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# Association of Additive Risk of Pioglitazone Use with the Presence of CYP1A1 Polymorphisms in the Occurrence of Bladder Cancer

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## ABSTRACT
Tumor of urinary bladder nowadays is regarded as one of the most prevalent human cancer allover our planet. Many predisposing factors play a crucial role in the pathogenesis of this tumor including endogenous and exogenous blamed causes. Certain polymorphism of CYP1A1 gene recently has been linked to the occurrence of bladder cancer. Pioglitazone that used for treatment of diabetes mellitus type II for long time carry a risk impact on induction of this tumor.
**Aim of this study:** To evaluate the risk of using of pioglitazone in patients who carry CYP1A1 polymorphism to induce bladder carcinoma.
**Materials and method:** This study was conducted from 2017 to 2019, 80 patients with bladder cancer after being medically diagnosed and were assessed if using of pioglitazone with presence of CYP1A1 polymorphisms associated with high risk of CA bladder. DNA was extracted and molecular detection was performed to detect single nucleotide polymorphisms (SNPs) at genetic sites using PCR and PCR-RFLP techniques.
**Results:** There was additive risk by using of pioglitazone for long time (at least 1 year) in occurrence of CA bladder in individuals with CYP1A1 polymorphisms.
**Keywords:** CA bladder, pioglitazone. CYP1A1 polymorphisms
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## INTRODUCTION
Bladder cancer (CA bladder) is regarded as one of the most common human cancers that affect urothelial tissues (Antoni, Ferlay et al. 2017). It has been estimated that more than 100000 persons every year is diagnosed with CA bladder (Kamat, Hahn et al. 2016). Many concerned factors play significant role in the occurrence of this cancer include genetic factors, smoking, many chemicals (like aromatic amines, benzopyrene) and some drugs like pioglitazone (AMEIN, HAMDY et al. 2016). Many of these risk factors play important role in disturbances of DNA functions that may eventually causing abnormal cell proliferation (Sanli, Dobruch et al. 2017).One of the pronounced genetic factors that associated with increased incidence of CA bladder is the presence of CYP1A1 polymorphisms (Feki-Tounsi, Khlifi et al. 2017). The impact of this polymorphism on the incidence of bladder CA is greatly varying in the world (Verma, Sharma et al. 2018). On the other hand many researches demonstrate that some drugs many intensify the risk of this tumor like pioglitazone (( it is proved anti-diabetic drug that acting by potentiation of PPAR-gamma receptors (Tuccori, Filion et al. 2016) that eventually reduces peripheral insulin resistance and increase glycemic control predicted by improvement in Hb $A_1C$ level)) (Zameer 2018).

## MATERIAL AND METHODS
The study enrolled 80 type II diabetic patients with bladder cancer. Among these patients, 45 persons were on pioglitazone (30 mg/day) for 2-2.5 years. Samples were collected from Hussein Teaching Hospital / Oncology Center in Kerbala, Iraq.
DNA was extracted, PCR technique was used to detect genetic defects in the study genes, where primers were used in CYP1A1: c.*1189T>C a gene.
F:5'-CAGTGAAGAGGTGTAGCCGC-3'
R:5-'TAGGAGTCTTGTCTCATGC C -3'
The PCR program used to amplify CYP1A1: c. * 1189T>C a gene is 94°C for 5 min for the initial denaturation, 35 cycles with 94°C for 45 sec, 59°C for 45 sec, and 72°C for 45 sec, and 72°C for 5 min for the final extension.
The PCR product was digested by MspI (HpaII) in CYP1A1: c.*1189T >C a gene to two fragments of 209 and 133 bp for T allele, and the C allele 342 bp fragment.
The data was expressed as (1) for sample with CYP1A1 polymorphism and (0) for negative samples, then these data were processed by using Chi-square test using sigma-plot software V.13.

## RESULTS AND DISCUSSION
This research demonstrate that there is significant association between using of pioglitazone and the presence of CYP1A1 polymorphism 1189T>C at $p < 0.05$ (P=0.011769). This finding was due to many mechanisms, the most notable one is that presence of this polymorphism causing genomic instability (AMEIN, HAMDY et al. 2016).Over-expression of CYP1A1 polymorphism was shown to prohibit the protective apoptotic defense mechanism specifically against CA bladder (Verma, Sharma et al. 2018)
On the other hand, using of pioglitazone was shown to increase the risk for CA bladder due to abnormal activation of PPAR-gamma that may induce abnormal proliferation of urothelial cell (Ripamonti, Azoulay et al. 2020). This effect was not noticed for rosiglitazone suggesting that the risk of CA bladder is drug specific rather that drug class specific (Tuccori, Filion et al. 2016).

## CONCLUSION
It can be concluded that assess the risk of pioglitazone use in patients bearing CYP1A1 polymorphism for induction of bladder carcinoma.

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