UQU Medical Journal

Original Article

Comparative Study between Thiazolidinediones and Other Oral Anti-Diabetic Drugs in Type 2 Diabetes Mellitus

Sami H Hammadi and Ghassan S Nouman*

Departments of Pharmacology& Toxicology and Pathology, Faculty of Medicine, Umm Al-Qura University, P.O.Box 7607, Makkah, Saudi Arabia*

Received: November 26, 2009 *Accepted: December 23, 2009*

دراسة مقارنة بين الثيازوليدينيديونز و باقي أدوية السكري التي تعطى بالفم لمرضى السكري من النوع الثاني

د. سامي حسين محمود حمادي و د. غسان سالم أسعد نعمان

قسم علم الأدوية و السموم و قسم علم الأمراض بكلية الطب* – جامعة أم القرى – مكة المكرمة –

المملكة العربية السعودية. ص. ب. : 7607

الملخص العربي

الأساس العلمي: إن مرض السكري يؤدي إلى خلل مجموعة كبيرة من وظائف الجسم المختلفة. و هناك نوعان من مرض السكري , النوع الأول و النوع الثاني. وفي الحقيقة فان النوع الثاني من مرض السكري هو الأكثر انتشارا من النوع الأول. و تعتبر السمنة و العوامل الوراثية من الأسباب التي تؤدي إلى مقاومة الجسم لعمل هرمون الأنسولين و بالتالي حدوث السكري من النوع الثاني. تعتبر مجموعة الثيازوليدينيديونز من المجاميع الدوائية الحديثة نسبيا لعلاج السكري من النوع الثاني عن طريق الفم و ذلك من خلال زيادة حساسية المستقبلات لهرمون الأنسولين. و من المعتقد أن هذه المجموعة تعمل من خلال تنشيط بعض مستقبلات نواة الخلية المعروفة باسم PPAR-γ . و قد لوحظ أن هذه المجموعة لها تأثير ايجابي على تصلب الشرايين و مؤشرات الالتهاب من خلال تقليل عامل الانقراض الورمي ألفا (TNF-α) .

أهداف البحث: تهدف هذه الدراسة إلى تحديد تأثير مجموعة الثيازوليدينيديونز على مستوى السكر في الدم و كذلك مستوى دهون الدم و مقارنتها بأدوية السكري الأخرى التي تعطى بالفم (البيجوانيدز و السلفانيليورياز) لمرضى السكري من النوع الثاني.

وسائل و طرق البحث: تشمل الدراسة 200 مريض سكري من النوع الثاني تم تقسيمهم إلى أربع مجموعات حسب العلاج الذي يأخذنه. ثلاث مجموعات منهم كانوا يأخذون أدوية السكري بالفم و المجموعة الرابعة كانت تتبع نظام غذائي و تدريبي فقط. هناك أيضا 50 شخصا غير مصابين بمرض السكري (طبيعيين) وكانوا هم المجموعة الضابطة. وقد سجلت النتائج التغير في مستوى السكر الصائم و بعد الأكل بساعتين و السكر التراكمي

و الكوليستيرول الكلي و الكوليستيرول المنخفض الكثافة و الكوليستيرول العالي الكثافة و الدهون الثلاثية لجميع المجموعات التي أدرجت في الدراسة بما فيها المجموعة الضابطة.

النتائج: أظهرت نتائج البحث حدوث تحسن لمرضى السكري من النوع الثاني للمجموعة التي أخذت عقار الثيازوليدينيديونز ليس فقط بالنسبة لضبط سكر الدم كما في المجموعات الأخرى و لكن أيضا تحسن مقاومة الأنسجة لهرمون الأنسولين و تحسن مؤشرات عوامل الخطر في الجهاز الدوري بما فيها خلل دهون الدم و سمنة الأحشاء.

الخلاصة: أثبتت هذه الدراسة التأثير الجيد لمجموعة الثيازوليدينيديونز على تصلب الشرايين لمرضى السكري من النوع الثاني بالإضافة لكونهم علاج لمرضى السكري من هذا النوع.

ABSTRACT

Background: Diabetes mellitus (DM) is a heterogenous group of disorders, it is two types: type 1 and type 2 DM. Type 2 DM is more common than type 1 DM. Obesity and genetic factors may lead to insulin resistance and development of type 2 DM. Thiazolidinediones (TZDs) are a new class of oral anti-diabetic drugs that act as insulin sensitizer. The anti-diabetic actions of TZDs are believed to be mediated by their interaction with the nuclear receptor peroxisome proliferators-activated receptor-gamma (PPAR-γ). TZDs also may have a series of effects on atherosclerosis, and have been shown to possess anti-inflammatory properties were evidenced through their suppressive effects and reduction of tumor necrosis factor-alpha (TNF-α). ***Objective:*** This study was designed to determine the effects of TZDs on blood glucose and lipid profiles and compare it to other oral anti-diabetic drugs (Biguanides and Sulfonylurea) in patients with type 2 DM.

