention and treatment of nephropathy in rats. Based on these evidences, a number of studies have examined the effects of the Thiazolidinediones on the prevention or treatment of DN. Such investigations still continue because in addition to the different methods and populations under study, the results of all these studies are not in line with each other.

Variables investigated in these studies include a wide range. Some studies have directly taken into consideration variables related to the kidneys such as kidney weight and microscopic lesions in animal models or other indicators of renal function (BUN, Cr, and urinary protein excretion). For example, in a non-blinded clinical trial, 44 patients with DN were randomly divided into two groups and received Pioglitazone or Glipizide. Although the amount of proteinuria in the group of patients receiving Pioglitazone indicated a decrease, however, such a difference was not significant. The researchers of this study have attributed such a lack of significant difference to advanced nephropathy in these patients (20).

With regard to the effects of Pioglitazone and Gliclazide on the DN, Katavetinet al. reported that FBS and HbA_1c significantly decreasedinbothgroupsafter12weeks. This was the only significant finding reported and both had similar 65 effects on micro albuminuria (21). Pioglitazone- compared with Placebo-not only controlled BS but also significantly and progressively decreases the amount of Proteinuria to 40%. The amount of urinary type IVC ollagen in Ovulation has been reduced and this reduction was not statistically significant though (22).

Systematic review of studies conducted in 2010 indicates that Thiazolidinediones can bear beneficial effects on albumin excretion and proteinuria in patients with DN problems. Clinical trials in this area are recommended (23) in order for various aspects to be specified.

Different studies like the current study have investigated serum levels of inflammatory markers which are associated with atherosclerosis and nephropathy instead of indicators directly measuring renal function and its tissue status. As expected, the results of the studies revealed differences regarding selected markers as well as the effect of Pioglitazone. In this case, there has been no consensus yet.

Agarwal, et al. studied the impact of Pioglitazone on 136 patients with diabetes. They found out that Pioglitazone significantly reduced CRP levels in such patients (24). Considering the effects of Pioglitazone and Gliclazide on DN, Ziaee, et al. acknowledged the significant positive effects of these two drugs on decreasing CRP and WBC taken after 4 months (25).

In our study, although the level of Hs-CR was reduced in Glibenclamide group, there was no significant difference between two groups. Given that our study was conducted over a longer period of time, the reduction of CRP might only lasts for short-term

period. Another similar study carried out in Iran had dissimilar results and a reduction in CRP levels has been reported for a group having Metformin compared to the group taking Pioglitazone. This randomized clinical trial was conducted on 40 patients with DMII. The results showed that Metformin and Pioglitazone were significantly decreased in both Hs-CRP and HbA_1c after three months. Meanwhile, the mean change in Metformin group was higher than Pioglitazone group (26).

In addition, controlling BS, as well as the follow-up treatment period may also contribute to changes in CRP levels. In the above-mentioned study, the group taking Metformin significantly achieved a better control of BS then the group having Pioglitazone. HbA_1c also experienced a greater reduction of Pioglitazone level.

In our study, there was no such difference. Interpreting the findings foregrounds considering the amount of a dose and the BS control status. In our study, both groups achieved an acceptable BS control level and no difference was also observed between two groups. This result is in the same line with those of most other studies (20, 25).

TAO and MDA levels are among indicators of oxidative stress which have been considered to be associated with diabetes complications (27). TAO amount begins to decline in the early stages of diabetes (28) and is associated with the amount of protein excretion (29). In our study, although the level of TAO in patients taking Glibenclamide was elevated, such difference was not statistically significant between the two groups. There are not any similar studies available measuring this indicator and investigating the effect of Pioglitazone or other BS-lowering medications which can be used for comparison. Considering the scope of TAO changes, it is better to conduct further studies with more samples taken, and this number of samples is probably not enough to illustrate the changes(30).

MDA amount also did not change through taking the targeted medications in our study. Few studies have examined the MDA level with regard to the use of Thiazolidinediones the results of which are consistent with the results of our study and its levels have not changed significantly (25). Another inflammatory indicator named serum ferritin level was also investigated in our study which did not change significantly in the both groups despite the proper control of BS.

Ferritin is another inflammatory indicator which is identified to be associated with DN in DMII. Nevertheless, these relationships have complications. For example, ferritin level in patients with DMII, regardless of the duration of diabetes or the status of kidney damage, is also related to BS control, and rises in case of poor control of BS (31).

