ASIAN JOURNAL OF PHARMACEUTICAL AND CLINICAL RESEARCH

INNOVARE ACADEMIC SCIENCES Knowledge to Innovation

Vol 8, Issue 2, 2015

ISSN - 0974-2441

Research Article

METFORMIN AND SULFONYLUREAS EFFECT ON THE BLOOD LEVEL OF PROSTATE SPECIFIC ANTIGEN

YOUSIF ELRAIH AHMED[1], ISMAT HASSAN ALI[2], MOHAMMED ELIMAM AHAMED[2,3]*

[1]Atomic Energy Council, Sudan Academy of Sciences, Khartoum, Sudan. [2]Department of Chemistry, Faculty of Science, King Khalid University, Abha, Saudi Arabia. [3]Sudan Atomic Energy Commission, Khartoum, Sudan. Email: mohammedelimam@yahoo.com

Received: 05 September 2014, Revised and Accepted: 06 October 2014

ABSTRACT

Objective: The aim of this study was to investigate the effect of metformin and sulfonylurea on the blood level of prostate specific antigen (PSA).

Methods: 26 Type 2 diabetic patients under metformin treatment and 42 patients under sulfonylurea treatment were involved in this study, their age ranges were (50-83) and (51-73), respectively. The patients were followed for 9 months, and three blood samples were obtained from each patient; after 3, 6 and 9 months. The blood samples were collected in ethylenediaminetetraacetic acid tubes, and the plasma was separated and kept at −20°C. Enzyme-linked immunosorbent assay technique was used to determine the PSA level.

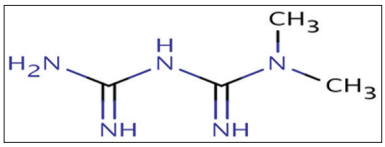
Results: Regarding the PSA results of the patients under metformin treatment, the mean values and ranges of the first, second and third samples were 0.51 (0.0-2.66), 0.6 (0.0-2.77) and 0.7 (0.0-3.42) ng/ml, respectively. Concerning the PSA results of the patients under sulfonylurea treatment, the mean values and the ranges of the first, second and third samples were 3.6 (0.0-39.2), 4.4 (0.0-46.4) and 5.9 (0.0-67.7) ng/ml, respectively.

Conclusion: Metformin and sulfonylureas affected the blood PSA level in the Sudanese Type 2 diabetic patients, but the sulfonylureas had the highest effect.

Keywords: Metformin, Sulfonylureas, Risk factors, Prostate cancer.

INTRODUCTION

Metformin is a biguanide anti-hyperglycemic drug. It is the first-line choice for the treatment of Type 2 diabetes, in particular, in over weight and obese people with normal kidney function. Metformin is the only anti-diabetic drug that is capable of preventing the cardiovascular complications of diabetes through reducing the blood concentration of low-density lipoprotein, cholesterol, and triglycerides [1,2]. It is well-known that, metformin had less effect on body weight compared to sulfonylureas and insulin [3]. Metformin therapy may be used for the people at risk for Type 2 diabetes mellitus (DM) to decrease their chance of developing the disease [4]. Concerning the management of gestational diabetes, metformin is safe as insulin [5].

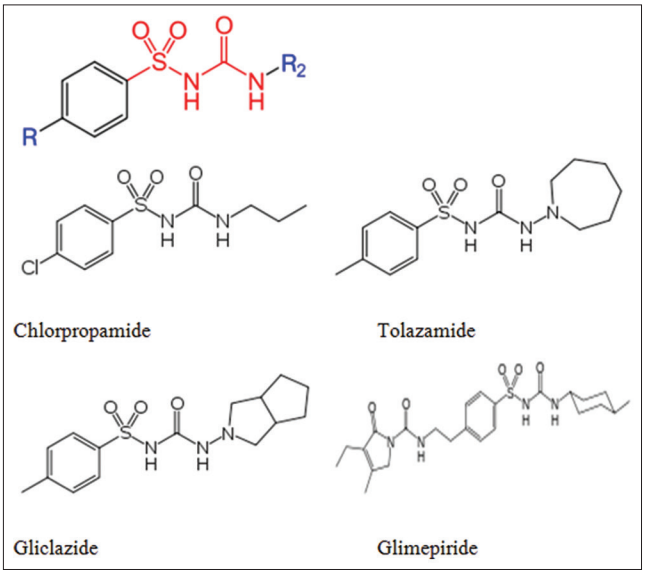


Metformin structure: Obtained from the drug bank at http://www.drugbank.ca/drugs/DB00331.

