보건학석사학위논문

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- For the 2009 naïve BPH patients of Republic of Korea -

2형 당뇨로 인한 메트포민 복용이 전립선 비대증 악화에 미치는 영향

- 한국의 **2009**년도 신규 전립선비대증 환자를 대상으로 **-**

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서울대학교 대학원

보건학과 보건학전공

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Abstract

Association of Metformin as treatment of Type 2 Diabetes and progression of Benign Prostate Hyperplasia

- For the 2009 naïve BPH patients of Republic of Korea -

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Background: As a prevalent and progressing disease, Benign Prostate Hyperplasia (BPH) comes along with proliferation of the periurethral and transition zones of the prostate and difficulty of voiding urine. BPH is a common disease in men over 40 years old and the prevalence of BPH increases as aging; men older than 70 years old show 80% of prevalence rate. A progressive condition of BPH causes symptoms which require treatment and the treatment option for BPH can be categorized into non-invasive treatment including watchful waiting and medical treatment and invasive treatment including prostatectomy. Surgical treatment is suggested as the last option for treating BPH patients since it can bring complications after surgery.

Type 2 Diabetes Mellitus (T2DM) is also prevalent and well known disease which leads

complications in many organ systems. History of association of BPH and Diabetes dates back up to decades. Underline mechanism of association of BPH and diabetes is suggested that insulin resistance with secondary hyperinsulinemia and hyperglycemia is the key role for prostate enlargement. Hyperinsulinemia increases level of Insulin-like Growth Hormone 1(IGF-1) which predisposes to have higher risk of BPH. Hyperglycemia increases cytosolic-free calcium in smooth muscle cells and neural tissues, leading to sympathetic nervous system activation contributing in more severe LUTS independent of prostatic enlargement. While T2DM is a negative factor for progression of BPH, few studies discovered that metformin, commonly used drug to treat T2DM, inhibits proliferation of prostate. Though association of prevalence of BPH and T2DM has a few evidences, association of progression of BPH, T2DM and medication of T2DM; metformin, lack of data and evidence. More studies should be done to find out clearer association with T2DM and the progression of BPH by metformin intake.

Objective: The aim of this study is to analyze association of type 2 Diabetes Mellitus and Benign Prostate Hyperplasia with metformin by investigating patients who newly diagnosed BPH in 2009 and follow up occurrence of prostatectomy to measure progression of BPH until June 2017 with claims data of HIRA in Korea.

Method: This study used claims data of the Health Insurance Review and Assessment Service of BPH patients in 2009 in Korea. The registered analysis number of the data requested by the Health Insurance Review and Assessment Service is M20180205893, which is applied to the remote access system and granted access to data. Detailed medical data including diagnosis data, prescribed drugs including Metformin and drugs for treating BPH and surgery information were used to obtain general conclusion about associations between T2DM, Metformin and prostatectomy among BPH patients. Each patient's information from different tables was joined by join key for each patient. Confounding variables were defined by literature review. Frequency analyses were

performed to examine the characteristics of the data, and the incidence rate of prostatectomy of BPH patients was estimated by 10,000 person year. After Proportional Hazard assumption test, the cox proportional hazard model was used to estimate the hazard ratio for prostatectomy of BPH patients with T2DM-metformin, T2DM non-metformin and without T2DM was measured. Moreover, total drug dose of Metformin was calculated per each Metformin intake T2DM group during look back period to consider dose effect of Metformin.

Results: Among 211,648 patients diagnosed as naïve BPH in 2009 who requires medical treatment, 13,926 patients were BPH with T2DM and 197,722 patients were BPH without T2DM. Among BPH naïve patients with T2DM, 11,050 were metformin group and 2,872 were non-metformin group. From the baseline characteristics, those with T2DM were older than those without T2DM (P<0.0001) and had more hypertension (P<0.0001). Total 7,672 patients received prostatectomy until June 2017. Average age of patients who received prostatectomy is higher than those who didn't receive prostatectomy (P<0.0001). The overall incidence of prostatectomy per 10,000 men was estimated to be 52.899 (CI: 38.725 to 83.438), while the incidence of prostatectomy per 10,000 of BPH patients without T2DM was estimated to be 53.061 (CI: 33.919 to 85.724). Incidence of prostatectomy per 10,000 men with T2DM - metformin seems to be slightly lower than that of BPH patients without T2DM by reaching 48.606 (CI: 33.919 to 85.724) while T2DM patients without metformin incidence increases up to 57.497 (CI: 39.874 to 103.035). The hazard ratios according to T2DM-metformin were found to be 0.860 for prostatectomy (P value=0.007), which drives a conclusion of T2DM comorbid patients with Metformin are at lower risk of receiving prostatectomy. Among subject patients in age group under 65 years old, T2DM with Metformin group showed lower HR of prostatectomy with 0.758(P-value=0.006). When dose of Metformin was considered, Metformin-High group showed significantly low risk of prostatectomy with HR 0.756(P

value=0.005)

Conclusion: From this study, although Diabetes is a risk factor of BPH, the characteristics of Diabetes patients; less likely to undergo surgeries due to complications and well managed diabetes can be helpful on managing BPH. Moreover Metformin's underline mode of action might block the progression of BPH. Though Diabetes can raise risk of progression of BPH, emphasizing managing Diabetes in their earlier stage and maintaining compliance of medication can lessen the risk of progression of BPH including prostatectomy and intake of Metformin can bring helpful outcome in managing progression of BPH.

Keywords: Benign Hyper Plasia, Metformin, Type 2 Diabetes Mellitus, Prostatectomy, Cox proportional hazard model

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Introduction

1) Background

1. Benign Prostate Hyperplasia, a prevalent and progressing disease

Though epidemiology and pathophysiology of benign prostate hyperplasia haven't yet clearly discovered (1), BPH, Benign Prostate Hyperplasia, is described with presence of proliferative process of the cellular elements of the prostate, an enlarged prostate, or the voiding dysfunction caused by prostatic enlargement and bladder outlet obstruction (2).

BPH occurs in the periurethral and transition zones of the prostate and its histological characteristics can be defined as the proliferative process of epithelial and stromal elements of the prostate gland.(3) Benign Prostate Enlargement (BPE) or even Benign Prostate Obstruction (BPO) along with progressive development of symptoms (Lower Urinary Tract Symptoms, LUTS); difficult to urine (BPE) or impair to urine (BPO), are clinically manifested findings of BPH(4). The term 'Lower Urinary Tract Symptoms (LUTS)' including voiding or storage symptoms is commonly used with BPH since BPH is associated with LUTS secondary to ensuing prostate enlargement. (5)

BPH is common especially in men over 40 years old and currently, make BPH as the fourth most prevalent disease in men aged 50 years old.(6) According to diverse studies related to prevalence of BPH or LUTS, the prevalence of BPH/LUTS increases with age, reported that the prevalence of BPH reaches up to 80% of men who are older than 70 years-old (5, 7).

Due to progressive condition of BPH, leaving BPH untreated causes serious

complications including acute urinary retention and surgeries related to BPH which might last for a long period of time(8). Prevalence of BPH also has considerable influence on socioeconomic factor by costing over $3 billion every year.(9) Since diverse factors of BPH/LUTS are related to aging, as life expectancy extends, socioeconomic burden increases with personal burden.

According to diverse guidelines of treating BPH including American Urology Association (AUA) and European association of Urology (EAU), there are four primary options for the treatment of BPH: watchful waiting, pharmacologic therapy, minimal invasive procedures, and surgeries(10). For the patients with non-bothersome symptoms and for those who less likely to take medication due to complications, adverse events and costs, watchful waiting is often chosen.

