

Systemic and local diseases associated with the development of diabetic macular edema among Japanese patients with diabetes mellitus

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Abstract

Background

Diabetic macular edema (DME) causes severe vision loss among patients with diabetes mellitus (DM). We aimed to investigate systemic and local diseases associated with the development of DME among a Japanese population.

Methods

A total of 3.11 million Japanese subjects who were registered in the database of the Japan Medical Data Center from 2005 to 2014 were analyzed. Subjects with DM were defined as individuals who had been prescribed any therapeutic medications for DM, and associated diseases were analyzed. The periods analyzed were one year before the development of DME among patients with DME and one year before the last visit to an ophthalmic clinic among patients without DME.

Results

A total of 17,403 patients with DM satisfied the inclusion and exclusion criteria, and 420 patients developed DME. Univariate analysis revealed significant associations between 55 diseases, including 39 systemic and 16 local diseases, and DME development. The logistic analysis identified 21 systemic diseases and 10 local diseases as significant factors associated with DME development. Various types of systemic and local diseases were associated with DME development.

Conclusion

Subjects with DM who present these risk factors must be carefully monitored to prevent visual impairment.

Background

The prevalence of diabetes mellitus (DM) continues to increase worldwide, and diabetic retinopathy (DR) remains a leading cause of vision loss in many countries. [1, 2] The reported prevalence of DR among patients with DM varies widely, from 1–40%. [3–9] According to Yau et al., approximately 93 million people suffer from DR, 17 million are diagnosed with proliferative DR (PDR), and 21 million are diagnosed with diabetic macular edema (DME) worldwide. [10]

PDR is the most common vision-threatening retinopathy, but DME is responsible for most of the vision loss experienced by patients with DM, and it remains the major cause of vision loss among patients with DM with or without PDR. Although many previous population-based or hospital-based studies

have focused on the prevalence of DME, few large-scale studies have focused on the incidence of DME. The annual incidence rates of DME among previous studies have shown varied widely from 0.01 to 6.0%. [11–15]

Previous epidemiological studies have also identified several risk factors associated with DR, including many systemic and lifestyle factors, nephropathy, obesity, alcohol consumption, hematological markers of anemia, hypothyroidism, inflammation, endothelial dysfunction, hyperglycemia, hypertension, dyslipidemia, diabetes duration, ethnic origin, pregnancy, and puberty. [10, 16–21]

There were some risk factors associated with DME development, including duration of diabetes, hemoglobin A1c, blood pressure, nephropathy, higher cholesterol, retinal and vitreous inflammation, and oxidative stress in the retina [22], but inconsistencies exist among reports; [23] additionally, the precise roles of these factors in the pathogenesis of DME are not well defined. In addition, risk factors for DME may differ from those for DR. Some epidemiological studies have examined the prevalence, incidence, and risk factors for DM and DR, including studies employing the Japan Diabetes Clinical Data Management Study Group (JDDM). Unfortunately, an insufficient number of studies have focused on DME in Japan. Currently, the main therapeutic procedures for DME are laser photocoagulation, vitrectomy, and anti-vascular endothelial growth factor (VEGF) injections, but these approaches are not always effective. In addition to the three approaches mentioned above, targeted therapies potentially ameliorate some of the identified risk factors. Here, we investigated systemic and local factors associated with DME development in a large-scale study based on the health insurance claim database in Japan.

Methods

This study was performed in accordance with the Declaration of Helsinki and was approved by the Institutional Ethics Review Board (IRB) of the University of Yamanashi. The IRB approved this study without requiring written informed consent from any patients because no data used in this study contained any personal information.

Database

We used the health insurance claim database from the Japan Medical Data Center (JMDC), which

contains medical data for patients using Employee Health Insurance, one of two major public insurance providers covering employees and their dependents. The JMDC was established in 2002 and is the largest medical database in Japan. The details of this database have been described elsewhere. [24–26] Briefly, the database records all individual medical claims from different hospitals, clinics, and pharmacies via a computer-aided post-entry standardization method and an anonymous linkage system for patients using the same insurance provider. This database enables the aggregation of all claims for the same patient without duplicating medical claims.

