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順天堂醫事雜誌

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(942nd issue)

JUNTENDO MEDICAL JOURNAL

順天堂醫事雜誌

The History of *Juntendo Medical Journal*

This *Juntendo Medical Journal* has been published under the Japanese name *Juntendo Igaku* (順天堂医学) from 1964 to 2012. However, the origin of *Juntendo Medical Journal* dates back to the oldest medical journal in Japan, *Juntendo Iji Zasshi* (順天堂醫事雜誌), which had been published between 1875 and 1877 (total of 8 issues). Between 1885 and 1886, Juntendo issued a limited release of a research journal titled *Houkoku* [*Juntendo Iji Kenkyukai*] (報告) for a total of 39 issues.

In 1887, *Juntendo Iji Kenkyukai Houkoku* (順天堂醫事研究會報告) was published with the government's approval and we used to regard this as the first issue of *Juntendo Medical Journal*. Since then, *Juntendo Medical Journal* has undergone a series of name changes: *Juntendo Iji Kenkyukai Zasshi* (順天堂醫事研究会雜誌), *Juntendo Igaku Zasshi* (順天堂医学雑誌), and *Juntendo Igaku* (順天堂医学).

Now in commemoration of the 175th anniversary of Juntendo University, starting with the first volume issued in 2013 (Volume 59 Number 1), we return to *Juntendo Medical Journal*'s original Japanese title in 1875-*Juntendo Iji Zasshi* (順天堂醫事雜誌). We also reconsidered the numbering of the journal and set the first issue in 1875 as the initial publication of *Juntendo Medical Journal*. The Volume-Number counting system and the English name *Juntendo Medical Journal* started in 1955 from the January 10 issue. Although this is not our intension, we will retain the Volume-Number counting system to avoid confusion. However, Volume 59 Number 1 will be the 882nd issue, reflecting the sum of all issues to date: 8 issues of *Juntendo Iji Zasshi* (順天堂醫事雜誌), 39 issues of *Houkoku* [*Juntendo Iji Kenkyukai*] (報告) (47 issues combined), and 834 issues from *Juntendo Iji Kenkyukai Houkoku* (順天堂醫事研究會報告) in 1887 to the present.

出典：小川秀興（OGAWA Hideoki, M.D., Ph.D.）：順天堂醫事雜誌（Juntendo Medical Journal）2013；59：6-10.

本誌は昭和39年（1964年）から平成24年（2012年）末まで『順天堂医学』として刊行されてきた．しかし，その起源は明治8年（1875年）から10年（1877年）にかけて発刊された日本最古の医学誌『順天堂醫事雜誌』（計8巻）にある．さらに明治18年（1885年）から19年（1886年）まで，会員限定配本として順天堂醫事研究會の雑誌『報告』（計39集）が発行されている．

その後『順天堂醫事研究會報告』が明治20年（1887年）に官許を受けて公刊されたので，順天堂ではこれを通刊1号としてきた．以来，『順天堂醫事研究会雑誌』，『順天堂医学雑誌』，『順天堂医学』と名称を変更して刊行されてきた．

今般，順天堂が創立175周年を迎える平成25年（2013年）の59巻1号を期して，本来の名称である『順天堂醫事雜誌』と復刻し，その起源である明治8年（1875年）第1巻をもって創刊号（通刊第1号）とすることとした．従来の巻号と欧文誌名は，昭和30年（1955年）1月10日発行のものを1巻1号としており，欧文誌名もこれより付け始めたもので不本意であるが，混乱を避けるためにこれらを継承する．ただし，通刊数は明治8年（1875年）から19年（1886年）にかけて刊行された『順天堂醫事雜誌』8巻分と順天堂醫事研究會の雑誌『報告』39集，計47巻分を通巻834号に加え，59巻1号を通刊882号とした．

出典：小川鼎三，酒井シヅ：順天堂医学　1980；26：414-418.
小川秀興：順天堂醫事雜誌　2013；59：6-10.

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The Juntendo Medical Society

From the illustrator: When taking a walk as usual, I feel sad because we can hardly see flowers blooming in the winter season. During that time, I found a tree with a lot of red fruit which made me glad. Then I drew a picture of glabrous sarcandra herb (Sarcandra glabra), a traditional Japanese New Year's plant used for flower arrangement, with best wishes for a happy new year.

Reviews

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P4 Medicine for Heterogeneity of Dry Eye: A Mobile Health-based Digital Cohort Study

TAKENORI INOMATA[1, 2, 3, 4], JAEMYOUNG SUNG[1], ALAN YEE[1, 2], AKIRA MURAKAMI[1, 2], YUICHI OKUMURA[1, 2], KEN NAGINO[1, 2, 3], KENTA FUJIO[1, 2], YASUTSUGU AKASAKI[1, 2], AKIE MIDORIKAWA-INOMATA[3], ATSUKO EGUCHI[3], KEIICHI FUJIMOTO[1, 2], TIANXIANG HUANG[1, 2], YUKI MOROOKA[1, 2], MARIA MIURA[1, 2], HURRAMHON SHOKIROVA[1], KUNIHIKO HIROSAWA[1, 2], MIZU OHNO[1, 2], HIROYUKI KOBAYASHI[3]

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During the 5th Science, Technology, and Innovation Basic Plan, the Japanese government proposed a novel societal concept -Society 5.0- that promoted a healthcare system characterized by its capability to provide unintrusive, predictive, longitudinal care through the integration of cyber and physical space. The role of Society 5.0 in managing our quality of vision will become more important in the modern digitalized and aging society, both of which are known risk factors for developing dry eye. Dry eye is the most common ocular surface disease encountered in Japan with symptoms including increased dryness, eye discomfort, and decreased visual acuity. Owing to its complexity, implementation of P4 (predictive, preventive, personalized, participatory) medicine in managing dry eye requires a comprehensive understanding of its pathology, as well as a strategy to visualize and stratify its risk factors.

Using DryEyeRhythm®, a mobile health (mHealth) smartphone software (app), we established a route to collect holistic medical big data on dry eye, such as the subjective symptoms and lifestyle data for each individual. The studies to date aided in determining the risk factors for severe dry eye, the association between major depressive disorder and dry eye exacerbation, eye drop treatment adherence, app-based stratification algorithms based on symptomology, blink detection biosensoring as a dry eye-related digital phenotype, and effectiveness of app-based dry eye diagnosis support compared to traditional methods. These results contribute to elucidating disease pathophysiology and promoting preventive and effective measures to counteract dry eye through mHealth.

Key words: dry eye, big data, mobile health, smartphone application, P4 medicine

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Introduction

Healthcare in the Society 5.0 era: P4 Medicine

Society 5.0 is a novel, human-oriented societal vision proposed during the 5th Science, Technology, and Innovation Basic Plan aimed to promote economic development and resolve various social problems through a highly integrated cyber and physical space[1]. As part of this vision, healthcare is also presumed to go through a major overhaul with an emphasis placed on providing patient- and public-oriented, predictive, and longitudinal care that can be performed in an unintrusive manner within one's daily life. Medicine envisioned in Society 5.0 utilizes a modern concept of medical big data through mobile health (mHealth) and various mobile device-attached sensors, collecting data on patient-based symptomology, biosensor inputs, and multi-omics in a frequent, longitudinal, remote, real-time, and bidirectional fashion. Such new forms of medical big data can subsequently be integrated to the traditional medical big data, such as electronic medical health records and epidemiologic reports, to be analyzed by artificial intelligence (AI) and generate newfound values of P4 (predictive, preventive, personalized, participatory) medicine[2-7].

Healthcare and the COVID-19 pandemic

The declaration of the coronavirus disease 2019 (COVID-19) pandemic by the World Health Organization (WHO) has dramatically affected the healthcare system[8-10]. Non-contact and non-intrusive examination techniques have been heavily relied on to minimize the spread of the severe acute respiratory syndrome coronavirus 2 during necessary care, resulting in a global transition to incorporate aspects of telemedicine[11]. Interestingly, this acceptance of telemedicine brought attention to the limitations of traditional medicine, such as unnecessary referrals to specialists, long waiting time, and crowded hospital environments[12]. Now gaining traction, digital transformation is offering new solutions to current healthcare problems, including simple remote screening assessments, remote monitoring devices, various app features, AI-assisted diagnosis, and drone-assisted drug delivery system. Considering glaucoma management, a comprehensive work-up on visual acuity, intraocular pressures, visual field tests, and dilated fundus exams is typically expected to be performed at a specialized facility. During the COVID-19 pandemic, while offering on-site care for severe and worsening cases of glaucoma, a protocol can be formulated to triage stable and mild severity patients and offer remote monitoring through portable devices, such as smartphones[12]. Such an approach can be implemented to other chronic diseases, and efforts to determine reliable digital phenotypes for remote monitoring is crucial for digital advancement.

The worldwide movement toward developing and embracing various non-intrusive life-oriented ocular exams and diagnostic devices have been noted in recent literature[3,4]. We developed two smartphone apps, each to collect patient-reported outcomes (PRO) on dry eye and hay fever with ongoing analyses on the accrued big data[13-16]. Other products include an app for visual acuity check, smartphone-attachable slit-lamp microscope, screening app for diabetic retinopathy, and an app for glaucoma evaluation[17-20]. Considering the change associated with Society 5.0 and COVID-19 pandemic, healthcare appears to be shifting toward predictive, longitudinal care within one's daily life and away from the traditional facility-based care using mHealth as a central catalyst.

Symptomology of Dry Eye and its Stratification

Considering the continuing digitalization of modern society, the sheer quality and number of visual screen time are increasing, underscoring the visual impact to one's quality of life (QoL)[21]. Dry eye is a prevalent ocular disease estimated to be affecting 1 billion patients worldwide and 20 million in Japan alone[22-24]. Additionally, the aging society, combined with the rapid digitalization that occurred during the pandemic is presumed to escalate the incidence of dry eye in the future[23,25-27]. Dry eye presents a wide range of subjective symptoms, including ocular dryness, eye discomfort, decreased vision, and generalized fatigue[28-31], which demonstrates a high degree of heterogeneity in its symptomology on an individual basis. Dry eye symptoms have been reported to negatively affect one's quality of vision and work productivity, ultimately resulting in financial burden and societal economic loss[32-38]. However, the mainstay approach to dry eye management revolves around post-facto treatment

of symptoms and suppression of further exacerbation; dry eye currently has no cure[39]. To establish the groundwork to effectively intervene and prevent further damage in a personalized manner, a cross-hierarchical and -sectional approach may be necessary to analyze comprehensive data on each patient and stratify disease-associated risk factors[3, 5].

DryEyeRhythm® smartphone application

The DryEyeRhythm® app was initially developed using Apple Inc.'s (Cupertino, CA, USA) open-source framework ResearchKit[14]. This app was released in November 2016 and September 2020 for the iOS and Android versions, respectively, under a consignment contract with the Juntendo University Graduate School of Medicine, Tokyo, Japan, and InnoJin Inc., Tokyo, Japan. It is freely available on Apple's App Store and Google Play. Figure 1 shows the description of the user experience of DryEyeRhythm®. Following installation of DryEyeRhythm® on a mobile device, users are requested to provide electronic consent (eConsent) for participation in the associated research. Table 1 shows the survey items of DryEyeRhythm®. Upon providing eConsent, users enter their basic information, including age, sex, height, weight, race, educational status, income, and visual acuity, as well as a detailed medical history through the app interface. Users are offered daily tasks to evaluate dry eye-related symptoms, such as a blink sensoring test, answering subjective symptom questionnaires (i.e., Ocular Surface Disease Index questionnaire; OSDI)[28, 40, 41], and entering information on the lifestyle patterns. As optional tasks, users can complete an evaluation of the depression symptoms (Zung Self-rating Depres- sion Scale, SDS)[42-44] and work productivity (Work Productivity and Activity Impairment Questionnaire)[45]. Figure 2 shows example screenshots of DryEyeRhythm® on a mobile device. The welcome screen of the app can be seen in Figure 2a. Users provided information according

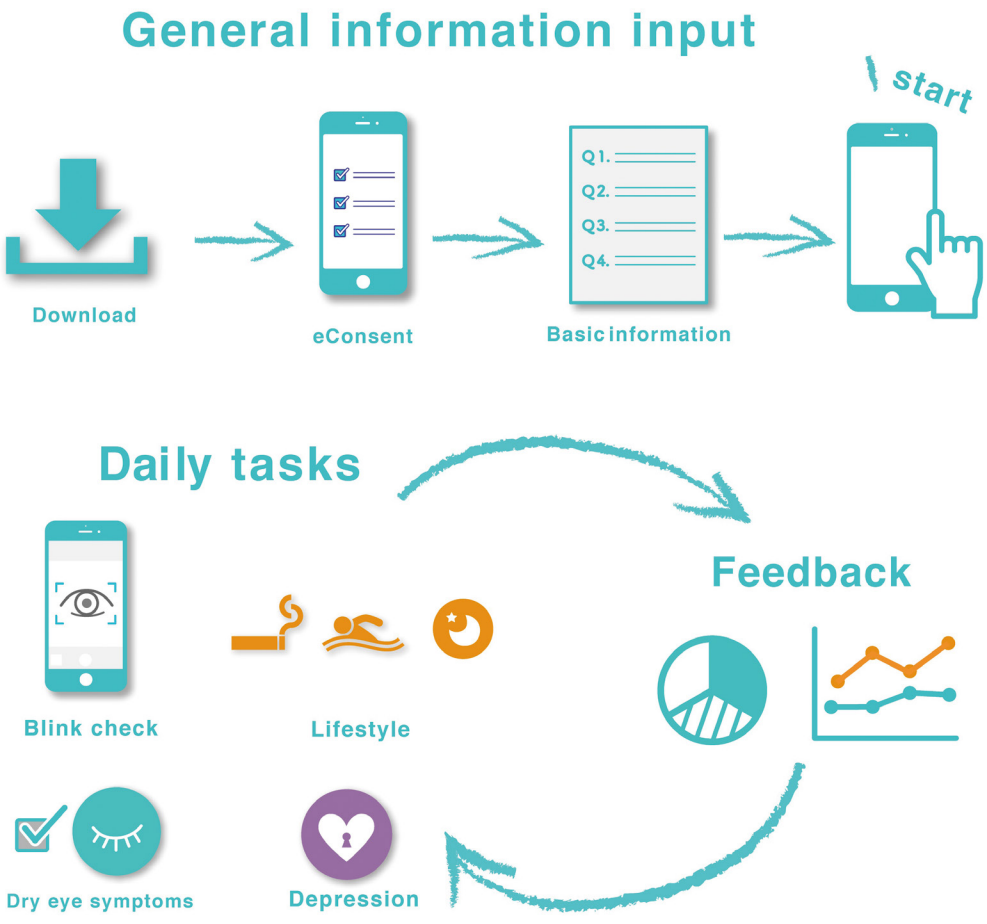

Figure 1 Description of user experience for DryEyeRhythm®
The figure is used from Inomata T. et al.[6] with permission.

Table 1 Survey items of DryEyeRhythm®

Category	Items
Demographic information	Height, Body weight, Age, Sex, Race, Education, Income, Visual acuity
Medical history	Hypertension, Diabetes, Blood disease, Brain disease, Collagen disease, Heart disease, Kidney disease, Liver disease, Malignant tumor, Respiratory disease, Hay fever, Mental illness including Depression, Schizophrenia, and other than depression and schizophrenia, Past dry eye diagnosis, Ophthalmic surgery including cataract surgery, LASIK, and other than cataract and LASIK, Medication, Eye drop
Lifestyle habits	Coffee, Contact lens use, Screen exposure time, Periodic exercise, Sleeping time, Steps, Smoking, Water intake, Feces
Subjective symptoms	Daily subjective symptoms including eye itching, asthenopia, headache, mental fatigue, stiffness and pain of body axis muscles, and stress, Ocular Surface Disease Index, Zung Self-rating Depression Scale, Work Productivity and Activity Impairment Questionnaire
Blink	Blink counts, Maximum blink interval
Functional visual acuity*	Right visual acuity, Left visual acuity
Others	Latitude, Longitude, Temperature, Humidity, Atmospheric pressure, Weather, Step count

LASIK, Laser in Situ Keratomileusis
*Latest version of DryEyeRhythm® (after released September 1st, 2020) exclude functional visual acuity function.

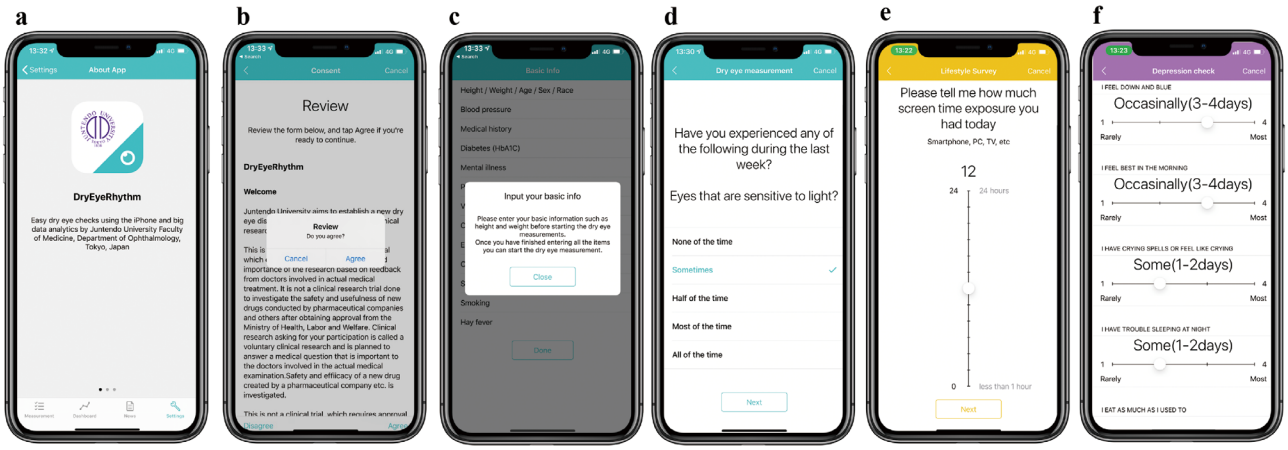

Figure 2 Screenshots of DryEyeRhythm®
(a) Welcome screen, (b) eConsent, (c) screen for entering participant characteristics, (d) Ocular Surface Disease Index questionnaire, (e) lifestyle information questionnaire, and (f) depressive symptoms questionnaire. The figure is used from Eguchi A. et al.[49] with permission.

to the given instructions, including eConsent (Figure 2b), demographic information (Figure 2c), Japanese version of OSDI (Figure 2d), lifestyle patterns (Figure 2e), and SDS (Figure 2f).

Mobile health-based digital cohort studies using DryEyeRhythm®

Table 2 shows the published studies using the DryEyeRhythm® app. Seven articles were published between December 11, 2018 to April 25, 2022[6, 14, 30, 46-49]. The study types included six cross-sectional studies and one observational study. The number of included participants ranged between 82 to 5,265 participants. Published journals included Ophthalmology, JAMA Ophthalmology, Ocular Surface, Journal of Medical Internet Research, Japanese Journal of Ophthalmology, and npj Digital Medicine.