As BPH progresses, patients complain symptoms to doctors and to lessen symptoms, pharmacological therapy with either an alpha-adrenergic blocker and/or a 5 alpha-reductase inhibitor (5ARI) are often chosen as the initial treatment. After certain period of treatment with drugs, minimal invasive procedures including the various transurethral thermotherapy treatments are following options, while surgical therapies include procedures such as transurethral resection of the prostate, transurethral incision of the prostate, transurethral laser vaporization, and open simple prostatectomy are considered when patients have larger prostate volume and unsolved symptoms after medical therapy. Under the BPH treatment guideline, prostatectomy is suggested as the last option and BPH treatment guideline suggests condition for receiving prostatectomy as prostate size greater than 30ml. (11)

2. Type 2 Diabetes Mellitus and its association of BPH

Diabetes is a historic and world-wide health issue which leads complications in many organ systems, disables and even death to some patients. Together with the other three major non-communicable disease; cardiovascular disease, cancer and respiratory disease, diabetes is among top 10 causes of death globally.(12) It's global predominance is expected to reach 51% from 366 million in 2011 to 552 million in 2030(13).

Growing number of obese population, increasing urbanization and diminishing physical activities brings rapid increasing prevalence rates of diabetes in Asia(14). In China, the rate of diabetes almost tripled from 2.6% to 9.7% over the past decade(15), while the rate of diabetes recorded 4.9% in 1985 and 8.3% in 2007 in Taiwan(16). Situation in Korea is parallel with global trend, supported by several cohort studies and national surveys (17, 18). According to a recent study in Korea using data based on The Health Screening Service of the NHIS(National Healthcare Insurance Service), the prevalence of Type 2 Diabetes Mellitus(T2DM) in Korea appeared to be 10.9% in 2013(19).

Research on association of BPH and T2DM dates back to 20 years ago, when Hammarsten J analyzed association of BPH with each factors of Metabolic syndromes, including diabetes (20). Increasing risks of BPH due to accompanied diabetes were measured in several studies by analyzing association of hyperinsulinemia and BPH(21-23). Hyperinsulinmia usually occurs as a result of early stage of diabetes and progresses to diabetes, and directly linked to an increase in the level of free insulin-like growth hormone 1 (IGF-1)(24), which lead patients with higher level of IGF-1 predispose to have higher risk of BPH (21-23).

Among studies on association of severity of BPH and Diabetes, in the INord-Trondelag Health Study, Men with diabetes were more likely to have an IPSS ≥8 than their non-diabetic counterparts were (OR: 1.3; 95% CI: 1.1-1.5) (25). In the prospective single institutional study with 501 men in Egypt showed significant positive correlation between duration of Diabetes Mellitus treatment and mean prostate volume (r= 0.147, P= 0.034)(26). A study with 305 men to find out whether metabolic disorders in Aging Men contribute to Prostatic Hyperplasia eligible for transurethral resection of the prostate showed possibility of further research by showing patients eligible for transurethral resection of the prostate were significantly more likely to have Metabolic syndrome(p = 0.018) and diabetes (p = 0.0477) compare to those who aren't.(27)

3. Hypothesized mechanisms of association of BPH and diabetes

Several studies done as a trial to understand underline mechanism of association of BPH and diabetes suggested that insulin resistance with secondary hyperinsulinemia is associated with prostatic enlargement (28, 29). Hyperinsulinemia is associated with an increased sympathetic nervous system activity and this increased activity may lead to increased smooth muscle tone of the prostate, contributing in more severe LUTS independent to prostatic enlargement(30)(31). The Insulin-like Growth Factor, IGF, pathway may also result the association between insulin resistance and BPH. Since structure of insulin and IGF-1 are similar to each other, insulin can bind IGF-1's receptor and activate a complex pathway influencing prostate cell growth and proliferation. Alternatively, as insulin increases, binding of IGF-1 on protein-1 increases.

Another factor related to diabetes is hyperglycemia and this may play a role by increasing cytosolic-free calcium in smooth muscle cells and neural tissues,

leading to sympathetic nervous system activation.

Other possible mechanisms including the increase in peripheral sympathetic nerve tone and activity of the autonomic nervous system caused by hyperinsulinemia(32), and hypoxia caused by DM-induced vascular damage(33) have been proposed to associate the development of BPH with type 2 DM.

4. Metformin, a treatment for T2DM and its association of BPH.

Diverse types of drug can be used to treat T2DM including biguanide, sulfonylurea, meglitinide, thiazolidinedione and alpha glucosidase inhibitor and relatively recent one, DPP4 inhibitor. Each category acts slightly different to control T2DM patients and have different mode of action. Compare to other categories, Metformin is well known to improve insulin resistance by lowering insulin level.(34)

Beneficial effects on preventing and treating cancers of Biguanide drugs have been studied over 10 years. Metformin, a representative biguanide drug has long history over 50 years and is the most widely used drug to treat type 2 Diabetes Mellitus. By lowering insulin level effectively, metformin derives better outcomes in cancer patients who are dealing with problem of higher insulin and c-peptide levels.(34) Reduced circulating insulin leads to a subsequent down-regulation of the phosphoinositide-3-kinase (PI3K) axis. The androgen receptor pathway which is followed by the phosphoinositide-3-kinase (PI3K) pathway is the second major driver of growth of prostate cancer. The PI3K axis becomes subsequently down-regulated when insulin level is decreased.(35)

Besides beneficial effects of Metformin on cancers including prostate cancer,

studies of discovering association of Metformin and proliferation of prostate has been published. According to a study done with rats with increased prostate weight and prostate index by medication of testosterone, metformin inhibited pathological alterations induced by testosterone.(36) Another in vitro study with benign prostate enlargement cell showed protective effect of metformin on BPH by inhibiting IGF-1. (37)

5. Confounding factors

Charlson Comorbidity Index

Since diverse medical histories could have impact on BPH and T2DM, the Charlson Comorbid Index, CCI, a method to weight comorbid conditions was calculated for each patient with ICD-10 algorithm developed by Quan et al. (38)

BPH medical treatment, a confounder for Prostatectomy.

Alpha blocker and 5 alpha reductase inhibitor is widely used to treat BPH. These drugs not only lessen the bothering symptoms but also reduce the risk of progression to AUR and prostate surgery (39-43). MTOPS, the first clinical studies to assess the effect of medical therapy on the risk of overall clinical progression of BPH, suggested that delaying the initiation of 5ARI therapy in men who receive combination therapy for BPH is associated with a higher likelihood of clinical progression.(40)

Most of the patients get prescription of alpha blocker for medical treatment and 5 alpha reductase inhibitor is often combined when the prostate volume is large. Two different medications; alpha blocker and 5 alpha reductase inhibitor, have different mode of action; alpha blocker-relaxing the muscle in prostate so that

lessen the voiding symptoms of BPH patients and 5 alpha reductase inhibitor-delaying proliferation of prostate epithelial cell.

2) Necessity of this study.

The prevalence of T2DM and BPH among men over 40 years increase as aging which lead an expectation of higher prevalence and comorbidity of those two diseases as world enters super aging society. Hence, studies, usually done by single institution or studies with limited number of patients, focused on increasing risk of BPH when Metabolic syndrome or T2DM was accompanied(25-27) and underlying hypothesized mechanism of association of characteristics of T2DM and BPH(20, 32, 33).

BPH is a progressing disease, and as it progresses, necessity to receive treatment increases by offering higher possibility to receive surgical treatment, which in turn higher risk and higher cost burden to patients. Therefore, histologic progression of disease should be considered when BPH is treated. Though association of prevalence of BPH and T2DM has a few evidences, association of progression of BPH and T2DM lack of data and evidence. Moreover, association of T2DM on BPH becomes more complicated when drugs to treat T2DM are considered.

Metformin is widely used to treat T2DM and it is also newly discussed with its protective effect on BPH. However until now, only one cohort study with Veterans showed metformin’s protective influence with relatively low hazard ratio (0.90) on BPH compare to sulfonylurea.(44) To find out clearer association of T2DM with metformin and the progression of BPH, a study to measure the ‘progression of BPH’ with consideration of metformin intake is needed.

3) Objective

The aim of this study is to analyze association of Type 2 Diabetes Mellitus and Benign Prostate Hyperplasia by investigating patients who newly diagnosed BPH in 2009 and follow up occurrence of prostatectomy to measure progression of BPH until June 2017 with claims data of HIRA in Korea.

Since severity of T2DM may defers from patients to patients, when the subject patients are categorized into T2DM accompanied group, types of medical treatment is considered. In addition, medical treatment type for treating BPH is also considered since 5alpha reductase inhibitor which is well known and widely used for treating BPH patients has mechanism to lessen the growth rate of prostate by inhibiting the action of 5 alpha reductase, reducing the concentration of dihydrotestosterone, the primary androgen involved in prostate growth(45).

