ORIGINAL ARTICLE

BLADDER CANCER IN PATIENTS WITH TYPE 2 DIABETES TREATED WITH PIOGLITAZONE, A COMPARATIVE STUDY

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Background: This study was conducted to determine the frequency of bladder cancer in diabetic mellitus type II patients treated with Pioglitazone as compared with diabetic mellitus type II patients treated with other oral therapy or insulin therapy. **Methods:** It was a comparative; cross sectional survey in it 1,168 patients were selected from Medical and Endocrinology out-patient departments of Jinnah hospital, Lahore and a Periphery Diabetic using non-probability purposive sampling. Patients with Duration of Type 2 Diabetics more than or equals to 2 years, both male and female aged above or equal to 40 years were selected in the study. In Group A, type 2 diabetic patients taking Pioglitazones for ≥2 years were selected and in group B type 2 Diabetic patients taking oral hypo-glycaemic or insulin were selected. The ethical committee of Allama-Iqbal Medical College, Lahore, approved this study. **Results:** Five hundred & eighty-four patients of Group A and 584 Patients of group B were selected in the study. In group A, 321 (54.97%) were male and 263 (45.03%) were female, whereas in group B 317 (54.28%) were male and 267 (45.72%) were female. Mean age of the group A patients was 47.01±8.27 years and mean age of group B patients was 58.97±8.14years. In group A mean duration of diabetes was 8.65±3.72 years and in group B the mean duration of diabetes was 10.86±4.48 years. Mean duration of Pioglitazone use was 6.92±2.28 years. Overall none of the patient was reported with the bladder cancer in the study. **Conclusions:** It is concluded from the study that none of the patient from either group was reported with bladder cancer haematuria and UTI. It is suggested that a randomized control trials should be conducted to single out the association of bladder cancer in patients with type II diabetes.

Keywords: Diabetes mellitus; Pioglitazone; Bladder cancer; Pakistan

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INTRODUCTION

Globally, about 60% of the Patients with Diabetes mellitus belong to Asia.[1]The trends have revealed that prevalence of diabetes has been doubled during the last decade from 2.4–4.4%. In Pakistan prevalence of only uncontrolled diabetes mellitus is about 39%.[2]

In Pakistan the overall glucose intolerance, diabetes mellitus with impaired glucose tolerance, is higher in urban areas as compared to rural area.[3] In the consequence of diabetes the pioglitazone therapy is prescribed. Patient reported the side effects of naso-pharyngitis, headache[4] and in some it leads to bladder cancer.[5]

In a recent French cohort study the association of thiazolidinediones (TZDs) with bladder cancer was found. The reported incidence of bladder cancer was 4.9 per million per year.[6] TZDs is not used as first line therapy for treating Type II diabetes but it improves insulin sensitivity through their action at peroxisome proliferator activated receptors (PPARs) gamma receptors. It was also reported that people who were taking Pioglitazones more than 2 years were at the risk of bladder cancer.[7] In meta-analytic studies and review articles reveals that the patients of type two diabetes treated with pioglitazone had slightly higher risk than controls.[8] In another study it was found that after 1 year each pioglitazone use increases the risk of bladder cancer.[9]

This study was conducted to find out the Frequency of bladder carcinoma in patients treated with TZDs therapy. This study will be the base line study to determine prevalence of bladder cancer in TZDs treated patients in Pakistan.

MATERIAL AND METHODS

It was a comparative; cross sectional survey in it 1,168 patients were selected from Medical and Endocrinology out-patient departments of Jinnah hospital, Lahore and a periphery diabetic using non-probability purposive sampling. Patients with duration of type 2 Diabetics more than or equals to 2 years, both male and female aged above or equal to 40 years were selected in the study.

In Group A, type 2 diabetic patients taking pioglitazones for ≥2 years were selected and in group B type 2 diabetic patients taking oral hypo-glycaemic or insulin were selected. This study was approved by the ethical committee of Allama Iqbal Medical College, Lahore.