Metformin decreases hyperglycemia primarily by suppressing glucose production by the liver [6,7], increasing insulin sensitivity and by enhancing peripheral glucose uptake (by inducing the phosphorylation of glucose transporter 4 enhancer factor [8] and by decreasing absorption of glucose from the gastrointestinal tract [9].

The most common adverse effect of metformin is gastrointestinal upset, including diarrhea, cramps, nausea and vomiting [10]. The most serious potential side effect of metformin is the rare complication; lactic acidosis due to impaired liver uptake and increased production of lactate from the intestine [6].

Sulfonylureas are a class of anti-diabetes drugs that are used in the management of DM Type 2. All the sulfonylureas contain a sulfonylurea moiety in their structure, and they are of different types. They act by increasing insulin release from the beta cells in the pancreas. Sulfonylureas are ineffective where there is an absolute deficiency of insulin production such as in Type 1 diabetes or post-pancreatectomy [11].



The general structures of sulfonylureas. Obtained from the Wikipedia at http://en.wikipedia.org/wiki/sulfonylurea.

Sulfonylureas bind to an ATP-dependent K (K_{ATP}) channel on the cell membrane of pancreatic beta cells. This inhibits a tonic, hyperpolarizing efflux of potassium, thus causing the electric potential over the membrane to become more positive. This depolarization opens voltage-gated Ca^{2+} channels, which leads to increased fusion of insulin granulae

with the cell membrane, and therefore increased secretion of (pro) insulin. There is some evidence that sulfonylureas also sensitize β-cells to glucose. Sulfonylureas reduce serum glucagon level, which induce hypoglycemia [11].

Sulfonylureas are well-known to induce hypoglycemia [12], weight gain mainly as a result their effect to increase insulin levels and thus utilization of glucose and other metabolic fuels [10]. Other side-effects are: Abdominal upset, headache and hypersensitivity reactions. It is unsafe to use sulfonylureas during pregnancy [13]. Sulfonylureas can cause loss of beta cells from the pancreas [14,15]. Decline in beta cell function over time and therapy have been seen in sulfonylureas treatment compared to metformin [16].

Prostate specific antigen (PSA) is a 33 KD single chain glycoprotein secreted mainly by the epithelial cells of the prostate gland. PSA is a serine proteinase with the functions of liquefying semen in the seminal coagulum, allowing sperm to swim freely and it is believed to be involved in dissolving the cervical mucus allowing the entry of sperm into the uterus [17].

PSA exists in serum in at least three different forms: Free PSA, α-2-macroglobulin bounded PSA and α-1-anti-chymotrypsin bounded PSA. It is present in small quantities in the serum of men with healthy prostates but is often elevated in the presence of prostate cancer or other prostate disorders [18,19].

The aim of this article is to investigate the effect of prolonged usage of metformin and sulfonylureas on the blood level of PSA.

METHODS

This study involved two groups of Type 2 diabetic patients; 26 patients under metformin and 42 patients under sulfonylureas for more than 5 years. This study was implemented in Sudan - Khartoum at Gaber Abo Elez diabetic center. The age ranges of the metformin and sulfonylureas patients were (50-83) and (51-73), respectively.

This study was conducted after approval from the authorities of Gaber Abo Elez diabetic center and after patients' informed consent.