Controlling these confounders will be described in detail in latter part of this paper. An appropriate statistical model will be presented to clarify the association between T2DM and progression of BPH; prostatectomy by correcting covariates and confounders. The main goal of this study is to enhance awareness on association of T2DM and BPH; each of the most prevailed disease among men over their mid age and importance of preventing T2DM or taking care of disease properly to avoid other comorbidities which can cause diverse social and individual economic burden. By clarifying the underlying mechanisms that may link these two pathologic conditions, it would be the first step to lessen the prevalence of comorbidity of two diseases.

To summarize, the impact of comorbid T2DM on newly diagnosed BPH patients who require medical treatment will be measured through this study by

defining prostatectomy as depending variable. Additionally severity of T2DM and categorizing prescribed BPH drug will be considered to minimize effect of confounder.

The detail purposes of this study are as follows:

-To assess the association between Type 2 DM with Metformin and the occurrence of Prostatectomy among BPH patients by following them until June 2017.

Ⅱ Materials and Methods.

1) Data source

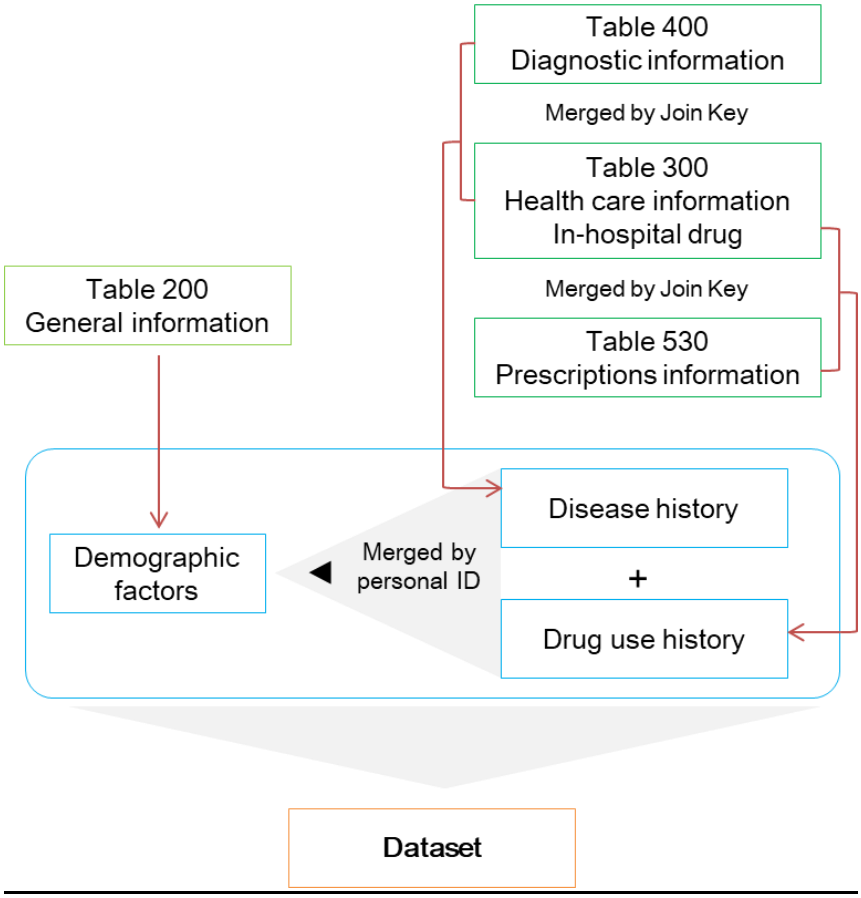
Claims data from Health Insurance Review & Assessment Service.

Korea's national health insurance system covers whole nation and this contains detailed medical data including diagnosis data, prescribed drugs and surgery information. To obtain general conclusion about associations between T2DM, prostatectomy among BPH patients, medical claims data from Health Insurance Review & Assessment Service (HIRA) in Korea were used.

In the claims data of HIRA, Table 200 provides its general information; patient status, date of visit, age and regional information of the visited health care center. Table 400 includes diagnostic information, and specific information on healthcare services provided including surgery can be obtained and Table 300 while Table 530 provides information about prescribed drugs.

Demographic factors from the data in Table 200 are extracted and then Join key for each statement number is used to merge 4 tables which contain different types of information. To enroll newly diagnosed BPH patient with medical treatment, each patient's past and current history of medical treatment and diagnosis were checked from Table 300, Table 530 and Table 400. To check prostatectomy, T300 were merged with merged information of enrolled patients by using the join key. The pipeline for the dataset configuration is shown in the following Figure 1.

Figure 1. Dataset Configuration



2) Study design

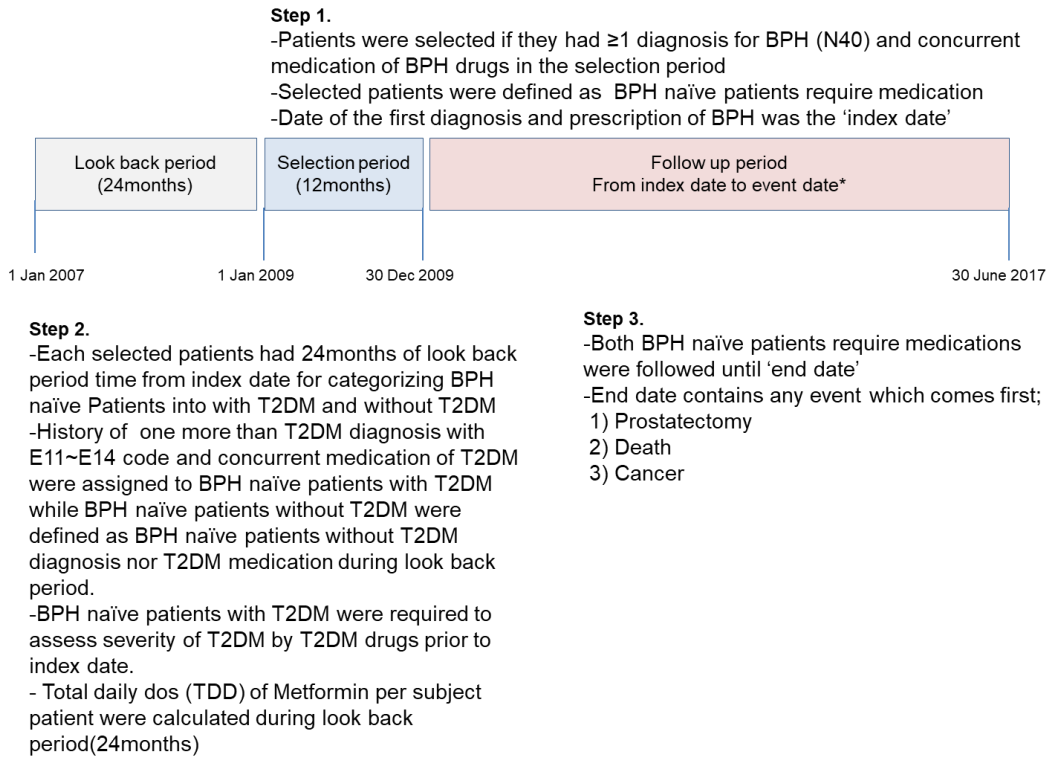
Attained data of demographic information, the medical care and prescription of the men over their 40 years in January 2007-June 2017 from HIRA through the remote access system was used.

