博士論文（要約）

Study on the incidence of interventions for diabetic retinopathy and serious lower-limb complications and its related factors in patients with diabetes using real-world large claims database
（大規模レセプトデータを用いた糖尿病患者における網膜症治療と下肢切断の発生率とその関連因子に関する研究）

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論文の内容の要旨

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1.　INTRODUCTION

Currently, the number of patients with diabetes is increasing rapidly worldwide, which is a major public health concern. Blindness owing to diabetic retinopathy and amputation owing to diabetic limb complications such as severe diabetic ulcers and/or gangrene are serious complications that cause profound changes in the quality of life of affected individuals. The major trends in the prevalence, incidence, and risk factors of the progression of diabetic retinopathy and lower-limb complications have been reported from various viewpoints. However, in practice, patients with diabetes present at various stages. These include the early stage, when diabetic retinopathy is detected at screening; the clinical stage, when symptoms of hyperglycemia appear; the referral stage, when the patient is referred to endocrinologist; and the advanced stage, when complications appear. Accordingly, most physicians start treatment for diabetic complications at various stages. For them, the real-world incidence of diabetic retinopathy or lower-limb complications requiring immediate interventions would be the most useful. However, few studies have examined the frequency of using the interventions for diabetic retinopathy or diabetic foot complications using the real-world data during long treatment periods. The greatest strength of a medical claims database is the ability to track the same patient even when he or she visits different clinics or hospitals.

In this study, 1: To estimate the IR of interventions for diabetic retinopathy and serious lower-limb complications, such as laser photocoagulation (LPC), vitrectomy (VR), and lower-limb amputation (LLA), in patients who were newly prescribed diabetic drugs and those who had been using them continuously by used a large medical claims database, 2: To investigate whether the basic attributes of the patients, such as age and gender, affected the incidence of diabetic complications that require treatment, 3: To illustrate the temporal changes of cumulative incidence of each intervention whether the incidences of interventions for complications had decreased in recent years as clinical care and treatment environments had improved.

2. MATERIALS AND METHODS

2.1 Research Design and Setting

This is a retrospective longitudinal study using health insurance claims data in Japan. We obtained health insurance claims data from JMDC Inc. JMDC Inc. has managed large claims databases and acquired data from some of the society-managed health insurance systems which are composed of large private companies' employees and their family members. The anonymous but individually traceable database includes patients' demographic characteristics, date of the medical service, diagnosis, procedures, prescription, and other health care services. JMDC Inc. codes the diagnosis on each claim according to the International Classification of Disease Version10 (ICD-10) 2003 version and the standard disease codes issued by the Japanese government's medical insurance calculation code sets. The number of beneficiaries included in the database of JMDC Inc. is 5,644,009 beneficiaries in 2018. We observed nine fiscal years from April 2009 to March 2018.

2.2 Patients

Among beneficiaries aged 20 to 74 years in the JMDC Inc. claims database from April 2009 to March 2018 in the observation period, we included patients who were taking at least one antidiabetic medication [injections (insulin or GLP-1 analog) or oral antihyperglycemic agents (A10 in the ATC classification system managed by the European Pharmaceutical Market Research Association)]. To clarify the difference in the incidence of complications between the newly treated patients with diabetes and those who have been previously treated for diabetes, we classified all the patients on antidiabetic medications into the following two groups: (1) those who were on antidiabetic medications after at least 6 months from the first date of his/her enrollment in the database (This six months are often referred to as the "washout period), defined as "patients with newly initiated antidiabetic medications" or Group 1, and (2) those who have been on antidiabetic medications within 6 months from the first date of his/her enrollment in the database, defined as "patients with continuing antidiabetic medication" or Group 2.

2.3 Outcome variables

Regarding the outcomes of the present study, we set LPC and VR for the intervention of diabetic retinopathy, and LLA for the intervention of serious diabetic limb complications. In the claims database, we detected the first appearance of a procedure code of LPC, VR and LLA.

2.4 Independent variables

The information on gender and birth month was obtained from the beneficiary's register; age was calculated as of the month of the first prescription of antidiabetic agents. We divided the patients into four groups based on their age: 20–39, 40–49, 50–59, and 60–74 years. We also divided the patients into those who were insured and those who were dependents of the insured breadwinner of a family. As for the type of prescription, we categorized the patients into two groups: those who received injections (at least one prescription of insulin and/or GLP-1 analogs) and those used only oral hypoglycemic agents. As for the type of DM, we classified the patients into type 1 DM and other types of DM (mostly type 2 DM). In addition, we used the Charlson comorbidity index (CCI) to understand complications as variables.

