ORIGINAL PAPER

Nagoya J. Med. Sci. **79**. 323 ~ 329, 2017
doi:10.18999/nagjms.79.3.323

Randomized controlled trial for assessment of Internet of Things system to guide intensive glucose control in diabetes outpatients: Nagoya Health Navigator Study protocol

Takeshi Onoue[1], Motomitsu Goto[1], Tomoko Kobayashi[1], Takashi Tominaga[1], Masahiko Ando[2], Hiroyuki Honda[3], Yasuko Yoshida[3], Takahiro Tosaki[4], Hisashi Yokoi[5], Sawako Kato[6], Shoichi Maruyama[6] and Hiroshi Arima[1]

[1]*Department of Endocrinology and Diabetes, Nagoya University Graduate School of Medicine, Nagoya, Japan*
[2]*Center for Advanced Medicine and Clinical Research, Nagoya University Hospital, Nagoya, Japan*
[3]*Innovative Research Center for Preventive Medical Engineering, Nagoya University, Nagoya, Japan*
[4]*TDE Healthcare Corporation Tosaki Clinic for Diabetes and Endocrinology, Nagoya, Japan*
[5]*Yokoi Kotobuki Clinic, Aichi, Japan*
[6]*Department of Nephrology, Nagoya University Graduate School of Medicine, Nagoya, Japan*

ABSTRACT

The Internet of Things (IoT) allows collecting vast amounts of health-relevant data such as daily activity, body weight (BW), and blood pressure (BP) automatically. The use of IoT devices to monitor diabetic patients has been studied, but could not evaluate IoT-dependent effects because health data were not measured in control groups. This multicenter, open-label, randomized, parallel group study will compare the impact of intensive health guidance using IoT and conventional medical guidance on glucose control. It will be conducted in outpatients with type 2 diabetes for a period of 6 months. IoT devices to measure amount of daily activity, BW, and BP will be provided to IoT group patients. Healthcare professionals (HCPs) will provide appropriate feedback according to the data. Non-IoT control, patients will be given measurement devices that do not have a feedback function. The primary outcome is glycated hemoglobin at 6 months. The study has already enrolled 101 patients, 50 in the IoT group and 51 in the non-IoT group, at the two participating outpatient clinics. The baseline characteristics of two groups did not differ, except for triglycerides. This will be the first randomized, controlled study to evaluate IoT-dependent effects of intensive feedback from HCPs. The results will validate a new method of health-data collection and provision of feedback suitable for diabetes support with increased effectiveness and low cost.

Keywords: type 2 diabetes, health guidance, Internet of Things, wearable device

INTRODUCTION

The worldwide prevalence of diabetes is increasing; preventing its onset and development is a healthcare priority.[1)] The cornerstone of diabetes treatment is improvement of lifestyle, with management of weight and physical activity because it is effective both for prevention of

Received: March 14, 2017; accepted: May 17, 2017

Corresponding author: Motomitsu Goto, M.D., Ph.D.
Department of Endocrinology and Diabetes, Nagoya University Graduate School of Medicine, 65 Tsurumai-cho, Showa-ku, Nagoya, 466-8550, Japan
Phone: +81-52-744-2142, fax: +81-52-744-2206, e-mail: goto@med.nagoya-u.ac.jp

diabetes onset[2-5] and good metabolic control of diabetes.[6,7] Both the American Diabetes Association and Japanese Diabetes Society recommend exercise therapy that combines aerobic exercise and resistance movement.[8,9] Nonexercise activity thermogenesis (NEAT) has been reported to be involved in control of obesity and diabetes aggravation.[10-13] However, lifestyle intervention requires extensive use of human resources and is costly. Further, it is not easy for healthcare professionals (HCPs) to evaluate patient lifestyle during consultations.

