The Influences of Metformin on Prostate in Terms of PSA Level and Prostate Volume

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Purpose: The effects of metformin on prostate volume and prostate-specific antigen (PSA) were investigated.

Materials and Methods: We enrolled 384 newly diagnosed diabetes mellitus (DM) patients and 152 controls all of whom were >50 years into our prospective cross-sectional observational study. The first group contained patients receiving metformin only, the second group patients were taking a mixture of medications, including metformin plus other oral anti-diabetics, and the third was the control group. Before beginning treatment, body mass indices (BMI) of all cases were obtained. Prostate volumes were evaluated using transabdominal ultrasonography at the sixth and twelfth months. Insulin, glycosylated hemoglobin (HbA1C), insulin sensitivity index (ISI), insulin-rich growth factor (IGF-1), PSA, free PSA, and total testosterone levels were measured.

Results: The differences in BMI between the first and third groups were statistically significant ($P < 0.05$). There were no statistical differences among the groups in terms of prostate volumes ($P > 0.05$). The differences between the groups for insulin, HbA1C, ISI, IGF-1 (somatomedin), PSA, free PSA, and total testosterone levels were not statistically significant ($P > 0.05$). Free PSA and total testosterone levels in groups 1 and 2 were not statistically different at the beginning of treatment and the sixth month ($p > 0.05$), but within groups 1 and 2, only PSA levels were different at the start of the study until completion. No differences were seen in the third group.

Conclusion: Metformin appears to cause a decrease in PSA levels. The mechanism and any effects on prostate tissue will be studied in future randomized, prospective studies.

Keywords: metformin; Prostate; PSA; prostate biopsy

INTRODUCTION

Prostate cancer (PCa) is the most common non-cutaneous cancer and the second-leading cause of cancer deaths in the United States (US). However, only ~16% of men diagnosed with PCa ultimately die from PCa because of effective treatments and biological indolence.[1] Although it has been suggested that the risk of several malignancies is increased in diabetes, there have been studies suggesting that the risk of (PCa) in diabetic patients is reduced second to lowering of testosterone levels during the state of hyperinsulinemia.[2] Metformin is a biguanide oral antihyperglycemic agent that abrogates hyperinsulinemia in individuals with and without diabetes.[3,4] It is a promising therapeutic agent for PCa[5] and may be useful for preventing and managing various cancer types through direct or indirect mechanisms.[2] However, there are some conflicting data in terms of its utility because the exact pharmacological mechanism of metformin is not clearly understood. If metformin is proven to affect prostate-specific antigen (PSA) levels, a more accurate assessment of the decision to take a biopsy in patients who have not been diagnosed with PCa or perhaps for prognostic purposes in PCa patients can be made according to the adjusted PSA value in patients using metformin. In this study, we investigated the effects of metformin on prostate volume and PSA, which is the most commonly used marker for the diagnosis and over the course of PCa.

MATERIALS AND METHODS

The study was designed as a prospective, cross-sectional observational study. Permission was obtained from the Regional Ethics Committee with the number of 80576354-050-99/86 and performed in accordance with the World Medical Association's Helsinki Declaration. The patients newly diagnosed with diabetes mellitus (DM) in patient groups 1 and 2 were enrolled into the study from the internal medicine clinic of our institute between 2013 and 2018, and the patients in the control group were enrolled from the check-up unit. Informed consent was obtained from all patients. All participants were chosen from a single center that is located in the east of our country.

A total of 2123 patients were evaluated for this investigation between 2013 and 2018. One-thousand five-hundred eighty-five patients were excluded due to concomitant disorders. We enrolled 536 patients (men) who were >50 years old with a PSA level < 4 ng/dL; 384 patients were newly diagnosed as diabetes mellitus (DM) at the beginning of the study as were the 152 controls and both sets were followed over a 12-month period. The determination of this time was based on the duration of the actions of five alpha-reductase inhibitors (at least six months) on the prostate.[6] For that reason, we evaluated the groups both at the sixth and 12th months. Lower urinary tract symptoms were evaluated by International Prostate Symptom Score (IPSS),

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Table 1. Baseline characteristics of patients.