The database includes data on age, sex, International Classification of Diseases 10th revision (ICD-10) diagnosis codes, the ICD-10 corresponding standard disease name master codes (referred as ICD-10 standard disease code), prescribed drugs, medical examinations, treatment, and the medical institution size, if medical records are available.

Inclusion and exclusion criteria

Subjects who were registered in the JMDC database between 2005 and 2014 and for whom medical records were available for more than one year were included. All registered data in the database were subject to the analysis. Subjects listed with any of the ICD-10 categories from E11 to E14 were extracted as candidates with DM. Among these subjects, subjects with a history of being prescribed any anti-DM drug, either an oral or injectable drug, were subject to the analysis. Subjects who terminated the Employee Health Insurance and for whom their subsequent insurance provider was unable to be identified and/or subjects for whom any of the aforementioned DM-related ICD-10 information was not confirmed in the final record during the investigated period were excluded. We eliminated the patients without DM who were diagnosed with central retinopathy, macular edema, maculopathy, or cystoid macular edema, because some of these subjects may have suffered from undiagnosed DM.

Definition of DME

Among subjects with DM, individuals with any of the following ICD10 sub-classification disease names (ICD10 disease code) were categorized as subjects with DME: diabetic maculopathy (E143), type 1 diabetic macula edema (E103), diabetic macula edema (E143), and type 2 diabetic maculopathy

(E113).

Comparison of DME-associated risk factors

We investigated risk factors associated with DME development by comparing the following two groups: a group of patients with DME and at least a one-year claim record before the development of DME and a group of patients without a DME diagnosis throughout the investigated period. Because we were unable to collect data regarding medical examination results for risk factors proposed in previous studies, including laboratory data, biological information, and genetic data, we focused on ICD-10 standard disease codes to identify risk factors associated with DME.

The current study compared ICD-10 standard disease codes for one year before DME development in a group of patients with DME and those for the most recent year in a group of patients without DME.

Statistical analysis

For the statistical analysis, the chi-square and Mann-Whitney U tests were used to compare demographics between the DME and DME-free groups.

According to suggestions from two experts in the field of medical statistics, Dr. Hiroshi Yokomichi and Dr. Tatsuhiko Saigo, we applied the criteria listed below to limit the ICD-10 codes for a proper analysis of the ICD-10 codes associated with the development of DME, because the total number of ICD-10 codes was 6,345, which may hinder the accurate analysis of factors associated with DME development.

As the first step, ICD-10 codes satisfying the following two conditions were eliminated: the total number of patients with the code was less than 0.1% of all enrolled subjects and fewer than five subjects were diagnosed with each ICD-10 standard disease code. The chi-square test was performed to identify associated disease codes, and codes with a P value of less than 0.05 were selected as significantly associated risk factors for DME using a univariate analysis. Codes categorized as significant risk factors in the univariate analysis were subjected to a multivariate logistic regression analysis and codes with a P value less than 0.05 were considered significantly associated risk factors.

Results

The total number of subjects registered in the database from 2005 to 2014 was 3,110,867. Of these subjects, the total number of patients with DM was 66,923, with a mean age of 53.4 ± 11.0 years.

Overall, 21,463 subjects had a DM-related local manifestation. After eliminating subjects who did not satisfy the inclusion criteria, 17,403 subjects with a mean age of 55.7 ± 10.8 years were included in the analysis. Four hundred twenty subjects were diagnosed with DME, with a mean age of 55.2 ± 10.0 years, and the demographics of the enrolled subjects are depicted in Table 1. DR was significantly more prevalent in males than females, but the incidence of DME development was not significantly different between males and females. Frequencies at which patients with and without DME visited medical institutions for diabetes treatment were 3.2 times/year and 2.9 times/1 year, respectively, which was not a significant difference. The two groups also showed same frequency of ophthalmological examinations (4.3 times/year). Among the total of 6,345 of ICD-10 standard disease codes, 86 codes were selected for investigating the ICD-10 codes associated with the development of DME.

