Effect of Patient Education for Diabetic Outpatients by a Hospital Pharmacist: A Retrospective Study

Yuko Ichiki, Daisuke Kobayashi, Toshio Kubota, Sahoko Ozono, Aya Murakami, Yusuke Yamakawa, Kazuya Zeki, and Takao Shimazoe

*Department of Clinical Pharmacy and Pharmaceutical Care, Graduate School of Pharmaceutical Sciences, Kyushu University; 3–1 Maidashi, Higashi-ku, Fukuoka 812–8582, Japan; and Kitakyushu City Moji Hospital; 3–1 Minamihonmachi, Moji-ku, Kitakyushu 800–0021, Japan.

(Received May 6, 2016; Accepted August 2, 2016; Advance publication released online August 29, 2016)

The number of patients with diabetes continues to increase in Japan, which means that education in disease management is important. However, there have been few investigations into the importance of hospital pharmacists performing outpatient education for diabetes mellitus in Japan. In the diabetes outpatient department of Kitakyushu City Moji Hospital, a pharmacist commenced patient education using check sheets before patients saw the physicians from 2012. We divided the patients into groups with an increase or decrease of hemoglobin A1c (HbA1c) level after 6 months from the start of patient education. To assess the factors related to a decrease of HbA1c level, we compared background factors, and laboratory values between these two groups. In the patients whose HbA1c level decreased, the level was high at the start of patient education and they had less knowledge about their medications. To evaluate the impact of this patient education, we compared HbA1c values before patient education and after 6 months to determine the effect of providing education in the diabetes outpatient department. In the HbA1c ≥ 8% group, the HbA1c level decreased significantly during 6 months of patient education. These results suggest that patient education by hospital pharmacists can be effective if HbA1c level is high at the start of education. This is the first report about the usefulness of patient education by a hospital pharmacist for improvement of HbA1c level in diabetic outpatients in Japan.

Key words — hospital pharmacist; diabetic outpatient; patient education; hemoglobin A1c; insulin; antidiabetic drug

INTRODUCTION

The objectives of treating diabetes are prevention of the onset and progression of complications and maintenance of quality of life by preserving health. In the 1990s, the Diabetes Control and Complications Trial, the UK Prospective Diabetes Study, and the Kumamoto Study showed that complications of microvascular disease decreased when blood glucose was controlled at a lower level. It was also reported that the risk of complications was much lower when hemoglobin A1c (HbA1c) level was below 6.9%. In 2013, the Japanese diabetes guideline stated that treatment goal of HbA1c level is less than 7.0 % in agreement with the American Diabetes Association. More than 7 million people have diabetes in Japan, and it is necessary for outpatients to receive appropriate medical treatment in order to achieve the target value of HbA1c.

Foreign reports have shown that it is essential to improve the adherence of patients with type 2 diabetes, and that patient education is important for this purpose. There have been many reports from the US about the importance of pharmacist participation in education. Ip et al. reported that intervention by pharmacists in primary care led to a decrease of HbA1c level after 12 months. This report supports the need for pharmacists to participate in the treatment of ambulatory diabetic patients. In addition, Spence et al. reported that improvement of adherence and a decrease of HbA1c level were achieved by face-to-face counseling of patients with poor glycemic control. Furthermore, Xin et al. showed that adherence and clinical outcomes were improved by hospital pharmacists providing pharmaceutical care working together with doctors. Moreover, patient education about type 2 diabetes, prescription medications and necessary lifestyle changes in the diabetes outpatient department leads to a decrease of HbA1c level. American pharmacists have more responsibilities than Japanese pharmacists. For example, they can prescribe medications since the introduction of the Collaborative Drug Therapy Management system, while this is not still allowed for Japanese phar-
Pharmacists. They also conduct drug therapy by collaborating with doctors in the ambulatory department. However, hospital pharmacists rarely participate in the treatment of diabetic outpatients in Japan, and therefore the effects of such intervention are still unclear. One reason is that the Japanese national health insurance system does not cover pharmacist activities in diabetes outpatient departments and only covers outpatient medications. At our hospital, we did not conduct patient education for ambulatory diabetic patients until March 2012, in spite of having many diabetes patients with poor glycemic control. We thought that hospital pharmacists could make an important contribution to the management of diabetic outpatients, so we started patient education from April 2012 based on the following process. First, patient education was performed using check sheets to access the problem about the treatment of diabetes medications before the patient saw the doctor. Then the pharmacist provided the information obtained about the patient to the doctor, after which the doctor asked the pharmacist to conduct patient education again as needed.