There is no study available that has investigated the effect of Thiazolidinediones on ferritin level in patients with DN specifically. However, the amount of ferritin was proved to be declined through using Pioglitazone in non-diabetic patients with nonalcoholic fatty liver disease in a 12-week period (32).In another study that was conducted on people with diabetes, ferritin level remained unchanged through using Pioglitazone, but has decreased through using insulin (33).In this study, kidney status was not among the purposes. However, the results are somewhat in line with the results obtained in our study.

PPAR-γ is expressed in monocytes and macrophages, and its expression is increased

in case these cells are stimulated (34). During differentiation of macrophages and their activation, PPAR-γ agonists have inhibitory effect on the expression of proinflammatory genes and experimental results show that PPAR-γ agonists have specific effect on secretion of IL-1, IL-6 and TNF-α from monocytes (35).

However, these results should be interpreted with respect to the complex inflammatory cascade. In addition to the fact that production of IL-6, CRP and TNF-α are associated with the status of fatty tissue of the body, IL-6 is the main inducer of CRP production in the liver and the production of IL-6 is also greatly affected by TNF-α-induced (36). On the other hand, the study by Mohanty et al indicates that Thiazolidinediones are not able to reduce TNF-α in obese diabetic patients despite the reduction of CRP amount (36).

In our study, although the participants were equal regarding their weight, their body mass index was not considered which is recommended to be taken into consideration for further studies.

Conclusion

In this clinical trial, controlling BS was appropriate in patients with DMII in the both groups. Changes in oxidative and inflammatory indicators (ferritin, TAO and MDA levels) and indicators of kidney function (Cr and BUN) were not significantly different in the both groups.

Table.I Comparison of oxidative and inflammatory markers in patients of Glibenclamide group at before and after intervention

	Before intervention	After intervention	P
FBS	239.4 ± 55.7	144.6 ± 38.6	<0.005
Hs-CRP	3.6 ± 3.4	1.9 ± 2.4	0.020
TAO	0.9 ± 0.4	1.0 ± 0.3	0.352
MDA	2.6 ± 0.9	2.4 ± 0.7	0.265
Ferritin	136.5 ± 147.7	87.4 ± 106.1	0.115
Creatinine	1.5 ± 0.1	1.5 ± 0.1	0.503
BUN	40.3 ± 12.6	39.4 ± 11.3	0.321
HbA_1c	8.6 ± 0.9	7.2 ± 1.0	<0.005

Table.II Comparison of oxidative and inflammatory markers in patients of Pioglitazone & Glibenclamide group at before and after intervention

	Before intervention	After intervention	P
FBS	223.8 ± 48.9	141.8 ± 37.2	<0.005
Hs-CRP	4.5 ± 4.2	3.5 ± 3.5	0.370
TAO	0.9 ± 0.3	0.8 ± 0.4	0.407
MDA	2.7 ± 0.9	2.1 ± 0.6	0.008
Ferritin	163.4 ± 190.2	132.4 ± 162.6	0.715
Creatinine	1.5 ± 0.1	1.5 ± 0.1	0.477
BUN	33.7 ± 9.9	31.7 ± 9.2	0.014
HbA_1c	8.4 ± 0.7	7.1 ± 0.7	<0.005

References

1-Pantelis A. Sarafidis, Panagiotis C. Stafylas , Panagiotis I. Georgianos , Athanasios N. Saratzis , Anastasios N. (2010). Lasaridis. Effect of Thiazolidinediones on Albuminuria and Proteinuria in Diabetes:A Meta-analysis. American Journal of Kidney Diseases, Vol 55, No 5 (May),pp 835-847.

2- Stacey Ruiz1, Pablo E. Pergola, Richard A. Zager, and Nosratola D. (2013). Vaziri. Targeting the transcription factor Nrf2 to ameliorate oxidative stress and inflammation in chronic kidney disease. Kidney International 83, 1029–1041.

3-Rajiv Agarwal. (2006). Anti-inflammatory effects of short-term pioglitazone therapy in men with advanced diabetic nephropathy. Am J Physiol Renal Physiol ,290, F600–F605.