Analyses were carried out after eliminating the personally identifiable information from the result of remote analysis. A cohort of patients diagnosed of BPH with medical treatment in 2009 was created. The diagnosis of BPH was defined as having the diagnosis of BPH (N40.0 in International Classification of Diseases, 10th revision) in whole diagnosis and concurrent prescription of drug (Alpha blocker or 5alpha reductase inhibitor) ≥2 times in 2009.(Table1) In order to make cohort with naïve BPH patients, each patient had 2 years of look back period without any diagnosis of BPH with neither N40-code nor prescription history of BPH drug.(Figure 2)

Table 1. Medication for BPH

Category	Molecule	Code
Alpha Blocker	Tamsulosin	234601AXX, 234603ACR
	Alfuzosin	104803ATR
	Doxazsoin	14910XXXX
	Terazosin	23550XXXX
	Silodosin	50420XXXX
	Naftopidil	61420XXXX
5ARI (5-Alph-Reductase-Inhibitor)	Dutasteride	458801ACS
	Finasteride	159001ATB

Figure 2. Study design



Study cohort was categorized into BPH patients with T2DM and BPH patients without T2DM by investigating each patient's medical history related to T2DM during the look back period. T2DM was defined when the patient had diagnosis of T2DM (E11~E14 in international classification of Diseases, 10th version) in whole diagnosis and concurrent prescription of T2DM. T2DM patients were then sub-categorized into those who take Metformin and those who do not take Metformin. Drugs which were available in look back period (2 years back from the index date) but invalid after index date were still counted for analyzing for T2DM. Recently released medication; SGL-2 inhibitor and DPP-4 inhibitor were not contained. (Table2)

Table 2. Medication for T2DM

CATEGORY	MOLECULE	CODE
Biguanide	Metformin	19150XXX
Sulfonylurea	Glibenclamide	165402ATB
	Gliclazide	16560XXXX
	Glimepiride	16570XXXX
	Glipizide	165801ATB
	Gliquidone	165901ATB
Meglitinide	Mitiglinide	486101ATB
	Nateglinide	43020XXXX
	Repaglinide	37950XXXX
Thiazolidinedione	Pioglitazone	43190XXXX
	Rosiglitazone	34800XXXX
Alpha glucosidase inhibitor	Acarbose	10060XXXX
	Voglibose	24900XXXX
Single tab of Metformin with other Metformin+	Glibenclamide	471900ATB, 421100AT, 443400ATB, 443500ATB
	Glimepiride	474200ATB, 474300ATB
	Rosiglitazone	452900ATB, 452700ATB, 469100ATB, 471800ATB

The incidence and timing of prostatectomy was defined by having surgery code of prostatectomy (Table 3). Among treatment options of BPH, prostatectomy is considered when severe voiding symptoms accompanied by BPO due to excessively enlarged prostate.

To measure progression of BPH within claims data, 4 types of prostatectomy were defined as the outcome which describes progression of BPH.

Table 3. Types of Prostatectomy

Types of Prostatectomy		Code
Prostatectomy	Transurethral resection	R3975
	Open prostatectomy	R3950
	Photoselective vaporization	R3976
	Holmium laser enucleation	R3977

Patients diagnosed with prostate cancer (ICD10, C61) or having claims suggesting a prior prostatic surgery, inflammatory diseases of the prostate, neurological diseases or conditions that could affect LUTS during the look back period were also excluded (Table 4).

Table 4. Exclusion criteria for subject patients.

DIAGNOSIS		ICD-10 or KD codes
Malignant neoplasm of the prostate		C61
Parkinson disease		G20
Secondary parkinsonism		G21
Parkinsonism in disease classified elsewhere		G22
Dementia in Parkinson disease(G20+)		F02.3
Multiple sclerosis		G35
Hemiplegia, Cerebral palsy and other paralytic syndromes, other paralytic syndromes		G80-G83
Cerebrovascular diseases		I60-I69
Neoplasm of uncertain or unknown behavior of the prostate		D40.0
Benign neoplasm of the prostate		D29.1
Acute urinary retention		R33
Inflammatory diseases of the prostate		N41
Thermal therapy		R3516
Prostatectomy	Transurethral resection	R3975
	Open prostatectomy	R3950
	Photoselective vaporization	R3976
	Holmium laser enucleation	R3977

3) Confounding

To control confounding, we included a set of baseline covariates which were potentially associated with BPH and the risk of progression of BPH defined as prostatectomy in the statistical models. In addition to age, hypertension and BPH medication categorized by alpha blocker and 5 alpha reductase inhibitor,

5ARI, were considered.

During the look back period of each subject patient, Charlson Comorbid Index (CCI) was calculated with ICD 10 code per each patient and the patients' comorbid status was categorized by CCI and the CCI for each patient was considered as confounder in further statistical analysis.

To manage confounding effect of BPH medication including alpha blocker and 5ari, patients' initial BPH medical treatments were categorized into 3 groups; patients with alpha blocker only, patients with 5ARI only and patients with combination therapy with alpha blocker and 5ARI.

4) Statistical analysis

Analyses included all patients meeting the inclusion criteria. Analyses were also stratified according to the following pre-specified sub cohorts at index date by severity of T2DM; mild T2DM with taking on the 1st category of drug, metformin, moderate T2DM with taking 2 categories of drug including the 1st category and severe T2DM with taking more than 3 types of drugs including the 1st and the 2nd categories.

Hazard ratios are reported for comparisons between BPH without T2DM (reference) and BPH with T2DM. Patients were censored if they reached the end of follow up without prostatectomy. Cox proportional-hazards regression models, adjusted for potential confounding factors (age, hypertension, alpha blocker drug usage, 5ARI drug usage) were used to compare cohorts (expressed as HR and 95% confidence interval [CI])

Before analyzing cox model, proportional hazard assumption was checked. The survival curves for two strata; BPH with T2DM and BPH without T2DM have hazard functions that are proportional over time (P value =0.357). P-value <0.05 was considered statistically significant.

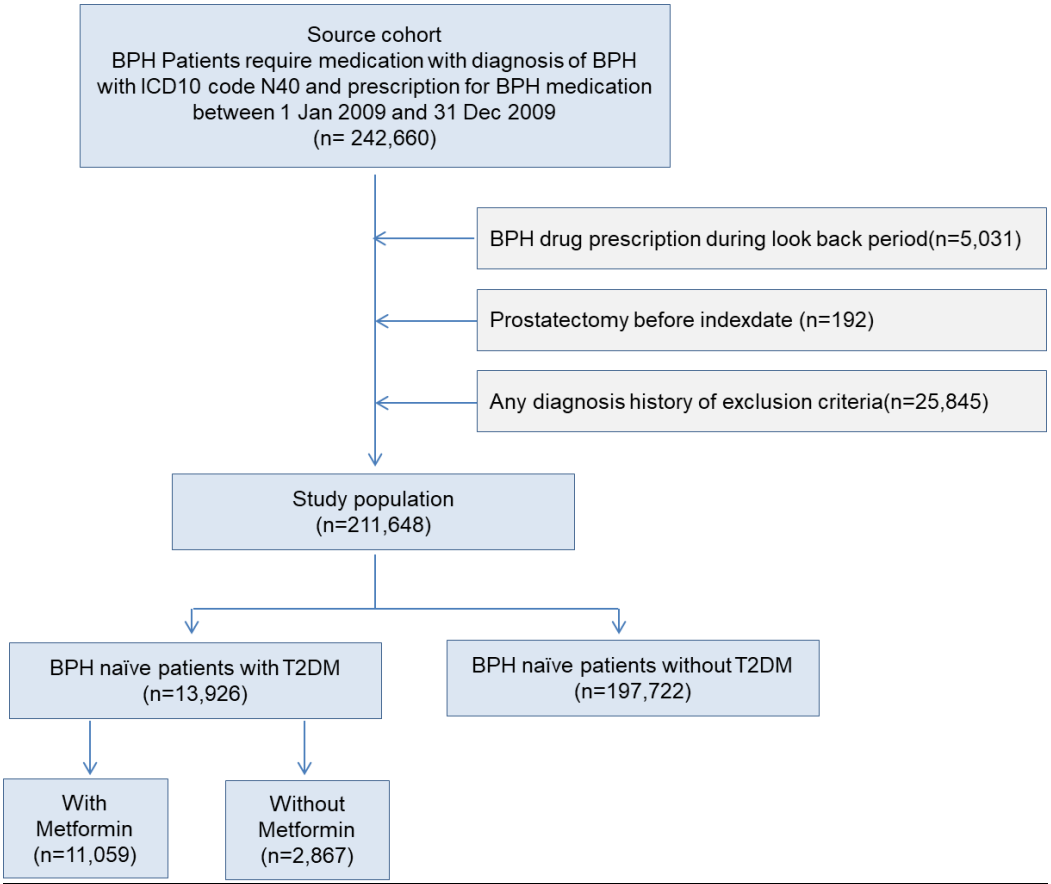
In the stratified analysis, to consider dose effect of Metformin on prostatectomy, total daily drug dose of Metformin was calculated per each subject patients during the look back period (24 months). Daily drug dose of Metformin is 2g according to World Health Organization (WHO), and after calculation, Metformin take group was sub categorized into Metformin Low, Mid, High group.