The patients were followed for 9 months and three blood samples were obtained from each patient, at the beginning and after 6 and 9 months. The blood samples were collected in ethylenediaminetetraacetic acid tubes, and the plasma was separated and kept at −20°C enzyme-linked immunosorbent assay (ELISA) technique was used for the determination of the PSA level.

The analysis procedure was done according to the instructions of the ELISA from DRG company (Cat.Nr./Kat.nr: 3719).

RESULTS AND DISCUSSION

Results

Regarding the results of the first sample of the patients under metformin, the PSA range was (0.0-2.66 ng/ml), the mean was 0.51 ng/ml and the standard deviation was 0.82. The results of the second sample showed that the range was (0.0-2.77 ng/ml), the mean was 0.6 ng/ml and the standard deviation was 0.88. Concerning the third sample, the range was (0.0-3.42 ng/ml), the mean was 0.7 ng/ml and the standard deviation was 1.01.

Regarding the variation between the mean values of the PSA in the first, second and third samples of the patients under metformin. When the mean of PSA of the first sample was compared to its mean in the second sample, there was insignificant variation (p=0.16), also there was insignificant variation when the mean of PSA in the third sample was compared to its mean in the second sample (p=0.19). However, there was significant variation when the mean PSA value of the third sample was compared to the PSA mean in the first sample (p=0.013).

When the PSA change in the first, second and the third samples of the metformin patients was studied, the PSA was increasing from the first to the third sample in 12 patients (46.3%), 5 patients were characterized by decreasing PSA values (19.2%), the PSA concentration was constant in 3 patients (11.5%), the PSA increased in the second sample and decreased in the third sample in 5 patients (19.2%) and the PSA decreased in the second sample and increased in the third sample in 1 patient (3.8%) (Fig. 1).

The results of the PSA of the patients under sulfonylureas treatment are presented in (Table 1). However, the ranges and means of the PSA were increasing.

When the means of the first, second and third samples were compared to each other's, there was significant variation between mean 1 and mean 2 (p=0.012), significant variation between mean 2 and mean 3 (p=0.008) and significant variation between mean 1 and mean 3 (p=0.004).

There were four patterns of the PSA changes in the patients under sulfonylureas treatment. 23 patients showed increasing PSA concentration (54.8%), 7 patients were with constant PSA concentration (16.7%), the PSA concentration was increased in the second sample and decreased in the third sample in 3 patients (7.1%) and the PSA of 9 patients decreased in the second sample and increased in the third (21.4%) (Fig. 2).

Age group wise, the mean values of the PSA was increasing in the samples of all the different age groups of the patients under metformin and sulfonylureas. However, the highest increase was seen in the

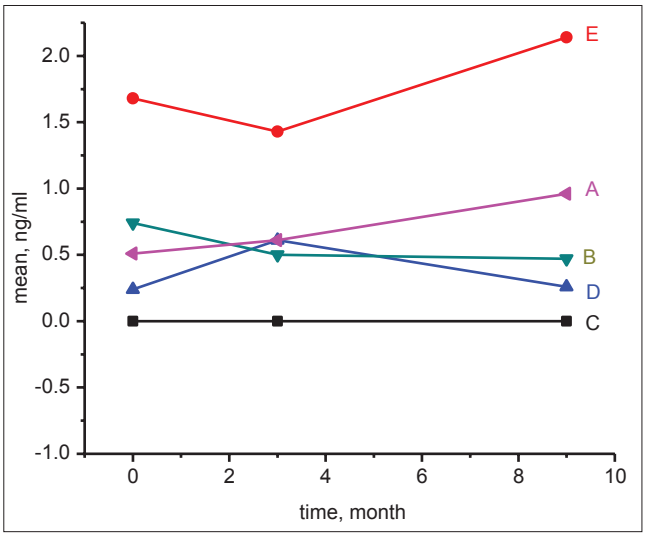


Fig. 1: The different patterns of prostate specific antigen (PSA) changes in the diabetic patients under metformin treatment, The A, B, C, D and E lines show the different patterns of the PSA changes in the diabetic patients under metformin treatment. A; increasing, B; decreasing, C; constant, D; increased then decreased, E; decreased then increased