Table 1 Demographics of enrolled subjects

	Number	mean age \pm SD (yrs.)	rate of male (%)
All entry subjects	17,403	55.7 ± 10.4	65.0
Subjects with DME	420	55.7 ± 10.8	62.6
Subjects without DME	16,983	56.2 ± 10.1	65.0

(SD; standard deviation, DME; diabetic macular edema)

Systemic factors associated with DME development: multivariate analysis

Systemic risk factors associated with DME development are shown in Table 2. Femoral head fractures showed the highest odds ratio (OROR, 7.04), followed by hyperlipidemia (OR 6.67), and impending

abortion (OR 6.14). In contrast, four factors, chronic eczema (OR 0.12), ureterolithiasis (OR 0.13), hay fever (OR 0.13) and osteoarthritis of the knee (OR 0.55), were identified as factors that negatively associated with DME development (Table 3).

Local factors associated with DME development: multivariate analysis

Ten local risk factors associated with DME development were revealed (Table 4). Retinal vessel occlusion showed the highest risk (OR 8.28), followed by eye movement disorder (OR 5.99).

Intraocular lens insertion and posterior vitreous detachment were identified as significant factors in the univariate analysis but not in the multivariate analysis. No ICD-10 codes were identified as local factors suppressing DME development.

Results of the univariate analysis for systemic and local factors associated with DME are summarized in Additional Tables 1 to 4.

Table 2 Systemic risk factors associated DME development: multivariate analysis

ICD10 standard disease name	Odd ratio	lower 95% CI
Femoral neck fracture	7.04	1.94
Hyperlipidemia	6.67	2.26
Impending abortion	6.14	2.35
Ménière syndrome	5.20	1.44
Cervical contusion	4.93	1.64
Chest contusion	4.75	1.77
Dysmenorrhea	4.72	1.62
Arthritis	4.68	1.58
Shoulder arthritis	3.84	1.54
Diabetic ketoacidosis	3.28	1.62
Vessel lumen mass	2.99	1.02
Postoperative of Percutaneous Coronary angioplasty	2.96	1.01
Lower leg skin ulcer	2.83	1.09
Arrhythmia	2.82	1.20
Diabetic nephropathy	2.52	1.56
Proteinuria	1.90	1.05

Table 3 Systemic suppressive factor of DME development: multivariate analysis

ICD10 standard disease name	Odd ratio	lower 95% CI	upper 95% C
Knee osteoarthritis	0.55	0.34	0.89
Ureter lithiasis	0.13	0.02	0.96
Hay fever	0.13	0.02	0.96
Chronic eczema	0.12	0.02	0.89

(ICD10; International Classification of Diseases 10th revision, DME; diabetic macular edema, CI; confidential interval)

Table 4 Local risk factors of DME development: multivariate analysis

ICD10 standard disease name	Odd ratio	lower 95% CI	upper 95% CI
Retinal vessel occlusion	8.28	2.62	26.16
Ocular movement disorder	5.99	2.01	17.82
Accommodative paralysis	4.95	1.50	16.33
Scleritis	4.63	1.27	16.88
Corneal disease	4.01	1.08	14.94
Ocular pain	3.21	1.08	9.61
Retinal hemorrhage	2.85	1.48	5.47
Vitreous hemorrhage	2.06	1.41	3.01
Myopic astigmatism	1.56	1.25	1.96
Conjunctivitis	1.35	1.05	1.73

(ICD10; International Classification of Diseases 10th revision, DME; diabetic macular edema, CI; confidential interval)