Ⅲ. Results

1) Characteristics of study population

Subjects who were diagnosed as BPH patients in 2009 with ICD 10 code N40 were used for analyses. 242,660 subjects who satisfy the definition of Naïve BPH patient were available; more than 2 times of diagnose of BPH with ICD10 code N40 and concurrent prescription of BPH medication in the claims data of HIRA in Korea. Subjects who satisfy the following conditions were excluded. Those who have claims suggesting a prior prostatic surgery, prostate cancers, inflammatory diseases of the prostate, neurological diseases which might have impact on LUTS were excluded. See the table 4 for further information about exclusion criteria. Figure 3 shows the summary for subject filtering described so far.

Figure 3. Patient selection flowchart.



*exclusion criteria (Table 4)

Among 211,620 study population, after investigating their previous disease history, 13,922 were comorbid with T2DM and 197,698 didn't have T2DM history. From the baseline characteristics, those with T2DM were older than those without T2DM (P<0.0001) and had more hypertension (P<0.0001). Table 5 shows more information on baseline characteristics of BPH naïve patients with T2DM and without T2DM.

Table 5. Baseline characteristics according to comorbidity of T2DM

	Total		BPH withT2DM		BPH without T2DM		P value
	n	(%)	n	(%)	n	(%)	
Age	61.4±11.0		64.9±9.4		61.2±11.0		<0.0001
40	33,523	(15.8)	842	(6.0)	32,681	(16.5)	
50	60,136	(28.4)	3100	(22.3)	57,036	(28.9)	
60	64,933	(30.7)	5332	(38.3)	59,601	(30.1)	
>=70	53,056	(25.1)	4652	(33.4)	48,404	(24.5)	
Diagnosed area							<0.0001
Seoul (Capital)	43,399	(20.5)	2,605	(18.7)	40,794	(20.6)	
Metropolitans	60,239	(28.5)	3,955	(28.4)	56,284	(28.5)	
Small town	108,010	(51.0)	7,366	(52.9)	100,644	(50.9)	
Initial BPH treatment							0.469
Alpha blocker only	143,815	(67.9)	9,413	(67.6)	134,402	(67.9)	
5ARI only	15,409	(7.3)	1,048	(7.5)	14,361	(7.3)	
Combination	52,424	(24.8)	3,465	(24.9)	48,959	(24.8)	
CCI, N (%)							0.038
≤1	167,479	(79.1)	10,981	(78.9)	156,498	(79.1)	
2-3	26,214	(12.4)	1,751	(12.6)	24,463	(12.4)	
≥4	17,927	(8.5)	1,189	(8.5)	16,738	(8.5)	

Table 6. Baseline characteristics of T2DM patients according to metformin prescription.

	T2DM with Metformin		T2DM without Metformin		P value
	n	(%)	n	(%)	
Age	64.7±9.4		65.9±9.6		<0.0001
40	691	(6.2)	151	(5.3)	
50	2,518	(22.8)	582	(20.3)	
60	4,256	(38.5)	1,076	(37.5)	
>=70	3,594	(32.5)	1,058	(36.9)	
Diagnosed area					<0.001
Seoul (Capital)	2,025	(18.3)	580	(20.2)	
Metropolitans	3,113	(28.2)	842	(29.4)	
Small town	5,921	(53.5)	1,445	(50.4)	
Initial BPH treatment					0.596
Alpha blocker	7489	(67.8)	1923	(67.0)	
5ARI only	820	(7.4)	227	(7.9)	
Combination	2741	(24.8)	722	(25.1)	
CCI, N (%)					0.996
≤1	2,247	(78.4)	8,734	(79.0)	
2-3	357	(12.5)	1,394	(12.6)	
≥4	262	(9.1)	927	(8.4)	

Among BPH naïve patients who comorbid with T2DM, those who take Metformin for treatment are younger than those who do not take Metformin. Hypertension comorbidity and BPH treatment did not show difference (Table 6).

Subject patients where followed until June 30th in 2017 and during the follow up period, total 7,672 patients received prostatectomy. Average age of patients who received prostatectomy is higher than those who didn't receive prostatectomy (P<0.0001). Detail information about BPH naïve patients categorized by prostatectomy are described in Table 7.

Table 7. Baseline characteristics according to prostatectomy operation.

	BPH patients received Prostatectomy		BPH patients didn't receive Prostatectomy		P value
Total number	7,672		203,976		
	n	(%)	n	(%)	
Age	65.6± 8.2		61.3±11.0		<0.0001
40	186	(2.4)	33,337	(16.4)	
50	1,527	(19.9)	58,609	(28.7)	
60	3,486	(45.4)	61,447	(30.1)	
>=70	2,473	(32.3)	50,583	(24.8)	
Diagnosed area					<0.0001
Seoul (Capital)	2,008	(26.2)	41,391	(20.3)	
Metropolitans	2,112	(27.5)	58,127	(28.5)	
Small town	3,552	(46.3)	104,458	(51.2)	
Initial BPH treatment					<0.0001
Alpha blocker only	4,622	(60.2)	139,193	(68.2)	
5ARI only	490	(6.4)	14,919	(7.3)	
Combination	2,560	(33.4)	49,864	(24.5)	
CCI, N (%)					<0.0001
≤1	5677	(74.0)	161,802	(79.3)	
2-3	1167	(15.2)	25,047	(12.3)	
≥4	827	(10.8)	17,100	(8.4)	

Baseline characteristics of Patients who received Prostatectomy were analyzed by their comorbidity of T2DM and described in Table 8. Among patients who received prostatectomy, those with T2DM are older than those without T2DM. While hypertension comorbid rate among BPH with T2DM were higher, when it comes to prostatectomy, hypertension comorbid rate among BPH with T2DM showed lower rate compare to prostatectomy received patients without T2DM. Table 9 shows descriptive analysis of prostatectomy received T2DM patients categorized by metformin intake. Due to insufficient event number none of differences between metformin intake and non-intake group appeared.

Table 8. Baseline characteristics according to T2DM among BPH patients who received prostatectomy.

	BPH with T2DM		BPH without T2DM		P value
	n	(%)	n	(%)	
Age	67.6±6.9		65.5±8.3		<0.0001
40	3	(0.7)	183	(2.5)	
50	44	(9.8)	1,483	(20.6)	
60	222	(49.0)	3,264	(45.2)	
>=70	184	(40.6)	2,289	(31.7)	
Diagnosed area					0.196
Seoul (Capital)	107	(23.6)	1,901	(26.3)	
Metropolitans	140	(30.9)	1,972	(27.3)	
Small town	206	(45.5)	3,346	(46.4)	
Initial BPH treatment					0.184
Alpha blocker only	291	(64.2)	4,331	(60.0)	
5ARI only	24	(5.3)	466	(6.5)	
Combination	138	(30.5)	2,422	(33.5)	
CCI, N (%)					0.036
≤1	339	(74.8)	5,338	(74.0)	
2-3	77	(17.0)	1,090	(15.1)	
≥4	37	(8.2)	790	(10.9)	

Table 9. Baseline characteristics according to metformin prescription among BPH patients with T2DM who received prostatectomy.