Risk factors for severe dry eye

Upon conducting a large-scale crowd sourced clinical research using DryEyeRhythm®, we were able to collect comprehensive, individualized medical big data on dry eye, and identify the risk factors associated with dry eye symptom exacerbations[14]. DryEyeRhythm® was downloaded 18,225 times between November 2016 and November 2017. Odds ratios (95% confidence interval) of each user-reported factors on developing severe dry

Table 2 Published articles using DryEyeRhythm®

Authors	Publication date	Study type	Sample size	Age, mean (SD) or median (IQR)	Women rate, n (%)	Findings	Journal
Inomata T et al.[14]	December 11, 2018	Cross-sectional study	5,265	27.2 (12.4)	3,500 (66.5)	This study identified the risk factors for severe dry eye.	*Ophthalmology*
Inomata T et al.[47]	January 1, 2020	Cross-sectional study	4,454	27.9 (12.6)	2,972 (66.7)	This study identified the risk factors for symptomatic dry eye and undiagnosed dry eye.	*JAMA Ophthalmology*
Inomata T et al.[46]	April 18, 2020	Cross-sectional study	4,454	27.9 (12.6)	2,972 (66.7)	This study identified the association between dry eye and depressive symptoms.	*Ocular Surface*
Inomata T et al.[48]	June 26, 2020	Cross-sectional study	4,454	27.9 (12.6)	2,972 (66.7)	This study identified and stratified the individuals with contact lens-associated dry eye and its risk factors.	*Journal of Medical Internet Research*
Eguchi A et al.[49]	January 8, 2021	Cross-sectional study	2,619	26 (19-40)	1,701 (64.9)	This study determined the eye drop type and usage frequency and identified risk factors for no eye drop use in individuals with symptomatic dry eye in Japan.	*Japanese Journal of Ophthalmology*
Inomata T et al.[6]	December 20, 2021	Cross-sectional study	3,593	27 (20-41)	2,147 (59.8)	This study developed a novel smartphone-based digital phenotyping to stratify heterogeneous symptoms of dry eye into seven clusters and identified the specific profiles and risk factors in each cluster.	*npj Digital Medicine*
Okumura Y et al.[30]	April 25, 2022	Observational study	82	37.4 (11.0)	35 (42.7)	This study determined the reliability, validity, and feasibility of the DryEyeRhythm® app for the diagnosis assistance of dry eye.	*Ocular Surface*

SD, standard deviation; IQR, interquartile range

eye subjective symptoms were calculated for 5,265 users who provided basic information, medical history, lifestyle patterns, and OSDI. Dry eye symptoms were considered severe if the reported ODSI total score was above or equal to 33 points[28, 40]. Identified factors included younger age by 1 year, 0.99 (0.98-0.99); female sex, 1.85 (1.60-2.14); collagen disease, 2.81 (1.34-5.90); depression, 1.68 (1.23-2.29); current contact lens (CL) use, 1.24 (1.09-1.41); hay fever, 1.18 (1.04-1.33); higher on-screen time by 1 hour, 1.02 (1.01-1.03); and smoking, 1.53 (1.31-1.79). Of the identified factors, current CL use, on-screen time, and smoking are modifiable risk factors that may be helpful when advising patients on lifestyle pattern adjustments to prevent dry eye exacerbation. While the identified factors from this study were largely referenced by various previous epidemiological studies[22, 50], the advantage of an mHealth approach lies in the comparable results attained by analyzing big data collected from a single, large-scale crowd sourced clinical study. These results highlight the validity of incorporating mHealth principles in clinical studies and may possess implications on the future direction of research methodologies.

Characteristics and risk factors for undiagnosed symptomatic dry eye

Using the data generated by Japanese users who downloaded DryEyeRhythm® between November 2016 to January 2018, the characteristics of undiagnosed dry eye was evaluated. A total of 21,394 discrete, individualized data was generated during this time[47]. Among the 4,454 participants included in the study, 53.8% (2,395 users) reported dry eye symptoms without a formal diagnosis of dry eye.

Risk factors associated with undiagnosed dry eye included younger age by 1 year, 0.99 (0.987–0.999); male sex, 1.99 (1.61–2.46); collagen disease, 0.23 (0.09–0.60); mental illnesses other than depression and schizophrenia, 0.50 (0.36–0.69); ophthalmic surgery other than cataract and laser in-situ keratomileusis (LASIK), 0.41 (0.27–0.64); current CL use, 0.64 (0.54–0.77); and history of CL use, 0.45 (0.34–0.58). Presence of these risk factors can elevate the clinicians' suspicion for an undiagnosed dry eye, aiding in prompt prevention and effective management through risk factor modification.

Association between dry eye and depression symptoms

The association between mental health and QoL has been gaining attention in recent years, and reports suggest that dry eye shares numerous risk factors with depression, such as disruption of hormonal, metabolic, and neurologic balance, resulting in an increased likelihood of comorbidity[22,51–53]. Upon examining the connection between the symptoms of depression and dry eye, the results demonstrated that increasing dry eye severity is associated with symptoms of depression[46]. Notably, the results of this study demonstrated an increased likelihood (3.29 times) of developing depressive symptoms in patients with severe dry eye compared to healthy controls. A hierarchical clustering heatmap of the respective 12 and 20 items of OSDI and SDS visualized the association between each of the item pairs of dry eye and depression questionnaires (Figure 3a). In particular, the environmental factors of dry eye subjective symptoms (OSDI items 10, 11, 12) correlated with the depressive symptoms. With continuous monitoring of the dry eye symptoms, suspicion for comorbid depressive symptoms can be raised upon identification of patients with severe dry eye and interventions can be promptly deployed to prevent or treat dry eye–associated depression.

Survey of eye drop type, usage frequency, and risk factors of no eye drop use for individuals with symptomatic dry eye

Timely intervention and management through topical eye drops is crucial for preventing dry eye progression[54]. Of the 2,619 individuals with symptomatic dry eye in this study, 1,876 individuals reported no usage of topical drops[49]. The most common eye drops used among the individuals were artificial tears (53.4%), hyaluronic acid 0.1% (33.1%), and diquafosol sodium 3% (18.7%). Figure 3b represents a visualized map of various combinations of eye drops used by individuals. The results also revealed that a significant portion of individuals with symptomatic dry eye were not using the recommended dosage of topical drops, raising concerns of decreased adherence. Risk factors (the odds ratio [95% confidence interval]) for no eye drop use were younger age by 1 year, 0.97 (0.97–0.98); body mass index, 1.04 (1.01–1.07); brain disease, 0.38 (0.15–0.98); collagen disease, 0.30 (0.13–0.68); mental illness other than depression and schizophrenia, 0.65 (0.45–0.93); cataract surgery, 0.12 (0.02–0.59); ophthalmic surgery other than cataract and LASIK, 0.55 (0.34–0.88); current CL use, 0.47 (0.38–0.57); history of CL use, 0.58 (0.43–0.77); >8 h on-screen time, 1.38 (1.05–1.81); <6 h sleep time, 1.24 (1.01–1.52); >9 h sleep time, 1.34 (1.04–1.72); and water intake, 0.97 (0.94–0.98). Monitoring dry eye symptoms and medication administration could aid clinicians in accurately understanding the effects of the medications and selecting effective personalized treatment strategies by escalating the intervention when appropriate. In addition, clinicians can more effectively initiate a motivational discussion with the patient to promote and ensure treatment adherence, rather than preemptive treatment escalation.

Stratifying heterogenous symptomologies and using digital phenotypes for P4 medicine

Dry eye is a multifactorial disease, in which a complex interaction exists between environmental, host, and lifestyle factors that ultimately affects the disease onset, progression, and prognosis[22]. Therefore, preventive and predictive measures to halt the onset altogether, as well as personalized or stratified approaches for intervention based on each patient's risk factors are considered ideal[3]. For such strategies, a comprehensive individualized dataset must be first accrued, followed by a cross-hierarchical and cross-sectional analysis. This may elucidate a better understanding behind dry eye symptom heterogeneity, providing a foundation for treatment stratification based on personalized factors[3].

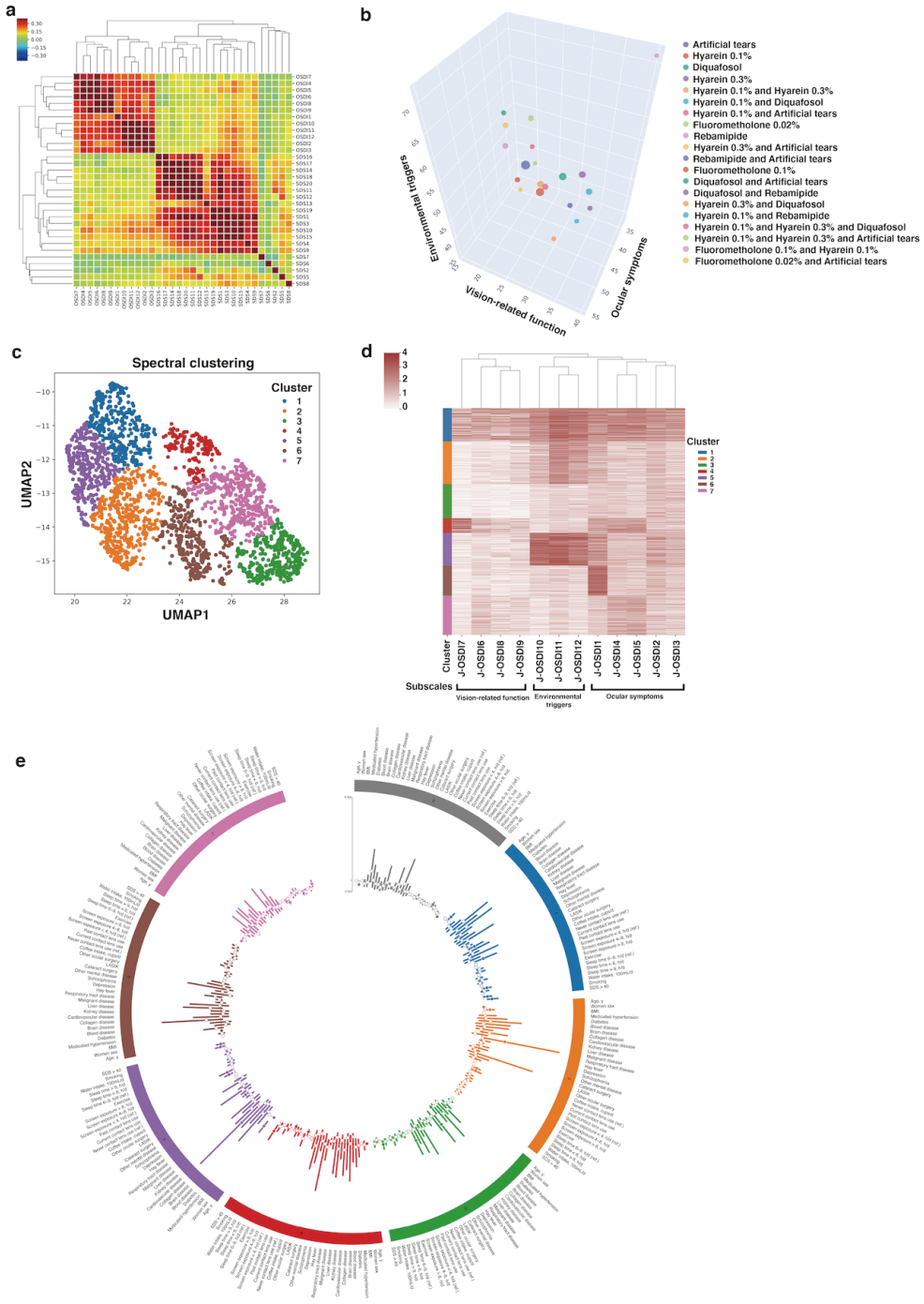

Figure 3 Characteristic visualization of symptomatic dry eye using collected comprehensive dry eye related health data and biosensoring data by DryEyeRhytm®

(a) The heatmap of the correlation between each item of the Ocular Surface Disease Index (OSDI) and Self-rating Depression Scale (SDS) questionnaires. (b) A bubble chart of representative combinations of types of eye drops used by symptomatic dry eye individuals based on data from the subscales of the OSDI. Among the total 51 combinations, the top 20 eye drop combinations are shown. The X-axis represents the ocular symptoms score, the Y-axis represents the vision related-function score, and the Z-axis represents the environmental triggers score based on the OSDI questionnaire. The bubbles represent the proportion of the combinations of eye drops used. (c) Dimension reduction of individuals with symptomatic dry eye—via Uniform Manifold Approximation and Projection with spectral clustering identified by unsupervised clustering analysis (n=2,619 individuals collected by DryEyeRhythm®)—depicted seven clusters when stratified for subjective symptoms based on the 12 items of the Japanese version of OSDI. (d) Fraction of individuals within each cluster visualized on the left most panel, along with a corresponding heat map of subjective symptoms from individuals within the identified clusters. (e) Risk factors for each cluster in symptomatic dry eye compared with other clusters visualized in a circular layout. The figures are used from a; Inomata T et al.[46], b; Eguchi A. et al.[49], and c–e; Inomata T. et al.[6], with permission.

In an effort to combine bioinformatics and AI technology for dry eye research, we developed a smartphone app, DryEyeRhythm®, which can generate comprehensive medical big data on dry eye through smartphone-attached biosensors and user-provided information[6]. A total of 3,593 participants who provided consent between November 2nd, 2016 and September 30th, 2019 were included in the study. The Uniform Manifold Approximation and Projection (UMAP) algorithm was utilized for dimension reduction of the heterogeneous dry eye symptoms, yielding 7 unique subgroups based on the collection of subjective symptoms (Figure 3c). Subsequent visualization of the characteristics of each subgroup was performed through hierarchical clustering (Figure 3d) or a multivariate logistic regression analysis (Figure 3e). Additionally, the performance of maximum blink interval (MBI)[55, 56] as a digital phenotype was tested for each identified subgroup using the blink biosensoring feature of the DryEyeRhythm® app (Figure 4a). In the subgroups with dry eye, a decrease in the app-measured MBI was observed (Figure 4b). Furthermore, each stratified subgroup displayed distinct MBI changes (Figure 4c). This suggests that the detection of blinking patterns through smartphone apps could be valuable in dry eye screening, as well as predicting the disease subtype.

In this study, dry eye was stratified into unique subtypes that elucidated a pattern based on the symptom heterogeneity, and a novel digital phenotype was identified. Based on the dry eye subtype identified by the DryEyeRhythm® app, personalized regimens to mitigate unique subtype-associated risk factors could be possible and clinicians may be able to provide a tailored preventive and interventional plan. This highlights the potential role of mHealth and the generated medical big data in creating a personalized health profile related to dry eye, including symptoms and lifestyle patterns, which have strong implications in bringing principles of P4 medicine to the field of dry eye management.

Diagnostic performance of dry eye mHealth app

To determine the diagnostic capabilities of DryEyeRhythm® through electronic subjective symptom questionnaires and digital phenotyping, the app-based OSDI results and MBI (Figure 4a) measurements were collected from 82 participants above the age of 20 years who visited the Juntendo University Hospital-associated ophthalmology clinic between July 2020 and May 2021. True diagnosis of dry eye was determined using the criteria proposed

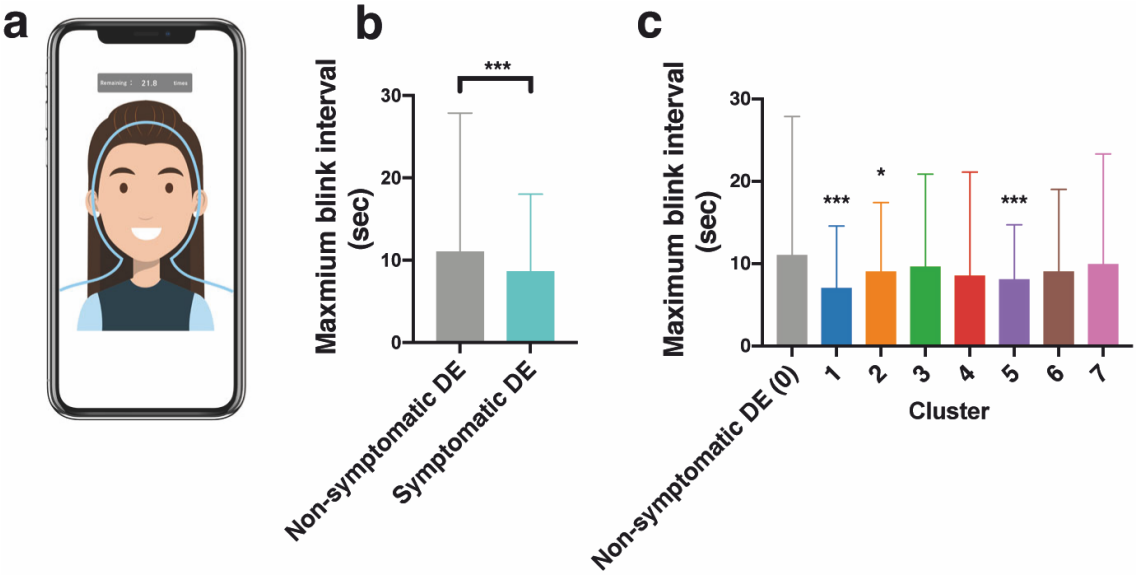

Figure 4 Blink sensoring by DryEyeRhythm®
(a) The duration of the participant's maximum blink interval (MBI) was recorded by DryEyeRhythm®. (b) MBI was significantly shortened in symptomatic dry eye vs. non-symptomatic dry eye (8.6 s vs. 11.0 s, $^{***}P<0.001$) (c) MBI each cluster (Kruskal-Wallis test, n=3,593, $^{*}P=0.016$, $^{***}P<0.001$). DE, dry eye. The figure is used from Inomata T. et al.[6] with permission.

by the Asia Dry Eye Society, which was used to evaluate the diagnostic performance of DryEyeRhythm® [57]. The area under the curve of the resultant receiver operating characteristic curve was 0.910. The sensitivity and specificity of DryEyeRhythm® was 91.3% and 69.1%, respectively, suggesting that DryEyeRhythm® may be an ancillary non-invasive, non-contact tool for dry eye diagnosis.

Discussion

Considering the advancements toward healthcare envisioned in the Society 5.0 plan, efforts have been placed to create a medical system that enables ubiquitous care that allows patients and the public to receive non-intrusive care within one's daily life. To realize the framework and improve the quality of dry eye management, the disease heterogeneity and multifactorial nature should be better understood along with efforts to implement P4 medicine in patient care. In this review, a series of studies using DryEyeRhythm® to collect comprehensive individualized data on dry eye, including subjective symptoms and disease-associated lifestyle patterns, were discussed to further understand dry eye as a pathology and discover means to implement principles of P4 medicine. mHealth apps appear to be well-suited in creating a holistic dataset for each user, utilizing user-provided data and biosensor data through (now common) smartphone sensors (i.e., camera, touchscreen, global positioning system). mHealth has become more accessible for creating robust medical data sets, which provide insights on disease variability and heterogeneity that traditional methodologies have struggled to provide. Ultimately, this may be the beginning of providing personalized prevention plans, interventions, and behavioral modifications.

mHealth has been receiving attention as a novel and effective route of collecting big medical data[5, 7, 58, 59]. mHealth, as defined by the WHO, refers to the "medical and public health practice supported by mobile devices, such as mobile phones, patient monitoring devices, personal digital assistants, and other wireless devices.[60]" In modern research, mHealth smartphone apps are being utilized as a complement to traditional research methodologies[3, 4]. The use of mHealth apps has several advantages: 1) frequent, longitudinal, remote, and real-time data collection, 2) biosensoring through smart device-attached sensors, and 3) bidirectional participatory medicine. If consent for participation is obtained through the app, the added accessibility and outreach through minimizing the need to physically visit a research facility may be beneficial. In addition, depending on how the data is processed and stored, the comprehensive dataset can stay individualized[4, 58, 61]. By integrating medical and biosensor data collected through mHealth apps using bioinformatics and AI technology, new aspects of disease processes and variability could be further unveiled.

Recent clinical studies on PRO underscored the importance of including subjective perspectives of patients as part of a routine clinical evaluation[62, 63]. The studies on electronic PRO (ePRO) collected through mHealth apps showed satisfactory reliability and validity[13, 14]. One common limitation of mHealth apps was the frequent reliance on self-administered questionnaires, which do not sufficiently reflect the clinical findings and could be prone to biases. However, the blink biosensoring technology included in DryEyeRhythm® adds an objective clinical finding as part of the dry eye evaluation, augmenting its accuracy as an ancillary diagnostic tool[6, 30]. The role of various digital user inputs and lifestyle patterns sensed by smart device sensors that translates into digital phenotypes demonstrates potential in stratifying and visualizing one's disease presentation, which helps bring in new values of P4 medicine into its care.

With an ever-evolving form of medical big data, mHealth appears to be an effective method to capture large data sets and perform a data-driven cross-hierarchical, cross-sectional approach that previous methodologies have struggled to perform[5]. Its application may be extrapolated beyond dry eye to better understand numerous pathologies in an era of integrated cyberspace and physical space. Additionally, the real-time data collection on one's health and lifestyle and analysis with minimal intrusion enables lifelong medical care that allows providers to rapidly provide tailored medical needs for patients and public based on incoming data[6, 7]. Considering traditional facility-oriented medicine, a paradigm shift toward a life-oriented healthcare is expected. With the recent changes that accompanied the COVID-19 pandemic, the demand for non-intrusive life-oriented medicine is expected to

increase globally, and its research will likely build upon the current foundation laid by mHealth to adopt the four key pillars of P4 medicine.