2.5 Statistical analysis

First, the patient characteristics at the time of the first prescription of antidiabetic medication were analyzed. We then described the cumulative incidences of intervention for diabetic complications using the Kaplan–Meier method according to the specific subject characteristics. The first month in which they enrolled in the insurance or when claims data collection by the JMDC Inc. started was set as start point of observation. The first prescription for antidiabetic agents after start point of observation was defined as time point zero. The time to the first event was defined as the interval between time point zero and the month in which the first of each intervention was performed. Patients' follow-up was censored at the final month of our observation (March 2018) or the final month of his/her enrollment in the database for the patients who did not experience these interventions. The cumulative incidences and unadjusted overall time to the development of these interventions in the groups were delineated by Kaplan–Meier analysis and examined by log-rank tests. Cox's regression model identified the association of covariate for each intervention modality. A generalized linear model with a log lank distribution was used to model the incidence of each intervention according to the patients' characteristics (age group, gender, drug category, insurance status, types of DM, and CCI). In addition, to investigate the temporal changes of interventions, we divided those patients of Group 1 and Group 2 into two periods. Period 1 observed the interventions that happened during former 5 years (April 2009–March 2014) for those with first prescription from April 2009 to March 2013, and Period 2 observed the interventions that happened during latter 5 years (April 2013–March 2018) for those with first prescription from April 2013 to March 2017. The cumulative incidences for each intervention were compared between the two periods.

3. RESULTS

3.1 Baseline characteristics and IR of each intervention

Table 1 shows the characteristics of those in Group 1 consisting of 42,788 patients, among whom approximately 70% were men and 7% had received insulin and/or GLP-1 analogs since the initial prescription. Table 2 shows the characteristics of those in Group 2 consisting of 85,337 patients; the proportion of gender were about the same as that in Group 1, though the proportion of users of insulin and/or GLP-1 analog were over 15%. In Group 1, the IR of first LPC, VR, and LLA were 7.12 (95% CI: 6.61–7.67), 2.57 (2.26–2.91), and 0.24 (0.16–0.36) per 1000 person-years, respectively (Table 1). In the intervention for ocular complications, the IR of women tended to be higher than that of men and the IR of all interventions of insulin and/or GLP-1user were higher than for the users of oral antidiabetic agents. Furthermore, the IR of all the interventions was higher for the dependents than the insured individuals. In Group 2, the IR of the first LPC, VR, and LLA were 9.14 (8.73–9.56), 3.34 (3.10–3.60), and 0.33 (0.26–

0.42) per 1000 person-years, respectively (Table 2). In the intervention for ocular complications, the IR of women tended to be higher than that of men. The IR of those with an older age, Type 1 diabetes, insulin and/or GLP-1 users and high CCI score tended to be high in all interventions. In addition, similar to the result in Group 1, the IR for all the interventions was higher for the dependents than for the insured individuals.

3.2 Hazard ratios for each intervention

Cox's regression analysis of the incidence of each intervention among Group 1 and Group 2 are shown in Table 3 and Table 4, respectively. In Group 1, older age was associated with an increased hazard ratio of the interventions for retinopathy after adjustment by Cox's regression hazard models. The users of insulin and/or GLP-1 analog were associated with increased risk of all the interventions. Gender differences of hazard ratio were found in LPC and LLA. In addition, the hazard ratios of dependents tended to be higher than that of insured individuals in all the interventions. In Group 2, a similar trend was observed. Being older was mostly associated with an increased hazard ratio of interventions. The hazard ratio of insulin and/or GLP-1 users tended to be high for all the interventions. The hazard ratios of dependents were also larger than that of insured individuals for all of the interventions. Higher CCI scores tended to be associated with larger hazard ratios in all the interventions.

3.3 Comparison of the time series of cumulative incidence for each intervention

Figure 2-7 shows comparison of the cumulative incidence for each intervention between Period 1 and Period 2 in Group 1 and Group 2. This was calculated using Kaplan–Meier method. In Group 1, the incidence of LPC and VR for Period 1 and Period 2 did not differ over time ($p = 0.90$, $p = 0.83$, respectively), the incidence of LLA was approximately halved ($p = 0.01$). In Group 2, the incidence of all the interventions for Period 1 and Period 2 did not differ over time.

4. Discussion and Conclusions

Based on the real-world claims data, we showed that the IR of LPC, VR, and LLA for patients with newly initiated antidiabetic medications were 7.12, 2.57, and 0.24 per 1000 person-years, respectively. Those for patients with continuing antidiabetic medication were about 1.3 times higher than the above group. Insulin and/or GLP-1 users were associated with a higher IR for these interventions. The hazard ratio of all the interventions tended to be higher for dependents than for the insured person himself or herself in both groups. While there was a limited change in the cumulative IR of the intervention for retinopathy, the incidence of LLA declined by half. The results of present study that investigated the IR of each intervention for severe diabetic retinopathy and diabetic serious lower-limb complications using large-scale real-world claims data are important and useful information for clinicians when considering the timing of referrals to ophthalmologists, dermatologists, and orthopedists in a clinical situation.