Materials and Methods: A total of 200 type 2 diabetic patients were included in this study and were divided into four groups according to their treatment: three groups were on oral anti-diabetic drugs and one group was on diet and exercise. 50 normal subjects were used as a normal control group. The changes in fasting blood glucose, post-prandial blood glucose, glycosylated hemoglobin, total cholesterol, low density lipoprotein, high density lipoprotein and triglycerides, were monitored in order to compare the effects of oral anti-diabetic agents as well as diet and exercise on these previous variables.

Results: Data from this study of TZDs in patients with type 2 DM indicated benefits not only in terms of glycemic control but also in terms of reduced insulin resistance and improved markers of cardiovascular risk. In addition, TZDs may reduce dyslipidemia and visceral obesity.

Conclusion: This study demonstrate an anti-atherogenic effect of TZDs in type 2 diabetic patients with respect to its anti-diabetic effect.

Keywords: Diabetes Mellitus (DM), Thiazolidinediones (TZDs), Blood Glucose, Lipid Profile, Anti-inflammatory effects.

INTRODUCTION

Diabetes mellitus (DM) is a clinical syndrome characterized by varying degrees of insulin hypo-secretion and/or insulin insensitivity leading to hyperglycemia. Lack of insulin affects the metabolism of carbohydrates, protein and fat, which lead to metabolic alterations, and it causes a significant disturbance of water and electrolytes homeostasis[1-3].

DM is divided into two groups based on their requirements for insulin: Insulin-Dependent Diabetes Mellitus (IDDM) and Non-Insulin-Dependent Diabetes Mellitus (NIDDM). In 1997, The American Diabetes Association (ADA) reclassified DM according to the etiology into (type 1 DM) which is equivalent to IDDM, and (type 2 DM) which is equivalent to NIDDM[2,4].

Type 1 DM most commonly affects juveniles; however, it may occur among adults with an acute onset. Type 1 DM is characterized by an absolute deficiency of insulin caused by massive β-cell lesions or necrosis. As a result of the destruction of β-cells, the pancreas fails to respond to ingestion of glucose, and type 1 DM shows the classical symptoms of insulin deficiency (polydipsia, polyphagia, polyuria and ketoacidosis) [4,5].

Type 2 DM (NIDDM) Mature or Adult Onset DM is the commonest form of DM. In contrast to type 1 DM, the onset is slow and the metabolic alterations observed are less than those of type 1 DM (for example, type 2 diabetic patients typically are non-ketotic) [4,5].
On average, patients with type 2 DM retain approximately 50% of their β-cell mass, resulting in variable insulin levels (normal or raised insulin level when compared with normal subjects), but are inappropriately low for degree of hyperglycemia present[1,4].

Groups at higher risk to develop type 2 DM include those with family history of type 2 DM, middle aged to elderly (age older than 40 years)[3], obese (especially visceral obesity), sedentary lifestyle and those on high-fat or high-caloric diet[2]. Insulin resistance is simply defined as a state of reduced sensitivity of tissues of the body to the action of insulin[6]. Insulin resistance may be due to an abnormal insulin molecule, over production of Tumor necrosis factor-alpha (TNF-α) in (obesity or inflammation) and/or target tissue defects (decreased number or mutations of insulin receptors) which is the most common cause of insulin resistance in type 2 DM[3].

Insulin resistance is often associated with increased body weight, cardiovascular disease (CVD) and secretion of proinflammatory cytokines such as TNF-α or interlukin-1 or 6 (IL1 / IL6)[7]. Therefore, insulin resistant state in type 2 DM is proinflammatory and potentially a proatherogenic process[8]. Individuals with insulin resistance and type 2 DM exhibit atherogenic dyslipidemia that has been associated with adverse cardiovascular (CV) outcomes. This dyslipidemic profile is characterized by increased triglycerides (TGs) levels, decreased high-density lipoprotein (HDL) levels and increase small, low-density lipoprotein (LDL) particles. These particles are more susceptible to penetrate vessel wall more easily, and are thus more atherogenic[9-15].The oral anti-diabetic drugs are classified by their actions into

either Hypoglycemic drugs (Sulfonylurea & non-sulfonylurea insulin secretagogues) or anti-hyperglycemic drugs (Metformin & Thiazolidinediones) [16].