Table 1: PSA ranges, means and standard deviation of the samples from the diabetic patients under sulfonylureas

Statistical parameter	First	Second	Third
Range (ng/ml)	0.0-39.2	0.0-46.4	0.0-67.7
Mean	3.6	4.4	5.9
Standard deviation	8.05	8.85	11.99

PSA: Prostate specific antigen

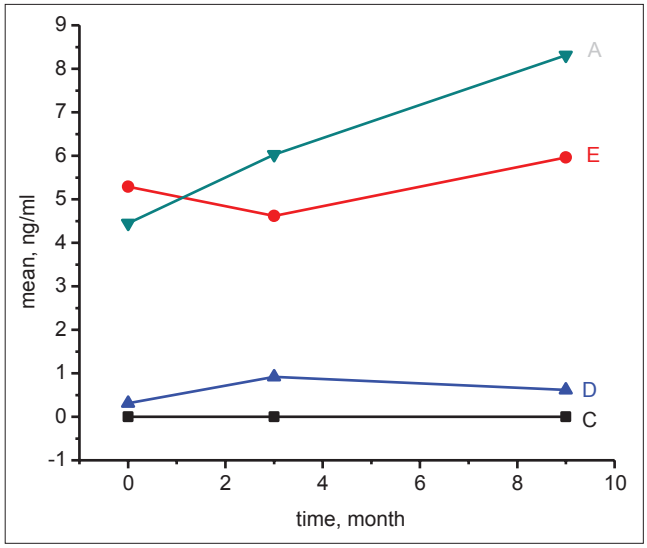


Fig. 2: The different patterns of prostate specific antigen (PSA) changes in the diabetic patients under sulfonylureas treatment, there were four patterns of PSA changes in the diabetic patients under sulfonylureas. A; increasing, C; constant, D; increased then decreased and E; decreased then increased. Unlike metformin, there was no decreasing pattern of PSA concentration

Table 2: Age ranges and the PSA changes in the patients under metformin and sulfonylurea treatment

Treatment	Age range	PSA result (ng/ml)					
		Range			Mean		
		1	2	3	1	2	3
Metformin	40-60	0.00-2.66	0.00-2.77	0.00-3.42	0.46	0.54	0.72
	≥61	0.00-1.99	0.00-2.45	0.00-2.84	0.56	0.67	0.67
Sulfonylurea	40-60	0.0-22.51	0.0-23.45	0.0-28.15	2.10	4.08	2.84
	≥61	0.0-39.20	0.6-46.42	0.59-67.71	5.87	7.74	10.49

PSA: Prostate specific antigen

patients with more than 60 years of those who are under sulfonylureas (Table 2).

The highest PSA increase was seen in the patients under sulfonylureas treatment with age more than 60 years old.

DISCUSSION

This study showed that the metformin usage increased the PSA and the risk of prostate cancer. There were five patterns of PSA changes, increasing (12/46.3%), decreasing (5/19.2%), constant (3/11.5%), increased then decreased (5/19.2%) and decreased then increased (1/3.8%). As a conclusion metformin was associated with increased risk (increased PSA and decreased then increased) for prostate cancer in 47.6% (46.3% + 1.3%) of diabetic patients and was associated with decreased risk for prostate cancer in 38.4% of the diabetic patients (decreasing 19.2% + increased then decreased 19.2%).

Similar to our finding, Rothermundt *et al.* [20] stated that metformin treatment for prostate cancer patients yielded objective PSA responses, e.g. prolongation of PSA doubling time in 52.3% of the patients and the PSA was decreased by more than 50% in two patients (4.5%), however, in our study metformin was associated with decreased PSA concentration in 38.4% of the patients.