In this study, we assessed the factors related to a decrease of HbA1c level after hospital pharmacist conducted patient education for diabetic outpatients. We also divided the patients into 3 groups according to their baseline HbA1c values, and compared the changes of HbA1c level after 6 months of patient education to evaluate the effects of pharmacist intervention.

**METHODS**

**Patient Enrollment** Among 88 patients with type 2 diabetes mellitus who consulted our diabetic outpatient department on Wednesday or Friday morning from 1 April 2012 to 31 March 2014, we extracted 65 patients who received patient education from pharmacist more than once. The exclusion criteria included patients without the requisite medical records (23 patients), patients taking steroids (4 patients), patients entering a nursing home (1 patient), and a history of hospitalization for diabetes training within 6 months before the start of patient education (2 patients). As a result, 30 patients were excluded and 35 patients, whose prescriptions were not changed for 3 months before the education, were selected. This study was carried out with the approval of the Ethics Committee of Kyushu University Hospital (approval number: 26-323).

**Patient Education** We interviewed each patient individually using a check sheet (Fig. 1), and the pharmacist wrote down the results. The hospital pharmacist who conducted patient education was a Local Certified Diabetes Educator. Using the check sheets, we assessed the following 12 items: oral medications adherence, injection adherence, understanding of drugs, appetite, nausea, defecation, hypoglycemia, sleep, back pain, other side effects, number of drugs, and anxiety about the financial burden of the treatment. The pharmacists obtained patient’s prescription data before the interview, and they conducted the education according to the prescribed antidiabetic drugs. Then the pharmacist confirmed the following four items: the patient’s level of stress, the patient’s level of anxiety, the patient’s understanding of the insulin injection procedure, and the patient’s level of vigor. Patient education was conducted in a separate room next to the examination room in order to maintain privacy and was done while patients were waiting for the doctor. The average duration of patient education was 20 min.

The details of patient education were written in the clinical records and the pharmacist reported the information to the doctor with the check sheets. The pharmacist confirmed the levels of aspartate aminotransferase (AST), alanine aminotransferase (ALT), γ-glutamine transpeptidase (γ-GTP), serum creatinine (SCr), total cholesterol (T-Cho), low-density lipoprotein (LDL), high-density lipoprotein (HDL), and triglycerides (TG). The pharmacist added comments about any abnormal items. If side effects such as hypoglycemia were suspected and a change of treatment was recommended, or the patient wished to change treatment, the information was recorded in the clinical records. In such cases, the pharmacist attended the doctor’s examination with the patient.

**Analysis of Factors Influencing the Change of HbA1c Level** We divided the patients into groups with an increase or decrease of HbA1c level according to the change during 6 months from the start of patient education. We compared background factors, check sheet items, and laboratory values between these two groups. HbA1c values were determined according to the national glycohemoglobin standardization program (NGSP). One of 4 choices (1 to 4) was selected by the patients for each check sheet item, and we evaluated difference between those selecting 1 or 2
and those selecting 3 or 4.

**Stratified Analysis of the Changes of HbA1c Level during Patient Education** Based on the guidelines of the Japanese Diabetes Society, we also divided the subjects into 3 groups based on HbA1c values (HbA1c<7%, 7% ≤ HbA1c<8%, and HbA1c ≥ 8%). We compared background factors at the start of patient education and laboratory values of the three groups. We also compared HbA1c level between start time of patient education and 6 months after at each group.