4- Anit Lamichhane, Suvarna Prasad, Neeru Bhaskar, Jasbir Singh and Rajesh Pandey. (2012). Malondialdehyde (MDA): an oxidative stress marker in type II Diabetes mellitus with and without complications. Current Trends In Biotechnology And Chemical Research Vol 2, No 2 (July-December), pp 110-112.

5- Xiangjin Xu , Pin Chen , Quanlin Zheng, Yanqiao Wang, Wenyu Chen. (2011). Effect of pioglitazone on diabetic nephropathy and expression of HIF-1a and VEGF in the renal tissues of type 2 diabetic rats. Diabet and clinical practice, 63-69.

6- Colleen Flynn and George L. (2013). Bakris. Noninsulin glucose-lowering agents for the treatment of patients on dialysis. Nat. Rev. Nephrol, 9, 147–153.

7- Uk Prospective Diabetes Study Group. (1998). Efficacy of atenolol and captopril in reducing risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 39. Br Med J ,317,713–720.

8- Brenner, Bm, Cooper, Me, De Zeeuw, D, Et Al. (2001). Effects of losartan on renal and cardiovascular outcomes in patients with type 2 diabetes and

nephropathy. N Engl J Med ,345,861–869.

9- LEWIS, EJ, HUNSICKER, LG, CLARKE, WR, et al. (2001). Renoprotective effect of the angiotensin-receptor antagonist irbesartan in patients with nephropathy due to type 2 diabetes. N Engl J Med ,345,851–860.

10- Guan, Y, Zhang, Y, Schneider, A, Et Al. (2001). Peroxisome proliferator-activated receptor-gamma activity is associated with renal microvasculature. Am J Physiol Renal Physiol ,281,F1036–F1046.

11- Bakris, Gl. (2003). Hypertension and nephropathy. Am J Med, 115 (Suppl 8A),49S–54S.

12- Hsueh, Wa, Nicholas, Sb. (2002). Peroxisome Proliferator-Activated Receptor-gamma in the renal mesangium. Curr Opin Nephrol Hypertens, 11,191–195.

13- Guan, Y, Breyer, Md. (2001). Peroxisome proliferator-activated receptors (PPARs): Novel therapeutic targets in renal disease. Kidney Int ,60,14–30.

14-Nakamura, T, Ushiyama, C, Osada, S, Et Al.(2001). Pioglitazone reduces urinary podocyte excretion in type 2 diabetes patients with microalbuminuria. Metabolism, 50,1193–1196.

15-Nicholas, Sb, Kawano, Y, Wakino, S, Et Al. (2001). Expression and function of peroxisome proliferator-activated receptor-gamma in mesangial cells. Hypertension, 37,722–727.

16-Wolf, G, Ziyadeh, Fn. (1999). Molecular mechanisms of diabetic renal hypertrophy. Kidney Int, 56,393–405.

17-Cordonnier, Dj, Pinel, N, Barro, C, et al. (1999). Expansion of cortical interstitium is limited by converting enzyme inhibition in type 2 diabetic patients with glomerulosclerosis. The Diabiopsies Group. J Am Soc Nephrol ,10, 1253–1263.

18-Baylis, C, Atzpodien, Ea, Freshour, G, Engels, K. (2003). Peroxisome proliferator-activated receptor [gamma] agonist provides superior renal protection versus angiotensin-converting enzyme inhibition in a rat model of type 2 diabetes with obesity. J Pharmacol Exp Ther ,307,854–860.

19-Rajiv Agarwal, Chandan Saha, Meher Battiwala, Nina Vasavada, Timothy Curley, Shawn D Chase. (2005). A pilot randomized controlled trial of renal protection with pioglitazone in diabetic nephropathy ,Kidney International ,68, 285–292.

20-Yanagawa, T, Araki, A, Sasamoto, K, Et Al. (2004). Effect of antidiabetic medications on microalbuminuria in patients with type 2 diabetes. Metabolism ,53,353–357.

21-Katavetin P, Eiam-Ong S, Suwanwalaikorn S. (2006).Pioglitazone Reduces Urinary Protein and Urinary Transforming Growth Factor-β Excretion in Patients with Type 2 Diabetes and Overt Nephropathy. J Med Assoc Thai,89 , 170-176.

22-Sarafidis PA, Stafylas PC, Georgianos PI, Saratzis AN, Lasaridis AN. (2007). Effect of Thiazolidinediones on Albuminuria and Proteinuria in Diabetes: A Meta-analysis. Am J Kidney Dis ,55,835-847.