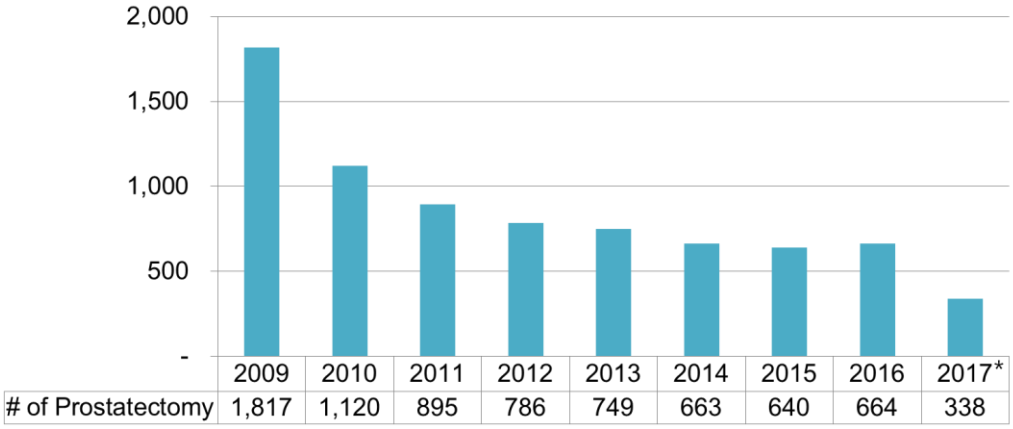
	With Metformin		Without Metformin		P value
	n	(%)	n	(%)	
Age	65.6±8.2		66.7±6.8		0.139
40	2	(1.9)	1	(0.3)	
50	11	(10.3)	33	(9.5)	
60	55	(51.9)	167	(48.1)	
>=70	38	(35.9)	146	(42.1)	
Diagnosed area					0.705
Seoul (Capital)	85	(24.5)	22	(20.8)	
Metropolitans	105	(30.3)	35	(33.0)	
Small town	157	(45.2)	49	(46.2)	
Initial BPH treatment					0.585

Alpha blocker only	219	(63.1)	72	(67.9)	
5ARI only	18	(5.2)	6	(5.7)	
Combination	347	(31.7)	28	(26.4)	
CCI, N (%)					0.603
≤1	262	(75.5)	77	(72.6)	
2-3	59	(17.0)	18	(17.0)	
≥4	26	(7.5)	11	(10.4)	

2) Incidence of Prostatectomy

Incidence of prostatectomy was estimated to examine overall status of prostatectomy due to BPH. Annual occurrence of prostatectomy is described in Figure 4.

Figure 4. Annual incidence of Prostatectomy



	2009	2010	2011	2012	2013	2014	2015	2016	2017*
# of Prostatectomy	1,817	1,120	895	786	749	663	640	664	338

*Data in 2017 is limited up to June.

The incidence of prostatectomy was determined by setting the person-year and multiplied by 10,000. The overall incidence of prostatectomy per 10,000 men was estimated to be 52.899 (CI: 38.725 to 83.438), while the incidence of prostatectomy per 10,000 of BPH patients without T2DM was estimated to be 53.061 (CI: 33.919 to 85.724). Incidence of prostatectomy per 10,000 men with

T2DM who take metformin seems to be slightly lower than that of BPH patients without T2DM by reaching 48.606(CI: 33.919 to 85.724) while T2DM patients without metformin incidence increases up to 57.497(CI: 39.874 to 103.035). More information on incidence rate can be found from Table 10.

Table 10. Incidence of Prostatectomy according to T2DM and metformin.

	The number of event	Incidence per 10,000people	95% CI	
Total	7,672	52.899	38.725	83.438
BPH without T2DM	7,219	53.061	33.919	85.724
BPH with T2DM, Metformin	347	48.606	33.919	85.724
BPH with T2DM, non Metformin	106	57.497	39.874	103.035

3) Cox proportional hazard model of Prostatectomy

To assess the status of prostatectomy of BPH naïve patients, the incidence per 10,000 men were estimated. As described from the previous part, T2DM and prostatectomy can be influenced by other risk factors. Therefore, effects of CCI, age, diagnosed region, diagnosed hospital level, and category of BPH medication need to be adjusted and the Cox proportional hazard models are applied.

For Cox proportional hazard model, the T2DM was set as the main exposure and fitted to the Cox proportional hazards model (Table 11). The hazard ratios according to T2DM were found to be 0.86 for prostatectomy (P value<0.01). This means that BPH naïve patients having T2DM are at lower risk of receiving

prostatectomy.

As patients' age increases, risk of receiving prostatectomy also increases with Hazard ratio 1.05 (P value<0.0001). Those BPH patients who diagnosed BPH from metropolitan or small towns show lower risk to receive prostatectomy with Hazard ratio 0.85 and 0.73 respectively. Compare to BPH patients who prescribed alpha blocker only on their first index date, those patients who prescribed combination therapy with alpha blocker and 5ARI showed higher risk to prostatectomy by showing hazard ratio 1.48. Patients who less visit hospital are less likely to receive prostatectomy supported by analysis of the OPD number categories with hazard ratio 0.796. When patients were diagnosed as BPH in upper level of hospital including 2^{nd} and 3^{rd}, they were more likely to receive prostatectomy. (HR 1.32, 1.51)

Table 11. Hazard ratios for prostatectomy according to T2DM, metformin, and baseline characteristics.

	HR[1]	95%CI		P-value
T2DM				
No (Reference)				
Yes without Metformin	0.94	0.78	1.14	0.557
Yes with Metformin	0.86	0.77	0.96	0.007
Age	1.05	1.04	1.05	<.0.0001
CCI	1.00	0.99	1.02	0.587
Region				
Capital (reference)				
Metropolitans	0.80	0.75	0.85	<.0.0001
Small town	0.69	0.66	0.73	<.0.0001
BPH medication				
Alpha blocker only (reference)				
5ARI only	0.99	0.90	1.09	0.811
Combination	1.40	1.34	1.48	<.0.0001
OPD[2] number				
Upper 25% (reference)				
Upper 50%	0.95	0.90	1.02	0.142
Lower 50%	0.90	0.84	0.96	<0.001
Lower 25%	0.78	0.73	0.83	<.0.0001
Diagnosed hospital type				
1st (reference)				
2nd	1.27	1.19	1.32	<.0.0001
3rd	1.32	1.57	1.51	<.0.0001

[1]Hazard ratio calculated by Cox proportional hazards regression after adjustments for age, area of hospital, initial BPH medication, hypertension, and outpatient department visits

[2]OPD: Out Patient Department number

4) Stratified analysis by age group

Considering that average age of BPH patients with T2DM and without T2DM was significantly different, additional stratified analysis was done by age group. Among subject patients in age group under 65 years old, T2DM with Metformin group showed lower hazard ratio of prostatectomy with 0.76 (P-value<0.01). However, in the group of age over 65, none of the group showed statistically significant difference.

Table 12. Stratified analysis for the risk of prostatectomy according to age

	without T2DM	T2DM without Metformin	T2DM with Metformin
Age<65			
Events	3,189	39	103
Hazard ratio (95% CI)	1.00 (reference)	1.20(0.87-1.64)	0.76(0.62-0.92)
P value		0.269	0.006
Age>=65			
Events	4,030	67	244
Hazard ratio (95% CI)	1.00 (reference)	0.88(0.69-1.12)	0.90(0.79-1.03)
P value		0.283	0.113

5) Stratified analysis by cumulative dose of Metformin

When TDDD of Metformin was considered, among the group of without T2DM, T2DM without Metformin, T2DM with Metformin Low, T2DM with Metformin Mid, and T2DM with Metformin high, T2DM with Metformin high group showed significantly low risk of prostatectomy with HR 0.76 (P value<0.01)

Table 13. Hazard ratios for prostatectomy according to T2DM and metformin dose.

	HR[1]	95%CI		P-value
Without T2DM(Reference)				
With T2DM non Metformin	0.94	0.78	1.14	0.556
With T2DM Metformin LOW	0.88	0.73	1.06	0.165
With T2DM Metformin MID	0.95	0.79	1.13	0.526
With T2DM Metformin HIGH	0.76	0.62	0.92	0.005

6) Sensitivity Analysis

Among the BPH naïve patients who were categorized into BPH without T2DM, there is still possibility of diagnosing T2DM after each patient's index date. To verify consistency of results, sensitivity analysis of hazard ratios for prostatectomy according to T2DM and metformin after excluding T2DM patients diagnosed after index date was done. (Table 14) After excluding T2DM patients diagnosed after index date, result was consistence by HR 0.86 (P-value 0.007) in T2DM with metformin.