**Statistical Analysis** One-way ANOVA, Student's t-test, Fisher's exact test, or the paired t-test was used for statistical comparisons. JMP version 11 was employed for statistical analysis all data are presented as the mean ± S.D.

**RESULTS**

**Factors Influencing the Change of HbA1c Level after 6 Months of Patient Education** Among the 35 patients, 21 were men and 14 were women. The mean age, height, and weight were 70.7 ± 10.2 years, 159.3 ± 9.0 cm, and 61.2 ± 10.8 kg. The mean HbA1c level was 7.6 ± 1.6% (Table 1). The number of education sessions during the 6-month period was 2.3 ± 1.2. After 6 months of patient education, HbA1c level decreased in 15 patients (HbA1c-decreased group) and HbA1c level increased in 20 patients (HbA1c-increased group). There were no significant differences of the age, height, weight, and laboratory values between these 2 groups. The numbers of patient education sessions were also similar.

The mean baseline HbA1c level was 8.5 ± 1.9% in the HbA1c-decreased group and it was significantly higher than that of the HbA1c-increased group (7.0 ± 0.8%, p=0.004) (Table 1). The percentage of patients who answered that they understood the effects of their medications was 53% in the HbA1c-decreased group, which was significantly lower than in the HbA1c-increased group (95%, p=0.011) (Table 2). There were no differences between the two groups with regard to the frequency of adverse events, the number of prescribed drugs, dissatisfaction with the financial burden, and the evaluations made by the pharmacist.

**Changes of HbA1c Level from before to after the Start of Patient Education** There were 12 patients in the HbA1c<7% group, 13 patients in the 7% ≤ HbA1c<8% group, and 10 patients in the HbA1c ≥ 8% group (Table 3). These 3 groups showed no differences with respect to sex, age, height, and weight. The number of patient education sessions was also similar. Moreover, there were no differences of laboratory values, except for baseline HbA1c level before the

---

Fig. 1. Check Sheet for Diabetes Medications

| Questionnaire       | Contents  |
|---------------------|-----------|
|                     | No  | Yes   |
| 1 Did you take drugs regularly? | 1   | 2    | 3    | 4    |
| 2 Did you inject insulin regularly? | 1   | 2    | 3    | 4    |
| 3 Do you understand drug effects? | 1   | 2    | 3    | 4    |
| 4 Do you have an appetite? | 1   | 2    | 3    | 4    |
| 5 Do you have nausea? | 1   | 2    | 3    | 4    |
| 6 Do you have defecation? | 1   | 2    | 3    | 4    |
| 7 Do you have an experience of hypoglycemia? | 1   | 2    | 3    | 4    |
| 8 Can you sleep? | 1   | 2    | 3    | 4    |
| 9 Do you have a back pain? | 1   | 2    | 3    | 4    |
| 10 Do you have an experience of other side effects? | 1   | 2    | 3    | 4    |
| 11 Do you feel that too much drugs are prescribed? | 1   | 2    | 3    | 4    |
| 12 Are you anxious about economic load? | 1   | 2    | 3    | 4    |

**Evaluation of the pharmacist**

| Evaluation of the pharmacist | Contents  |
|-----------------------------|-----------|
|                            | No  | Yes   |
| 1 He (She) is tense.       | 1   | 2    | 3    | 4    |
| 2 He (She) feels uneasy.   | 1   | 2    | 3    | 4    |
| 3 He (She) understands insulin injection procedure. | 1   | 2    | 3    | 4    |
| 4 He (She) is vigorous.    | 1   | 2    | 3    | 4    |
Table 1. Patient Background

|                          | Total n=35 | HbA1c-decreased group n=15 | HbA1c-increased group n=20 | p-value |
|--------------------------|------------|-----------------------------|-----------------------------|---------|
| Sex (M/F)                | 21/14      | 11/4                        | 10/10                       | 0.296   |
| Age (years)              | 70.7±10.2  | 70.7±7.5                    | 70.7±11.9                   | 0.996   |
| Height (cm)              | 159.3±9.0  | 161.4±6.7                   | 157.7±10.0                  | 0.242   |
| Weight (kg)              | 61.2±10.8  | 62.0±10.6                   | 60.6±10.8                   | 0.748   |
| Number of patient education | 2.3±1.2   | 2.3±1.5                     | 2.3±1.0                     | 0.938   |