The Internet of Things (IoT) enables networking and connection of objects to the Internet, and has expanded sufficiently to allow connection of wearable devices and measurement instruments such as body-weight scales with Bluetooth or near field communication (NFC). It is thus easy to record health data and transfer it to cloud services where it is accessible by both patients themselves and their physicians. These technologies make it possible to collect large volumes of health data such as daily activity, body weight (BW), and blood pressure (BP) automatically. Applications compatible with devices that measure health-related data are readily available, and some have been evaluated.[14-17] However, these applications are designed primarily to present data to the user; the feedback functions are limited.

In previous randomized clinical trials evaluating the use of IoT devices in diabetic patients,[18-21] the control groups were not given measuring instruments comparable to the intervention group.[18-21] Therefore, the outcomes of the intervention included effects of both the health data measurement itself and the feedback using IoT. To evaluate the effectiveness of diabetes health guidance using IoT, evaluation of the feedback using collected data is required.

For this study, we developed a new health guidance system (the "IoT system") using IoT technologies. Daily health activity data and BW and BP are linked to each other and collected, and are then provided for the patients themselves and HCPs using the application and an Internet cloud service. The IoT system enables HCPs to evaluate patient lifestyle and to provide appropriate feedback. The effect of the IoT-system feedback is to be compared with those obtained in a control group using health measurement instruments that do not have a data transmission function, but allowed self-management of health data. Data were provided not only to the primary care physicians for feedback but also to study investigator HCPs in a remote call center for feedback using the IoT system. Providing these patient health data to HCPs may contribute to improved control of diabetes, BW and BP through self-management and more appropriate health guidance by HCPs.

In this manuscript, we outline the study protocol of the randomized controlled trial designed to evaluate the effect of the IoT-system; we also report the characteristics of registrants at the time of registration completion.

METHODS

Trial design

This multicenter, open-label, randomized (1:1), parallel group study is designed to compare the impact of intensive health guidance on diabetic outpatients using an IoT system with conventional medical guidance on glucose control. The study protocol was approved by the ethical committee of Nagoya University Graduate School of Medicine (No. 2016-0152). All enrolled patients provided written consent to participate after they were informed of the purpose of the study as well as the potential risks and benefits. The trial is listed in the Japanese University Hospital Medical Information Network Clinical Trials Registry (UMIN-CTR: UMIN 000022480).

Patients

Patients are eligible for inclusion if they 1) are outpatients at the two participating clinics, and 2) have glycosylated hemoglobin (HbA1c) ≥6.5%. Patients are excluded if they 1) are on dialysis, 2) are treated with insulin, 3) have severe diabetic nephropathy (estimated glomerular filtration rate < 30 mL/min/1.73 m^2), 4) cannot properly operate the devices to be used, or 5) are judged by their physician as not able to participate.

Registration and randomization

Participants are recruited from two participating clinics where they meet with the study coordinator who provides them with an information brochure and a consent form. After consent, the coordinator has access to a web-based registration and follow-up system developed by the Center for Advanced Medical and Clinical Research of the Nagoya University Hospital and enters the information required for enrollment. The system automatically determines the eligibility of each patient and randomly assigns him/her in equal numbers to the IoT or non-IoT group with a dynamic allocation strategy using a minimization method. Stratification includes the clinic that the patient visits, HbA1c (>8% or ≤8%), sex, age (>65 or ≤65), BMI (>25 kg/m^2 or ≤25 kg/m^2), and the use or nonuse of oral diabetes agents.

Interventions

Patients in the IoT group are provided with smartphones (Kyocera S301, Kyoto, Japan) programmed with the study-specific application (https://play.google.com/store/apps/details?id=jp.ac.nagoyau.lifestylemonitoring&hl=ja), Bluetooth-enabled activity trackers (TOSHIBA Actiband WERAM1100, Tokyo, Japan), Bluetooth-enabled BP monitors (A&D UA-851PBT-C, Tokyo, Japan), and Bluetooth-enabled body weight scales (A&D UC-411PBT-C). All devices can transmit measurement data over a wireless network to a cloud server. IoT system patients, primary care physicians (local HCPs) and study investigator HCP in a remote call center (remote HCP) can view the health data (exercise volume, exercise time, step counts, circadian rhythm, changes in BW and changes in BP, and number of access events) transmitted by each smartphone. Remote HCP at the call center call patients once monthly to provide feedback the accomplishment of personal goals, activity volume, and weight change.