Parameters	Group 1 n=216	Group 2 n=168	Group 3 n=152	*p*
Age	58.81 ± 8.28	59.52 ± 8.54	60.89 ± 7.14	>0.05
BMI	29.81 ± 2.9	28.48 ± 2.5	26.32 ± 6.9	*0.027
For prostate volume				
First	28.33 ± 15.1	27.01 ± 9.39	27.42 ± 10.4	> 0.05
6th month	28.16 ± 15.4	27.18 ± 8.6	28.01 ± 10.7	
12th month	27.09 ± 14.13	26.75 ± 9.5	28.12 ± 18.3	
For PSA				
First	1.59 ± 1.86	1.56 ± 1.59	1.64 ± 1.56	> 0.05
6th Month	1.24 ± 1.29	1.46 ± 1.48	1.67 ± 1.31	
12th Month	1.22 ± 1.25	1.15 ± 1.29	1.64 ±1.38	
For free PSA				
First	0.3 ± 0.23	0.32 ± 0.28	0.41 ± 0.35	> 0.05
6th Month	0.36 ± 0.42	0.35 ± 0.34	0.36 ± 0.36	
12th Month	0.3 ± 0.35	0.24 ± 0.26	0.45 ± 0.38	
For total Testosterone				
First	360.4 ± 129.11	399.01±167.46	349.8 ± 146.7	> 0.05
6th Month	325.68 ± 106.64	403.8 ± 179.41	340.42 ± 134.48	
12th Month	356.51 ± 136.48	370.06 ± 174.71	365.74 ± 144.58	
For insulin				
First	5.39 ± 1.92	6.8 ± 2.73	5.22 ± 1.44	> 0.05
6th month	5.16 ± 1.88	6.4 ± 1.48	5.03 ± 1.35	> 0.05
12th Month	5.27 ± 1.61	6.62 ± 2.56	4.96 ± 1.68^{+}	0.02
For HbA1C				
First	8.29 ± 1.76	9.37 ± 1.43	-	> 0.05
6th month	7.48 ± 1.28	8.11 ± 1.34	-	
12th month	7.52 ± 1.23	7.95 ± 0.99	-	
For ISI				
First	2.02 ± 1.3	2.73 ± 1.32	1.25 ± 0.38	> 0.05
12th month	1.81 ± .22	2.44 ± 1.19	1.31 ± 0.53^{+}	0.004
For IGF-1 (somatomedine)				
First	170.26 ± 75	182.00 ± 53.08	146.62 ± 32.5	> 0.05
12th month	179.26 ± 76.8	191.29 ± 44.3	140.63 ± 34.7+	0.02

*Statistical difference between first and third groups, $p < 0.05$
+Statistical difference between second and third groups, $p < 0.05$
Prostate-specific antigen (PSA), free PSA, and total testosterone in ng/dl
Insulin reference range: 1.9–23 microunits/ml
Abbreviations: Insulin-like growth factor (IGF)-1 (somatomedine) reference range: 78–258 ng/ml HbA1C: glycosylated hemoglobin; BMI: body mass index; IGF-1: insulin-like growth factor; ISI: insulin sensitivity index