[Blood test value before patient education]

|                          |            | HbA1c (%) | AST (IU/L) | ALT (IU/L) | γ-GTP (IU/L) | Scr (mg/dL) | T-Chol (mg/dL) | LDL-Chol (mg/dL) | HDL-Chol (mg/dL) | TG (mg/dL) |
|--------------------------|------------|-----------|------------|------------|--------------|-------------|----------------|------------------|------------------|------------|
| HbA1c-decreased group n=15 |            | 7.6±1.6   | 25.5±15.7  | 26.1±22.0  | 43.3±60.5    | 0.9±0.4     | 194.9±40.7     | 113.7±40.0      | 62.3±17.3       | 169.8±227.3 |
| HbA1c-increased group n=20 |            | 8.5±1.9   | 24.9±11.0  | 25.4±14.4  | 32.5±29.3    | 0.9±0.3     | 194.2±43.2     | 117.2±41.5      | 62.8±20.2       | 126.4±49.2  |

Aspartate aminotransferase (AST), alanine aminotransferase (ALT), γ-glutamyl transpeptidase (γ-GTP), serum creatinine (Scr), total cholesterol (T-Chol), low-density lipoprotein (LDL), high-density lipoprotein (HDL), and triglycerides (TG). Mean±S.D.; Sex: Fisher’s exact test; Others: Student’s t-test. *p<0.05.

Table 2. Answers of the Patients and Evaluations of the Pharmacists

|                          | HbA1c-decreased group n=15 | HbA1c-increased group n=20 | p-value |
|--------------------------|-----------------------------|-----------------------------|---------|
| [Patient self-assessment items] (%) |                   |                     |         |
| I took drugs every day.   | 86 (12/14)                 | 100 (20/20)              | 0.163   |
| I was injected daily.     | 83 (5/6)                   | 100 (6/6)                | 1.000   |
| I understand the drug effects | 53 (8/15)                 | 95 (19/20)               | 0.011*  |
| I have an appetite.       | 100 (15/15)                | 90 (18/20)               | 0.496   |
| I have nausea.            | 0 (0/15)                   | 5 (1/20)                 | 1.000   |
| I have defecation.        | 93 (14/15)                 | 85 (17/20)               | 0.619   |
| Hypoglycemia happened.    | 13 (2/15)                  | 10 (2/20)                | 1.000   |
| I can sleep.              | 87 (13/15)                 | 60 (12/20)               | 0.134   |
| I have a back pain.       | 7 (1/15)                   | 0 (0/20)                 | 0.429   |
| Other side effects happened. | 7 (1/15)                 | 15 (3/20)                | 0.619   |
| I feel prescribed drugs too much. | 33 (5/15)             | 40 (8/20)                | 0.737   |
| Economic burden is a concern. | 33 (5/15)               | 40 (8/20)                | 0.737   |

[Evaluation of the pharmacist]

|                          |                      |                  |                  |
|--------------------------|----------------------|-----------------|-----------------|
| Tense state              | 7 (1/15)             | 5 (1/20)        | 1.000           |
| Uneasy state             | 20 (3/15)            | 45 (9/20)       | 0.163           |
| Understand the injection procedure | 67 (4/6)        | 67 (4/6)        | 1.000           |
| Vigor state              | 93 (14/15)           | 90 (18/20)      | 0.737           |

Percentages (%) were indicated by dividing the number of selecting 3 or 4 by total subjects for each item at the check sheet for diabetes medications. Fisher’s exact test; *p<0.05.

In the HbA1c≥8% group, HbA1c level decreased from baseline (9.5±1.7%) to after 6 months (8.4±1.9%) (p=0.015, Fig. 2). In the HbA1c<7% group, HbA1c level increased significantly after 6 months (6.9±0.6%) of patient education. On the other hand, there were no significant changes in the 7%≤HbA1c<8% group.