In conclusion, as the aspects of the Society 5.0 plan comes to fruition, forms of lifelong, non-intrusive, and predictive medicine are expected to emerge. Evolving concepts of medical big data collected through mHealth-through smartphones, wearables, and Internet of Medical Things devices-and AI technology may help bring in new values derived from the principles of P4 medicine to the current system. This warrants a societal discussion to identify technology and strategies that could help transform the healthcare system into one that is more effective and beneficial for patients and the public in our progress toward Society 5.0.

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Author contributions

TI conceived of the concept of this paper and was major contributor in writing the manuscript. JS and AY were the major contributors in writing the manuscript. TI, YO, KN, KF, YA, AMI, AE, and HT contributed to the development of the study protocol and collected the data. TI, YO, KN, and AMI performed the data analysis and data visualization. TI, YO, AMI, and AE performed funding acquisition. All the authors reviewed the advanced the concepts within the paper and drafted the manuscript. All the authors read and approved the final manuscript.

Conflicts of interest statement

The DryEyeRhythm® application was created using Apple's ResearchKit (Cupertino, CA, USA) along with OHAKO, Inc. (Tokyo, Japan) and Medical Logue, Inc. (Tokyo, Japan). TI, YO, and AMI are the owners of InnoJin, Inc. (Tokyo, Japan), which developed DryEyeRhythm®. TI reported receiving grants from Johnson & Johnson Vision Care, SEED Co., Ltd., Novartis Pharma K.K., and Kowa Company, Ltd., outside the submitted work, as well as personal fees from Santen Pharmaceutical Co., Ltd., and InnoJin, Inc. The remaining authors declare no competing interests.

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Reviews

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A Narrative Review of Current Status and Future Perspective of Telemedicine for Parkinson's Disease, Dementia, and Intractable Neurological Diseases in Japan

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The coronavirus disease 2019 pandemic has uncovered several inherent problems in society. While the demand for telemedicine surged worldwide and some countries responded flexibly, in Japan, most telemedicine services were limited to telephone consultations, and full-fledged telemedicine did not become widespread. In addition, the digitalization process in both medicine and wider society lags behind some other nations. It is necessary to accelerate digital transformation in healthcare to build a sustainable society that is resilient to crises, such as new pandemics. In particular, as Japan is facing an issue of super-aged society, a sustainable care model for people with Parkinson's disease, dementia, and intractable neurological diseases should be established.

Many neurodegenerative and intractable neurological diseases are progressive; as the disease progresses, patients could become difficult to visit specialists. Although online medical care has many advantages, it does not provide the same quality of information as face-to-face consultations.

However, new technology can overcome the limitations of online medical care. As an evolutionary direction for telemedicine, three-dimensional telemedicine technologies are being developed, which enable online medical treatment to be delivered as if the patient was sharing the same space. Telemonitoring can enable the objective and continuous evaluation of patient information at home through the use of motion capture, wearable devices, and other devices. The advancement of digital transformation in medical care should be a game-changer in accumulating big data and analyzing it using artificial intelligence.

Key words: Parkinson's disease, dementia, telemedicine, wearable devices, artificial intelligence

Introduction

The coronavirus disease 2019 (COVID-19) pandemic uncovered inherent problems in society. While the demand for telemedicine surged worldwide and some countries responded flexibly[1], in Japan, most telemedicine services were limited to telephone consultations, and full-fledged telemedicine did not become widespread[2]. Moreover, the digitalization process in medicine and wider society

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lags behind some other nations. It is necessary to accelerate digital transformation (DX) in healthcare to build a sustainable society that is resilient to crises, such as new pandemics. In particular, as Japan is facing an issue of super-aged society, a sustainable care model for people with Parkinson's disease, dementia, and intractable neurological disorders should be established[3].

Many neurodegenerative and intractable neurological diseases are progressive, making patients increasingly difficult as the disease progresses to visit a specialist that could be located some distance away[4]. In addition, symptoms may fluctuate within a day, and for appropriate management, it is necessary to accurately monitor not only symptoms during outpatient visits but also fluctuations in symptoms at home. Currently, however, few methods can objectively identify symptoms. Therefore, the importance of information and communication technology (ICT) applications and DX in healthcare is recognized as key to solving these problems.

Telemedicine technology can improve access to medical specialists. With the spread of COVID-19, telemedicine has gradually spread in Japan[2]. Augmented reality (AR) and virtual reality (VR) technologies are expected to advance telemedicine technology and be applied to telerehabilitation and other areas. Wearable devices are a solution to objectively monitor patient conditions. By monitoring the patient 24 h a day with wearable devices, it is possible to objectively and continuously evaluate the patient's condition at home outside of medical examinations. In addition, the vast amount of big data obtained from monitoring with wearable devices may lead to the discovery of digital biomarkers and the development of diagnostic and therapeutic assistance programs through analysis using artificial intelligence (AI).

This review provides an overview of the current status and future perspectives of ICT and DX research in intractable neurological diseases.

Methods

In this narrative review, we searched the literature on the current status of telemedicine in Parkinson's disease and intractable neurological diseases in Japan, published in English in PubMed. A search strategy identified relevant references using the terms Parkinson's disease, intractable neurological diseases, and telemedicine. Only original articles were included. We also discussed the limitation of current telemedicine and future perspectives of ICT and DX research to improve telemedicine.

Results

We found that five articles fulfilled the criteria[2,4-7]. Four studies include PD[2,4,6,7], one study includes amyotrophic lateral sclerosis, spinocerebellar degeneration, and multiple system atrophy, as well as PD[6], and one study included spinocerebellar ataxia[5]. Three research used tablet[2,4,7] and two research used telephone as ICT[5,6].

Discussion

Telemedicine and online medical care

Many intractable neurological diseases are progressive, and as they progress, it becomes difficult for patients to visit specialists that may be located some distance away. In particular, aging is a risk factor for neurodegenerative diseases such as Parkinson's disease, and with the advent of an aging society, the number of intractable neurological diseases is increasing[8]. However, because specialists are unevenly distributed in urban areas, it is difficult for patients with intractable neurological diseases in rural areas, where there are many elderly people, to access specialist care[4]. One solution to improving access to specialists is telemedicine, which provides medical care remotely, and telehealth, which provides prevention and health promotion. Regardless of distance, health services using ICT are called eHealth or digital health and include various types of devices, such as wearable devices and smartphone applications[9].

In telemedicine, the Ministry of Health, Labour and Welfare (MHLW) in Japan defines "online medical care" as real-time medical treatment between a doctor and a patient, in which the doctor examines and diagnoses the patient using ICT devices and transmits diagnostic results and prescriptions[10]. To date, there have been several restrictions on online medical care covered by national insurance. It is limited to patients with chronic disease and followed up for at least three months. Face-to-face visits must be scheduled at least every three months, with emergency cases seen within 30 min. Since the revision in 2022, fees

for online medical care have also increased, similar to face-to-face consultations. In addition, time and distance requirements between medical institutions and patients, as well as limitations on the percentage of online medical care, were eliminated. Therefore, online medical care has been promoted.

Telemedicine for Parkinson's disease, dementia, and intractable neurological disease

A previous review reported that telemedicine is an effective tool for the rapid evaluation of patients in remote locations that require neurological care for various neurological diseases, including dementia, neuromuscular diseases, multiple sclerosis, headache, trauma, and movement disorders[11]. Since the first study reporting the feasibility of remote assessment of motor symptoms in Parkinson's disease in 1993[12], studies, including randomized controlled studies, have reported the usefulness of videoconferencing telemedicine in this field[4].

In Japan, the first pilot study of telemedicine for Parkinson's disease using an iPad was conducted in 2014[4]. This study showed the safety and feasibility of telemedicine care for patients with Parkinson's disease. Following this evidence, Juntendo University Hospital started a telemedicine service for Parkinson's disease and other intractable neurological diseases in 2017[2]. In this service, the physician sees patients through the iPad and sends a prescription to patients as needed. Then, patients can get their medication from their nearest pharmacy (Figure 1). This service is now commonly provided in Japan. In a survey conducted during the first year of the service, both patients and caregivers were highly satisfied with the service and particularly appreciated the reduction in the burden of hospital visits[2]. In 2018, the MHLW approved "online medical care" in telemedicine to be covered by national insurance. Although the number of users of our telemedicine service was limited to approximately 20 patients per month, the COVID-19 pandemic led to a rapid five-fold increase in the number of users. We also started a trial of doctor-to-patient with doctor-type (D to P with D) online medical care and online second opinions. However, while demand for telemedicine surged and patients' tolerance for online medical care increased with the spread of COVID-19[13], most telemedicine services were limited to telephone consultations, and fully fledged telemedicine did not become widespread in Japan. In addition, there are limitations to the current online medical care services. Although online medical care has many advantages, it does not provide the same information as face-to-face consultations. The COVID-19 pandemic uncovered inherent problems in society and showed that medical care, as well as the whole society, is behind in the digitalization process. It is necessary to accelerate digital transformation in healthcare to build a sustainable society that is resilient to crises, such as new pandemics.

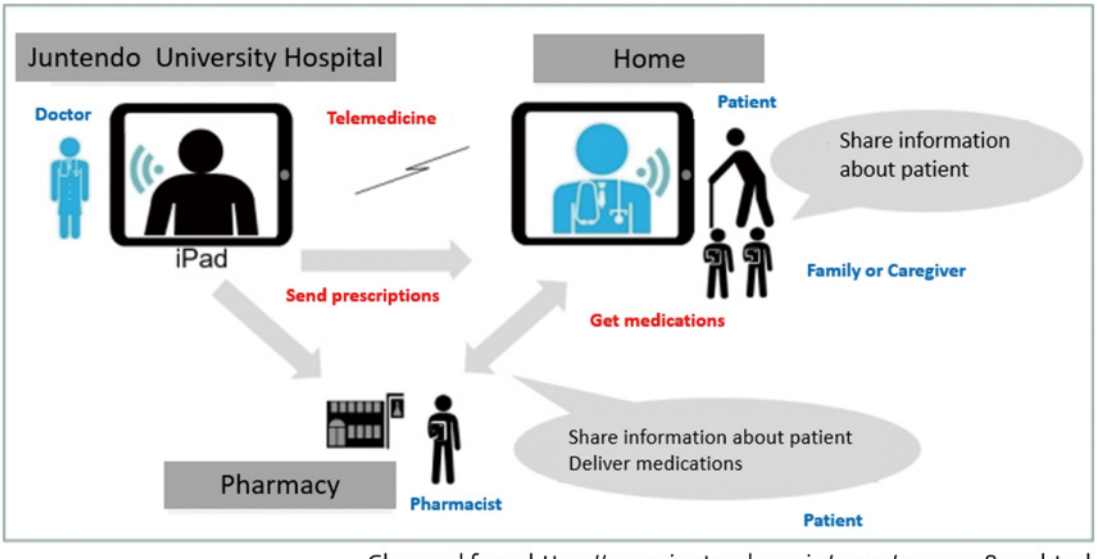

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Figure 1 Telemedicine service in Juntendo University Hospital

Digital transformation for Parkinson's disease practice

Telemonitoring is a telemedicine technology that compensates for the weaknesses of current online medical technology. Using wearable devices and smartphone applications makes it possible to evaluate patient information objectively and continuously at home[14]. Furthermore, an evolutionary direction for telemedicine includes technologies that enable three-dimensional video calls, facilitating online medical treatment as if the patients were sharing the same space as the doctors[15]. Furthermore, digitization in medicine will allow the accumulation of big data and its analysis through AI.

Three-dimensional telemedicine

One way to advance telemedicine treatment technology is the application of AR and mixed reality (MR) three-dimensional telemedicine technology. Three-dimensional telemedicine produces a three-dimensional hologram via a head-mounted display, which is scanned using an RGB depth camera in real-time[15]. By wearing the head-mounted display, the doctor and patient can see each other and share the space as if they were right in front of each other, even though they are not. The advantages of three-dimensional online medical care are that it provides a more realistic examination environment and can be used to scan three-dimensional motion data of the entire body, which can be analyzed using AI. In the future, if AI-based algorithms can display relevant information in real-time in an MR space to assist physicians, such as frequency and the type of tremor, it might enhance the ability of non-specialists and provide an accurate evaluation aid.

In addition, medical applications of VR are underway[16]. In particular, multiple studies on VR rehabilitation have been reported. The metaverse is the ultimate concept of further development of extended reality (XR) technologies, such as AR, VR, and MR. A metaverse is a three-dimensional virtual space or service built within a computer network. Users can freely experience various objects through their avatars in the metaverse space via computers or VR headsets. For example, at Juntendo University Hospital (Figure 2), a virtual hospital project has been started where

Figure 2 Virtual Juntendo hospital projects

patients and their families can virtually visit the hospital before coming, experience treatment methods, and interact with medical professionals and other patients (https://www.juntendo.ac.jp/news/20220413-05.html). It also allows hospitalized patients who have difficulty leaving the hospital to walk freely in a virtual space. In the future, we plan to examine whether mental health and other diseases can be improved through activities in the metaverse space.

Wearable devices

In addition to XR technologies, another way to review symptoms that cannot be examined easily using telemedicine is the application of wearable devices. Wearable devices can continuously and objectively monitor changes in a patient's condition in daily life outside the hospital through 24 h continuous monitoring. Indeed, the Apple Watch offers a movement disorder API that can distinguish between tremors and dyskinesia and monitor them separately[17]. Digital recording of an individual's movement symptoms is also expected to serve as a digital biomarker and is expected to become the basis for personalized medicine in the future[18].

Artificial intelligence

AI is a computer program that imitates human intelligence. The basis of AI is machine learning, which includes supervised and unsupervised learning. The development of deep learning has dramatically improved the capabilities of AI. AI has already been used in medical applications in the field of diagnostic imaging, and research is underway to treat neurological disorders. For example, technology has been developed to automatically determine tremors by simply holding one's hand over an infrared motion capturing device[19].

We developed an AI-based chatbot application for telemedicine[7]. Chatbots are programs that automatically converse with people, such as iPhone's Siri and Amazon's Alexa. Our AI-based chatbot was trained using several conversation scripts extracted from doctors' conversations with patients in their daily practice. Then, the AI-based chatbot selects from these scripts to converse with the patient. The application performs natural language processing based on the content of the conversation. In addition, it automatically displays a patient's health information report on a dashboard, which the doctor can use as a reference to provide regular or telemedicine care in less time. Our randomized controlled trial examined the efficacy and feasibility of the AI chatbot application. Twenty patients were randomized into a group that had only weekly remote conversations with the doctor and a group that had daily use of the AI chatbot in addition to a weekly conversation with their doctor to examine changes in facial expression and voice characteristics recorded during the remote discussion with physicians. AI chatbot intervention resulted in improvements in smiling and a decrease in filler words. This study indicated that daily conversations with an AI chatbot application could be applied to rehabilitation.

AI can save time for physicians by organizing the vast amount of information traffic, allowing physicians to focus on meaningful information, or by interviewing and rehabilitating patients instead of doctors and healthcare professionals. As a result, it might be possible for physicians to concentrate on their primary tasks, which only they can perform: listening to, sympathizing with, touching and examining, and healing patients.

Limitations

The most significant limitation of this study is the paucity of studies. In addition, as this is a narrative review, no quality ratings of these references were performed. We need more crossectional and longitudinal studies to elucidate this field.

Conclusion

Various technologies, such as telemedicine, AR/VR/MR, metaverse, wearable devices, and AI technology, are being applied to treat intractable neurological diseases. The current limitations of telemedicine may be overcome by DX using new technologies, such as wearable devices, three-dimensional telemedicine, and AI. DX in medicine is expected to lead to a revolution in which various medical professionals can collaborate across the boundaries of professions and provide more effective medical care using fewer resources. In addition, a paradigm shift may occur in which instead of patients visiting a hospital after developing a disease, people manage their health daily using

wearable devices and smartphone apps, consult online when the devices highlight a problem, and visit a hospital only when they need face-to-face medical care (Figure 3).

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Author contributions

The first draft of the manuscript was written by GO, and all authors commented on subsequent versions of the manuscript. All authors read and approved the final manuscript.

Conflicts of interest statement

GO has received grants from Grant-in-Aid for Scientific Research (Kakenhi) and Novartis Pharma K.K. and honoraria from AbbVie Inc., Boston Scientific Corporation, Eisai Co., Ltd., Kyowa Kirin Co., Ltd., Medtronic Japan Co., Ltd., Otsuka Pharmaceutical Co., Ltd., Sumitomo Dainippon Pharma Co. Ltd., and Takeda Pharmaceutical Company Limited.

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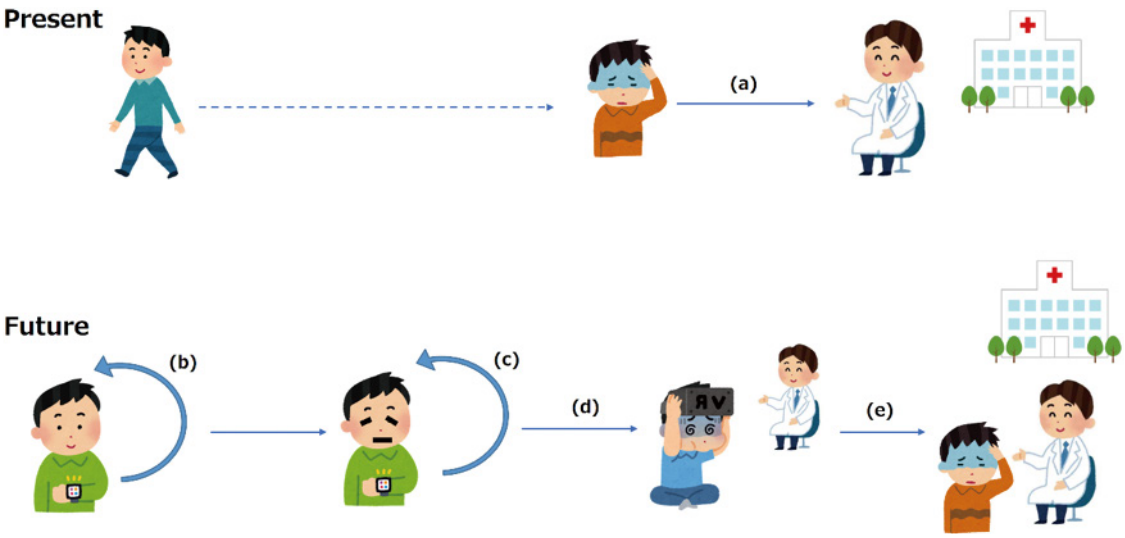

Figure 3 Paradigm shift in future medicine. (a) Patients see doctors when they get sick. (b) (c) People manage their health daily using wearable devices and smartphone apps. (d) People consult online when the devices highlight a problem. (e) Patients visit a hospital only when they need face-to-face medical care.

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Reviews

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Deep Brain Stimulation for Parkinson's Disease

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There is a long history of surgical treatment for Parkinson's disease (PD). Currently, deep brain stimulation (DBS) has been performed as promising treatment option for medically refractory PD. DBS is an adjustable and reversible treatment using implanted medical devices to deliver electrical stimulation to precisely targeted areas of the brain. DBS modulates neurological function of the target region. The most common target for PD is the subthalamic nucleus (STN). DBS is particularly indicated for patients suffering from motor complications of dopaminergic medication such as fluctuations and dyskinesia. Although there is currently no curative treatment for PD, a combination of medical treatment and DBS provide long-term relief of motor symptoms. In this review, I introduce history, mechanism, indication, clinical outcome, complication, long term outcome, timing of surgery, surgical procedure, and current new technology concerning DBS for PD.

Key words: Parkinson's disease, deep brain stimulation, subthalamic nucleus

Introduction

Parkinson's disease (PD) is a progressive nervous disorder caused by degeneration of dopamine-producing cells in the substantia nigra. The main symptoms are movement-related, including tremor, rigidity, bradykinesia, postural instability, gait disturbance, and so on. Other symptoms include autonomic, sensory, psychiatric and cognitive problem. Although there is currently no curative treatment for PD, motor symptoms of PD are initially treated with dopaminergic medications such as levodopa and dopamine agonists. In addition to medical treatment, there is a long history of surgical treatment for Parkinson's disease (PD)[1)]. After pioneering trials and errors, the current primary surgical treatment for PD is deep brain stimulation (DBS). To date, more than 170,000 patients worldwide have undergone DBS. DBS is a promising treatment option for patients with medically refractory PD.