Thiazolidinediones (TZDs) are a new class of oral anti-diabetic drugs that act as insulin sensitizer. The anti-diabetic actions of TZDs are believed to be mediated by their interaction with the nuclear receptor peroxisome proliferators-activated receptor-gamma (PPAR-γ). TZDs also may have a series of effects on atherosclerosis, and have been shown to possess anti-inflammatory properties were evidenced through their suppressive effects and reduction of tumor necrosis factor-alpha (TNF-α).[17]. It is recommended that people with moderate to severe CHF New York Heart Association (NYHA) class III-IV should avoid TZDs[18-20]. Careful monitoring approach should be followed for people who don't have symptoms of CHF but who do have one or more risk factors for CHF, physicians and patients should watch for signs of fluid retention. In these cases the drugs should be started at low doses[18-20]. Combination therapy of TZD and insulin should be observed for signs and symptoms of CHF and edema[2,21]. These drugs are contraindicated in patients with serious hepatic impairment or with ALT levels more than 2.5 times the upper limit of normal range [22].

TZDs exert their anti-hyperglycemic effect only in the presence of insulin. Therefore, it should not be used in patients with type 1 DM or for the treatment of diabetic ketoacidosis[23].

This study was designed to assess the relationships between the anti-diabetic and anti-atherosclerotic as well as the anti-inflammatory effects of the new class of oral anti-diabetic drug TZDs. Thereafter, to compare the beneficial effects of TZDs, with other conventional oral anti-diabetic agents used in the treatment of type 2 DM, through the assessment of blood glucose and lipid profiles.

MATERIAL AND PARTICIPANTS

The present study includes 200 patients with type 2 DM. Patients were divided into 4 groups, as well as 50 normal healthy subjects which were included as a 5th control group. The age of all participants ranged between 30 and 90 years. All of them gave informed consent.

***Group 1*:** Received TZDs (pioglitazone 30 mg/tablet once daily for 3 months)

***Group 2*:** Received sulfonylurea (diamicron 80 mg/tablet twice daily half an hour before breakfast and dinner for 3 months).

***Group 3*:** Received Metformin (glucophage 500 mg/tablet twice daily with meals for 3 months).

***Group 4*:** Type 2 diabetic patients on diet and exercise only.

***Group 5*:** Normal individuals were considered as the control group of the study**.** Five hospitals were involved in the study: AL-Noor Specialist Hospital (DM centre), Alawi Tunsi and his Brothers Hospital, Dr. Baksh Hospital, Al-Hada Armed Forces Hospital, King Abdulaziz Medical City National Guard Hospital.

METHODS

The participants (patients and control subjects), were subjected to medical examinations by their physicians that included: history taking and clinical examinations, routine laboratory investigations, Blood glucose profiles that include Fasting blood sugar level(FBS),Post-prandial sugar level (PPBS) 2 hours and Glycosylated hemoglobin (HbA1c). Lipid profiles that include Serum total cholesterol (T.C), low-density lipoprotein (LDL), high-density lipoprotein (HDL) and triglycerides level (TGs).

DM is diagnosed when FBS levels are 126 mg/dl or higher and PPBS levels greater than 200 mg/dl. HbA1c provides an accurate and objective measure of the average of the blood glucose concentration over the life of the hemoglobin molecule (approximately 3 months)[3]. The concentration of serum lipids: T.C, LDL, HDL and TG was measured at diagnosis and regularly thereafter. Ideally, lipid profiles, especially TG concentration is measured in fasting state.

SPSS (Statistical Package for Social Sciences) for windows version 10 was used in the description and analysis of this data. ONE WAY ANOVA and descriptive frequencies analysis tests were used for the comparison of differences between means and ranges respectively within each group. Data are presented as the mean ± standard deviation (SD), and $p<0.05$ was considered statistically significant.

RESULTS

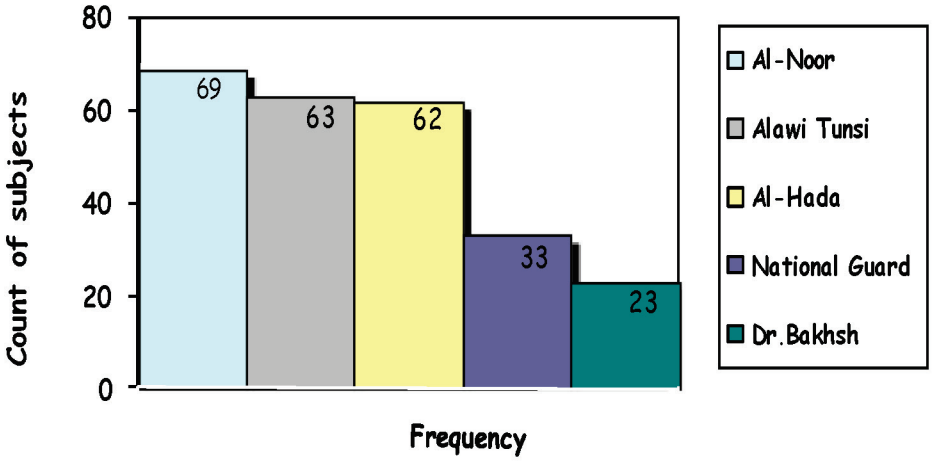

Figure 1: Distribution of the 250 subjects among the hospitals involved in the study.