Patients with bladder cancer diagnosis before starting pioglitazones, Infection of the prostate or bladder (on history and urine analysis), renal stones (on history and ultrasound KUB), Kidney or urinary tract malignancy or benign prostatic hyperplasia (on history and ultrasound KUB) were excluded from the study. Urine samples were collected according to standardized technique to determine haematuria (3–5 RBCs/HPF), ultrasound bladder was performed and if suggestive cystoscopy to confirm bladder carcinoma. The collected information was entered in SPSS-20. Mean and standard deviation was calculated for quantitative date like age, body mass index, duration of diabetes, and duration of drug given.

The qualitative variables like incidence of bladder cancer, haematuria, ultrasound bladder and cystoscopy were analysed as frequency and percentages. Student's *t*-test was applied to quantitative data to determine the mean difference. Chi square test was applied for qualitative data. A *p*-value of <0.05 was considered as statistically significant.

RESULTS

A total of 584 patients of Group A and 584 patients of group B were selected in the study. In group A, 321 (54.97%) were male and 263 (45.03%) were female, whereas in group B 317 (54.28%) were male and 267 (45.72%) were female. Mean age of the group A patients was 47.01±8.27 years and mean age of group B patients was 58.97±8.14years.

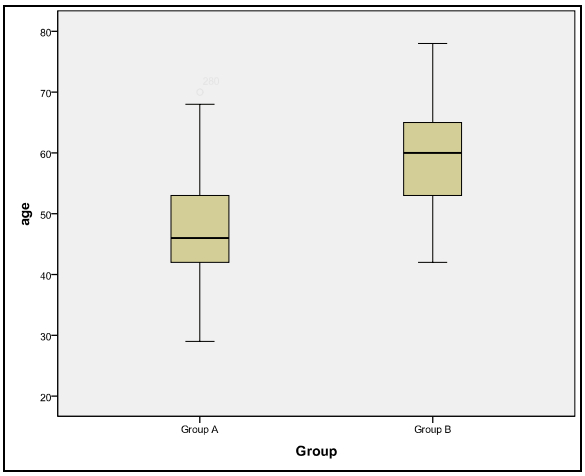
Among Group A 285 (48.80%) were normal weight, 283 (48.46%) were overweight and 16 (2.74%) were obese. Whereas in group B 25(4.28%) were normal weight, 286 (48.97%) were overweight and 273 (46.75%) were obese. BMI among both groups was statistically significantly different (*p*-value <0.001). In group A mean duration of diabetes was 8.65±3.72 years and in group B the mean duration of diabetes was 10.86±4.48years

In group A the mean duration of taking Oral hypoglycaemic was 7.039±2.22years and in group B the duration of taking oral hypoglycaemic was 9.579±4.14years. There was a statistically significant difference between both groups according to hypoglycaemic

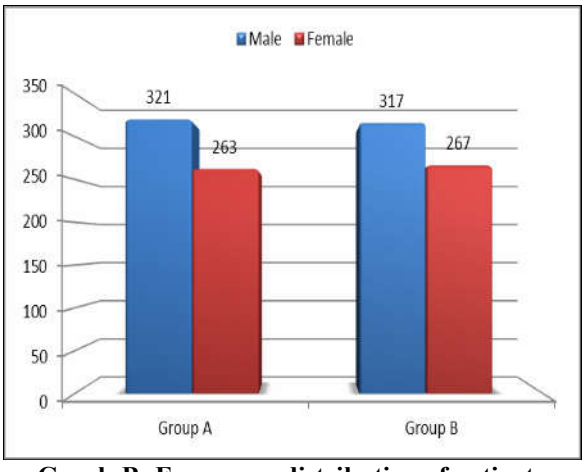
Table-1: Summary of study statistics

		Group A (TZD)	Group B (Insulin/Oral-glycaemic)	*p*-value
Age (Years)	≤45	292 (50%)	33 (5.65%)	<0.001*
	>45	292 (50%)	551 (94.35%)	
Male		321 (54.97%)	317 (54.28%)	0.933
Female		263 (45.03%)	267 (45.72%)	
BMI	Normal	283 (48.46%)	25 (4.28%)	<0.001*
	Overweight	285 (48.80%)	286 (48.97%)	
	Obese	16 (2.74%)	273 (46.75%)	
Smoker		70 (11.99%)	127 (21.75%)	0.002*
History of Diabetes	≤10 years	469 (80.31%)	317 (54.28%)	<0.001*
	>10 years	115 (19.69%)	267 (45.72%)	
Bladder Carcinoma		0 (0%)	0 (0%)	-