History of surgical treatment for Parkinson's disease

James Parkinson published "An essay on the shaking palsy" in 1817. However, the etiology and cure for this intractable disease long remained unknown. The concept of the extrapyramidal tract was proposed in the 1920s and direct surgery to the basal ganglia was attempted. In 1947, Spiegel and Wycis developed a stereotactic frame for humans, enabling less invasive surgery to the extrapyramidal tract[2)]. Stereotactic pallidotomy or thalamotomy was subsequently developed for the treatment of PD. However, the use of surgical treatment rapidly declined after the introduction of levodopa

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in 1969. Dopamine replacement therapy became a mainstay of the treatment of PD. However, some patients suffered from motor complications of dopaminergic medication such as fluctuation or dyskinesia. In 1992, Laitinen revived pallidotomy for patients with motor complications from levodopa[3].

In 1983, Langston found 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) as a neurotoxin causing PD[4]. Consequently, an animal model for PD using MPTP was developed and the pathophysiology of PD was clarified in detail. In 1989, Albin demonstrated the functional anatomy of the basal ganglia related to the pathophysiology of movement disorders[5]. Shortly after, Bergman demonstrated that motor symptoms of MPTP-treated monkeys were dramatically improved by lesioning of the subthalamic nucleus (STN)[6]. In 1993, Benabid et al developed deep brain stimulation (DBS) of the STN, a monumental work of surgical treatment of PD[7]. Subsequently, DBS of the globus pallidus internus (GPi) was introduced as an another treatment option.

DBS and its mechanism

DBS is a surgical treatment involving the implantation of medical devices to deliver electrical stimulation to precisely targeted areas of the brain. Expectation of DBS is based on functional alteration in the target area. The DBS system consist of three components: the implantable pulse generator (IPG), the lead with four or eight contacts, and the extension wire (Figure 1). DBS is an adjustable and reversible treatment. The IPG can deliver pulses with three variable parameters. Frequency (2-250 Hz), width (20-450 μsec), amplitude (0-20 mA), and the selection of the stimulating contact can be set by wireless telemetry.

Surgical treatment is based on the following functional alteration within the basal ganglia-thalamo-cortical circuit (Figure 2). In PD, increased

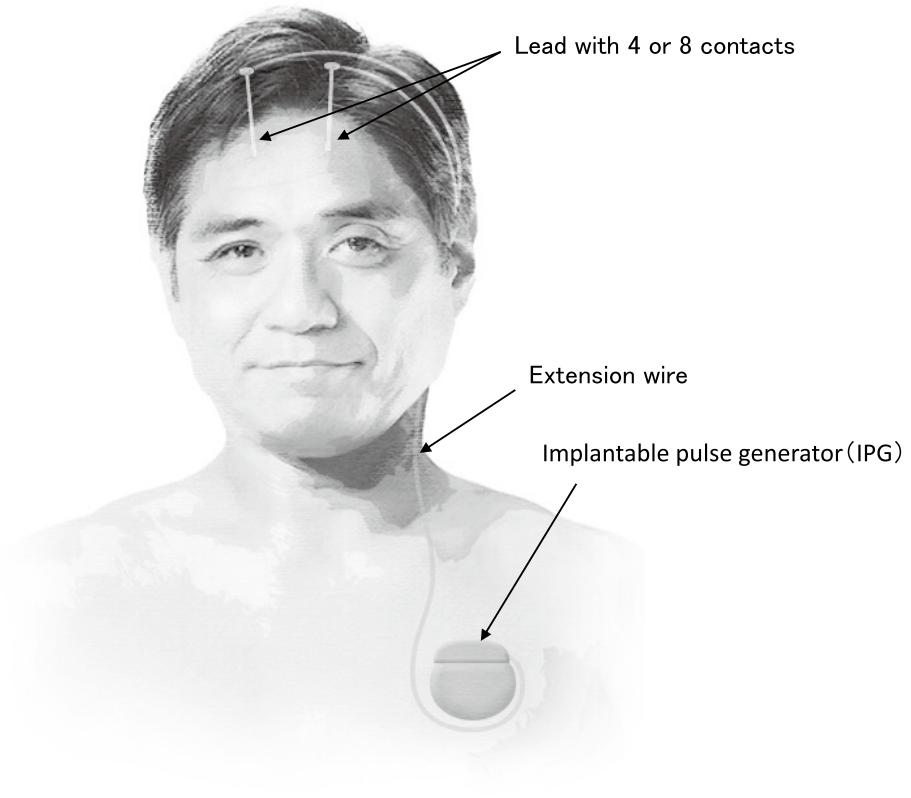

Figure 1 Outline of DBS system

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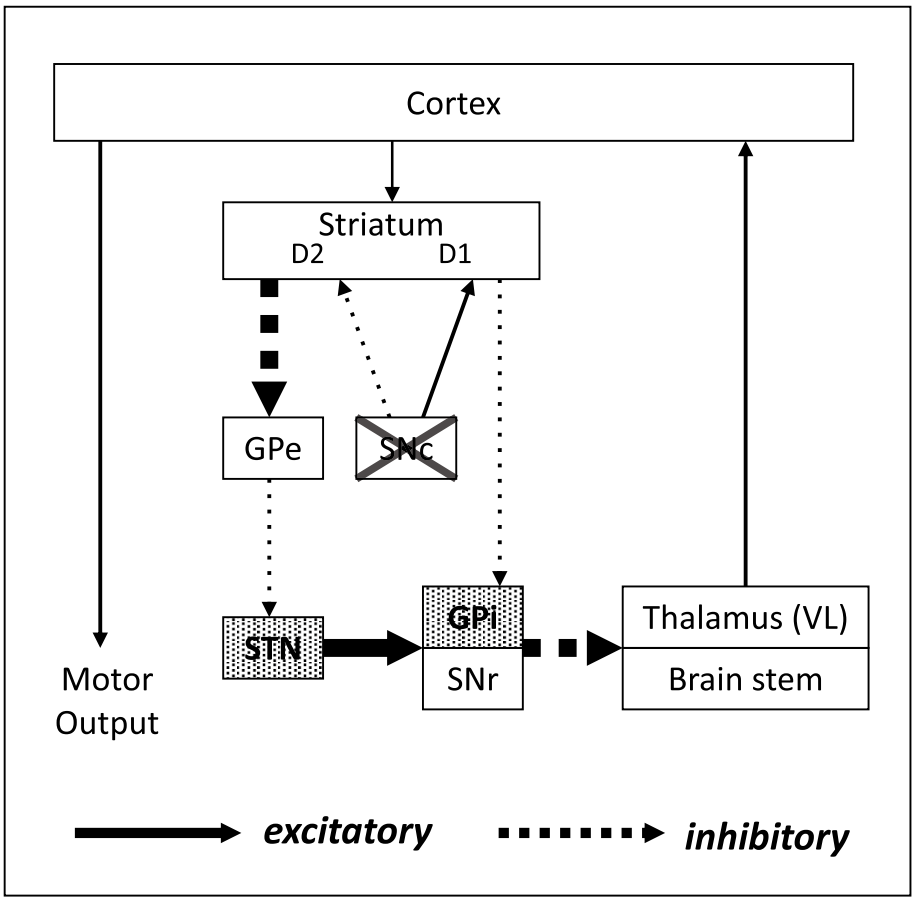

Figure 2 Pathophysiology of PD within the basal ganglia–thalamo–cortical circuit

excitatory activity of the STN caused by depletion of dopamine in substantia nigra pars compacta (SNc) abnormally activates the GPi which inhibit activity of the thalamus and thalamocortical neurons. The reduced thalamic and cortical activity account for the hypokinetic symptoms of PD such as rigidity and akinesia. Therefore, reducing the overactivity of STN or GPi through ablative procedure or DBS might have a considerable clinical effect in PD. DBS seems to produce a functional lesion in the brain and reduces activity in the focal area as well as ablative procedure. However, the true mechanism of the action in DBS is not well understood.

Indication of DBS for PD

Currently, there is no curative treatment for PD. First choice of treatment for PD is medical treatment. Therefore, what is required for surgical treatment in PD is to obtain improvement of symptoms that are difficult to improve with medical treatment, or to solve problems caused by medication. Symptoms that are difficult to improve with medical treatment include some tremors and axial symptoms. On the other hand, problems caused by medication include motor complications such as fluctuation and dyskinesia, and side effects of medication such as hallucinations, delusions, and impulse control disorders.

In considering indications for DBS[8], a correct diagnosis of idiopathic PD is essential. A good response to levodopa is a good indicator of a correct diagnosis of PD. Atypical parkinsonism or secondary PD are not indications for DBS. The most appropriate surgical candidate for DBS is a patient who suffers from the motor complications of dopaminergic medications such as fluctuation and dyskinesia. A patient who suffers from disabling tremor despite optimal medical treatment is also a good candidate for DBS. Furthermore, patients with dementia or active psychiatric issues are not indicated for DBS. Ideally, the patient should also be young (i.e., less than 70 years of age), although carefully-selected older patients can also be candi-

date. Some experts recommend excluding patients based on a mini-mental state examination cutoff score of 24.

As described below, STN-DBS can reduce the dose of antiparkinsonian dopaminergic medication with improved motor function. Therefore, it is indicated for patients suffering from medication-induced psychotic symptoms such as hallucinations and delusions[9].

Clinical outcomes

The theoretical target of DBS based on the pathophysiology of PD is the STN or the GPi. An early comparative study revealed the superiority of STN-DBS in improvement of motor scores in the medication-off period and reduction of dopaminergic medication[10]. Consequently, the STN has long been the most common target of DBS for PD.

STN-DBS results in a significant reduction in the Unified Parkinson's Disease Rating Scale (UPDRS) motor score in the medication-off state but does not alter the score in the medication-on state. STN-DBS effectively improves levodopa-responsive symptoms of PD and significantly reduces dyskinesia, motor fluctuation, and the dose of dopaminergic medication. Several controlled randomized studies demonstrated that STN-DBS yielded better outcomes in motor function and quality of life (QOL) than medical treatment alone for advanced PD patients[11-13].

According to a meta-analysis of early outcomes, STN-DBS improves UPDRS III motor scores in the medication-off state by 52% and UPDRS II activities of daily living (ADL) score by 50%. STN-DBS also reduces dyskinesia by 69%, the daily off period by 68%, and the dose of dopaminergic medication by 56%. Average improvement in quality of life (QOL) using PDQ-39 is 35%[14]. As a result, STN-DBS provides a second honeymoon period for patients suffering from the motor complications of dopaminergic medication.

Postural abnormality such as camptocormia or Pisa syndrome are one of the most difficult condition to treat. Postural abnormality could be corrected by DBS in some patient although the long-term benefit is limited[15]. Early introduction of DBS after onset of postural abnormality is beneficial.

The effect of STN-DBS on impulse control disorders (ICD) and dopamine dysregulation syndrome (DDS) is controversial[16]. Preexisting ICD or DDS is improved by considerable reduction of dopaminergic medication in some patients.

In this way, STN-DBS is currently the most effective surgical treatment for advanced PD because it has an overwhelming effect on motor symptoms and can solve many medication-induced problems by reducing the dose of dopaminergic medication.

Complications of DBS

A significant incidence of adverse effects associated with DBS in PD has been reported[17]. Most are mild and transient, but serious morbidity is also reported. According to a large study (1,183 patients)[18], the mortality rate during the first 30 postoperative days after stereotactic surgery is 0.4% and the permanent surgical morbidity rate is 1%. The morbidity is mainly caused by intracerebral hemorrhage (ICH) (2.2%). An analysis of adverse events in published data revealed that common surgery-related complications included 2.0% with symptomatic ICH and 2.0% with infections in 928 STN-DBS cases[19].

The neuropsychological aspects of STN-DBS have recently received considerable attention and many studies concerning neuropsychological outcome after STN-DBS have been performed[20]. Mood changes including hypomania or depression are common adverse effects in patients treated with STN-DBS. Most are usually transient in the immediate postoperative period. The spread of stimulation to the limbic STN seems to be a cause of altered mood states[21]. On the other hand, depression or apathy occurring several months after surgery often coincides with excessive reduction of dopaminergic medication, and is generally improved by increasing the dose.

There are many studies on cognitive outcomes after STN-DBS. Most concluded that STN-DBS is relatively safe from a cognitive perspective despite mild cognitive morbidity. A meta-analysis of cognitive sequelae revealed small but significant declines in executive function and verbal learning and memory, and moderate declines in both semantic and phonemic verbal fluency after STN DBS[22].

Several factors are considered to contribute to cognitive changes after STN-DBS. As the STN has widespread connections with basal ganglia and the

prefrontal cortex[21], the direct effect of stimulation may contribute to cognitive changes. Furthermore, the impact of surgical intervention or drastic postoperative reduction of dopaminergic medication may cause cognitive decline[23].

Long-term outcomes

There are many studies of long-term (more than 5 years) outcomes of STN-DBS[24]. In most studies, effects of STN-DBS were mostly preserved even 5 years after surgery. For each symptom, improvements in cardinal motor symptoms such as tremor, rigidity, and bradykinesia are well maintained 5 years after surgery. However, axial symptoms affecting speech, gait, and postural instability progressively worsened. These symptoms are refractory to both medication and DBS. The symptoms of gait disturbance or postural instability seem to be mediated by nondopaminergic mechanisms. STN-DBS improves only the dopamine-mediated motor symptoms. Therefore, the aggravation of axial symptoms reflects the progression of PD itself.

There have been a few reports on long-term outcomes of STN-DBS of greater than 5 years[25]. According to these reports, not only deterioration of axial motor symptoms but also cognitive decline affect worsening of ADL.

As for survival of patients with PD, Ngoga et al demonstrated that patients with STN-DBS have significantly longer survival than those who are treated only by medication. STN-DBS markedly reduces the death rate related to respiratory complications, such as pneumonia[26].

Timing of surgery

The timing of DBS surgery is one of current topics. The general course of PD with only medical treatment is shown in Figure 3A. After onset, patients remain well with medication for several years (honeymoon period). However, most patients subsequently suffer from motor complications of dopaminergic medication such as fluctuation and dyskinesia. In the advanced stage, treatment-resistant axial symptoms and cognitive decline appear. Until now, DBS has been considered as a last resort after medical treatment, and was usually introduced in the late phase of motor complications (Figure 3B). In this situation, patients could achieve a second honeymoon period after DBS, but treatment-resistant axial symptoms appeared in several years. Currently, early introduction of STN-DBS is recommended based on new evidence (EARLYSTIM study)[27]. This study demonstrated that STN-DBS also improved QOL and motor function in PD with early motor complications. In this situation, the second honeymoon period will be much longer (Figure 3C).

Surgical procedure

The surgical procedure for STN-DBS varies among centers[28]. There is some controversy about surgical aspects of DBS. Currently, DBS leads are implanted into the target area stereotactically under magnetic resonance imaging (MRI) guidance with physiological refinement by microelectrode recording (MER) under local anesthesia in most centers. DBS surgery proceeds logically, and although a certain amount of experience is required to make various decisions during surgery, anyone can complete it by performing several steps steadily.

As recent progress in MRI technology has enabled direct visualization of the STN, some groups avoid using MER for placement of the DBS lead. They insist that MER may increase the risk of ICH. The combination of MER and hypertension will definitely increase the incidence of bleeding. However physiological refinement by MER is the gold standard for identifying the STN and its borders. The optimal region for STN stimulation might be missed due to individual anatomical variations or intraoperative brain shift. In our own series, about 20% of cases required two or more trajectories to obtain sufficient activity of STN by MER[29].

Current new technology

Recent advancement of DBS device are remarkable. A conventional IPG has a primary cell battery, and IPG replacement surgery is necessary every 4-5 years. Currently, a rechargeable IPG is developed. Rechargeable IPG have a battery life of over 15 years.

MRI was not officially approved for patients with a conventional IPG. However, most current IPGs are MRI compatible under specific conditions of use.

The new technology of the multiple independent current control (MICC) provides independent current settings in eight contacts in one lead[30].

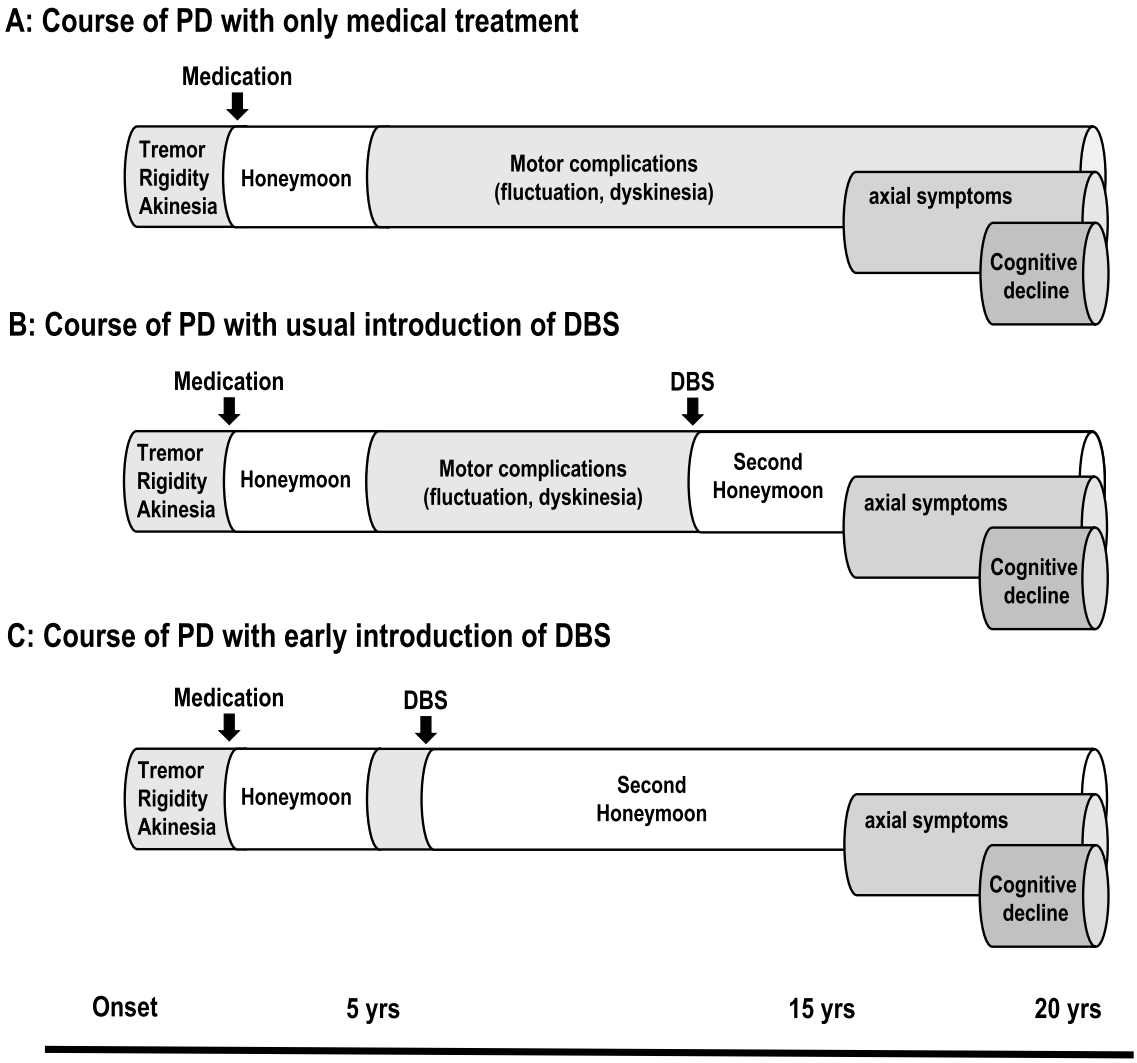

Figure 3 Timing of DBS in long-term course of PD

Amplitude of each contact is freely adjustable regardless of each impedance. Newly developed directional lead is constructed by 4 contact levels like a conventional 4-contact ring electrode, and total of 8 contacts. The middle two contacts consist of 3-segment electrode with each direction of 120 degree, and distal and proximal contacts are conventional ring electrode[31]. Combination of MICC technology and the directional lead enabled both vertical and horizontal current steering on purposes. Consequently, MICC directional lead is useful to explore more precise control of motor symptoms and also useful to avoid stimulation-induced adverse effect (Figure 4).