Figure 1 shows that of the 250 subjects of DM and control group, 27.6% were from Al-Noor, 25.2% from Alawi Tunsi, 24.8% from Al-Hada, 13.2% from National Guard and 9.2% Dr. Baksh Hospitals.

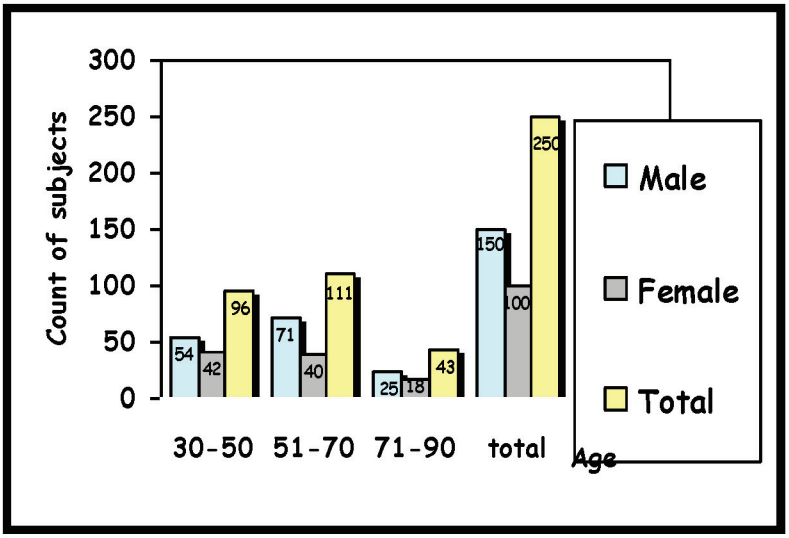

Figure 2: Distribution of the 250 subjects according to sex and age.

Figure 2 shows the male and female distribution among different age groups.

Table 1: Distribution of subjects according to reference ranges of glucose and lipid parameters.

Parameters	Reference Ranges	Diet and Exercise			Metformin			Sulfonylurea			TZDs		
		No. of Subjects (%)		Mean	No. of Subjects (%)		Mean	No. of Subjects (%)		Mean ±SD	No. of Subjects (%)		Mean
	Normal	Normal	Above	±SD	Normal	Above	±SD	Normal	Above		Normal	Above	±SD
FBS mg/dl	60-126	3 (12)	22 (88)	153 ± 20	10 (40)	15 (60)	154 ± 53	13 (52)	12 (48)	136 ± 27	8 (32)	17 (68)	**169 ± 88**
PPBS mg/dl	Less than 200	2 (12)	14 (88)	238 ± 20	11 (69)	5 (31)	214 ± 92	12 (75)	4 (25)	169 ± 40	8 (50)	8 (50)	**219 ± 84**
HbA1c %	4-7	9 (30)	21 (70)	9 ± 3	11 (37)	19 (63)	7.68 ± 2	12 (40)	18 (60)	7.44 ± 2	17 (57)	13 (43)	**7.17 ± 2**
T.C mg/dl	Less than 200	28 (93)	2 (7)	177 ± 19	18 (60)	12 (40)	193 ± 49	17 (57)	13 (43)	192 ± 41	19 (63)	11 (37)	**189 ± 30**
LDL mg/dl	Less than 100 up to 129	25 (100)	0	160 ± 8	23 (92)	2 (8)	90 ± 38	19 (76)	6 (24)	108 ± 36	21 (84)	4 (16)	**98 ± 43**
TGs mg/dl	Less than 150	23 (77)	7 (23)	176 ± 36	20 (67)	10 (33)	145 ± 57	23 (77)	7 (23)	172 ± 45	18 (60) Below 2 (7)	10 (33)	**142 ± 64**
HDL mg/dl	More than 50	Normal 1 (4)	Below 24 (96)	35 ± 6	Normal 4 (16)	Below 21 (84)	43 ± 12	Normal 7 (28)	Below 18 (72)	43 ± 11	Normal 11 (44)	Below 14 (56)	**45 ± 17**

Table 1 shows the normal reference ranges of glucose and lipid parameters. In addition, the number subjects who had achieved normal range and those who are above or below normal range in each group are illustrated.