and digital rectal examinations (DRE) was performed. The DM patients were separated into two groups according to their medications. Thus, three groups were formed. The first group consisted of patients who were taking metformin 2000 mg/day (split over two different times), and the second group consisted of those who were taking a mixture of medications that include metformin plus other oral anti-diabetics, including sulfonylurea and glinides. This group allowed us to clarify the effect of the oral anti-diabetic drugs on our results. The third group consisted of patients who did not have any diseases. Before beginning treatment, body mass indices (BMI) of all cases were obtained. The prostate volumes of all patients were counted using transabdominal ultrasonography (USG) by the same urologist in our clinic and recorded at the beginning of treatment. This ultrasonography was repeated at the sixth and 12th month of treatment. During the same period, the PSA, free PSA, glycosylated hemoglobin (HbA1C), and total testosterone levels were measured and reported. All blood samples were obtained at the same time of the day due to fluctuations in some blood values, such as total testosterone and when the patients were on an empty stomach, over the course of the day. In addition, insulin, insulin sensitivity index (ISI), and insulin-like growth factor (IGF)-1 (somatomedin) were measured at the beginning and at the12th month. All measurements for PSA and total testosterone were performed with the same kit. The Access Hybritech PSA assay, which is a two-site immunoenzymatic ('sandwich') assay, was used to measure PSA.

The parameters were analyzed between groups and also repetitive PSA measurements for the same patients were analyzed within groups.

In addition to these parameters, some parameters that could affect the results, including compliance to treatment, physical activity, and diet, were evaluated.

The comparative statistical analysis was made both between times in each group and between groups at different times in terms of the investigated parameters.

Exclusion criteria: The cases with problems that could increase PSA levels, such as lower urinary tract disorders and chronic prostatitis, the situations in which the international prostate symptom score (IPSS) is >7, urinary tract infections, abnormal digital rectal examination findings, patients with the PSA levels > 4 ng/dL, and patients who were using medications for other chronic diseases were excluded from the study in order to prevent their effects on PSA and total testosterone levels. These criteria were evaluated during the study period in order to catch the status of the new patients related to the exclusion criteria.

Statistical Analysis

The results are presented as mean ± standard deviation. The data were analyzed using SPSS 16.0 for Windows (SPSS, Inc., Chicago, IL, USA). Differences between the results in terms of investigated parameters were analyzed using paired-samples student t tests with regard to repeated parameters in groups, one-way analysis of

Table 2. The comparative results in groups 1 and 2 with regard to repetitive PSA measuremets for the same patients in groups.

Groups	Pretreatment PSA ng/dl	6th PSA ng/dl	12th PSA ng/dl	*p*
Group 1	1.59 ± 1.86*	1.24 ± 1.29	1.22 ± 1.25*	*0.049
Group 2	1.56 ± 1.59*	1.46 ± 1.48	1.15 ± 1.29*	*0.001
Group 3	1.64 ± 1.56	1.67 ± 1.31	1.64 ± 1.38	> 0.05

*Statistically significant between pretreatment and 12-month results

Table 3. The rates of the compliance with treatment and recommendations (diet and physical activity).

Parameters	Group 1 n=216 (%)	Group 2 n=168 (%)
Compliance with treatment	120 (55.5%)	72 (42.8%)
Compliance with physical activity	140 (64.8%)	56 (33.3%)
Compliance with diet	124 (57.4%)	68 (40.4%)

variance (ANOVA) in terms of the differences between groups, and chi-squared test for categorical parameters.

RESULTS

There were 216, 168, and 152 patients in groups 1, 2, and 3, respectively. Demographic variables were analyzed between groups (**Table 1**) and also repetitive PSA measurements for the same patients were analyzed within groups (**Table 2**).

The demographic characteristics of the groups are presented in **Table 1**. The differences between the first and third group for BMI were statistically significant (p = 0.027). There were no statistical differences among the groups in terms of prostate volumes ($p > 0.05$) as shown in **Table 1**. The differences between the groups with regard to HbA1C, PSA, free PSA., and total testosterone levels were studied during each period, including the beginning of the treatment and the sixth and 12th months ($p > 0.05$). Insulin levels, ISI, and IGF-1 (somatomedin) both at the beginning and at the 12th month ($p > 0.05$) were evaluated as shown in **Table 1**. Free PSA and total testosterone levels in groups 1 and 2 were not statistically different at the beginning of treatment and during the sixth month ($p > 0.05$), but within groups 1 and 2, only PSA levels were different by month 12 (p = 0.049) as shown in **Table 2**. No differences were seen in the third group.