Currently, pathological beta-oscillation recorded from the STN in local field potential recording is the most noteworthy phenomenon in the condition of PD[32]. The concept of the adaptive DBS is based on a closed-loop model (Figure 5). In adaptive DBS, stimulation amplitude is adjusted according to the detection of pathological beta-oscillation[33]. The world's first DBS case using commercialized adaptive DBS device was reported from Juntendo Nerima Hospital[34]. This case demonstrated that the stimulation successfully adapted to beta oscillation fluctuations without any stimulation-induced side effects. This new stimulation method provides new insights into the pathophysiological mechanisms of PD.

Conclusions

More than twenty years have passed since DBS was introduced in the treatment of PD in Japan. Currently, STN-DBS is the most promising surgical treatment option for patients with medically refractory PD. DBS is also used for other movement

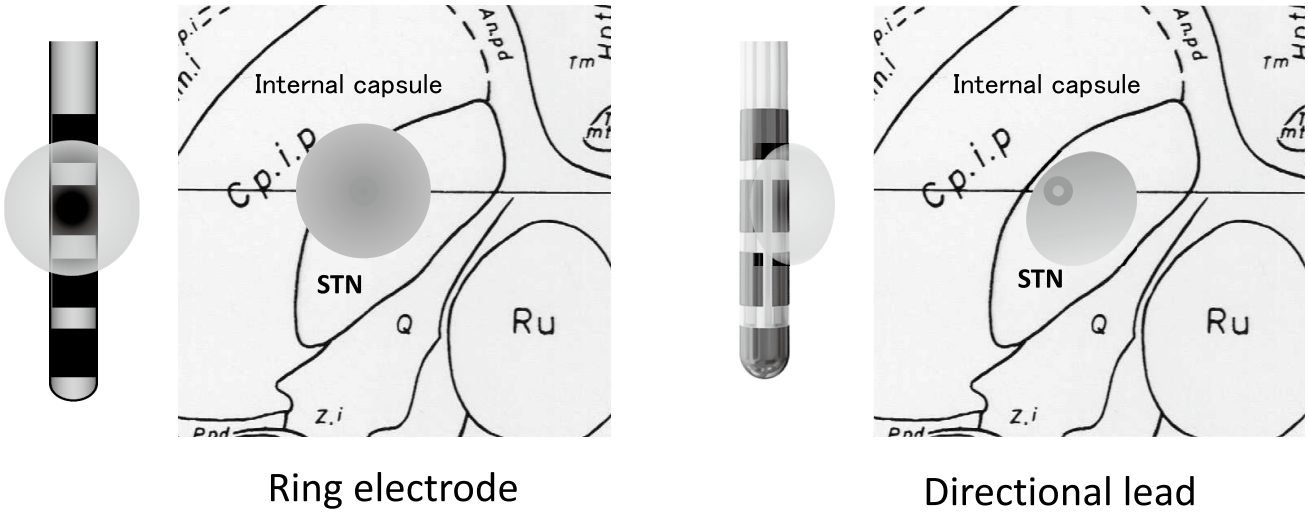

Figure 4 Current steering with directional lead
In the conventional ring electrode, increasing amplitude spread stimulation to the internal capsule and induce adverse effect (left). This adverse effect can be avoided by current steering using directional lead (right).

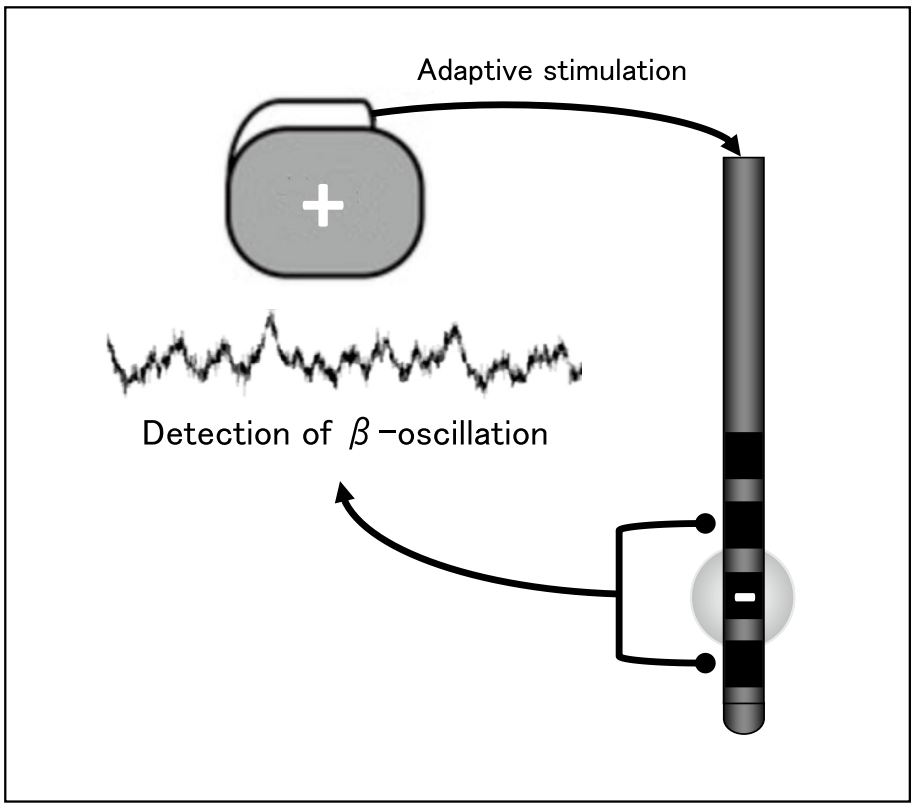

Figure 5 Concept of adaptive DBS

disorders and neuropsychiatric diseases. DBS has evolved along with the development of surgical procedures and device technology.

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Author contributions

AU wrote the manuscript.

Conflicts of interest statement

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Abstract

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Assessment of iPS Cell-derived Dopaminergic Progenitor Cells Properties with Long-term Passaging and Amplification

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Key words: induced pluripotent stem cell, neural stem cell, neurosphere, genomic stability, dopaminergic neuron

Dopaminergic (DA) progenitor cells derived from iPSCs have the potential as a resource of regenerative medicine for Parkinson's disease. Since the safety of cells derived from iPSCs requires a lot of quality assurance, mainly safety verification, autologous transplantation is difficult for practical use, and it is necessary to prepare cell stocks with guaranteed safety. Since undifferentiated iPSCs have genomic instability[1)], there is a risk of causing genomic structural abnormalities when large numbers are cultured for creating large stocks. On the other hand, differentiated cells are presumed to have a relatively stable genome structure, so we thought it would be safer to amplify them after induction. Neurospheres are an efficient method to expand the number of neural stem cells by passaging. However, it was unclear how long these properties, such as regional identity, proliferation, neuronal differentiation, and genomic stability, would be maintained. To reveal this problem, we passaged the neural stem cells using neurospheres differentiated from two types of healthy control-iPS cells from different somatic cells (201B7 and aTKA4) to ensure versatility and tried to evaluate the changes in their properties.

Primary Neurospheres (PNS) were induced from healthy control-derived human iPSCs (201B7 and aTKA4) after treatment with three inhibitors as previously described with purmorphamine and CHIR99021 to provide the regional identity of the ventral midbrain[2)]. Neurospheres were passaged every seven days to form secondary neurospheres (2NS), tertiary neurospheres (3NS), and so on up to 10NS. Then, the properties of neurospheres were evaluated by cell proliferation, qPCR, and Karyotype analysis. Then, neurospheres were differentiated into DA neurons in vitro and evaluated differentiation efficiency by immunostaining against Tyrosine Hydroxylase (TH), a dopaminergic neuron marker, and β-III-tubulin, a neuron marker.

The growth rates of neurospheres calculated by cell counts showed that cell proliferation of 201B7

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and aTKA4 were not changed until 10NS. qPCR analysis revealed that the expression levels of midbrain markers (EN1, FOXA2, LMX1A, and TH) were not changed after 2NS to 10NS, and the expression levels of forebrain markers (SIX3 and FOXG1) and hindbrain markers (HOXB4 and HOXC4) were low at 2NS and 3NS. Similar results were obtained for 201B7 and aTKA4. Immunocytochemical staining was performed with antibodies against TH. An immunofluorescence study performed on 2NS and 10NS showed that the percentage of TH+ neurons was 34.7±7.2% (201B7-2NS), 29.0±3.2% (201B7-10NS), 27.9±6.7% (aTKA4-2NS), 24.1±4.0% (aTKA4-10NS). These results showed that dopamine neuronal differentiation efficiency is stable from 2NS to 10NS. Chromosomal integrity, karyotyping, and genotyping of neurospheres were analyzed by Karyostat Array (ThermoFisher SCIENTIFIC). Whole Genome View showed that no new significant mutations were detected in 201B7 and aTKA4 after nine passages. Undifferentiated iPSC genomes are known to be unstable, and they are easily mutated by passaging. However, karyotyping results showed that they rarely mutate after their differentiation into neurospheres and subsequently passaging.

Ventral midbrain-specific neurospheres induced by our method can be maintained with stable quality for at least 70 days in any iPS cell lines. These results suggest that given the stability of the genome, neurosphere-based passaging and amplification is the preferred method for large-scale culture of neural stem cells.

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Author contributions

NR, TS, KI, and WA conceived and designed the experiments. TM and NR performed the experiments and analyzed the data. TM, KI, NH and WA wrote and revised the manuscript. All authors have reviewed and approved the manuscript.

Conflicts of interest statement

The authors declare that there are no conflicts of interest.

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Original Articles

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Concomitant Mitral Valve Surgery Versus No Intervention in Patients with Moderate Ischemic Mitral Regurgitation Undergoing Coronary Artery Bypass Grafting: A Propensity Score Analysis

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Objectives: Ischemic mitral valve regurgitation (IMR) in patients undergoing coronary artery bypass grafting (CABG) is associated with worse long-term outcomes. This study aimed to assess the impact of mitral valve repair with CABG in patients with moderate IMR.

Materials: This observational study enrolled 3,215 consecutive patients from the Juntendo CABG registry with moderate IMR and multivessel coronary artery disease who underwent CABG between 2002 and 2017.

Methods: The CABG alone and CABG with mitral valve surgery (MVs) groups were compared. The propensity score was calculated for each patient. Long-term all-cause death, cardiac death, and major adverse cardiac and cerebrovascular events (MACCEs) were compared.

Results: Our database had 101 patients who underwent CABG with moderate IMR. Propensity score matching selected 40 pairs for final analysis. MVs was associated with increased risks of postoperative atrial fibrillation, blood transfusion, and longer hospitalization. Long-term outcomes, including all-cause mortality, cardiac mortality, and the incidence of MACCEs were similar.

Conclusion: Surgical treatment of moderate IMR combined with CABG was related to increased risk of several non-fatal short-term complications when compared to CABG alone, with similar long-term outcomes. Further studies are needed to determine the effects of MVs in patients with moderate IMR and severe coronary artery disease.

Key words: ischemic MR, coronary artery bypass grafting, cardiac surgery

Introduction

Ischemic mitral regurgitation (IMR) is a disorder with poor prognosis caused by ischemic heart disease. The mechanisms of IMR involve mitral leaflet tethering due to papillary muscle displacement and increased interpapillary muscle distance, based on impaired left ventricular (LV) systolic function, LV remodeling and dilatation, and mitral valve annulus dilation[1, 2]. Thus, IMR is recognized as both a valvular disease and an LV disorder.

IMR severity is changed by preload, afterload, and the development of myocardial ischemia. It is known that LV reverse remodeling with improvement of myocardial ischemia leads to reduction of mitral regurgitation (MR)[2]. Thus, it is difficult to establish reliable treatment strategies for IMR, especially in cases of moderate IMR, where performing coronary artery bypass grafting (CABG) alone or CABG together with mitral valve surgery (MVs) remains controversial[3, 4].

This study compared the short-term and long-term outcomes of CABG alone and CABG together with MVs in patients with moderate IMR.

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Materials and Methods

Study design

This was a retrospective, observational cohort study of prospectively collected data. The protocol for this study was approved by our institutional research ethics committee (H20-0389). We applied Opt-out method to obtain consent on this study through oral information, without a written document. Consecutive patients who underwent CABG between 2002 and 2017 were examined. Patients who had multivessel coronary artery disease and moderate IMR were selected. Patients were further divided into two groups: those who underwent CABG alone and those who underwent CABG with MVs. Before propensity score matching, baseline characteristics were analyzed for the whole sample cohort. The propensity score was calculated for each patient from the results of multivariate logistic regression analysis. Long-term all-cause death, cardiac death, and incidence of major adverse cardiac and cerebrovascular events (MACCEs) were compared between the two groups. Exclusion criteria included any echocardiographic findings of degenerative (chordal or leaflet) mitral valve disease or ruptured papillary muscles. Patients who had a history of previous cardiac surgery were also excluded from the present study.

Patient data and follow-up

Patient data, including preoperative characteristics, operative data, and postoperative outcomes, were collected from the Juntendo CABG database. Remote outcomes were collected by serial contact (every 3 years) with patients or their families until September 2018. Study coordinators called participants to ask them about adverse events.

Study outcomes and definitions

The endpoints to compare the efficacy of the two strategies were hospital outcomes, all-cause death, and MACCEs. Postoperative death was defined as death within 30 days of surgery. Postoperative stroke was defined as a new stroke diagnosed on magnetic resonance imaging (MRI) or computed tomography (CT). Postoperative acute kidney injury was defined by a greater than 50% increase in serum creatinine level from baseline. Cardiac death was defined as death by myocardial infarction, congestive heart failure, arrhythmia, or sudden death. The definition of MACCEs included all-cause death, nonfatal myocardial infarction, target vessel revascularization, heart failure requiring hospital admission, and stroke.

Qualifying transthoracic echocardiography was performed before surgery. MR severity was defined based on the criteria recommended by the American Society of Echocardiography[5]. If leaflet or chordal abnormalities (i.e., primary MR) coexisted, these cases were excluded from the study.

Operative procedures

All patients underwent surgery with median sternotomy. In isolated CABG cases, off-pump coronary artery bypass (off-pump CABG), which involves performing CABG on the beating heart without cardiopulmonary bypass, was usually performed.

In CABG and MVs cases, cardiopulmonary bypass was established with ascending aorta and right atrial cannulation. Cardiac arrest was obtained with both antegrade and retrograde blood cardioplegia. The strategies for mitral valve intervention were left to the surgeons' discretion. Mitral valve repair was performed by restrictive mitral annuloplasty (MAP) using an artificial ring to correct annular dilatation. Mitral valve replacement was performed with preservation of the posterior leaflet or subvalvular apparatus. The techniques of mitral valve repair and the choice of prosthetic valve were determined by the surgeons.

Statistical analysis

Continuous variables are expressed as means ± standard deviation, and categorical data are tabulated as frequencies and percentages. These data were compared using Student's t-test or Mann-Whitney U test for continuous variables, and the χ^2 test or Fisher's exact test for categorical variables. The propensity score was calculated for each patient from the results of multivariate logistic regression analysis based on preoperative covariates as independent variables with CABG alone vs. CABG plus MVs as binary dependent variables. The following preoperative patient characteristics were the exploratory variables of the logistic regression model: sex, age, BSA, diabetes (yes/no), dyslipidemia (yes/no), hypertension (yes/no), esti-

mated GFR (mL/min/1.73m^2), history of cerebrovascular accident (yes/no), peripheral artery disease (yes/no), history of myocardial infarction (yes/no), LV ejection fraction, preoperative atrial fibrillation (yes/no).

Short-term postoperative complications were compared between the two groups. Long-term all-cause death, cardiac death, and MACCEs were compared, and the Kaplan-Meier method with the log-rank test was used for these survival analyses. A Cox proportional-hazards model was used to assess the association between the survival time of these events and one or more predictor variables, that were determined with reference to previous other studies. Values of $p<0.05$ were considered significant. All data were analyzed using SPSS version 23.0 for Windows (SPSS, Chicago, IL).

Results

Patients' characteristics and operative data

A total of 3,215 patients underwent CABG between 2002 and 2017. Of these patients, 101 who had multivessel coronary artery disease and moderate IMR were eligible for the study. These 101 patients were divided into two groups, 60 (59.4%) who underwent CABG alone and 41 (40.6%) who underwent CABG with MVs. Propensity score matching selected 40 pairs for final analysis. The p-value of the Hosmer-Lemeshow test for the model was 0.787, and the c-statistic (area under the ROC curve) was 0.707. The mean propensity score of the CABG alone group was 0.50±0.25, and that of the CABG plus MVs group was 0.58±0.22. A higher propensity score indicated a higher probability of undergoing CABG with MVs at baseline.

Comparison of baseline characteristics between the CABG alone and CABG plus MVs groups before and after propensity score matching is shown in Table 1. Even before propensity score matching, there were no significant differences between the two groups in the variables.

Operative parameters are shown in Tables 2 and 3. Overall, 95% of patients (n=38) in the CABG alone group underwent CABG without cardiopulmonary bypass (off-pump CABG). The number of coronary anastomoses was comparable between the

Table 1 Baseline characteristics of patients undergoing CABG alone vs. CABG + MVs

	Before matching			After matching		
	CABG (N=60)	CABG + MVs (N=41)	p-value	CABG (N=40)	CABG + MVs (N=40)	p-value
Age (y) mean ± SD	68.9 ± 9.4	68.2 ± 8.6	0.720	69.5 ± 9.6	68.2 ± 8.7	0.536
Sex male, n (%)	48 (80.0%)	33 (80.4%)	0.556	34 (85.0%)	32 (80.0%)	0.562
BSA (m^2), mean ± SD	1.63 ± 0.14	1.65 ± 0.12	0.478	1.63 ± 0.13	1.65 ± 0.12	0.660
Diabetes mellitus, n (%)	37 (61.6%)	21 (51.2%)	0.314	25 (62.5%)	21 (52.5%)	0.372
HbA1c (%), mean ± SD	6.4 ± 1.1	6.1 ± 1.2	0.225	6.4 ± 1.1	6.1 ± 1.2	0.255
Dyslipidemia, n (%)	42 (70.0%)	24 (58.5%)	0.234	28 (70.0%)	24 (60%)	0.348
Serum TG level (mg/dL), mean ± SD	118.0 ± 59.4	111.8 ± 46.2	0.576	115.0 ± 56.9	112.9 ± 46.2	0.857
Serum LDL cholesterol level (mg/dL), mean ± SD	102.8 ± 38.8	100.8 ± 29.7	0.787	93.6 ± 36.4	100.5 ± 30.0	0.363
Hypertension, n (%)	46 (75.4%)	30 (75.0%)	0.689	34 (85.0%)	30 (75.0%)	0.263
Estimated GFR (mL/min/1.73m^2), mean ± SD	50.3 ± 27.8	48.6 ±39.2	0.808	48.2 ± 24.7	49.6 ± 30.2	0.850
History of cerebrovascular accident, n (%)	10 (16.6%)	5 (12.1%)	0.373	7 (17.5%)	4 (10.0%)	0.336
Peripheral artery disease, n (%)	8 (13.3%)	7 (17.0%)	0.777	6 (15.0%)	7 (17.5%)	0.765
History of myocardial infarction, n (%)	8 (13.3%)	8 (19.5%)	0.403	5 (12.5%)	8 (20.0%)	0.363
BNP (pg/mL), mean ± SD	760.8 ± 1512.6	613.2 ± 781.0	0.574	504.7 ± 568.6	613.2 ± 781.0	0.480
LVEF (%), mean ± SD	41.1 ± 13.2	37.6 ± 16.5	0.251	37.5 ± 11.2	34.8 ± 14.5	0.382
Preoperative AF, n (%)	4 (6.6%)	7 (17.0%)	0.094	3 (7.5%)	7 (17.5%)	0.181
EuroSCORE II (%), mean ± SD	6.8 ± 8.6	7.5 ± 6.9	0.699	5.9 ± 7.7	7.5 ± 6.9	0.365
Japan SCORE (%), mean ± SD	5.6 ± 11.9	7.5 ± 12.2	0.497	5.5 ± 13.1	7.5 ± 12.2	0.516

Abbreviations: AF, atrial fibrillation; BNP, brain natriuretic peptide; BSA, body surface area; HbA1c, hemoglobin A1c; LVEF, LV ejection fraction; TG, triglycerides