Table 2: Multiple comparisons between the means of FBS leve

Drugs	Groups	Mean ± SD mg /dl	Significant (*p*-value)
Metformin	TZDs	169 ± 88	0.281
	Sulfonylurea	136 ± 27	0.193
	Diet & Exercise	153 ± 20	0.939
	Control	100 ± 12	0.000*
TZDs	Metformin	154 ± 53	0.281
	Sulfonylurea	136 ± 27	0.018*
	Diet & Exercise	153 ± 20	0.249
	Control	100 ± 12	0.000*
Sulfonylurea	Diet & Exercise	153 ± 20	0.220
	Control	100 ± 12	0.008*
Diet & Exercise	Control	100 ± 12	0.000*

* The mean is significant at the $p< 0.05$.

Table 3: Multiple comparisons between the means of PPBS level

Drugs	Groups	Mean ± SD mg /dl	Significant (p-value)
Metformin	TZDs	219 ± 84	0.823
	Sulfonylurea	169 ± 40	0.034*
	Diet & Exercise	238 ± 20	0.261
	Control	120 ± 7	0.000*
TZDs	Metformin	214 ± 92	0.823
	Sulfonylurea	169 ± 40	0.020*
	Diet & Exercise	238 ± 20	0.366
	Control	120 ± 7	0.000*
Sulfonylurea	Diet & Exercise	238 ± 20	0.002*
	Control	120 ± 7	0.021*
Diet & Exercise	Control	120 ± 7	0.000*

* The mean is significant at the $p< 0.05$.

Tables 2&3 show multiple comparisons of FBS and PPBG of diabetic patients on different therapeutic modalities

Table 4: Multiple comparisons between the means of HbA1c lev

Drugs	Groups	Mean ± SD mg /dl	Significant (p-value)
Metformin	TZDs	7.17 ± 2	0.278
	Sulfonylurea	7.44 ± 2	0.617
	Diet & Exercise	9 ± 3	0.013*
	Control	5 ± 1.2	0.000*
TZDs	Metformin	7.68 ± 2	0.278
	Sulfonylurea	7.44 ± 2	0.557
	Diet & Exercise	9 ± 3	0.000*
	Control	5 ± 1.2	0.000*
Sulfonylurea	Diet & Exercise	9 ± 3	0.003*
	Control	5 ± 1.2	0.000*
Diet & Exercise	Control	5 ± 1.2	0.000*

* The mean is significant at the $p< 0.05$.

Table 5: Multiple comparisons between the means of T.C level

Drugs	Groups	Mean ± SD mg /dl	Significant (p-value)
Metformin	TZDs	189 ± 30	0.637
	Sulfonylurea	192 ± 41	0.936
	Diet & Exercise	177 ± 19	0.075
	Control	119 ± 19	0.000*
TZDs	Metformin	193 ± 49	0.637
	Sulfonylurea	192 ± 41	0.695
	Diet & Exercise	177 ± 19	0.188
	Control	119 ± 19	0.000*
Sulfonylurea	Diet & Exercise	177 ± 19	0.089
	Control	119 ± 19	0.000*
Diet & Exercise	Control	119 ± 19	0.000*

* The mean is significant at the $p< 0.05$.

Table 4 shows that TZDs achieve the lowest HBA1c level (7.17%)

Table 6: Multiple comparisons between the means of LDL level

Drugs	Groups	Mean ± SD mg /dl	Significant (p-value)
Metformin	TZDs	98 ± 43	0.355
	Sulfonylurea	108 ± 36	0.048*
	Diet & Exercise	160 ± 8	0.000*
	Control	77 ± 11	0.129
TZDs	Metformin	90 ± 38	0.355
	Sulfonylurea	108 ± 36	0.285
	Diet & Exercise	160 ± 8	0.000*
	Control	77 ± 11	0.015*
Sulfonylurea	Diet & Exercise	160 ± 8	0.000*
	Control	77 ± 11	0.001*
Diet & Exercise	Control	77 ± 11	0.000*

* The mean is significant at the $p< 0.05$.

Table 7: Multiple comparisons between the means of HDL level

Drugs	Groups	Mean ± SD mg /dl	Significant (p-value)
Metformin	TZDs	45 ± 17	0.473
	Sulfonylurea	43 ± 11	0.901
	Diet & Exercise	35 ± 6	0.012*
	Control	49 ± 4	0.028*
TZDs	Metformin	43 ± 12	0.473
	Sulfonylurea	43 ± 11	0.553
	Diet & Exercise	35 ± 6	0.001*
	Control	49 ± 4	0.136
Sulfonylurea	Diet & Exercise	35 ± 6	0.008*
	Control	49 ± 4	0.038*
Diet & Exercise	Control	49 ± 4	0.000*

* The mean is significant at the $p< 0.05$.