Patients in the non-IoT group are provided with an ordinary activity trackers (Omron HJ-325, Kyoto, Japan), BP monitors (Omron HEM-7130-HP), and body weight scales (Tanita HD-660, Tokyo, Japan) that cannot transmit data over a wireless network. Participants in this self-managed control group use these conventional measurement instruments without routine physician or investigator feedback.

An overview of IoT system is shown in Figure 1, and a study flowchart is shown in Figure 2.

Outcomes

The primary outcome is glucose control measured by HbA1c at 6 months. Secondary outcomes include change in BW, BP, fasting blood glucose, total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, triglycerides, and changes of medication.

Sample size

Based on the results of a previous clinical trial,[22,23] the geometric standard deviation (SD) of change in HbA1c at the last observation period was assumed to be 0.7%. We estimated that at least 48 patients were required in each treatment group to confer a power of 80% to detect a significant difference of 0.4% change from baseline in the two groups at the end of the intervention. We thus planned to recruit 50 patients per group (100 in total) with consideration

for potential discontinuation or dropout of enrolled patients during the study period.

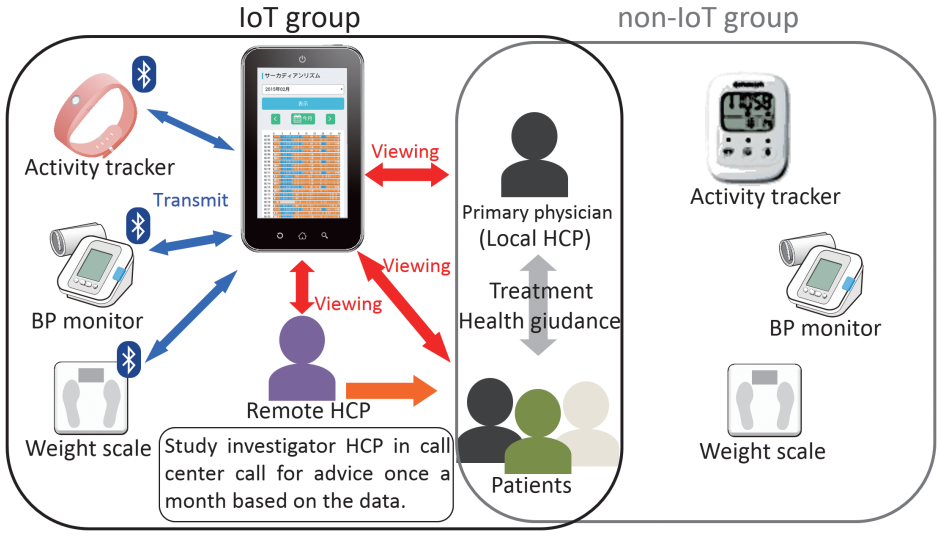

Fig. 1 An overview of the IoT system
Patients in the IoT group were provided with smartphones programmed with the study-specific application, activity trackers, BP monitors, and weight scales, all able to transmit measurement data by wireless network to a cloud server. Patients in the non-IoT group were provided with an ordinary activity tracker, BP monitors, and weight scales under the self-management of patients. IoT, Internet of Things; HCP, healthcare professional; BP, and blood pressure.