Table 2 Operative data of patients undergoing CABG alone vs. CABG + MVs

	CABG (N=40)	CABG + MVs (N=40)	p-value
Preoperative IABP, n (%)	2 (5.0%)	1 (2.5%)	0.556
Number of grafts selected, mean ± SD	2.7 ± 0.7	2.4 ± 0.7	0.142
Left internal thoracic artery, n (%)	39 (97.5%)	35 (87.5%)	0.090
Bilateral internal thoracic artery, n (%)	30 (75.0%)	19 (47.5%)	0.012
Radial artery, n (%)	3 (7.5%)	2 (5.0%)	0.644
Gastroepiploic artery, n (%)	20 (50.0%)	17 (40.2%)	0.501
Saphenous vein graft, n (%)	16 (40.0%)	25 (60.2%)	0.044
Number of distal anastomoses, mean ± SD	3.7 ± 1.4	3.6 ± 1.7	0.725
Off-pump surgery	38 (95%)	0 (0.0%)	
Operation time duration (min), mean ± SD	300.3 ± 74.4	468.2 ± 124.2	< 0.001
Aorta cross clump time (min), mean ± SD	-	105.8 ± 51.2	
Cardiopulmonary bypass (min), mean ± SD	159.0 ± 14.1	188.3 ± 76.0	0.586

Abbreviations: IABP, intra-aortic balloon pump

Table 3 Details of mitral valve procedures

Procedure	CABG + MVs (N=40)
Mitral annuloplasty (MAP) alone, n (%)	17 (42.5%)
MAP + Procedure of MV leaflet or subvalvular apparatus, n (%)	19 (47.5%)
Leaflet edge-to-edge repair, plication, chordal cutting, n (%)	7 (17.5%)
Chordal cutting, n (%)	5 (12.5%)
Papillary muscle approximation (PMA), n (%)	10 (25.0%)
LV reconstruction, n (%)	5 (12.5%)
Mitral valve replacement, n (%)	4 (10.0%)

Table 4 Preoperative echocardiography of patients undergoing CABG alone vs. CABG + MVs

	CABG (N=40)	CABG + MVs (N=40)	p-value
Left atrial diameter (mm), mean ± SD	44.7 ± 6.7	47.3 ± 8.8	0.192
Mitral annulus diameter (mm), mean ± SD	34.1 ± 5.5	31.5 ± 3.8	0.105
LV diastolic dimension (mm), mean ± SD	58.5 ± 7.3	59.2 ± 7.7	0.735
LV systolic dimension (mm), mean ± SD	48.6 ± 10.0	47.6 ± 11.5	0.720
LV EDVI (mL/m2), mean ± SD	101.9 ± 38.0	110.7 ± 41.3	0.388
LV ESVI (mL/m2), mean ± SD	64.6 ± 31.5	74.6 ± 39.8	0.278
ERO (PISA), mean ± SD	0.26 ± 0.06	0.26 ± 0.08	0.827
RV (PISA) (mL), mean ± SD	39.3 ± 10.8	42.5 ± 15.7	0.443
Tenting height (mm), mean ± SD	10.8 ± 2.3	9.8 ± 2.0	0.178
LVEF (%), mean ± SD	37.5 ± 11.2	34.8 ± 14.5	0.382

Abbreviations: Dd, diastolic dimension; Ds, systolic dimension; EDVI, end-diastolic volume index; ERO, effective regurgitant orifice; ESVI, end-systolic volume index; LV, left ventricular; LVEF, LV ejection fraction; RV, regurgitant volume

two groups (3.7±1.4 vs. 3.6±1.7; p=0.52). In the CABG alone group, the rate of using bilateral internal thoracic arteries was significantly higher (75.0% vs. 47.5%; p=0.012), and saphenous vein grafts were less likely to be used (40.0% vs. 62.5%; p=0.07). The mean operation time was significantly longer in the CABG plus MVs group than in the CABG alone group.

Preoperative echocardiogram data are shown in Table 4. The preoperative echocardiogram at base-

line showed no significant differences between the two groups in LV ejection fraction (LVEF) (39.3%±12.8% vs. 36.7%±15.5%), LV size (LVDd, Ds, EDVI, ESVI), mitral annular diameter size, and degree of IMR or tethering (ERO and RV(PISA), tenting height).

Short-term outcomes

The postoperative short-term outcomes are shown in Table 5. There was no early death in the CABG alone group, and only one death in the CABG plus MVs group (1.25% of all matched patients). The incidences of stroke, respiratory failure or pleural effusion, acute kidney injury, and re-exploration for bleeding were similar between the two groups. When compared with the CABG alone group, the incidences of postoperative atrial fibrillation (37.5% vs. 62.5%, p=0.025) and postoperative blood transfusion (40.0% vs. 75.0%, p=0.002) were higher, and the mean lengths of ICU stay and hospital stay (3.2 days vs. 6.0 days, p=0.084, 13.6 days vs. 18.1 days, p=0.035, respectively) were much longer in the CABG plus MVs group.

Long-term outcomes

The median follow-up period was 3.6 (1.4-8.1) years. Cumulative event-free curves with log-rank tests are shown in Figure 1. Long-term all-cause mortality, cardiac mortality, and the incidence of MACCEs were similar between the groups. There was no reoperation in both groups. Five-year survival rates for patients in the CABG alone group and in the CABG plus MVs group were 80% and 77%, respectively. Concomitant MVs was not associated with an increased risk of long-term all-cause death or MACCE. Table 6 shows Hazard ratios of several risk factors for long-term all-cause mortality, cardiac mortality, and the incidence of MACCEs, calculated by a Cox proportional-hazards model. History of cerebrovascular accident was an independent risk factor for these long-term events.

Discussion

This propensity matched study evaluated the

Table 5 Hospital outcomes of patients undergoing CABG alone vs. CABG + MVs

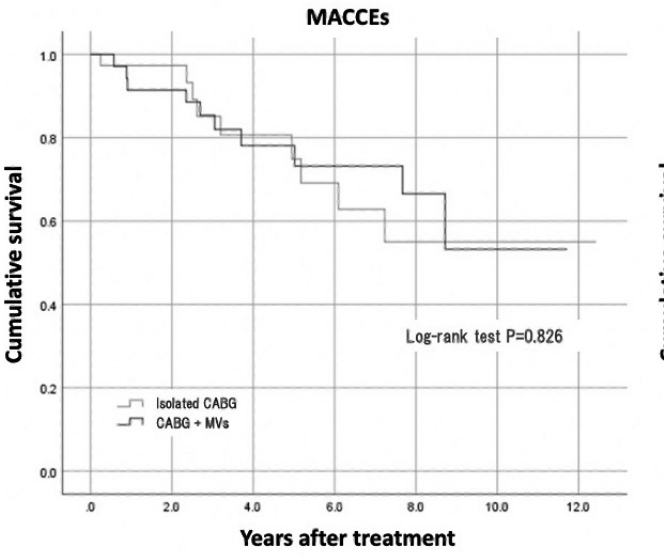
A) All 101 patients

	CABG (N=60)	CABG + MVs (N=41)	p-value
In-hospital death, n (%)	3 (5.0%)	2 (%)	0.676
Postoperative AF, n (%)	22 (36.6%)	26 (63.4%)	0.007
Postoperative stroke, n (%)	1 (1.6%)	1 (2.4%)	0.650
Respiratory failure / Pleural effusion, n (%)	13 (21.6%)	13 (31.7%)	0.183
Acute kidney injury, n (%)	6 (10.0%)	6 (14.6%)	0.343
Blood transfusion, n (%)	25 (41.6%)	31 (75.6%)	0.001
Re-exploration for bleeding, n (%)	0 (0.0%)	1 (2.4%)	0.406
Length of ICU stay (day), mean ± SD	3.2 ± 3.5	5.8 ± 9.2	0.089
Length of hospital stay (day), mean ± SD	13.4 ± 8.4	17.7 ± 9.8	0.021

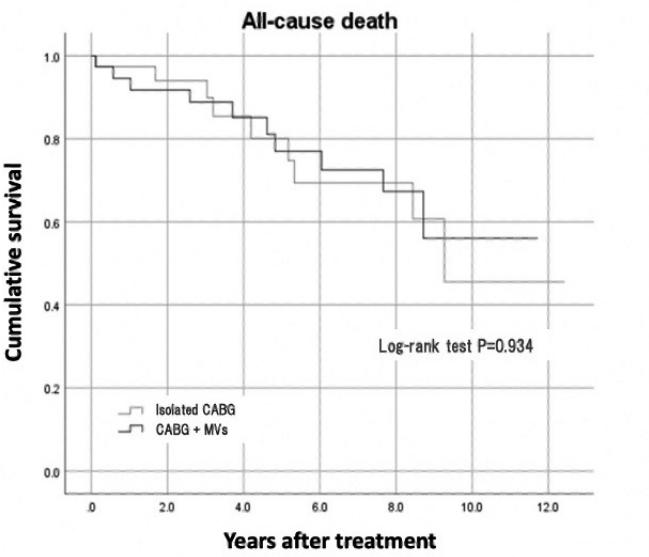
B) Matched patients

	CABG (N=40)	CABG + MVs (N=40)	p-value
In-hospital death, n (%)	0 (0.0%)	1 (2.5%)	0.314
Postoperative AF, n (%)	15 (37.5%)	25 (62.5%)	0.025
Postoperative stroke, n (%)	1 (2.5%)	1 (2.5%)	1.0
Respiratory failure / Pleural effusion, n (%)	6 (15.0%)	12 (30%)	0.108
Acute kidney injury, n (%)	3 (7.5%)	6 (15.0%)	0.288
Blood transfusion, n (%)	16 (40.0%)	30 (75%)	0.002
Re-exploration for bleeding, n (%)	0 (0.0%)	0 (0.0%)	
Length of ICU stay (day), mean ± SD	3.2 ± 4.1	6.0 ± 9.3	0.089
Length of hospital stay (day), mean ± SD	13.6 ± 8.9	18.1 ± 9.6	0.035

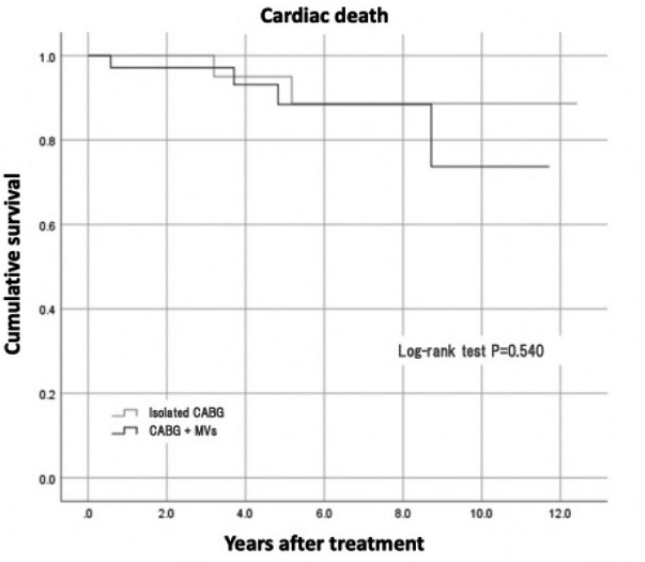
Abbreviations: AF, atrial fibrillation; LVEF, left ventricular ejection fraction



Years		1	2	3	4	5	6	7	8	9	10
CABG	At risk(N)	37	25	23	16	15	13	12	11	5	2
	Survival	97%	94%	94%	85%	80%	68%	68%	68%	58%	45%
CABG + MVs	At risk(N)	35	33	28	23	19	18	15	10	6	4
	Survival	95%	92%	89%	85%	77%	77%	72%	67%	56%	56%



Years		1	2	3	4	5	6	7	8	9	10
CABG	At risk(N)	37	25	22	16	14	12	9	8	3	2
	Survival	97%	97%	85%	81%	75%	69%	63%	55%	55%	55%
CABG + MVs	At risk(N)	33	33	26	20	18	15	13	7	5	4
	Survival	92%	92%	85%	78%	78%	73%	73%	67%	53%	53%



Years		1	2	3	4	5	6	7	8	9	10
CABG	At risk(N)	37	25	23	16	15	13	12	11	5	2
	Survival	100%	100%	100%	95%	95%	88%	88%	88%	88%	88%
CABG + MVs	At risk(N)	35	33	28	23	19	18	15	10	6	4
	Survival	97%	97%	97%	93%	88%	88%	88%	88%	74%	74%

Figure 1 Kaplan-Meier survival curves for all-cause death, cardiac death, MACCEs

short-term and long-term outcomes of CABG alone and CABG plus MVs in patients with moderate IMR. In this study, combined mitral valve treatment was associated with increased risks of several postoperative adverse events (atrial fibrillation, postoperative blood transfusion, and prolonged lengths of ICU stay and hospital stay), but short-term mortality and the incidences of stroke, acute kidney injury, bleeding, and respiratory failure were similar between the two groups.

Some studies have shown that off-pump CABG, compared with on-pump CABG, was associated

Table 6 Multivariable predictors for all-cause mortality, cardiac death, and MACCE

	Hazard ratios	95% confidence intervals	p-values
All-cause death			
Combined MV surgery	0.96	0.56 – 1.64	0.886
Age	1.02	0.98 – 1.07	0.179
Sex male	1.28	0.53 – 3.07	0.570
Diabetes mellitus	1.20	0.66 – 2.18	0.530
Peripheral vascular disease	0.90	0.37 – 2.17	0.815
History of cerebrovascular accident	2.51	1.07 – 5.88	0.047
Estimated GFR	0.99	0.98 – 1.01	0.828
LVEF	0.72	0.37 – 1.38	0.327
Cardiac death			
Combined MV surgery	0.97	0.59 – 1.59	0.917
Age	1.02	0.98 – 1.06	0.176
Sex male	1.30	0.58 – 2.87	0.506
Diabetes mellitus	1.06	0.62 – 1.82	0.819
Peripheral vascular disease	1.15	0.56 – 2.36	0.695
History of cerebrovascular accident	2.67	1.21 – 5.88	0.022
Estimated GFR	1.00	0.99 – 1.01	0.804
LVEF	0.67	0.37 – 1.18	0.164
MACCEs			
Combined MV surgery	0.96	0.56 – 1.65	0.897
Age	1.01	0.97 – 1.06	0.510
Sex male	1.16	0.50 – 1.77	0.720
Diabetes mellitus	1.08	0.59 – 1.97	0.799
Peripheral vascular disease	1.18	0.53 – 2.61	0.678
History of cerebrovascular accident	2.63	1.17 – 5.93	0.027
Estimated GFR	1.00	0.99 – 1.01	0.426
LVEF	0.84	0.44 – 1.62	0.618

Abbreviations: MACCEs, major adverse cardiac and cerebrovascular event

with lower risks of mortality, stroke, renal failure, RBC transfusion, prolonged ventilation, inotropic support, and intra-aortic balloon pumping support, especially in higher risk patients[6–8]. In the present study, despite the fact that almost all isolated CABGs were performed without cardiopulmonary bypass, short-term mortality, cerebrovascular events, kidney injury, and respiratory failure were similar between two groups. This result suggests that combined MVs, which needs cardiopulmonary bypass, can be performed in patients with moderate IMR as safely as off-pump CABG. Probable explanations for this finding are improvements of cardiopulmonary bypass, cardioplegia, anesthesia, and perioperative medications[9, 10].

Furthermore, during this study's long-term follow-up period, both groups were similar in all-cause death, cardiac death, and the incidence of MACCEs. In addition, postoperative reverse remodeling was observed in both groups. These findings were consistent with two recent prospective, randomized trials[11, 12]. These studies, which randomized 301 patients with moderate IMR to undertake isolated CABG or CABG plus MAP, showed that moderate or severe residual MR was more frequently observed in patients undergoing CABG alone, but

showed no difference between the two procedures in LV reverse remodeling, mortality, overall adverse events, and readmissions at two years after operation.

On the other hand, these results contradicted other previous studies[13, 14]. Fattouch and colleagues reported the first prospective, randomized study of moderate IMR, comparing patients with undergoing CABG alone or CABG plus MAP for an average of 32 months[13]. They showed that the addition of MAP to CABG significantly improved LV reverse remodeling, severity of MR, and NYHA functional class compared with CABG alone. Similarly, the Randomized Ischemic Mitral Evaluation (RIME) trial[14], which was another randomized study of moderate IMR, demonstrated that oxygen consumption, severity of MR, plasma B-type natriuretic peptide levels, and LV reverse remodeling were improved in patients assigned to CABG plus MVs compared to those assigned to CABG alone. These studies proved the beneficial effects of CABG plus MVs in patients with moderate IMR by showing that concomitant mitral valve restoration not only reduced the degree of severity of mitral valve regurgitation, but also provided an improvement in the NYHA functional class. Therefore, in deciding on additional MVs, the presence of symptoms such as dyspnea, shortness of breath, and heart failure, might be important, which means MR bears more clinical and prognostic significance.

Why various results were observed in studies that compared CABG alone and CABG plus MVs for patients with moderate IMR? One can only speculate on these discrepancies between the results of these studies. Since the mechanisms of IMR are various and complicated[1, 2], patients' characteristics at baseline might be heterogeneous and imbalanced among these studies. For example, when comparing the three clinical trials mentioned above, in the study by Fattouch and colleagues[13] and in the RIME trail[14], patients had significantly higher rates of previous MI and larger LV size, and remodeling was more advanced than in the CTSN trial[12] at baseline. Postoperative echocardiogram showed that the degree of reverse LV remodeling was greater in the first two studies than in the CTSN trial. In each of the three studies, the combined procedure group had a higher rate of postoperative residual or recurrent MR, but there was no significant difference in mortality. What can be inferred from these studies is that combined MVs for moderate IMR is not associated with increased long-term survival, instead, it may contribute to improvement of other endpoints, including LV reverse remodeling, MR grade, and cardio-humoral factors, especially in patients with larger ventricles and advanced LV remodeling at baseline. Conversely, patients with smaller ventricles at baseline can obtain the benefit of LV reverse remodeling from CABG alone to the same extent as CABG plus MVs.

About other factors to predict LV reverse remodeling after CABG, several studies have demonstrated that the presence of preoperative viable myocardium is closely related to improvements in LV reverse remodeling and downgrading of IMR. Reliable improvement in MR after surgery was limited to those who had viable myocardium and less LV dyssynchrony between papillary muscles for patients with moderate IMR who underwent isolated CABG[15, 16]. Conversely, patients whose cardiac muscle has suffered ischemic changes for a long period and are less likely to have sufficient viable cardiac muscle, and those who have fewer or no bypass target to the posterior-inferior-lateral area are not better off with isolated CABG. Unfortunately, myocardial viability were not included in many randomized trial mentioned above, and also in this analysis.

Therefore, to decide whether to perform MVs at the time of CABG in patients with moderate IMR, we should know which patient may benefit most from CABG plus MVs rather than CABG alone. Preoperative evaluation of several factors, such as MR severity, left atrium enlargement or mitral annulus dilatation, LV size and remodeling degree, severity of LV dysfunction, presence of LV scar tissue or myocardial viability, and presence of an efficient bypass target to the posterior-inferior-lateral area, might be helpful to determine the surgical plan[3, 12]. To assess these variables, preoperative stress echocardiography and cardiac catheterization, single photon emission computed tomography (SPECT), and functional cardiac MRI are preferred, if possible[17, 18]. However the ability to predict MR response to CABG alone is still poor because there has been insufficient validation.

In addition, we should also consider patient factors or comorbidities such as age, frailty, number

of bypass targets, renal failure, respiratory failure, peripheral artery disease, thoracic aortic calcification, arteriosclerosis, previous cerebral infarction, etc. The surgeon's experience with MVs is important as well, because the effect of mitral valve repair depends on the accuracy with which it is performed, and if the surgeon lacks experience with mitral valve repair, not adding MVs may be better in order to decrease the duration and total risk of the operation.

This study had several limitations that could affect the interpretation of our findings. Despite the prospective collection of operative data, this was a retrospective study in a single institution. Although propensity score analysis was performed, the number of patients was small because moderate IMR is an uncommon disease. This study was susceptible to various sources of bias. The decision for MVs was not decided based on specific preoperative criteria, and the surgeon determined the surgical details of CABG or MVs, based on various center/patient-specific factors. In addition, myocardial variables such as local wall motion score or viability were not included in this analysis, therefore the relationship between myocardial variables and long-term prognosis were not investigated in this study. Finally, another limitation is that clinical outcomes related to heart-failure symptoms such as NYHA class were not assessed, and neither were improvements in patients' quality of life and physical function, which might be a benefit of a lower incidence of postoperative MR by additional MVs, as some studies have reported.