A lot of studies investigated the usage of metformin in combination with other cancer drugs to treat different cancers including, breast, liver, lung and prostate cancers and the majority stated better outcomes when using metformin with other cancer drugs like docetaxel [21,22] metformin also improve the response towards radiotherapy [23]. Decensi *et al.* [24] study indicated that metformin was associated with a 30% reduction in cancer incidence in individuals with Type 2 diabetes compared with other diabetic treatments. Clements *et al.* [25] concluded that metformin is useful in overcoming the side effects of androgen deprivation therapy, and it showed antineoplastic activity in prostate cancer.

In an *in-vitro* study on prostate cancer cell line, Demir *et al.* in 2014 [26] found that metformin inhibited the growth and migration of the prostate cancer celine.

However, Patel *et al.* in 2010 [27] stated that metformin has no better outcomes when used after radical prostatectomy for localized cancer, Margel *et al.* in 2013 [28] found that there is no association between metformin usage and the risk for prostate cancer while Zhang *et al.* [29] concluded that metformin can reduce the risk and mortality of liver, breast, pancreatic and colorectal cancers and it has no beneficial effect on the incidence of prostate cancer. Wright and Stanford [30] found that metformin usage was associated with borderline decrease in the risk of prostate cancer in Caucasian - Americans and there was no association between metformin use and the risk of prostate cancer in African - Americans. In 2013 Franciosi *et al.* [31] stated that metformin was not associated with risk of breast, lung, ovary, prostate, uterus, bladder and kidney cancers, while Currie *et al.* [32] found that metformin is associated with lower risk of colon and pancreas cancer and it is not associated with the risk of prostate or breast cancer. Hsieh *et al.* [33] found that metformin is associated with lower risk of liver and colon cancers. Similar to the previous studies Azoulay *et al.* stated [34] that metformin did not reduce the risk of prostate cancer in diabetic patients Type 2. From the above literature it is clear that metformin decreases the risk of cancer in some patients and it has no effect on the risk in other patients, so detailed molecular studies should be implemented in the two groups to answer why metformin decreased the risk in some patients and why it did not affect the risk of prostate cancer in other patients.

Regarding the effect of sulfonylureas on the PSA level and the risk of prostate cancer, this study revealed that the sulfonylureas significantly increased the mean PSA concentration and the risk of prostate cancer. There were four patterns of PSA changes; increasing (54.8%), constant (16.7%), increased then decreased (7.1%) and decreased then increased (21.4%). Unlike metformin, there was no patient with decreasing PSA concentration. We can assume that the overall percentage of sulfonylureas patients with increasing PSA is 76.2% (54.8% increasing + 21.4% decreased then increased) and 7.1% of the sulfonylurea patients were with decreased.

The findings of the previous researches about sulfonylureas and the risk of cancer as general are as follows: Hitron *et al.* in 2012 [35] stated that diabetic patients under sulfonylureas are more susceptible to high-grade tumors compared to non-diabetic individuals. A retrospective study conducted in United Kingdom concluded that patients under sulfonylureas are more likely to develop solid tumors [32]. Similar to the study of Currie *et al.* [32], Hsieh *et al.* [33] stated that Taiwanese diabetic patients under sulfonylureas are at risk of breast and lung cancers. Soranna *et al.* [36] stated that metformin and not sulfonylureas reduced the risk of pancreatic and colorectal cancers.

CONCLUSION

The conclusions of this study are:

1. The mean PSA concentration in the diabetic patients under treatment of metformin was increasing, and the difference between the means was significant when the mean of PSA concentrations of sample one was compared to that of sample three
2. 47.6% of the diabetic patients under metformin were characterized

by increasing PSA concentration, which means increased risk of prostate cancer while 38.4% of them were characterized by decreasing PSA concentration, i.e. reduced risk of prostate cancer

3. Similar to the patients under metformin, diabetic patients under sulfonylureas had increasing mean values of PSA and the difference between the three means was significant (mean 1 to mean 2, mean 1 to mean 3 and mean 2 to mean 3)
4. 76.2% of the sulfonylureas patients were characterized by increasing PSA values i.e., increased risk of prostate cancer, and 7.1% of them were with decreasing PSA concentration, which means they were with decreased risk for prostate cancer.