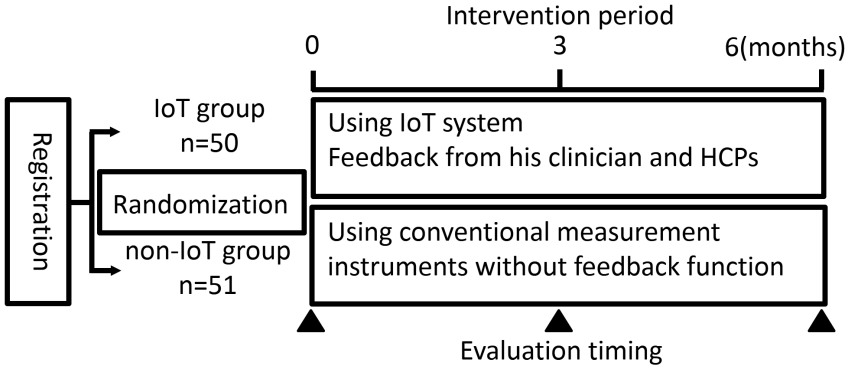

Fig. 2 Study flowchart. IoT, Internet of Things; HCP, healthcare professional

Statistical analysis

Continuous variables were expressed as means ± SD. Between-group differences in baseline values of continuous variables were tested for significance with the two-sample *t*-test, and values of nominal variables were compared using the Chi-square test. The primary outcome, change in HbA1c from baseline to 6 months, will be evaluated in each group and compared by analysis of

covariance (ANCOVA). Baseline HbA1c, sex, age, BMI, and the use or nonuse of diabetes oral agents were included as covariates. A linear mixed model including treatment period, treatment group, an interaction term for treatment group and period, HbA1c at entry, sex, age, BMI at entry, and the use or nonuse of diabetes oral agents as fixed effects will be used to compare the change in HbA1c from baseline at 3 and 6 months in the two groups.

Secondary outcomes, (BW, BP, fasting blood glucose, total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol and triglycerides at 3 and 6 months), will be analyzed with linear-mixed effect models that include treatment period, treatment group, an interaction term between treatment group and period, value at entry, sex, age, BMI at entry, and the use or nonuse of diabetes oral agents as fixed effects. Changes of medication are classified as increased dose, no change, and decreased dose, and analyzed using the Mantel-extension test stratified by sex, age (>65 or ≤65), BMI at entry (>25 kg/m^2 or ≤25 kg/m^2), and the use or nonuse of diabetes oral agents. Differences are considered significant at $P < 0.05$ for all statistical analyses.

RESULTS

The study enrolled 101 patients, 50 in the IoT group and 51 in the non-IoT group, at the two participating outpatient clinics. Baseline characteristics are shown in Table 1. The mean participant age was 57.1 ± 12.5 years, 45% were women, the mean BMI was 26.2 ± 4.8 kg/m^2, mean HbA1c was 7.2 ± 0.6%, and mean fasting blood glucose was 145 ± 45 mg/dL. No between-group differences in baseline characteristics were observed except for triglycerides, which were lower in the IoT group than in the non-IoT group ($P = 0.01$). There were no intervention-related severe adverse events.

Table 1 Baseline characteristics of the study population

	Total (n=101)	IoT group (n=50)	non-IoT group (n=51)	P-value
HbA1c (%)	7.2±0.6	7.2±0.6	7.2±0.7	0.92
Age (years)	57.1±12.5	56.8±13.0	57.4±12.1	0.81
Sex				
Female	45	23	22	0.19
Male	56	27	29	
Body weight (kg)	70.4±16.1	71.3±16.3	69.4±16.0	0.54
Body mass index (kg/m^2)	26.2±4.8	26.4±4.8	26.1±4.9	0.75
Blood pressure (mmHg)				
Systolic blood pressure	125±12	125±11	124±13	0.51
Diastolic blood pressure	75±8	74±9	75±8	0.68
Blood glucose (mg/dl)	145±45	138±41	152±47	0.13
Total cholesterol (mg/dl)	191±41	187±39	195±43	0.30
Triglyceride (mg/dl)	170±104	144±73	196±123	0.01
HDL cholesterol (mg/dl)	53±14	51±12	54±17	0.29
LDL cholesterol (mg/dl)	107±31	107±34	107±28	0.95
Serum creatinine (mg/dl)	0.68±0.19	0.69±0.21	0.66±0.18	0.44

Use of hypoglycemic drugs	96	48	48	0.56
Use of antihypertensive drugs	47	21	26	0.21
Use of lipid-lowering drugs	50	24	26	0.66

IoT, Internet of Things; HDL, high-density lipoprotein; LDL, low-density lipoprotein. Data are means ± standard deviation.