In conclusion, the present study showed that surgical treatment of moderate IMR combined with CABG could be performed as safe as isolated CABG (off-pump CABG). In contrast, surgical treatment of moderate IMR did not improve long-term outcomes, including all-cause mortality, cardiac mortality, and the incidence of MACCEs. In patients with moderate IMR, the indication for concomitant mitral valve surgery and the problem of whether to replace or repair, and whether to add subvalvular and leaflet approaches to ring annuloplasty, remain controversial. Further studies are necessary to determine the effects of MVs and optimal selection of patient with moderate IMR with severe coronary artery disease.

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Author contributions

JL analyzed and interpreted the patient data, and was a major contributor in writing the manuscript. KK contributed to the design of the work, and revised the manuscript critically. YT was a major contributor in the acquisition of data for the work. All authors read and approved the final manuscript.

Conflicts of interest statement

The authors declare that there are no conflicts of interest.

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Original Articles

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Inhibition of Insulin Secretion Induces Golgi Morphological Changes

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Objectives: The role of autophagy in pancreatic β cells has been reported, but the relationship between autophagy and insulin metabolism is complex and is not fully understood yet.
Design: We here analyze the relationship between autophagy and insulin metabolism from a morphological aspect.
Methods: We observe the morphological changes of β cell-specific Atg7-deficient mice and Atg5-deficient MIN6 cells with electron microscopy.
Results: We find that Atg7-deficient β cells exhibit a marked expansion of the endoplasmic reticulum (ER). We also find that the inhibitory state of insulin secretion causes morphological changes in the Golgi, including ministacking and swelling. The same morphological alterations are observed when insulin secretion is suppressed in Atg5-deficient MIN6 cells.
Conclusions: The defect of autophagy induces ER expansion, and inhibition of insulin secretion induces Golgi swelling, probably via ER stress and Golgi stress, respectively.

Key words: autophagy, pancreatic β cells, ER, Golgi, diazoxide

Introduction

Pancreatic β cells are specialized for the synthesis and secretion of insulin. Because insulin is a hormone that regulates glucose utilization, pancreatic β cells play an essential role in the body by efficiently mobilizing intracellular organelles. For example, mitochondria promote glucose-responsive insulin secretion via the ATP synthesis. Therefore, when mitochondria become dysfunction, insulin secretion is substantially reduced. In the rough endoplasmic reticulum (ER), preproinsulin is biosynthesized[1, 2]. The pre-sequence corresponds to a signal peptide, which is cleaved after translocation into the ER to form proinsulin[3]. After transport to the Golgi apparatus, proinsulin is included into insulin secretory granules and transported out of the cell. During this process, proinsulin is cleaved to become mature

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insulin in the secretory granules[4]. In the β cell, the ER is continually subjected to high levels of ER stress in order to synthesize large amounts of insulin, and hence, further elevated stress enhances the ER stress response and induce cell death[5]. Thus, various organelles function has been analyzed, whereas their morphological observations have not yet been fully analyzed.

Autophagy is a cellular function in which intracellular components are enclosed by a double membrane and are digested by fusing with lysosomes[6]. Autophagic structures are considered as a type of organelle because they are consisted by bio-membranes and perform specific cellular functions. However, unlike other organelles, the number of autophagic structure fluctuates depending on the environment in which the cell is placed. In a steady state, a small amount of autophagic structures degrades small amount of proteins for maintaining cellular homeostasis. On the other hand, under stressful conditions, a large amount of autophagic structures are generated to degrade vast amount of proteins and even organelles[7]. Many papers have reported the role of autophagy in pancreatic β cells. For example, induction of autophagy has been reported in pancreatic β cells of mice challenged with a high-fat diet and of type 2 diabetes model mice. In mice lacking Atg7, an essential molecule for autophagy, in pancreatic β cells, glucose-responsive insulin secretion becomes abnormal, and thereby, the mice showed hyperglycemia after 6 weeks of age[8]. On the other hand, it has been reported that insulin granules are not a substrate for autophagy[9, 10]. Therefore, the relationship between autophagy and insulin metabolism is complex and is not fully understood yet. In order to obtain data to solve this problem, we here analyzed the morphology of organelles in autophagy-deficient pancreatic β cells.

Materials and Methods

Mammalian cell culture

MIN6 cells were kindly provided by Prof. J. Miyazaki (Osaka University). Atg5 KO MIN6 cells were generated by the CRISPR/Cas9 system[10] (Cong et al., 2013). Briefly, a 20-bp mouse Atg5-targeting sequence (GAGAGTCAGCTATTTGACGT) was synthesized (Eurofins) and introduced into px330 (Addgene). MIN6 cells were co-transfected with the plasmid and pcDNA3.1 (Invitrogen), which contains the neomycin gene, and G418 selection (800 μg/ml) was initiated 24 hr later. After 48 hr selection, the MIN6 cells were re-seeded to allow single colony formation. The knockout of Atg5 was confirmed by anti-Atg5 immunoblot. Cells were grown in modified Dulbecco's modified Eagle's medium (DMEM high glucose, Nacalai) supplemented with 0.25 mM 2-mercaptoethanol, 55 U/mL penicillin, 55 g/mL streptomycin, and 11% (v/v) fetal bovine serum in a humidified 5% CO2 incubator at 37°C. For the analysis of glucose depletion, cells were stimulated in low glucose (135 mM NaCl, 3.6 mM KCl, 1.5 mM CaCl2, 0.5 mM NaH2PO4, 0.5 mM MgCl2, 2 mM NaHCO3, 10 mM HEPES, 0.1% BSA, and 2.5 mM glucose, pH 7.4) or control KRB buffer (135 mM NaCl, 3.6 mM KCl, 1.5 mM CaCl2, 0.5 mM NaH2PO4, 0.5 mM MgCl2, 2 mM NaHCO3, 10 mM HEPES, 0.1% BSA, and 25 mM glucose, pH7.4) after PBS wash.

Mice

$Atg7^{flox/flox}$: Rip-cre mice were generated by the crossbreeding of $Atg7^{flox/flox}$ mice with Rip-cre mice[10, 11]. To suppress insulin secretion, 50 mg/kg Diazoxide (SIGMA) was added by peritoneal administration for an hour before perfusion-fixation. Mice were bred in a 12 hr light /12 hr dark cycle at approximately 23°C and 40% relative humidity at the Laboratory for Recombinant Animals of Tokyo Medical and Dental University, Tokyo, Japan. This animal facility is operated according to the NIH guidelines. The Tokyo Medical and Dental University Ethics Committee for Animal Experiments approved all experiments in this study, and all experiments were performed according to their regulations.

Electron microscopy

Mammalian cells were fixed by a conventional method (1.5% paraformaldehyde and 3% glutaraldehyde in 0.1 M phosphate buffer, pH 7.4, followed by an aqueous solution of 1% Osmium Tetroxide). Fixed samples were embedded in Epon 812, and thin sections (70-80 nm) were then cut and stained with uranyl acetate and lead citrate for observation under a Jeol-1010 electron microscope (Jeol) at 80 kV[12, 13].

Results

Morphological characteristics in wild-type pancreatic β cells

First, to analyze the morphological characteristics of pancreatic β cells, we isolated islets from wild-type mice and observed by electron microscopy. Unlike other sort of cells, a large amount of insulin granules were present inside the pancreatic β cells (Figure 1A). In addition, well-developed mitochondria, ER, and Golgi apparatus were observed (Figure 1B), all of which were considered to be actively functioning. Only a few autophagosome was observed (Figure 1C).

Autophagy-deficient pancreatic β cells show inclusion body formation and endoplasmic reticulum expansion

Next, we generated mice lacking Atg7 in pancreatic β cells by cross-breeding $Atg7^{flox/flox}$ mice with Rip-cre mice[10, 11]. These mice have been shown to have pancreatic β cells in which autophagy does not occur. We observed Atg7-deficient β cells by electron microscopy, and there was no significant difference in the amount or location of insulin granules from wild-type β cells (Figure 2A). On the other hand, the most significant change was the presence of inclusion bodies (Figure 2A), whose internal structure was a dense meshwork of filamentous assemblies (Figure 2B), in a large number of cells. Because p62 is known to accumulate in Atg7-deficient β cells and the electron microscopic findings are completely identical to the previously reported p62 granules[14], this inclusion body was considered to be a p62 granule.

Another significant morphological change was observed in the ER, which was observed to have a bulging lumen and a small amount of ribosomes attached to it (Figure 2C), as well as layered ER (Figure 2D). Such abnormal ER morphology is often observed in the cells with excess ER stress[15]. The structures within the ER lumen are fibrous (Figure 2C), and judging by their shape, they were suspected to be unfolded polypeptides. In pancre-

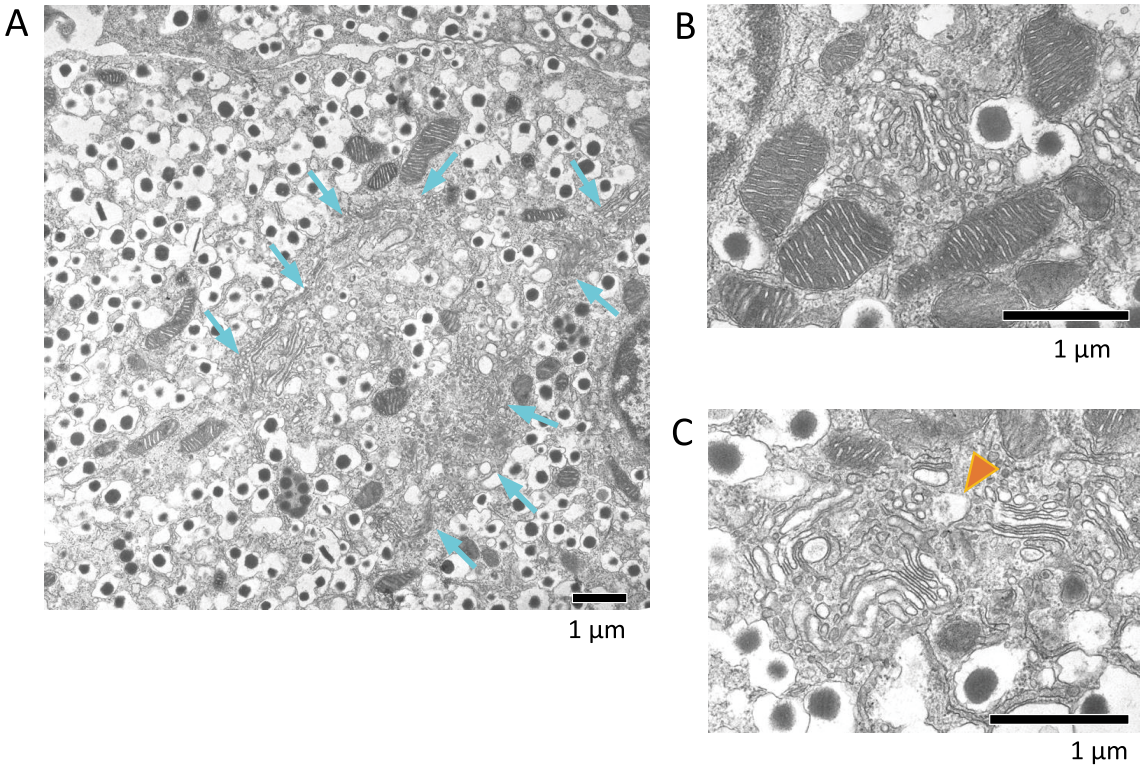

Figure 1 EM analysis of β cells from wild-type mice
Islet is isolated from wild-type mice, and β cell was observed by EM. (A) The cytoplasm is filled with insulin granules. In the center of them, there is a Golgi apparatus (blue arrows). (B) Mitochondria are energized. (C) Ribbon shaped-Golgi apparatus is surrounded by insulin granules. Small-sized autophagic vacuole (orange arrowhead) is existed close to Golgi apparatus.

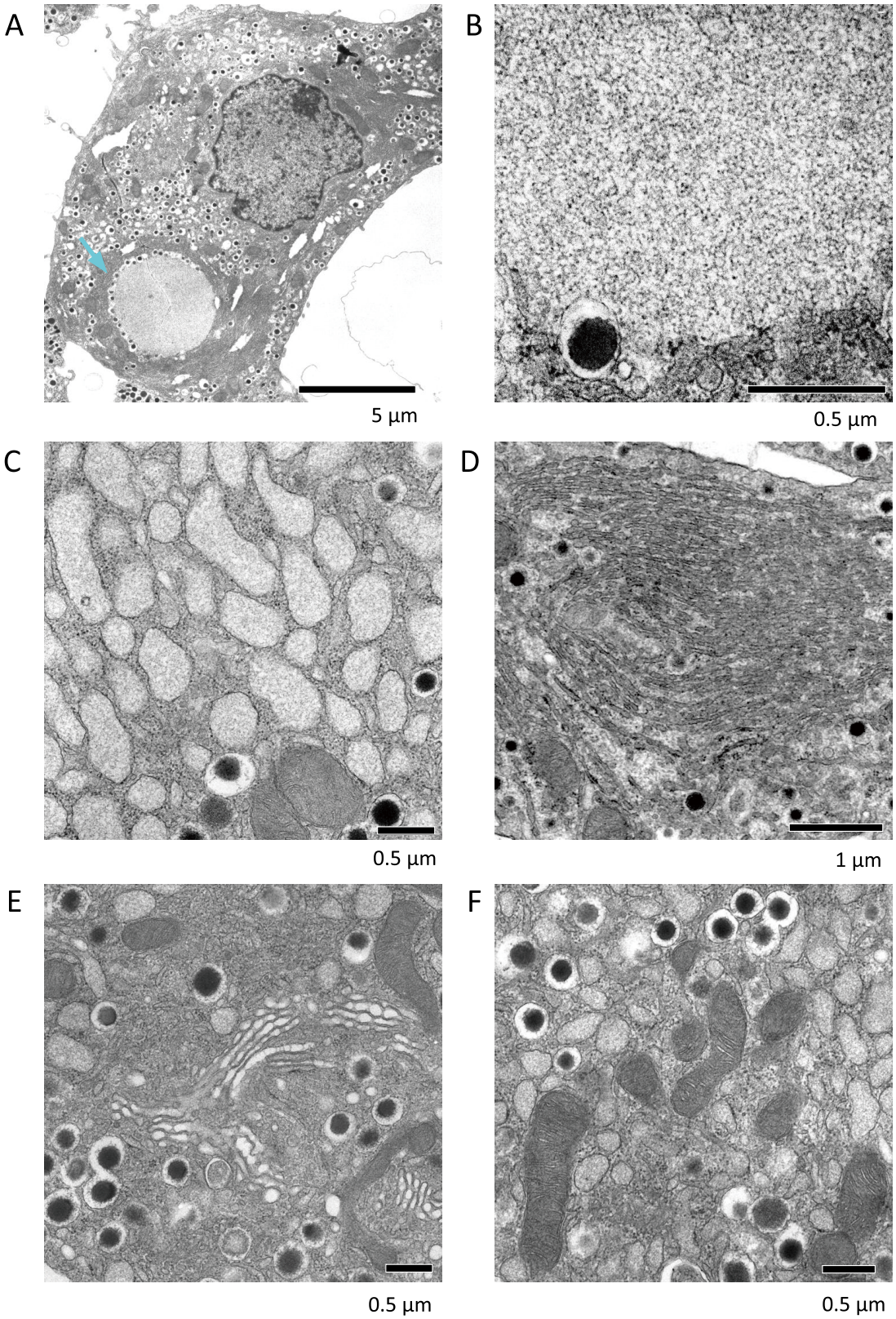

Figure 2 EM analysis of β cell from β cell-specific Atg7-deficient mice
The pancreas from Atg7$^{flox/flox}$: Rip-cre mouse was perfusion-fixed and β cell was observed by EM. (A) We observed representative inclusion body (blue arrow). Such structure was not observed in wild-type β cells. (B) Magnified image of inclusion body containing a dense meshwork of filamentous assemblies. (C, D) Abnormal morphology of the ER. (C) Rough ER with small number of ribosomes was remarkably swollen with fibrous structures. In (D), layered ER was also observed. (E, F) Normal morphology of the Golgi and mitochondria. Golgi apparatus (E) and mitochondria (F) were morphologically intact.

atic β cells, at least, proinsulin or islet amyloid polypeptide (IAPP), a peptide consisting of 37 residues[16], were considered to be accumulated in the ER lumen. Furthermore, because IAPP, but not insulin, is degraded by autophagy[10,17], IAPP could be one of the structures in the ER of Atg7-deficient β cells. No major abnormalities were observed in the Golgi apparatus or mitochondria (Figure 2E, F).

Inhibition of insulin secretion causes Golgi morphology abnormalities

Diazoxide, a KATP channel activator, is used as a therapeutic agent for insulinoma because of its pharmacological effect of inhibiting insulin secretion[18]. When Atg7$^{flox/flox}$: RIP-Cre mice were treated with Diazoxide to suppress insulin secretion, the number and size of inclusions increased, with a diameter of nearly 5 μm (Figure 3A, B). In some cases, four inclusions were found in a single cell (Figure 3C). The abnormalities of the ER became more pronounced, with the appearance of ERs with progressive lumenal swelling (Figure 3B) and spiral-like stratified ERs (Figure 3D), suggesting that ER stress had progressed. In addition, abnormalities in Golgi morphology were newly observed; mini stacks of the Golgi and swelling of the cisterna (Figure 3E, F), which should be induced by the accumulation of insulin granules in the Golgi apparatus.

MIN6 cells also show Golgi deformation under insulin secretion inhibition

MIN6 cells are a glucose-responsive insulin-secreting cell line derived from mouse pancreatic β cells[19]. Absence of Atg5, a molecule required for autophagy execution as well as Atg7, in this cell line did not show any abnormal structures, including inclusion body formation and a bulging ER lumen, unlike Atg7-deficient pancreatic β cells (Figure 4A, B). This difference may be due to the difference between in vivo β cells and lineage β cells. The Golgi apparatus was also normal in morphology under normal culture condition (Figure 4A, B). However, when the glucose concentration was lowered and insulin secretion was suppressed[10], as similar situation with Diazoxide-treatment, Golgi was mini-stacked and swelling of the cisterna were evident both in wild-type MIN6 cells and Atg5-deficient MIN6 cells (Figure 4C, D). These results suggest that the alteration of Golgi morphology is induced by suppression of insulin secretion in MIN6 cells like pancreatic β cells.

Discussion

In this study, we analyzed the influence of autophagy in pancreatic β cells from a morphological aspect. We found that the analysis of Atg7-deficient β cells revealed a pronounced ER dilatation, which is generally induced by the abnormality of protein turnover. In the case of β cells, insulin and IAPP, which are specifically synthesized in β cells, are thought to be involved in this morphological alteration. However, insulin degradation involves proteolytic systems distinct from autophagy, called stress-induced nascent granule degradation (SINGD)[9] and Golgi membrane-associated degradation (GOMED)[10,12,20,21]. SINGD is a cellular function in which newly synthesized insulin granules are degraded by direct fusion with lysosomes, while GOMED is a function in which insulin granules are wrapped in the Golgi membrane followed by the degradation after fusion with lysosomes. Unlike SINGD and GOMED, autophagy has been reported to play little role with respect to insulin degradation, suggesting that insulin might not be involved in the morphological alternation of the ER. On the other hand, with regard to IAPP, it was reported that Atg7 deficiency in human IAPP-expressing mice increased IAPP amyloid and caused glucose intolerance[22], indicating that IAPP is a substrate for autophagy degradation. Therefore, IAPP might be involved in the ER alteration induced by autophagy deficiency.

In pancreatic β cells, IAPP is degraded by autophagy, while insulin granules are not. This finding demonstrated the substrate specificity of autophagy, and there are many other similar examples. For example, in the final differentiation of erythrocytes, ribosomes, but not mitochondria, are degraded by autophagy[21,23]. Although the precise reason of different sensitivity against autophagy between IAPP and insulin is unidentified, this might be owing to the recognition by autophagic adaptor proteins.