Discussion

Although the global incidence of DM is increasing, the global incidence of DR has been reported to be decreasing. [27] This finding might be explained by improvements in the control of systemic risk factors in patients with DM. DM-related severe local complications are one of the main causes of blindness worldwide. According to a recent study, DME is causing an increasing number of visual impairments in patients with DM. [22] DME, which does not result in total blindness, but in severe vision loss, may instead be the main DM-associated severe local complication. Second, advances in

optical coherence tomography technology have enabled the identification of DME much more precisely and less invasively than before. Some previous studies have investigated factors associated with DME. However, many of these studies employed a cross-sectional design. [22, 23, 28–32] Although several studies have investigated factors associated with DME development, [14, 33–37] these studies did not report associations between concomitant and systemic diseases with DME. In the present study, we investigated factors associated with DME development among more than 6,000 ICD-10 standard disease codes using a large claim dataset in Japan. Many of the systemic factors significantly associated with the development of DME were considered related to the presence of a severe metabolic impairment, including hyperlipidemia, diabetic ketoacidosis, vessel lumen mass, postoperative of percutaneous coronary angioplasty, lower leg skin ulcer, arrhythmia, diabetic nephropathy, and proteinuria. DM has been identified as an important risk factor for osteoporosis-associated fracture. [38, 39] Among female subjects with type 1 DM, diabetic ketoacidosis in pregnancy can result in an impending abortion. Since DM sometimes results in peripheral vestibular damage and predicts a poor prognosis of typical vestibular pathologies, some patients suffer from benign paroxysmal positional vertigo that is one symptom of Ménière syndrome. Poor visual function due to DME may contribute to increase the risk of falls, resulting cervical and chest contusions. Female patients with DM are more likely to report very irregular menstrual cycles. [40] Although the present study identified arthritis as a risk factor for developing DME, Tentolouris et al. reported a negative correlation between arthritis and DM. [41] However, the impact of DM on the incidence of rheumatoid arthritis is not well established.

The present study also revealed some systemic factors that negatively associated with the development of DME. Some previous studies reported a significantly higher prevalence of primary osteoarthritis among subjects with DM than among subjects without DM, as well as significant associations with glycemic control and the duration of diabetes. Obesity may be associated with the onset of osteoarthritis [42–44]. We are unsure why the present study showed a negative impact of orthoarthritis on DME. According to Taylor et al., diabetes may increase the risk of kidney stone formation by altering the composition of the urine, and insulin resistance may play a role in stone

formation. [45]

Several systemic diseases and local diseases that have not been reported to be related to DME development were identified. Interestingly, some factors were identified as negative factors. An explanation for the finding that hay fever and chronic eczema were selected as factors associated with a significant negatively associated factor of DME development may be an impairment in the auto-immune function, as DM deteriorates the auto-immune function and a significantly lower prevalence of allergic rhinitis was observed in subjects with metabolic syndrome, high blood pressure, or impaired fasting glucose levels. [46]

Many previous studies have focused on the effects of DM on pathological conditions and disorders. Few studies have investigated factors associated with the development of DME in a large sample. We were unable to precisely investigate the status of glycemic control and severity of DM complications in the present study. Further studies are necessary to clarify these points.

Although some significantly associated systemic factors identified in the current study are consistent with previous reports, some of the identified factors have never been reported to be associated with the development of DME. In addition to diseases that have been reported to serve as risk factors to date, such as renal and circulatory disorders, orthopedic and dermatological diseases were identified to be associated with the development of DME. These diseases may have been identified because the current study included more than 6,000 diseases in the analysis. Furthermore, some factors were found to be negatively associated with DME. Currently, information about the mechanisms of these factors in DME development is limited, and these data must be confirmed in further investigations. Previous papers have reported some local factors associated with DME development, including DR severity, [33, 34, 47] cataract surgery, [35] and ocular inflammation, [37] consistent with the current results. The current study discovered some new local factors associated with DME development, some of which are related to systemic and local DM complications. Retinal vessel occlusion showed the highest OR and was selected as a disease often observed in subjects with retinal circulation disorders and severe diabetic retinopathy. Additionally, eye movement disorder and accommodation paralysis are strongly associated with DME development.