DISCUSSION

The IoT refers to the creation of networks of devices other than computers that contain electronics, applications, and/or sensors, and that have Internet connectivity. Using the IoT, new possibilities may be created by uploading health data from health measurement instruments such as activity metering devices, body weight scales and blood pressure monitors to Internet sites. The vast amount of health data collected using IoT can provide more information than previously possible to both patients and HCPs. A significant benefit of the IoT is the provision of patient-appropriate feedback by HCPs based on the large amount of collected and transmitted data.

A few clinical trials of IoT devices have been conducted in diabetic patients,[18-21] but they did not evaluate the effect of feedback based on evaluation of IoT data. This study will be the first randomized controlled study to purely evaluate the effect of intensive feedback from HCPs using IoT. The study results will provide much needed information on the use of health data collected from internet-connected devices and the provision of IoT system feedback suitable for diabetes support. Such a system will be economical and will make effective use of limited medical resources.

ACKNOWLEDGMENTS

This study includes the following researchers: clinical research coordinator, Keiko Katagiri, Mieko Torii, Takahiro Imaizumi, Kyoko Kikuchi, Manabu Hishida, Takuya Ozeki, Koji Inagaki, Asuka Hachiya, Misao Niwa, and Noriko Shibata. This study was funded by Ministry of Economy, Trade and Industry of Japan.

CONFLICT OF INTEREST

Innovative Research Center for Preventive Medical Engineering, Nagoya University received a research funding from Toyota Motor Corporation; however, the sponsor had no control over the interpretation, writing, or publication of this work. Takahiro Tosaki received an honoraria from Eli Lilly, Astellas, MSD, and Takeda; however, the honoraria are not directly associated with this study.

REFERENCES

1) Rahelić D. 7TH EDITION OF IDF DIABETES ATLAS--CALL FOR IMMEDIATE ACTION. *Lijec Vjesn*, 2016; 138: 57–58.
2) Tuomilehto J, Lindström J, Eriksson JG, Valle TT, Hämäläinen H, Ilanne-Parikka P, *et al.* Prevention of type 2 diabetes mellitus by changes in lifestyle among subjects with impaired glucose tolerance. *N Engl J Med*, 2001; 344: 1343–1350.