In this study, we find that inhibition of insulin secretion causes morphological changes in the Golgi apparatus. When the transport of molecules, including insulin, to the extracellular and plasma membrane via the Golgi is blocked, Golgi is usually

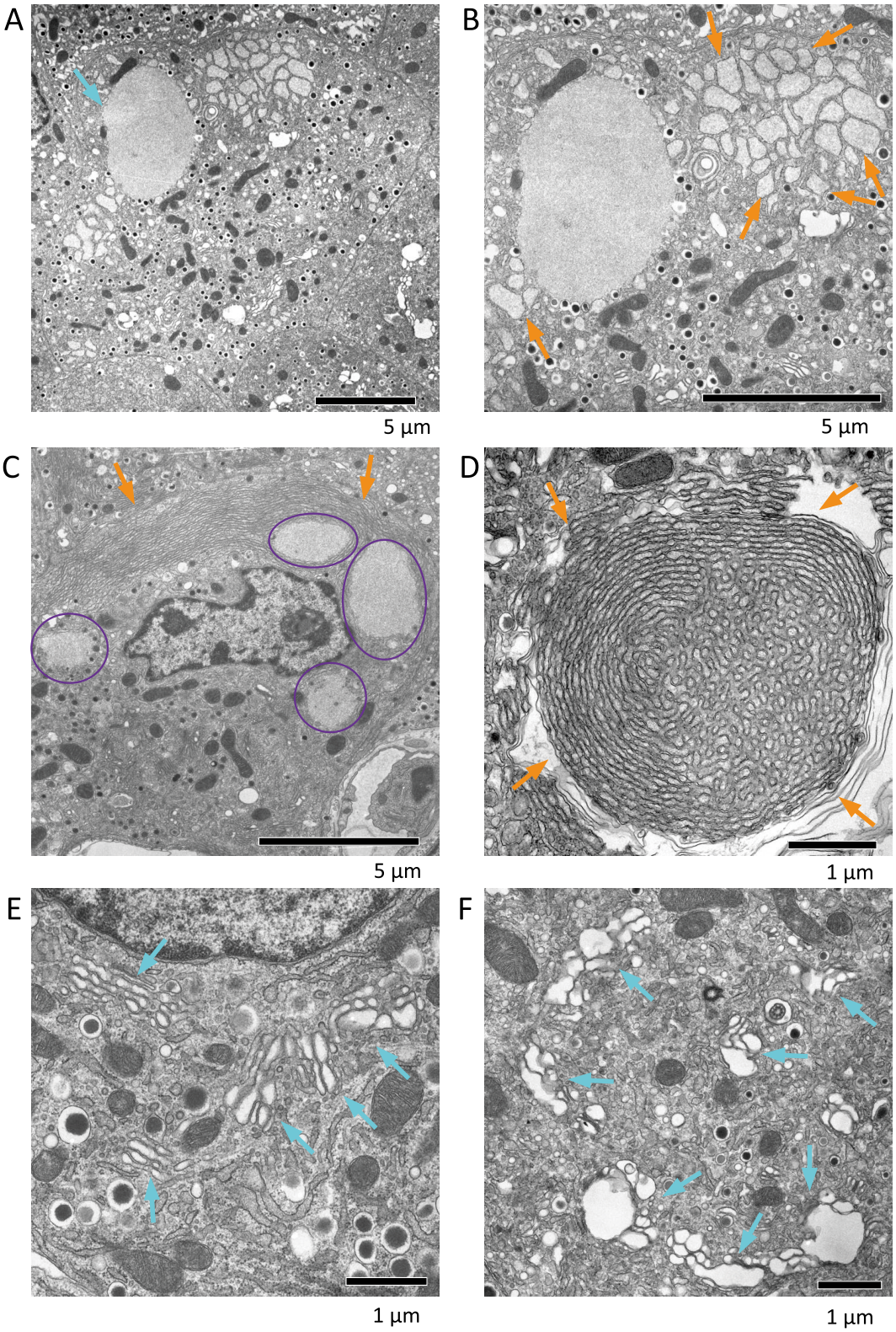

Figure 3 EM analysis of β cell from β cell-specific Atg7-deficient mice upon diazoxide treatment
Diazoxide was treated intraperitoneally to $Atg7^{flox/flox}$: Rip-cre mice for 1 hour. Then, the mice were perfusion-fixed and β cells were observed by EM. (A) Inclusion body was enlarged (blue arrow). (B) Magnified image of (A). Inclusion body contained a dense meshwork of filamentous assemblies, and rough ERs were remarkably swollen (orange arrows). (C) The four inclusion bodies (purple circles) and layered ER (orange arrows) were observed. In (D), layered ERs were assembled in a whirlpool (orange arrows). (E, F) Abnormal morphology of the Golgi apparatus. Golgi apparatus were separated into mini-stacks (blue arrows in E) and swollen (blue arrows in F).

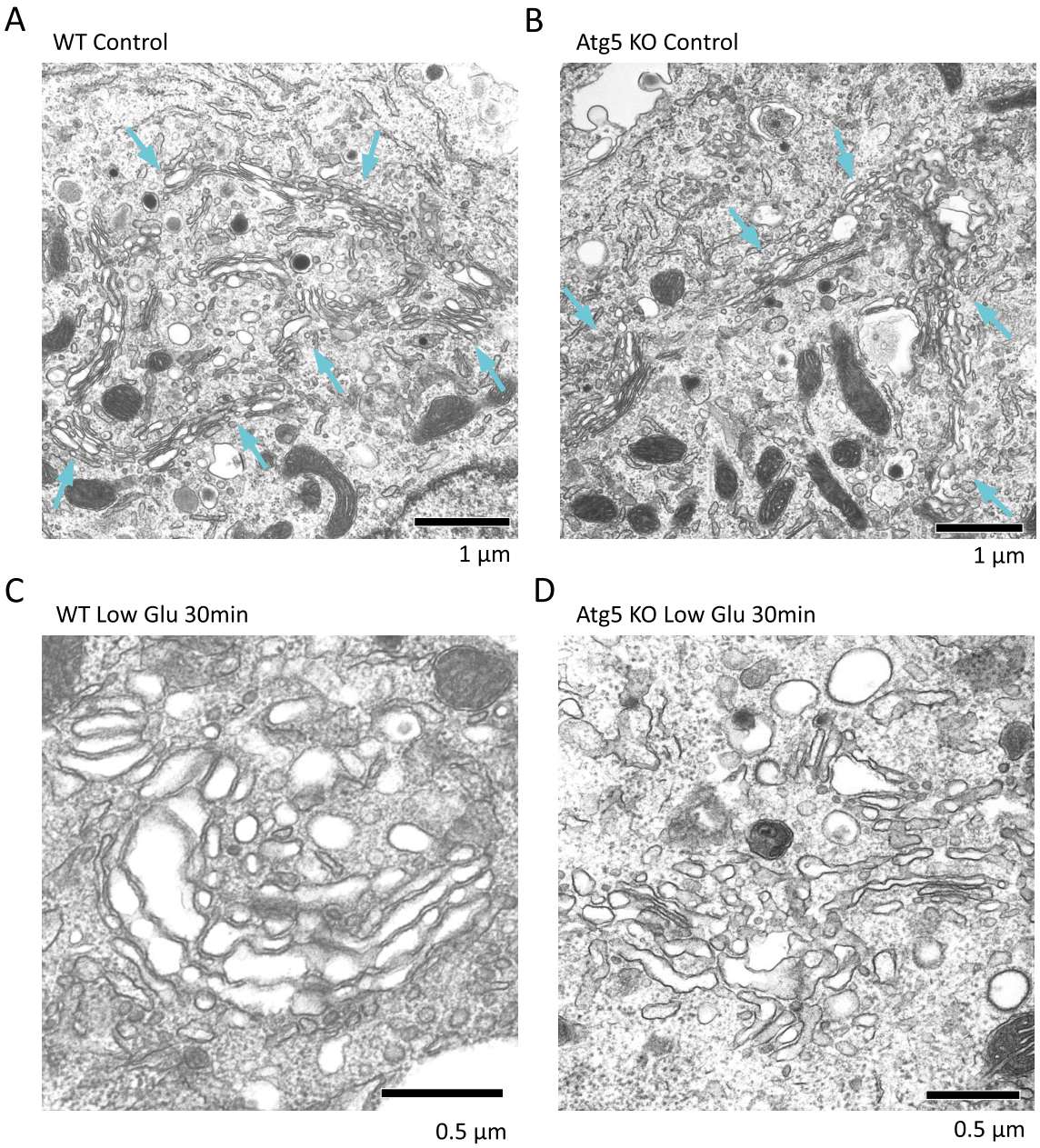

Figure 4 EM analysis of MIN6 cells
(A, B) EM analysis revealed no difference between wild-type MIN6 cells (A) and Atg5-deficeint MIN6 cells (B). In both cells, Golgi apparatus (blue arrows) localized at the center of the cells. (C, D) Glucose deprivation generated mini-stacked Golgi and Golgi swelling both in wild-type MIN6 cells (C) and Atg5-deficeint MIN6 cells (D).

deformed to become ministack-Golgi and swelling. The cause of Golgi deformation is thought to be the simultaneous morphological changes required to execute GOMED to degrade the retained molecules, in addition to the changes that occur passively due to molecular retention in the Golgi[10, 20]. Specifically, Golgi swelling appears to be a passive response owing to substance retention, while mini-stacking is a process necessary for GOMED execution.

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Author contributions

S S, H S and S A designed the experiments, developed the workflow, analyzed the data. T I, H S, H Y, H Y and S K performed the experiments. S S, Y N and H W wrote the manuscript; Y N and H W participated in study conceptualization and helped improve the manuscript. All authors read and approved the final manuscript.

Conflicts of interest statement

The authors declare that there are no conflicts of interest.

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Publication List

Juntendo Medical Journal
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Pediatric General and Urogenital Surgery

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A dagger (†) denotes doctoral works by non-Japanese students.

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Neurosurgery

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Instructions to Authors

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編 集 後 記

"History never repeats itself, but it does often rhyme." This quote, most often attributed to the American writer and humorist best known under his pen name, Mark Twain, has survived the test of time. Looking back over my own experiences that meandered from discoveries in plant molecular genetics to teaching first-year medical students at Juntendo Medical School, I see the rhymes.

In 1989, the young but already famous rising star, Gerald R. Fink, who, having just switched from yeast to plant molecular genetics, wrote an editorial in the prestigious journal Cell calling for a greater proportion of plant research funding to be reallocated from traditional schools of agronomy (where matters of practical importance to farming are studied) to the exciting new possibilities opened up by plant gene engineering. His opinions resonated with many young academicians in the top plant biology departments around the world. However, a distinguished older scientist and fellow member of the US National Academy of Sciences shot back with an editorial in The Plant Cell. There, Joseph E. Varner welcomed Gerald Fink's new-found enthusiasm for plant research, but argued that traditional agronomic research (which responds to local weather and soil conditions, especially as new plant varieties are released) could not be neglected. Varner argued that although very welcome, the new tools do not replace the old: "After every last method and insight of the molecular biologist is applied, the agriculturist still must deal with soil structure, drainage, and mineral nutrients and how these may affect productivity. There will always be decisions about till or no-till, when and how to irrigate, what crop in which field, yield per acre versus return on investment, store or sell, and so on and so on." Indeed, history has affirmed Varner's views. Plant gene engineering has produced valuable plant varieties that are more insect resistant, can use cheaper and less toxic weed-killers, and in some cases are more nutritious, but farmers still wait for the advice of their local schools of agronomy before planting any of these.

Today we face a similar situation in advanced medical care. There are many exciting technologies on the horizon that hold promise for new ways to fight disease. However, the task of comparing treatment methods and evaluating effectiveness and safety from the patient's point of view, and public health from society's view, still depends on institutions like Juntendo University and its hospitals where the patient's clinical outcome is, and will always be, the focus. Many of the professors at Juntendo are involved in the formulation of national clinical guidelines, and much of our research arises from patients' real problems. Recognizing opportunities depends on what Louis Pasteur called "the prepared mind," an attitude we also strive to keep. The articles in this issue of the Juntendo Medical Journal reflect these priorities.

Robert F. Whittier
Division of Medical Education, Juntendo University

イラスト作者より

散歩していても、この時季は花を見かけることはほとんどなく寂しいのですが、そんな中、紅い実をたくさんつけている木に出合いうれしくなります。新しい年を迎え、つつがなく良い事が沢山あります様に、と願いをこめて千両を描きました。(宮道明子)

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抄　録

順天堂醫事雑誌
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ドライアイの多様性に対するP4医療：モバイルヘルスを用いたデジタルコホート研究

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Society 5.0 で実現する医療では，サイバー空間とフィジカル空間の高度な融合により，医療施設中心型の医療から患者・市民を中心とした日常生活圏で予見的・生涯的な医療が行われる．とりわけ，高齢化･デジタル化の進む現代社会において視機能の質は Quality of Life の向上に重要である．

ドライアイは本邦で 2,000 万人が罹患する最も多い眼疾患の一つであり，今後も増加が予想される．ドライアイの多様な症状による視覚の質の低下は生涯に渡り Quality of Life の低下を起こす．ドライアイは，環境因子，生活習慣，宿主因子などが複合的に関連する多因子疾患である．Society 5.0 の実現を目標としたドライアイの診療の質の向上には，個々人の自覚症状の多様性の理解や関連する病因の見える化・層別化による予防・予測・個別化・参加型医療からなる P4 Medicine が重要である．

そこで，我々はドライアイ研究用スマホアプリ「ドライアイリズム®」を用いて，個々人のドライアイの症状や生活習慣などに関する包括的ドライアイ関連健康ビッグデータを収集している．これまでの我々の研究からドライアイ症状の重症化因子の解明，ドライアイ未診断者の特徴，ドライアイ症状の重症化と抑うつ症状との関連，ドライアイのアドヒアランス調査，ドライアイの多様な症状の層別化アルゴリズムの創出と瞼目のバイオセンサリングによるデジタルフェノタイピング手法の開発，ドライアイ研究用スマホアプリ「ドライアイリズム®」のドライアイ診断能を明らかにした．これらの成果はドライアイ患者に対して，ドライアイの多様な病態の解明と，モバイルヘルスによる個別の早期の予防および効果的な介入につながる可能性があり，将来のドライアイ診療の P4 Medicine という新たな価値の創出に資するものと考えられる．

キーワード：ドライアイ，ビッグデータ，モバイルヘルス，スマートフォンアプリケーション，P4 医療

この抄録は，順天堂醫事雑誌 69 巻 1 号，p2-13，2023 掲載の『P4 Medicine for Heterogeneity of Dry Eye: A Mobile Health-based Digital Cohort Study』の和文抄録です．

抄　録

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パーキンソン病・認知症・神経難病における遠隔医療の現状と未来

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8)順天堂大学大学院パーキンソン病病態解明研究講座

COVID-19パンデミックは社会に内在する問題をあぶりだす機会となった．全世界的に遠隔医療の需要が急増し，柔軟に対応した国々もある一方で，本邦では本格的な遠隔医療は広がらず，多くは電話再診のみでの対応であった．本邦では医療のみでなく，社会全体のデジタル化の遅れが問題となっている．医療においてもデジタルトランスフォーメーション(DX)を加速し，新たなパンデミックなどの危機に強い，持続可能な社会を構築していくことが必要である．とくに，高齢社会に突入した本邦においては，加齢とともに急増するパーキンソン病や認知症疾患に対する持続可能な医療をどのように提供していくかが課題となる．

神経変性疾患や神経難病の多くは進行性であり，進行とともに遠方の専門医への通院自体が困難となる．専門医へのアクセスを改善するための方法の一つとして，遠隔医療がある．本邦では厚生労働省は，遠隔医療のうち，医師－患者間において，情報通信機器を通して，患者の診察及び診断を行い診断結果の伝達や処方等の診療行為を，リアルタイムで行う行為をオンライン診療とし，保険診療が可能となっている．オンライン診療には利点も多いが，対面診察と同様の情報が得られるわけではない．

オンライン診療の不足を補う遠隔医療技術として，これまでの２次元のビデオ通話を用いたオンライン診療を３次元化し，まるで同じ空間を共有しているかのようにオンライン診療を行うことができる技術が開発されている．また，モーションキャプチャーやウェアラブルデバイスなどを用いた遠隔モニタリングにより，患者の情報を在宅でも客観的かつ連続的に評価をすることができるようになる．さらに，これらのビックデータを蓄積し，人工知能によって解析することが可能となり，医療のパラダイムシフトがおこると考えられる．

キーワード： パーキンソン病，認知症，遠隔医療，ウェアラブルデバイス，人工知能

この抄録は，順天堂醫事雑誌69巻1号，p14-20，2023掲載の『A Narrative Review of Current Status and Future Perspective of Telemedicine for Parkinson's Disease, Dementia, and Intractable Neurological Disease in Japan』の和文抄録です．

抄　録

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パーキンソン病に対する脳深部刺激療法（DBS）

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パーキンソン病（PD）に対する外科治療には長い歴史がある．最近では薬物療法のみで症状コントロールが困難な PD に対して脳深部刺激療法（DBS）が広く行われている．DBS は体内植え込み式のデバイスにより脳内の特定のターゲットを電気刺激することで神経機能を調整して症状の改善を図る．現在 PD に対して最も有効な刺激ターゲットは視床下核（STN）である．

現状で根治的治療が無い PD に対する治療の第一選択はレボドパを中心とした薬物療法であることは論を待たず，PD 治療における外科治療に求められることは，薬物療法で改善困難な症状の改善を得ること，または薬物療法により引き起こされた問題の解決を図ることが不可欠である．特に STN-DBS は薬物療法で改善困難な振戦を改善するのみでなく，薬物療法により引き起こされるウェアリングオフやジスキネジアといった運動合併症を改善し，その長期的な効果も立証されている．また最近ではより早期に DBS を導入することでさらに長期にわたる症状の安定を得ることができることも示唆されている．

DBS 手術は MRI ガイド下の定位脳手術の手法に微小電極記録による神経活動評価を組み合わせて論理的に行われる．コンピューター技術の進歩により手術は従来に比べて格段に容易になり，精度や安全性も飛躍的に向上している．術中の様々な判断にはある程度の経験を要するが，いくつかのステップを着実にこなすことで完遂できる．

DBS における最近の新技術として，ディレクショナルリードでは刺激野の形状を自在に形成することが可能でより精密な刺激調整や刺激副作用回避に役立つ．また，adaptive DBS では刺激電極による LFP 測定から PD 症状のバイオマーカーであるとされる β-oscillation を検出し，その程度により刺激強度を自動調節することが可能になった．こうした新技術も加わり DBS はさらに洗練されつつある．

キーワード：パーキンソン病，脳深部刺激療法，視床下核

この抄録は，順天堂醫事雑誌 69 巻 1 号，p21–29，2023 掲載の『Deep Brain Stimulation for Parkinson's Disease』の和文抄録です．

順天堂医学会 会員の皆様

順 天 堂 医 学 会
会長　服部　信孝

順天堂医学会短期海外留学時助成金給付制度

順天堂医学会では短期海外留学時助成金給付制度を開始いたしました。

1. 要件

下記すべての要件を満たす者

(1) 順天堂大学（大学院を含む）の学生で 1 か月以上 12 か月未満の海外留学をする者

(2) 留学先の研究機関または財団などからの援助がない者

(3) 医学会の正会員として 1 年以上の経歴を有し、医学会費を完納している者

2. 申請書類

(1) 順天堂医学会短期海外留学時助成金申込書

(2) 所属長の推薦書

(3) 申請者の主な研究テーマ・研究業績

(4) 留学受け入れ機関の指導者からの推薦状

3. 助成金の給付金額

留学期間	助成金額
1 か月以上 4 か月未満	10 万円
4 か月以上 7 か月未満	20 万円
7 か月以上 12 か月未満	30 万円

4. 申請スケジュール（年 2 回）

申請期限	助成決定時期
6 月末	8 月
12 月末	2 月

5. 選考機関：順天堂医学会短期海外留学時助成金選考委員会

6. 助成後の義務

(1) 帰国後直近の順天堂医学会学術集会において研究成果の発表および、その内容を「順天堂醫事雑誌」に報告する。

(2) 帰国後は、順天堂大学またはその関連機関に原則として 3 年以上勤務する。

7. 本件の照会先

HP：https://www.juntendo.ac.jp/journal/membership/benefit_plan.html

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