REFERENCES

1. El Messaoudi S, Rongen GA, de Boer RA, Riksen NP. The cardioprotective effects of metformin. Curr Opin Lipidol 2011;22(6):445-53.
2. Malek M, Aghili R, Emami Z, Khamseh ME. Risk of cancer in diabetes: The effect of metformin. ISRN Endocrinol 2013;2013:636927.
3. Selvin E, Bolen S, Yeh HC, Wiley C, Wilson LM, Marinopoulos SS, *et al.* Cardiovascular outcomes in trials of oral diabetes medications: A systematic review. Arch Intern Med 2008;168(19):2070-80.
4. Knowler WC, Barrett-Connor E, Fowler SE, Hamman RF, Lachin JM, Walker EA, *et al*. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. N Engl J Med 2002;346:393-403.
5. Donovan PJ. Drugs for gestational diabetes. Aust Prescriber 2010;33:141-4.
6. Kirpichnikov D, McFarlane SI, Sowers JR. Metformin: An update. Ann Intern Med 2002;137(1):25-33.
7. Hundal RS, Krssak M, Dufour S, Laurent D, Lebon V, Chandramouli V, *et al.* Mechanism by which metformin reduces glucose production in type 2 diabetes. Diabetes 2000;49(12):2063-9.
8. Miller RA, Chu Q, Xie J, Foretz M, Viollet B, Birnbaum MJ. Biguanides suppress hepatic glucagon signalling by decreasing production of cyclic AMP. Nature 2013;494(7436):256-60.
9. Bailey CJ, Turner RC. Metformin. N Engl J Med 1996;334(9):574-9.
10. Bolen S, Feldman L, Vassy J, Wilson L, Yeh HC, Marinopoulos S, *et al.* Systematic review: Comparative effectiveness and safety of oral medications for type 2 diabetes mellitus. Ann Intern Med 2007;147(6):386-99.
11. Ashcroft FM. Mechanisms of the glycaemic effects of sulfonylureas. Horm Metab Res 1996;28(9):456-63.
12. Hemmingsen B, Lund SS, Gluud C, Vaag A, Almdal T, Hemmingsen C, *et al.* Intensive glycaemic control for patients with type 2 diabetes: Systematic review with meta-analysis and trial sequential analysis of randomised clinical trials. BMJ 2011 24;343:d6898.
13. Merlob P, Levitt O, Stahl B. Oral antihyperglycemic agents during pregnancy and lactation: A review. Paediatr Drugs 2002;4(11):755-60.
14. Maedler K, Carr RD, Bosco D, Zuellig RA, Berney T, Donath MY. Sulfonylurea induced beta-cell apoptosis in cultured human islets. J Clin Endocrinol Metab 2005;90(1):501-6.
15. Takahashi A, Nagashima K, Hamasaki A, Kuwamura N, Kawasaki Y, Ikeda H, *et al.* Sulfonylurea and glinide reduce insulin content, functional expression of K(ATP) channels, and accelerate apoptotic beta-cell death in the chronic phase. Diabetes Res Clin Pract 2007;77(3):343-50.
16. Eurich DT, Simpson SH, Majumdar SR, Johnson JA. Secondary failure rates associated with metformin and sulfonylurea therapy for type 2 diabetes mellitus. Pharmacotherapy 2005;25(6):810-6.
17. Balk SP, Ko YJ, Bubley GJ. Biology of prostate-specific antigen. J Clin Oncol 2003;21(2):383-91.
18. Catalona WJ, Richie JP, Ahmann FR, Hudson MA, Scardino PT, Flanigan RC, *et al.* Comparison of digital rectal examination and serum prostate specific antigen in the early detection of prostate cancer: Results of a multicenter clinical trial of 6,630 men. J Urol 1994;151(5):1283-90.
19. Velonas VM, Woo HH, dos Remedios CG, Assinder SJ. Current status of biomarkers for prostate cancer. Int J Mol Sci 2013;14:11034-60.