In addition to these, compliance to treatment, diet intervention, and physical activity were assessed at the 12th month, and their results are presented in **Table 3**. In general, compliance to treatment rates were lower in group 2.

DISCUSSION

Hyperinsulinemia and hyperglycemia are thought to promote carcinogenesis in patients with DM. Several meta-analyses have demonstrated that diabetes is associated with increased risk of some cancers, such as breast, endometrium, bladder, liver, colorectum, and pancreatic in addition to a decrease in the risk of PCa, but other studies do not demonstrate an association of hyperinsulinemia and hyperglycemia with an increase in the risk of cancer.[2,7–9] Thus, the evidence has been conflicting. For that reason, this situation needs further studies to clarify this matter.

There are conflicting data about the effect of metformin on controlling cancer.[2, 10–16] The effects of metformin, such as weight- and tissue-specific reducing effects [17,18] occur through several pathways. Because of its effect on colon cancer and hepatoblastoma[10] , activation of adenosine 5'-monophosphate-activated protein kinase (AMPK), which is a tumor suppressor protein kinase[19,20], has an inhibitory effect on protein synthesis and gluconeogenesis during cellular stress. AMPK also presents inhibitory effects on the mammalian target of rapamycin (mTOR), a downstream effector of growth factor signaling that is frequently activated in malignant cells[7] and has inhibitory effects on hypoxic inducible factor 1-alpha (HIF1-alpha).[21] According to a study by Ranasing, nonspecific HIF1-alpha inhibitors increase progression-free survival and reduce the risk of developing castrate-resistant PCa and metastases in patients on continuous androgen deprivation treatment.[21] Metformin can affect cancer development via one or all of these mechanisms.

Also, according to a study by Jayalath, mean PSA levels were 30% lower among metformin users compared to nonusers. PSA levels of intermediate- and high-dose metformin users were32% and 37% lower, respectively, compared to the low-dose group. PSA levels were not different between intermediate- and high-dose users.[22] Drugs that affect PSA levels may provide protective effects to PCa patients relative to those that decrease PSA levels. There are many conflicting sets of data about the effects of metformin on prostate tissue. If the effects of metformin on PSA levels and prostate tissue can be explained with respect to all aspects, these findings may provide a guide for PCa development and its course. In this study, we investigated the metformin effects to understand its effect on the prostate in terms of PSA levels and volume. Currently, the PSA test is the least invasive method that provides information on prostate tissue development. We have investigated the effect of metformin especially in terms of PSA level and prostate volume. If it causes a decrease in the PSA levels, this effect may then occur for multiple reasons and may be important while deciding for obtaining a prostate biopsy according to the adjusted PSA value. For example, it may only inhibit prostate tissue via protective effects on the prostate tissues for PCa.

We found that metformin and combination therapies caused a decrease in PSA levels at the 12th month versus baseline. The means of PSA at pretreatment and at the 12th month for group 1 were 1.59 ± 1.86 and 1.22 ± 1.25 (p = 0.049), respectively. The same parameters for group 2 were 1.56 ± 1.59 and 1.15 ± 1.29 (p = 0.001), respectively, as shown in **Table 2**. The difference in rates within groups were 0.37 and 0.41 for groups 1 and 2, respectively. The difference in rates between the groups for pretreatment and 12-month PSA values were statistically significant (**Table 2**), whereas the differences between groups 1 and 2 were not (**Table 1**). In fact, the main result, the PSA decline rate between baseline and 12th month, may not be attributed only to metformin since group 2 also demonstrated improvement. However, the decline rates between groups 1 and 2 are very close to each other. If the other drugs in group 2 affected the PSA levels in addition to the metformin effect, the PSA decline would decrease even further. For that

reason, the decline in PSA in group 2 may be attributed to the metformin effect. Also, since PSA values in both groups decreased compared to baseline values, it can be interpreted that this effect may be due to metformin. From another point of view, there were no statistical differences between groups 1 and 2 with regard to PSA levels (**Table 1**). This result could be based on the use of metformin in both groups. Nevertheless, prospective, randomized trials with larger study populations are needed to prove these findings.