23-Satoh N, Ogawa Y, Usui T, Tagami T, Kono S, Uesugi H, Sugiyama H, Sugawara A, Yamada K, Shimatsu A, Kuzuya H, Nakao K. (2003). Antiatherogenic effect of pioglitazone in type 2 diabetic patients irrespective of the responsiveness to its antidiabetic effect. Diabetes Care, 26(9), 2493-9.

24-Agarwal R. (2006). Anti-inflammatory effects of short-term pioglitazone therapy in men with advanced diabetic nephropathy. Am J Physiol Renal Physiol 290, F600–F605.

25-Ziaee A, Hashemipour S, GhavamS, Javadi A, Ghavam R, Barikani A, Esmailzadehha N. (, 2012). Comparison of Metformin and Pioglitazone on hs-CRP Levels in Patients WithType II Diabetes. Sci J Ilam Med Uni, 2, 28-36.

26-El Boghdady NA, Badr GA. (2012). Evaluation of oxidative stress markers and vascular risk factors in patients with diabetic peripheral neuropathy. Cell Biochem Funct, 4, 328-334.

27-Telci A, ÇakatayU , Salman S, Satman I, Sivas A. (2000). Oxidative protein damage in early stage Type 1 diabetic patients, Diabetes Research and Clinical Practice, Volume 50, Issue 3, Pages 213-223.

28-Sarah Lyn Prior, Ting Seng Tang, Geoff V. Gill, Steve C. Bain, Jeffrey W. (2011). Stephens, Adiponectin, total antioxidant status, and urine albumin excretion in the low-risk "Golden Years" type 1 diabetes mellitus cohort, Metabolism, Volume 60, Issue 2, Pages 173-179.

29-Hsu YH1, Huang MC, Chang HY, Shin SJ, Wahlqvist ML, Chang YL, Hsu KC, Hsu CC. (2013). Association between serum ferritin and microalbuminuria in Type 2 diabetes in Taiwan. Diabet Med, 30(11),1367-73.

30-Sumesh Raj, G. V. Rajan . (2013). Correlation between elevated serum ferritin and HbA1c in type 2 diabetes mellitus, Int J Res Med Sci, 1(1), 12-15.

31-Aithal GP, Thomas JA, Kaye PV, Lawson A, Ryder SD, Spendlove I, et al. (2008). Placebo-Controlled Trial of Pioglitazone in Nondiabetic Subjects With Nonalcoholic Steatohepatitis, Gastroenterology, Volume 135, Issue 4, Pages 1176-1184.

32-Agnès Hartemann-Heurtier, Marine Halbron, Jean-Louis Golmard, Sophie Jacqueminet, Jean-Philippe Bastard, Christine Rouault, Amine Ayed, Laurence Pieroni, Karine Clément, André Grimaldi. (2009). Effects of bed-time insulin versus pioglitazone on abdominal fat accumulation, inflammation and gene expression in adipose tissue in patients with type 2 diabetes, Diabetes Research and Clinical Practice, Volume 86, Issue 1, Pages 37-43.

33-Ricote M, Huang J, Fajas L, Li A, Welch J, Najib J, Witztum JL, Auwerx J, Palinski W, and Glass CK. (1998). Expression of the peroxisome proliferator-activated receptor _ (PPAR_) in human atherosclerosis and regulation in macrophages by colony stimulating factors and oxidized low density lipoprotein. Proc Natl Acad Sci USA ,95, 7614–7619.

34-Ricote M, Li AC, Willson TM, Kelly CJ, and Glass CK. (1998).The peroxisome proliferator-activated receptor-_ is a negative regulator of macrophage activation. Nature, 391, 79–82.

35-Yudkin JS, Stehouwer CD, Emeis JJ, Coppack SW. (1999). C-reactive protein in healthy subjects: associations with obesity, insulin resistance, and endothelial dysfunction: a potential role for cytokines originating from adipose tissue? Arterioscler Thromb Vasc Biol , 19, 972 – 978.

36-Mohanty P, Aljada A, Ghanim H, Hofmeyer D, Tripathy D, Syed T, Al Haddad W, Dhindsa S, and Dandona P. (2004). Evidence for a potent antiinflammatory effect of rosiglitazone. J Clin Endocrinol Metab 89,2728–2735.