20. Rothermundt C, Hayoz S, Templeton AJ, Winterhalder R, Strebel RT, Bärtschi D, *et al.* Metformin in chemotherapy-naive castration-resistant prostate cancer: A multicenter phase 2 trial (SAKK 08/09). Eur Urol 2014;66(3):468-74.
21. Spratt DE, Zhang C, Zumsteg ZS, Pei X, Zhang Z, Zelefsky MJ. Metformin and prostate cancer: Reduced development of castration-resistant disease and prostate cancer mortality. Eur Urol 2013;63(4):709-16.
22. Wang Y, Yao B, Wang Y, Zhang M, Fu S, Gao H, *et al.* Increased FoxM1 expression is a target for metformin in the suppression of EMT in prostate cancer. Int J Mol Med 2014;33(6):1514-22.
23. Zannella VE, Dal Pra A, Muaddi H, McKee TD, Stapleton S, Sykes J, *et al.* Reprogramming metabolism with metformin improves tumor oxygenation and radiotherapy response. Clin Cancer Res 2013;19(24):6741-50.
24. Decensi A, Puntoni M, Goodwin P, Cazzaniga M, Gennari A, Bonanni B, *et al.* Metformin and cancer risk in diabetic patients: A systematic review and meta-analysis. Cancer Prev Res (Phila) 2010;3(11):1451-61.
25. Clements A, Gao B, Yeap SH, Wong MK, Ali SS, Gurney H. Metformin in prostate cancer: Two for the price of one. Ann Oncol 2011;22:2556-60.
26. Demir U, Koehler A, Schneider R, Schweiger S, Klocker H. Metformin anti-tumor effect via disruption of the MID1 translational regulator complex and AR downregulation in prostate cancer cells. BMC Cancer 2014;14:52.
27. Patel T, Hruby G, Badani K, Abate-Shen C, McKiernan JM. Clinical outcomes after radical prostatectomy in diabetic patients treated with metformin. Urology 2010;76(5):1240-4.
28. Margel D, Urbach D, Lipscombe LL, Bell CM, Kulkarni G, Austin PC, *et al.* Association between metformin use and risk of prostate cancer and its grade. J Natl Cancer Inst 2013;105:1123-31.
29. Zhang P, Li H, Tan X, Chen L, Wang S. Association of metformin use with cancer incidence and mortality: A meta-analysis. Cancer Epidemiol 2013;37(3):207-18.
30. Wright JL, Stanford JL. Metformin use and prostate cancer in Caucasian men: Results from a population-based case-control study. Cancer Causes Control 2009;20(9):1617-22.
31. Franciosi M, Lucisano G, Lapice E, Strippoli GF, Pellegrini F, Nicolucci A. Metformin therapy and risk of cancer in patients with type 2 diabetes: Systematic review. PLoS One 2013;8(8):e71583.
32. Currie CJ, Poole CD, Gale EA. The influence of glucose-lowering therapies on cancer risk in type 2 diabetes. Diabetologia 2009;52(9):1766-77.
33. Hsieh MC, Lee TC, Cheng SM, Tu ST, Yen MH, Tseng CH. The influence of type 2 diabetes and glucose-lowering therapies on cancer risk in the Taiwanese. Exp Diabetes Res 2012;2012:413782.
34. Azoulay L, Dell'Aniello S, Gagnon B, Pollak M, Suissa S. Metformin and the incidence of prostate cancer in patients with type 2 diabetes. Cancer Epidemiol Biomarkers Prev 2011;20(2):337-44.
35. Hitron A, Adams V, Talbert J, Steinke D. The influence of antidiabetic medications on the development and progression of prostate cancer. Cancer Epidemiol 2012;36(4):e243-50.
36. Soranna D, Scotti L, Zambon A, Bosetti C, Grassi G, Catapano A, *et al.* Cancer risk associated with use of metformin and sulfonylurea in type 2 diabetes: A meta-analysis. Oncologist 2012;17:813-22.