In addition; according to our results, a significant reduction in PSA levels at the 12th month was shown within groups 1 and 2 (**Table 2**); however, no significant differences were established with regard to insulin, ISI, and IGF-1 (somatomedin) levels at six month in terms of our comparative results between groups 1 and 2. For that reason, the decrease in PSA levels can be associated with metformin use and/or diabetes improvements because of the presence of metformin use in both groups 1 and 2. However, further and more detailed studies are needed in order to clarify the factors related to PSA levels.

Although our results have been confirmed by Preston et al.[16] and Rothermundt et al.[17]. A study by Randazzo showed no significant differences in PSA levels or PCa incidence/grade in metformin patients.[14] In addition, Nordström et al.[12] and Merrick et al.[13] found no protective effects from aspirin, statins, or antidiabetic drugs in terms of PCa risk. Lee et al. found that metformin could reduce androgen-dependent cell growth and the expression of androgen receptor target genes by inhibiting androgen receptor function in prostate cancer cells.[15] Patel et al. showed the effects of metformin on clinical outcomes after radical prostatectomy in terms of biochemical recurrence of PSA level. They found that metformin use did not have any benefits in this group of patients.[8,11] However, according to their methodology, they analyzed this effect after radical prostatectomy.

In addition to these results, the BMI results should be taken into consideration. According to our results, BMI differences between the first and third groups were statistically significant ($p = 0.027$) as shown in **Table 1**. Goodwin and Becker showed that the weight-reducing effects of biguanides may partially explain their antitumor activity.[17,18] Again, high BMIs have been directly associated with risk of aggressive or fatal PCa. One possible explanation for this finding may be an effect of BMI on serum PSA levels.[23] According to some studies about the weight management resulting from metformin use, metformin may be a useful weight management aid in children in a clinical setting although the use of metformin for this purpose in children in a clinical setting has not been well described.[24,25] We believe that more clinical and histo-morphological studies should be performed to clarify this issue.

The relationship between PSA and total testosterone is well known. Thus, we also studied the relationship between metformin use and total testosterone in order to understand whether the effect of metformin is through the testosterone pathway. We found no relationship between metformin use and total testosterone ($P > 0.05$). Although testosterone levels within and among the groups were not statistically different from their baseline values, there was a slight decrease in groups 1 and 2 by the 12th month. This situation needs to be reevaluated in studies with larger numbers of patients.

We also investigated the effect of metformin use on prostate volume and benign prostate hyperplasia (BPH). There was no statistical difference among the groups in terms of prostate volumes ($P > 0.05$).

According to our results, although no statistical differences were established with regard to insulin, IGF-1 (somatomedin), HbA1C, and ISI values between groups 1 and 2, PSA and testosterone levels were a bit higher (statistically insignificant) in group 2, which was a bit higher for insulin, IGF-1, and ISI. This situation may be associated with the numbers of the groups and/or patient lifestyle because the patient lifestyles in group 2 is generally worse (unhealthier) than those in the group 1 (**Table 3**).

The limitations of our study were that no evaluation of diabetic patients was performed as a separate group who received anti-diabetic drugs other than metformin in addition to conducting the study only in a single center.

CONCLUSIONS

We found that metformin may decrease PSA levels. This should be taken into consideration in order to prevent other unnecessary interventions in this patient group when it is time to make a decision for prostate disease diagnosis and treatment. However, the findings of this study and mechanism in addition to any effects on prostate tissue will be studied in future randomized, prospective and histo-morphological studies. This issue needs to be re-studied for different doses or differently designed studies in order to clarify the effects and mechanisms of metformin actions on prostate tissue.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest

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