Table 14. Sensitivity analysis of hazard ratios for prostatectomy according to T2DM and metformin after excluding T2DM patients diagnosed after index date.

	No T2DM	T2DM without metformin	T2DM with metformin
Exclusion of T2DM after index date, N			
Events	7,110	106	347
HR	1.00	0.94	0.86
(95% CI)	(reference)	(0.78-1.14)	(0.77-0.96)
P-value		0.557	0.007

In the stratified analysis, BPH patients were categorized into 5 groups; No T2DM, T2DM without metformin, T2DM with metformin Low, T2DM with metformin MEDIUM and T2DM with metformin HIGH by considering comorbid of T2DM and cumulative dose of metformin during 24 months earlier than the index date. To consider cumulative dose of each enrolled patients after the index date, sensitivity analysis of hazard ratios for prostatectomy according to T2DM and metformin dose considered 1-2 years after index date was done (Table 15). T2DM with metformin LOW, MEDIUM and HIGH group were re-categorized per each year; 1 year after index date and 2 years after index date. T2DM with Metformin HIGH group showed lower risk of prostatectomy compare to the patients without T2DM by showing statistically significant HR in both periods.

Table 15. Sensitivity analysis of hazard ratios for prostatectomy according to T2DM and metformin dose considered 1-2 years after index date.

	HR	95% CI	P-value
1 year			
No T2DM	1.00 (ref)		
T2DM without metformin	0.98	0.78-1.25	0.882
T2DM with metformin LOW	0.95	0.83-1.09	0.475
T2DM with metformin MEDIUM	1.01	0.88-1.17	0.896
T2DM with metformin HIGH	0.84	0.72-0.98	0.029
2 years			
No T2DM	1.00 (ref)		
T2DM without metformin	1.02	0.79-1.33	0.869
T2DM with metformin LOW	0.89	0.76-1.04	0.137
T2DM with metformin MEDIUM	1.07	0.93-1.23	0.349
T2DM with metformin HIGH	0.86	0.74-1.01	0.062

Though prostatectomy is minimal invasive surgery, still lots of patients' condition might have influence on deciding surgery. Therefore, when a certain patient receive prostatectomy within 1 year after the index date of BPH

diagnosis, other factors except intake of metformin might have more influence. To clarify the metformin impact on prostatectomy on BPH patients, Sensitivity analysis of hazard ratios for prostatectomy according to T2DM and metformin after excluding events that occurred 1-4 years after the index date.(Table 16) In this sensitivity analysis, group of T2DM with metformin showed lower risk of prostatectomy compare to the patients without T2DM in washout of 1-4 year.

Table 16. Sensitivity analysis of hazard ratios for prostatectomy according to T2DM and metformin after excluding events that occurred 1-4 years after the index date.

	No T2DM	T2DM without metformin	T2DM with metformin
Washout of 1 year			
HR (95% CI)	1.00 (reference)	0.94 (0.75-1.19)	0.81(0.71-0.93)
P-value		0.610	0.002
Washout of 2 years			
HR (95% CI)	1.00 (reference)	1.00(0.78-1.29)	0.83(0.72-0.96)
P-value		0.996	0.014
Washout of 3 years			
HR (95% CI)	1.00 (reference)	0.98(0.74-1.30)	0.83(0.70-0.98)
P-value		0.883	0.024
Washout of 4 years			
HR (95% CI)	1.00 (reference)	1.03(0.75-1.41)	0.79(0.65-0.96)
P-value		0.870	0.016

IV. Discussion

This study demonstrates the incidence of prostatectomy of BPH naïve patients categorized by comorbidity of T2DM. Previous studies have shown that patients are likely to visit hospitals and seek medical care when they have bothersome

or more profound symptoms.(46-48) This aspect is also shown in this study by OPD number of patients; those patients with less OPD are less likely to have prostatectomy, more likely to have less symptoms due to less progression of BPH.

From the community-dwelling studies, a cohort study with men having American Urological Association Symptom Index 8 or greater, after 2 years of follow up, 4% of the study cohort received BPH surgery.(49) In the Proscar Long-Term Efficacy and Safety study with 4 year follow up period, 5% of the finasteride treated patients and 10% of placebo treated patients underwent BPH surgery.(50) Until now BPH surgery-prostatectomy was measured from BPH patients' cohort and had limited follow up period. However, in this study, study cohort was followed up almost 7 years and by defining naïve BPH patients, prostatectomy was used as the key to verify progression of BPH. Moreover, incidence of prostatectomy among BPH patients with T2DM and without T2DM was measured.

While previous studies analyzed association of Diabetes and Benign prostate hyperplasia and showed diabetes as a risk factor of BPH due to diverse pathophysiology including hyperinsulineamia and dyslipidemia,(28-32) studies done with diabetes patients who receive appropriate treatment to care diabetes are limited.

The result of this thesis shows BPH patients with T2DM are less likely to undergo prostatectomy and there are several reasons to be studied further.

The first reason is that T2DM patients are more likely to have complications after surgeries. When medical therapy becomes ineffective, prostatectomy by open surgery or transurethral resection of the prostate is considered.(51) However, multiple complications; urinary tract infection, strictures, sexual

dysfunction and blood loss are often associated with surgical treatment. Therefore, operators of the surgery are reluctant to decide prostatectomy to T2DM patients compare to patients without T2DM.

Another reason comes from the effect of metformin on proliferation of prostate. The insulin similar molecule IGF-1 plays critical role in the proliferation of prostate.(52) IGF-1 performs a fundamental role in regulation of a variety of cellular processes such as proliferation, differentiation, apoptosis, extracellular matrix expression, chemotaxis, and neovascularization (53-55). IGF-1 regulates the stromal-epithelial interaction through the paracrine pathway, and also that the activation of IGF-IR promotes the proliferation of prostatic epithelial cells via MAPK/AKT/Cyclin D pathway(52)

Metformin is prescribed as a first line medication for type 2 diabetes treatment and almost 120 million people are taking Metformin worldwide(56). Interestingly, recent studies have suggested this medication as a potential anti-proliferative agent. In prostatic cancer cell lines, metformin has been demonstrated to inhibit cell proliferation and block the cell cycle in the G_0/G_1 stage by activating the AMPK pathway (57, 58).

One study showed that metformin inhibits the proliferation of two being prostatic epithelial cell lines, BPH-1 and P69 in a dose dependent and time dependent manner(59). Moreover, this study addressed that IFG-1 is involved in the abrogation of cell proliferation induced by metformin.

Considering that all T2DM patients who were enrolled in this study were taking Metformin, the result of this study might offer hint of the role of Metformin as a protective action on BPH.

There are a few limitations of the present study. The database did not include clinical variables; such as prostate volume and the diagnosis of BPH and T2DM

were based only on the physician's opinion. The T2DM patients with BPH may have been underestimated because only patients who had visited the clinic were included in the analysis. Third, since patients who diagnosed with acute urinary retention were excluded, the incidence of surgery might be underestimated.

Ⅴ. Conclusion

The incidence of prostatectomy as an outcome of progression of BPH is different from patients with T2DM which were categorized by metformin and patients without T2DM. Patients with T2DM showed lower risk of prostatectomy compare to BPH patients without T2DM and the effect of metformin was significant when stratified analysis with age was done. BPH naïve patients with T2DM under the age 65 years old showed that intake of Metformin lessen the hazard ratio of receiving prostatectomy compare to BPH patients without T2DM while T2DM patients without Metformin did not show difference. Except the comorbidity of T2DM, older age and tendency to visit clinics often increased risk of prostatectomy.

From this study, although Diabetes is a risk factor of BPH, the characteristics of Diabetes patients; less likely to undergo surgeries due to complications and well managed diabetes can be helpful managing BPH by blocking the progression of BPH by Metformin's underline action. Though Diabetes can raise risk of progression of BPH, emphasizing managing Diabetes in their earlier stage and maintaining compliance of medication can lessen the risk of progression of BPH including prostatectomy.