This study also has several limitations. Because the subjects were limited to social insurance subscribers and subscribers to the national health insurance, another major insurance provider in Japan, were not considered, the target sample may be biased. National health insurance is managed by each municipality, increasing the difficulty of integrating and collecting data; thus, while these data were not included in this study. Since subjects in JMDC were employees and their dependents, it is possible that a significant number of senior citizens whose prevalence of DM could be higher than that in JMDC were not included in the database. National health insurance members must also be considered in the future. The use of the diagnosis codes of claims data as diagnostic criteria has several problems. First, the accuracy of the diagnosis is not necessarily high. An investigation of whether some reported risk factors were associated with DME development was impossible because the current database does not contain information about some factors, including the hemoglobin A1c level [14] and the severity of DR. [33, 34, 47] Genetic factors have also been reported to contribute DME development, such as genes related to VEGF and erythropoietin. [48-52] Unfortunately, claims data do not contain genetic information. In this study, we worked with epidemiological statisticians to accurately detect risk factors associated with DME development from many disease categories, but it was difficult to completely exclude the influence of confounding factors. We excluded some diseases due to a small number of patients, which may have factors that could not detect an association. Inconsistencies between previous reports and the current study may also be partially due to differences in the statistical methods applied. Previous studies have reported that there are differences between DR- and DME-associated factors. In this study, we focused on the factors associated with the development of DME. It will be necessary to examine the factors associated with to the development of DMR and DME using the same database in the future.

In this study, we clarified systemic and local diseases associated with DME development in Japan. Notably, many patients with DM do not undergo periodic eye examinations. Based on these results, factors associated with DME development should be closely monitored. Because DR is sometimes asymptomatic during the period in which laser photocoagulation should be applied, asymptomatic persons should be screened to minimize the risk of vision loss. As the number of DME patients is

expected to increase, further studies on the early detection and prevention of DME development are needed.

Conclusions

In this study, we clarified systemic and local diseases associated with DME development in Japan. Notably, many patients with DM do not undergo periodic eye examinations. Based on these results, factors associated with DME development should be closely monitored. Because DR is sometimes asymptomatic during the period in which laser photocoagulation should be applied, asymptomatic persons should be screened to minimize the risk of vision loss. As the number of DME patients is expected to increase, further studies on the early detection and prevention of DME development are needed.

Abbreviations

DM, diabetic mellitus; DME; diabetic macular edema, DR; diabetic retinopathy, PDR; proliferative diabetic retinopathy, CI, confidence interval; ICD-10, International Classification of Diseases 10th revision; JMDC, Japan Medical Data Center; OR, odds ratio; VEGF, vascular endothelial growth factor.

Declarations

- **Ethics approval and consent to participate**

This study was performed in accordance with the Declaration of Helsinki and was approved by the University of Yamanashi Ethical Review Board. Because the data used in this study do not contain any personal information, the Ethical Review Board agreed to allow this study to proceed without requiring written informed consent from all patients.

- **Consent for publication**

All authors agree with consent for publication.

- **Competing interests**

None of the authors have conflicts of interest with the information presented in this study.

- **Funding**

This study did not receive any funds.

- **Authors' contributions**

KK contributes designing and analyzing this study, and writing this paper. AK contributes collecting

and analyzing data.□All authors have read and approved the manuscript.

- **Availability of data and materials**

The data that support the findings of this study are available from the JMDC but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are however available from the authors upon reasonable request and with permission of the JMDC.

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Additional Table Legends

A detailed description of the factors associated with DME development and suppression is provided in Additional Tables 1, 2, 3 and 4, respectively.

Additional Table 1 Systemic risk factors associated with DME development: univariate analysis

(ICD10; International Classification of Diseases 10th revision, DME; diabetic macular edema, CI; confidence interval)

Additional Table 2 Systemic factors that suppressed DME development: univariate analysis

(ICD10; International Classification of Diseases 10th revision, DME; diabetic macular edema, CI; confidence interval)

Additional Table 3 Local risk factors associated with DME development: univariate analysis

(ICD10; International Classification of Diseases 10th revision, DME; diabetic macular edema, CI; confidence interval)

Additional Table 4 Local factors that suppressed DME development: univariate analysis

(ICD10; International Classification of Diseases 10th revision, DME; diabetic macular edema, CI; confidence interval)

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