Table 8: Multiple comparisons between the means of TGs level

Drugs	*Groups*	*Mean ± SD mg /dl*	*Significant (p-value)*
Metformin	TZDs	142 ± 64	0.837
	Sulfonylurea	172 ± 45	0.029*
	Diet & Exercise	176 ± 36	0.012*
	Control	141 ± 16	0.739
TZDs	Metformin	145 ± 57	0.837
	Sulfonylurea	172 ± 45	0.017*
	Diet & Exercise	176 ± 36	0.007*
	Control	141 ± 16	0.899
Sulfonylurea	Diet & Exercise	176 ± 36	0.729
	Control	141 ± 16	0.012*
Diet & Exercise	Control	141 ± 16	0.005*

* *The mean is significant at the p< 0.05.*

Tables 5-8 show multiple comparisons of different therapeutic modalities as well as diet and exercise on different lipid parameters (T.C., LDL-C, HDL-C, & T.Gs.)

DISCUSSION

Type 2 DM is characterized by hyperglycemia that develops due to a combination of insulin resistance and pancreatic insufficiency. Insulin resistance is often associated with the metabolic syndrome which includes: elevated TGs, T.C, LDL, low levels of HDL and other factors, which are risk factors for atherosclerosis and CVDs. Atherosclerosis is considered a result of inflammatory disease that is characterized by lipid accumulation in the arteries.

Our data showed that diabetic patients who received sulfonylurea had the best effect on their blood glucose profiles (FBS and PPBS) in comparison to the other anti-hyperglycemic drugs used and diet and exercise group. This might be due to the differences in the mode of actions of these drugs. Although sulfonylurea was the best of all drugs studied in lowering the levels of FBS and PPBS, still diabetic patients in all groups did not reach the target glycemic control and showed significantly elevated FBS and PPBS levels as compared to control group. Our results showed disagreement with a study done on 192 patients divided into two groups who received sulfonylurea and TZDs. FBS decreased to a more extent in the TZDs group as compared to the sulfonylurea group[24]. Unlike this previous study, we have not shown a significant fall in FBS with TZDs. Sulfonylurea also showed a significant difference in control of PPBS compared to TZDs, metformin and diet and exercise group.

Results of our study demonstrated that 32% of patients on TZDs achieved adequate glycemic control and 40% of patients on metformin achieved adequate glycemic control which is better compared to the results obtained by Kendall. who reported a percentage of 25-30% of patients who achieved adequate glycemic control with metformin and only 15-20% with TZDs [25].

In this study the three oral anti-diabetic drugs (TZDs, metformin and sulfonylurea) showed low levels of HbA1c which are statistically different from diet and exercise group. Patients on metformin, TZDs, sulfonylurea and diet and exercise had acceptable levels of HbA1c but are higher than the level of control group. There was a significant difference between control group in HbA1c levels compared to other groups.

Results of HbA1c in TZDs and sulfonylurea groups were close to each other. Similarly, a study which have been done by Pfutzner et al. on two groups receiving TZDs and sulfonylurea showed an equal and significant improvement of HbA1c[24]. Furthermore, the rate of HbA1c levels in our study is similar to what has been reported by Lebovitz et al. in a study done on 493 patients who had type 2 DM and randomized to receive TZD. Glycemic control improved significantly, as evidenced by reductions in HbA1c from a mean baseline value of 9.0% to 7.8% and 7.5% [26].

Anti-diabetic drugs used in this study as well as diet and exercise group have reduced the levels of T.C to levels within normal range but still higher than those in control

group. There was a significant difference in T.C levels between control group and other groups. There were no significant differences among other groups. In disagreement with our study, Pfutzner et al. showed that, there was a decrease in T.C level in the sulfonylurea group only and not in the TZD group as our study has shown[24].

In our study the three oral anti-diabetic drugs (TZDs, metformin and sulfonylurea) showed low levels of LDL which are statistically different from the diet and exercise group. Metformin showed a low level of LDL which are statistically different from sulfonylurea . Still LDL levels of all diabetic patients (four groups) are significantly higher than the control subjects. There was a significant difference between control group in LDL levels compared to TZDs, sulfonylurea and diet and exercise groups respectively, except for the group that received metformin.

Anti-diabetic drugs used in this study groups maintained HDL levels, despite low, but still within the normal range. The group on diet and exercise alone showed unexpectedly the lowest level which was significantly lower than all other groups. The three oral anti-diabetic drugs (TZDs, metformin and sulfonylurea) showed higher levels of HDL which were significantly different from diet and exercise group. There was a significant difference in HDL between control group and metformin, sulfonylurea and diet and exercise groups. The difference between TZDs group and control group was not significant. The HDL levels achieved in this study were close to each other in TZDs and sulfonylurea groups (45 and 43 mg/dl) respectively, a finding which disagrees with what had been reported by Pfutzner et al. that there was a significant increase in HDL levels with TZDs only compared to sulfonylurea[24].The findings of our results are supported by a study done on 18 patients who received TZDs and had a significant reductions in LDL and HDL levels which provide cardio-protective effects are significantly increased with treatment [27].