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국문 초록

2형 당뇨로 인한 메트포민 복용이 전립선 비대증 악화에 미치는 영향

- 한국의 2009년도 신규 전립선비대증 환자를 대상으로 -

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연구 배경: 연령이 증가함에 따라 높은 유병율을 보이는 전립선 비대증은 요로 상피 세포의 증식과 전립선 이행대의 팽창으로 정의 된다. 전립선비대증은 40세 이상의 남성에게 있어 매우 흔한 질환이며 노화에 따라 질병의 양상이 증가함에 따라 70대 이상의 남성에서는 80%의 유병률을 보인다. 전립선 비대증은 증상 악화 정도에 따라 대기요법, 약물 요법을 포함한 비침습적 치료나, 수술을 비롯한 침습적 치료로 이어진다. 수술 후 저장증상의 악화 등 다양한 부작용이 일어날 수 있기 때문에 수술적 치료는 전립선 비대증 치료의 마지막 단계로 추천 된다.

2형 당뇨는 신체의 다양한 장기에 합병증을 유발하는 높은 유병률을 보이는 질병이며 2형 당뇨와 전립선 비대증의 연관성에 대한 연구는 20여년 전부터 논의 되어왔다. 전립선비대증과 2형 당뇨의 연관성을 설명하는 기전은 이상지지혈증과 고인슐린증 두 가지로 대표된다. 고인슐린증은 Insulin-like Growth Hormone 1(IGF-1)의 농도를 증가시키며 전립선 내 근육의 비대를 유발하며 전립선 비대증을 악화 시킨다. 이상지지혈증은 평활근 세포의 cystosolic-free 칼슘을 증가하여 교감 신경의 반응을 자극하여 하부요로 증상

을 악화 시켜 전립선비대증을 더욱 악화한다. 당뇨는 전립선비대증의 악화 요인으로 보는 많은 연구들이 발표되어 왔으나 최근에 당뇨 치료제로 가장 널리 쓰이는 메트포민이 전립선 세포 증식을 억제하는 효과를 발현한다는 연구가 발표 되었다. 지금까지 당뇨와 전립선 비대증의 연관성에 대한 연구는 동반 비율이나 유병률, cross-sectional 한 연구가 대부분이었으나 당뇨 치료의 가장 기초적인 약제인 메트포민을 복용하는 당뇨 동반 환자에 대한 전립선 비대증 악화에 대한 연구는 미비하다.

연구 목적: 이 연구의 목적은 2형 당뇨에 따른 메트포민 복용과 전립선 비대증의 악화와의 연관성을 분석하기 위해 우리나라의 2009년도에 약물치료를 필요로 하는 전립선 비대증 신환으로 진단 된 환자들을 대상으로 진행 되었다. 전립선 비대증의 악화를 전립선 절제술로 정의하고, 대상 환자들을 2형 당뇨 없는 군, 있으면서 메트포민을 복용하는 군, 복용하지 않는 군으로 나눠 2017년 6월까지 전립선 절제술 여부를 파악하였다.

연구 방법: 본 연구는 한국의 전립선 비대증 신규 환자를 대상으로 한 2형 당뇨의 동반 유무에 따른 전립선 비대증 악화를 파악하기 위하여 2009년도에 전립선비대증으로 진단 받은 환자들의 심사평가원 청구데이터를 원격으로 활용하였다.(과제 번호는 M20180205893) 명세서, 진료내역, 처방전 관련 자료를 환자 식별 번호와 key 번호를 기준으로 통합하여 본 연구에 활용 될 자료를 구성하였다. 문헌 조사를 통해 분석에서 교란 요인의 설정 및 설명 변수의 선택을 실시 하였다. 자료의 특성을 알아보기 위해 빈도분석을 실시하였고, 전립선 비대증 환자들의 전립선 절제술 현황을 파악하기 위해 대상 환자들의 전립선 절제술 발생률을 추정하였다. 발생률의 추정은 10,000인-년을 기준으로 추정하였다. 비례위험 가정을 확인 한 후에 2형 당뇨를 동반한 전립선비대증 환자와 2형 당뇨를 동반하지 않은 전립선비대증 환자의 전립선 절제술 여부에 대한 위험 함수를 추정하였다. 2형 당뇨의 전립선 절제술로 정의된 전립선 비대증의 악화에 대한 위험비를 추정하기 위하여 콕스 비례 위험 모형을 활용하였다. 메트포민 복용량의 효과를 보기 위하여 index date기점 전 2년 동안 메트포민 복용 환자들의 메트포민 총 복용량을 구하여 메트포민 복용량 상, 중, 하로 나눠 추가 분석을 진행하였다.

연구 결과: 2009년 신규 전립선비대증으로 정의 된 211,648명 환자 중 13,926명의 환자는 2형 당뇨를 동반하였으며 197,722명의 환자는 2형 당뇨를 동반하지 않았다. 2형 당뇨를 동반한 군에서 메트포민을 복용한 군은 11,059명이었으며 메트포민을 복용하지 않은 군은 2,867명이었다. 2형 당뇨를 동반

한 환자군의 평균 나이가 상대적으로 많았으며(P<0.0001) 고혈압 동반 비율이 더 높았다(P<0.0001). 대상 환자들은 2017년 6월 30일까지 추적 관찰 되었으며 follow-up 기간 동안 총 7,672명의 환자가 전립선절제술을 받았다. 전립선절제술을 받은 환자의 평균 나이는 전립선절제술을 받지 않은 환자에 비해 고령이었다(P<0.0001). 10,000명의 전립선 비대증 환자 당 연간 전립선절제술 발생율은 52.899 (CI: 38.725 to 83.438) 이었으며 당뇨를 동반하지 않은 환자에게 있어서는 53.061 (CI: 33.919 to 85.724)을 보였다. 당뇨를 동반한 환자 중 메트포민을 복용한 군은 48.606(CI: 33.919 to 85.724)을 보이며 메트포민을 복용하지 않은 군의 발생율인 57.497(CI: 39.874 to 103.035)에 비하여 낮은 발생율을 보였다. 콕스 비례 위험 모형에서 2형 당뇨 동반한 메트포민 복용군은 전립선절제술에 대해 위험비가 0.86(P-value=0.007)로 추정되었으며 연령을 기준으로 층화 분석을 실시한 결과 2형 당뇨를 동반한 환자 중 메트포민을 복용한 65세 미만의 환자들의 경우에는 당뇨를 동반하지 않은 전립선비대증 환자에 비해 전립선 절제술을 받을 위험이 낮게 나타났다. (위험비 0.76, P-value=0.006) 메트포민 복용량이 반영 된 추가 분석 결과, 메트포민 복용량 高군에서 전립선 절제술에 대한 유의미하게 낮은 HR이 나타났다(위험비 0.76 P-value=0.005).

결론: 본 연구에서는 2형 당뇨가 전립선비대증의 악화에 미치는 영향과 더불어 2형 당뇨 환자들이 복용하는 메트포민의 영향에 대해 분석하였으며, 2형 당뇨 환자의 경우 전립선 절제술로 정의 된 전립선 비대증 악화에 2형 당뇨를 동반하지 않은 군에 비해 위험도가 낮은 것으로 보였다. 수술에 동반 되는 부작용에 대해 더 취약한 2형 당뇨를 동반한 군이 수술적 치료를 지양하는 성향이 반영 되었을 수 있으며, metformin을 복용 중인 환자로 구성 된 그룹의 경우 50-60대에서 당뇨 비동반 군보다 낮은 위험비를 보이면서 2형 당뇨 자체는 전립선 비대증의 위험 요인이나 2형 당뇨의 1차 약제인 Metformin이 가지는 예방적인 효과에 대한 근거로 해석 할 수 있다. 따라서 본 연구를 통해 전립선 비대증의 위험 요인에 대한 2형 당뇨에 대한 전립선 비대증과의 연관성과 더불어 2형 당뇨 치료 약제인 메트포민의 전립선비대증에 대한 예방적 효과에 대한 추가적인 연구의 필요성을 촉구한다.

주요어: 전립선비대증, 2형 당뇨, 메트포민, 콕스 비례 위험 회귀 모형, 전립선절제술

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