3) Knowler WC, Barrett-Connor E, Fowler SE, Hamman RF, Lachin JM, Walker EA, *et al.* Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. *N Engl J Med*, 2002; 346: 393–403.
4) Li G, Zhang P, Wang J, Gregg EW, Yang W, Gong Q, *et al.* The long-term effect of lifestyle interventions to prevent diabetes in the China Da Qing Diabetes Prevention Study: a 20-year follow-up study. *Lancet*, 2008; 371: 1783–1789.
5) Saito T, Watanabe M, Nishida J, Izumi T, Omura M, Takagi T, *et al.* Lifestyle modification and prevention of type 2 diabetes in overweight Japanese with impaired fasting glucose levels: a randomized controlled trial. *Arch Intern Med*, 2011; 171: 1352–1360.
6) Wing RR, Bolin P, Brancati FL, Bray GA, Clark JM, Coday M, *et al.* Cardiovascular effects of intensive lifestyle intervention in type 2 diabetes. *N Engl J Med*, 2013; 369: 145–154.
7) Umpierre D, Ribeiro PA, Kramer CK, Leitão CB, Zucatti AT, Azevedo MJ, *et al.* Physical activity advice only or structured exercise training and association with HbA1c levels in type 2 diabetes: a systematic review and meta-analysis. *JAMA*, 2011; 305: 1790–1799.
8) Colberg SR, Albright AL, Blissmer BJ, Braun B, Chasan-Taber L, Fernhall B, *et al.* Exercise and type 2 diabetes: American College of Sports Medicine and the American Diabetes Association: joint position statement. Exercise and type 2 diabetes. *Med Sci Sports Exerc*, 2010; 42: 2282–2303.
9) Gordon BA, Benson AC, Bird SR, Fraser SF. Resistance training improves metabolic health in type 2 diabetes: a systematic review. *Diabetes Res Clin Pract*, 2009; 83: 157–175.
10) Levine JA. Nonexercise activity thermogenesis—liberating the life-force. *J Intern Med*, 2007; 262: 273–287.
11) Levine JA, Vander Weg MW, Hill JO, Klesges RC. Non-exercise activity thermogenesis: the crouching tiger hidden dragon of societal weight gain. Arterioscler Thromb Vasc Biol, 2006; 26: 729–736.
12) Levine JA, Lanningham-Foster LM, McCrady SK, Krizan AC, Olson LR, Kane PH, *et al.* Interindividual variation in posture allocation: possible role in human obesity. *Science*, 2005; 307: 584–586.
13) Grøntved A, Hu FB. Television viewing and risk of type 2 diabetes, cardiovascular disease, and all-cause mortality: a meta-analysis. *JAMA*, 2011; 305: 2448–2455.
14) Brzan PP, Rotman E, Pajnkihar M, Klanjsek P. Mobile Applications for Control and Self Management of Diabetes: A Systematic Review. *J Med Syst*, 2016; 40: 210.
15) Kirwan M, Vandelanotte C, Fenning A, Duncan MJ. Diabetes self-management smartphone application for adults with type 1 diabetes: randomized controlled trial. *J Med Internet Res*, 2013; 15: e235.
16) Quinn CC, Shardell MD, Terrin ML, Barr EA, Ballew SH, Gruber-Baldini AL. Cluster-randomized trial of a mobile phone personalized behavioral intervention for blood glucose control. *Diabetes Care*, 2011; 34: 1934–1942.
17) Bhuyan SS, Lu N, Chandak A, Kim H, Wyant D, Bhatt J, *et al.* Use of Mobile Health Applications for Health-Seeking Behavior Among US Adults. *J Med Syst*, 2016; 40: 153.
18) Magid DJ, Olson KL, Billups SJ, Wagner NM, Lyons EE, Kroner BA. A pharmacist-led, American Heart Association Heart360 Web-enabled home blood pressure monitoring program. *Circ Cardiovasc Qual Outcomes*, 2013; 6: 157–163.
19) McMahon GT, Gomes HE, Hickson Hohne S, Hu TM, Levine BA, Conlin PR. Web-based care management in patients with poorly controlled diabetes. *Diabetes Care*, 2005; 28: 1624–1629.
20) Waki K, Fujita H, Uchimura Y, Omae K, Aramaki E, Kato S, *et al.* DialBetics: A Novel Smartphone-based Self-management Support System for Type 2 Diabetes Patients. *J Diabetes Sci Technol*, 2014; 8: 209–215.
21) Cho JH, Kim HS, Yoo SH, Jung CH, Lee WJ, Park CY, *et al.* An Internet-based health gateway device for interactive communication and automatic data uploading: Clinical efficacy for type 2 diabetes in a multi-centre trial. *J Telemed Telecare*, 2016.
22) Arambepola C, Ricci-Cabello I, Manikavasagam P, Roberts N, French DP, Farmer A. The Impact of Automated Brief Messages Promoting Lifestyle Changes Delivered Via Mobile Devices to People with Type 2 Diabetes: A Systematic Literature Review and Meta-Analysis of Controlled Trials. *J Med Internet Res*, 2016; 18: e86.
23) Orsama AL, Lähteenmäki J, Harno K, Kulju M, Wintergerst E, Schachner H, *et al.* Active assistance technology reduces glycosylated hemoglobin and weight in individuals with type 2 diabetes: results of a theory-based randomized trial. *Diabetes Technol Ther*, 2013; 15: 662–669.