In case of TGs, both metformin and TZDs groups showed significantly lower levels of TGs which are statistically different from sulfonylurea group. Also, both metformin and TZDs groups showed statistical significant difference in TGs compared to diet and exercise group. There was a significant difference between control group compared to sulfonylurea and diet and exercise groups, but for the TZDs and metformin there was no statistical difference. The group on TZDs showed a level of TGs (142 mg/dl) almost the same as the control group (141 mg/dl) and there were no statistical difference between the control group and the TZDs group. Also, the level of TGs in metformin receiving group (145 mg/dl) was close to that of control group (141 mg/dl). Results of TGs levels in TZDs group are supported by a study done on 9 patients with type 2 DM who received TZDs, and showed a decrease in TGs levels with treatment[28]. The study done by Pfutzner et al. is also in agreement with our results, that TGs levels improved significantly in TZDs group compared to sulfonylurea[24]. There is another study supporting ours which was conducted on 408 patients with type 2 DM who received TZDs (pioglitazone), showed that there were

significant increases in HDL levels, and significant decreases in TGs levels both of which were associated with improved glycemic control [28-32].

Regarding T.C, LDL and TGs levels, they were decreased significantly in type 2 diabetic patients who received TZDs. These findings are in agreement with a study of 136 Japanese patients with type 2 DM. After treatment with TZDs, T.C, LDL and TGs levels were decreased significantly. In contrast, our findings show elevated levels of HDL in TZDs group whereas, HDL remained unchanged in Japanese patients[33]. A total of 67 type 2 diabetic patients agreed to take part in the study done by Chu et al.[34], there was a fall in TGs in both metformin and TZDs groups but not in sulfonylurea group. These results are in agreement with ours except for sulfonylurea. T.C fall significantly on metformin, but again, this change was not different from that seen in the other groups. HDL increased significantly in the TZDs group. Comparing the three groups, the change seen with TZDs was significantly different from that seen with metformin and sulfonylurea. No change in total LDL cholesterol was seen in any group. These results are in agreement with our results in case of T.C but not for LDL and HDL [34].

The differences in the results achieved in our study compared to other studies may be due to the differences in methods of measurements and differences in populations. As we have noticed in case of lipid profile the three oral anti-diabetic drugs almost had achieved controlled levels but TZDs was the best.

This study showed that the anti-diabetic effect of TZDs is associated not only with significant improvements in glycemic control and reduction of insulin resistance, but also with a substantial beneficial impact on lipid profile. Therefore, TZDs may offer an added initial therapeutic strategy to treat DM-associated CVD in type 2 diabetic patients because of their anti-diabetic, anti-atherogenic and anti-inflammatory effects. However, further studies are needed to confirm these findings and to exclude any deleterious effect on other cardiovascular parameters.

REFERENCES

1. Cantrill JA. Diabetes Mellitus, 633-638. *In* Walker R and Edwar C (eds.), Clinical Pharmacology and Therapeutics, Churchill Livingstone 1999.

2. Krentz AJ. Churchill's Poket Book of Diabetes, Churchill Livingstone 2000; 2-20.

3. Frier BM and Fisher BM.. Diabetes Mellitus, 644-655. *In* Haslett C, Chilvers ER, Boon NA, and Colledge NR (eds.), Davidson's Principles and Practice of Medicine, Churchill Livingstone 2002.

4. Harvey RA, Champe PC, and Mycek MJ. *In* Pharmacology Lippincott's Ilustrated Reviews Lippincott. Williams and Wilkins 2000; 255-257.

5. Govan DT, Macfarane PS, and Callander R. Pathology Illustrated. Churchill Livingstone 1995; 821-823..

6. Visser M, Bouter L, McQuillan G, Wener M, and Harris T.. Insulin Resistance as a Proinflammatory State: Mechanisms, Mediators, and Therapeutic Interventions. JAMA 1999; 282:2169-2171.

7. Hu E, Liang P, and Spiegelman BM.. AdipoQ is a novel adipose-specific gene dysregulated in obesity. J Biol Chem 1996; 271:10697-10703.

8. Dandona P and Aljada A. A rational Approach to pathogenesis and treatment of type 2 diabetes mellitus, insulin resistance, and atherosclerosis. Am J cardiol 2002; 90:27-33.

9. Haffner SM, Lehto S, Ronnemaa T, Pyorala K, and Laakso M. Mortality from coronary heart disease in subjects with type 2 diabetes and in nondiabetetic subjects with and without prior myocardial infarction. N Engl J Med 1999; 339:229-234.