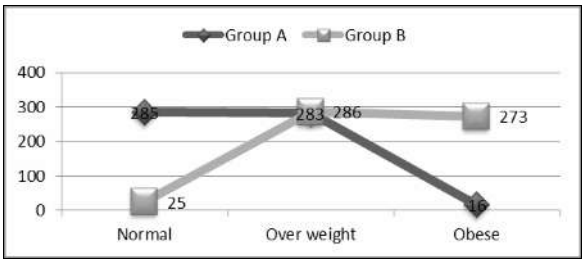
*Difference is significant at 0.05 level of significance



Graph-1: Age distribution among both groups



Graph-B: Frequency distribution of patients according to gender



Graph-C: Frequency distribution of Patients according to Body mass index

Table-2: Average duration of TZDs and Insulin usage in Years

	Mean	SD	95% Confidence Interval for Mean	
TZD	6.92	2.28	6.54	7.30
Insulin	2.56	3.204	2.02	3.09

Table-3: duration of oral hypoglycaemic in both groups

Groups	n	Mean	SD	Std. Error Mean
Group A	584	7.039	2.2179	0.1316
Group B	584	9.579	4.1375	0.2473

t-test 9.103

DISCUSSION

Burden of diabetic patients is increasing globally. In Pakistan the prevalence of diabetes mellitus varies from urban to rural area, it's been seen that prevalence of Diabetes Mellitus was higher in men as compared to women, whereas impaired glucose tolerance (IGT) was more frequent in women as compared to men.[3] In our study males were more frequent than women, female to male ratio was 1:1.97≈2. The mean age of the patients was also below 60years. Globally the high prevalence is found between 30–60 years of age group.[10]

In our study it was also observed that body mass index in patients treated with Pioglitazone (group A) was less than the BMI of diabetic patients taking insulin or oral medicine. Pioglitazone control glycemia and blood pressure despite increasing body mass index of the patient. It is also found that it helps in increasing serum adiponectin level which has anti-atheroscleroticaffect.[11] In insulin resistant patients the BMI has positive correlation with the insulin resistance.[12]

It is found that glycolysis occurs when using insulin and cancer cell get energy from glycolysis instead of tricarboxylic acid generate during anaerobic condition.[13] On the basis of it some scientist have associated insulin treated group with bladder cancer in contrast some associated the bladder cancer with Pioglitazone. The reported Bladder cancer incidence is approximately 8.94 per million per year in diabetic patients.[9] In contrast reported hazard ratio of 1.2 in pioglitazone as compared to 1.4 in control group.[7] According to a review article there was significant risk of bladder cancer in type II diabetes patient taking pioglitazone therapy. But when in-depth review was done, many bias and errors were found. It was found that instead of more than two years therapy, more than five-year therapy should be considered being risk factor. Another interesting fact was the patients reported in the studies had switched the therapies over the year.[14,15] A recent Meta analytic study has shown similar results to our study. But they have also revealed that there is very decreased risk of bladder cancer but the risk should be considered.[16]In this study among both group none of the patient reported with bladder cancer whether the patients taking oral medicine/insulin or Pioglitazone from more than 2 years. No patient was reported with urinary tract infection (UTI) of haematuria.

CONCLUSION

This study in contrast to previous studies observed no patient with bladder cancer was found. In this study Pioglitazone was associated with less BMI.

AUTHORS' CONTRIBUTION

AR and KK worked on the concept and design of the study. AR, BA and IK collected the data. AR analysed the data. AR and BA worked on the manuscript. AR prepared the final draft of the manuscript. KK supervised the study. All authors have read and approved the final draft of the manuscript.

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