10. MacGarry JD. Dysregulation of fatty acid metabolism in the etiology of type 2 diabetes. Diabetes 2001; 51:7-18.

11. Ovalle F and Bell DSH. Differing effects of thiazolidinediones on LDL sub fractions. Diabetes 2001; 50:453-454.

12. Parulkar AA, pendergrass ML, and Granda-Ayala R, Lee TR, Fonseca VA. Nonhypoglycemic effects of thiazolidinediones. Ann intern Med 2001;134:61-71.

13. Bays H. Atherogenic dyslipidemia in type 2 diabetes and metabolic syndrome: current and frther treatment options. Br J Diabetes Vas Dis 2003; 3:356-360.

14. Brunzell JD and Ayyobi AF. Dyslipidemia in the metabolic syndrome and type 2 diabetes mellitus. Am J Med 2003;115:24-28.

15. Kendall DM, Sobel BE, and Coulston AM. The insulin resistance syndrome and coronary artery disease. Coron Artery Dis 2003;14:335-348.

16. Laurence DR, Bennet PN, and Brown MJ. Clinical pharmacology. Churchill Livngstone.1997; 623-625.

17. Bell DS. Beneficial effects resulting from thiazolidinediones for treatment of type 2 diabetes mellitus. Postgrad Med 2003; 23:35-44.

18. Hirsch IB, Kelly J, Cooper S. Pulmonary edema associated with troglitazone therapy. Arch Intern Med 1999; 159: 1811.

19. Thomas ML, LIyd SJ. Pulmonary edema associated withrosiglitazone and troglitazone. Ann Pharmacther 2001; 35:123-124.

20. Nesto RW, Bell D, Bowon RO. Thiazolidinedione,use, fluid retention, and congestive heart failure. Circulation 2003; 108:2941-2948.

21. Okazaki R, Miura M, Toriumi M, Taguchi M, Hirota Y, Fukumoto S, Fujita T, Tanaka K, and Takeuchi A. Short-term treatment with troglitazone decreases bone turnover in patients with type 2 diabetes mellitus. Endocr J 1999; 46:795-801.

22. Avandia (package insert). Research Triangle Park 2003.

23. Zachary T and Bloomgarden MD. Thiazolidinediones. Diabetes Care 2005; 28:488-439.

24. Pfutzner A, Marx N, Lubben G, and Langenfeld M. Improvement of cardiovascular risk markers by pioglitazone is independent from glycemic control. J Am Coll Cardiol 2005; 45:1925-1931.

25. Kendall. Thizolidinediones. Diabetes Care 2004; 28:488-493.

26. Lebovitz HE, Dole JF, and Patwardhan R, Rappaport Eb, Freed MI. Rosiglitazone monotherapy is effective in patients with type 2 diabetes. J Clin Endocrinal Metab 2001; 86:280-288.

27. Kwietrovich PO Jr. The metabolic pathways of high-density lipoprotein; low-density Lipoprotein; and triglyceride. A current review Am J Cardiol 2000; 86:5-10.

28. Mayerson AB, Hundal RS, and Dufour S. The effects of rosiglitazone on insulin sensitivity, lipolysis, and hepatic and skeletal muscle triglyceride content in patients with type 2 diabetes. Diabetes 2002; 51:797-802.

29. Aronoff S, Rosenblatt S, and Braithwaite S. Pioglitazone hydrochlride monotherapy improves glycemic control in the treatment of patient with type 2 diabetes: A 6-month randomized placepo-controlled dose-response study. Diabetes Care 2000; 23:1605-1611.

30. Boyle PJ, King AB, and Olamsky L. Effects of pioglitazone and rosiglitazone on blood lipid levels and glaycemic control in patients with type 2 diabetes mellitus. Circ Res 2002; 24:378-396.

31. Kahn MA, St peter JV, and Xue JL. A prosterective, randomaized comparison of the metabolic effect of pioglitazone or rosiglitazone in patients with type 2

diabetes who were previously treated with proglitazone. Diabetes Care 2002; 25:708-711.

32. Mathisen AL, Schneider R, Rubin C, and Houser V. The effect pioglitazone on glucose control and lipid profile in patients with type 2 diabetes. Diabetologia 1999; 42:277-279.

33. Noriko S, Yoshioka S, Hiroko u, and Kazuwa N. Antiatherogenic effect of pioglitazone in type 2 diabetes patients irrespective of the responsiveness to its antidiabetic effect. Diabetes Care 2003; 26:2493-2499.

34. Chu NV, Caulfield M, Kong APS, Mudaliar SR, Kim DD, Kim DD, Henry RR, and Reaven PD. Differential effects of metformin and troglitazone on cardiovascular risk factors in patients with type 2 diabetes. Diabetes Care 2002; 25:542-549.