We assessed the relationship between the decrease
in HbA1c level and an increase in the dosage and/or
addition of other antidiabetic drugs in the HbA1c ≥ 8
% group. Three of the 10 patients in this group
received only oral drugs: two patients received a
dipeptidyl peptidase 4 (DPP-4) inhibitor and sulfonylurea (SU), and one patient received an α-
glucosidase inhibitor (α-GI), a biguanide (BG), and
SU. Five of the 10 patients were prescribed insulin
only: three patients used premixed insulin and two
patients used ultra-long acting insulin plus ultra-rapid
insulin. Two of the 10 patients were treated with both
oral drugs and insulin: one patient used premixed insu-
lin and an α-GI, and the other used premixed insulin
and a DPP-4 inhibitor. HbA1c levels decreased in
seven patients; five of these seven patients received
additional antidiabetic drugs or higher dosages of an-
tidiabetic drugs for 6 months. It is possible that the
decrease in HbA1c level in four of the five patients
was influenced by these additional antidiabetic drugs.
Three of them were treated with daily insulin doses of
18, 30, and 52 units at the start of patient education,
and were added with 2, 2, and 4 units of insulin,
respectively. Another one was increased of the dosage
and were added with 2, 2, and 4 units of insulin,
three of them were treated with daily insulin doses of
18, 30, and 52 units at the start of patient education,
and were added with 2, 2, and 4 units of insulin,
respectively. Another one was increased of the dosage
and were added with 2, 2, and 4 units of insulin,
respectively. Another one was increased of the dosage
and were added with 2, 2, and 4 units of insulin,
only oral drugs (DPP-4 inhibitor: 4 patients, BG: 1 patient, α-GI: 2 patients, DPP-4 inhibitor + SU: 1 patient, α-GI + BG: 1 patient, SU + TZD: 1 patient). Two of them were prescribed insulin (premixed insulin: 1 patient, DPP-4 inhibitor + premixed insulin: 1 patient).

DISCUSSION

In general, Japanese pharmacists are not active in the diabetes outpatient department. In this study, the hospital pharmacist conducted education of diabetic outpatients and we performed the first assessment of its effectiveness in Japan.

The results suggested that patients with a high baseline HbA1c level and poor understanding of their treatment were more likely to show improvement after receiving patient education from a pharmacist. We also showed that education was effective for patients with an HbA1c level of more than 8%.

At the start of patient education, HbA1c level was 8.5 ± 1.9% in the HbA1c-decreased group and 7.0 ± 0.8% in the HbA1c-increased group. The percentage of patients with good understanding of their medications was only 53% in the HbA1c-decreased group, which was relatively low. In this study, we did not assess the change of understanding after the patient education. However, foreign studies have shown that understanding of medications and adherence are improved by patient education. Therefore, the level of understanding might have been increased by education in our patients. In the HbA1c-increased group, 95% of the patients stated that they understood their medications, but this study was based on a questionnaire survey so it is possible that some patients misunderstood their drugs and gave wrong information to the pharmacist. Further investigation of this issue will be necessary.

There are several reports that assessed HbA1c value as the effect of intervention by pharmacists after four to six months. In this study we also assessed the HbA1c value after six months. In this study, HbA1c level improved in the HbA1c≥8% group after 6 months of patient education. Similar results were reported by Choe et al. They found that HbA1c level was decreased by pharmacist intervention using the primary care technique in patients with HbA1c levels of more than 8% (mean: 10 ± 1.8%). In addition, Spence et al. reported that face-to-face patient education might be effective. In the HbA1c ≥ 8% group, HbA1c levels of seven patients decreased. Two of these seven patients received their prescribed anti-diabetic drugs unchanged, and their HbA1c levels decreased after patient education. Therefore, the decrease in HbA1c might be caused by patient education by the hospital pharmacist. In three of the seven patients, the decrease in HbA1c level might have been influenced by the addition of insulin. However, the added doses of insulin were relatively low to explain the decrease in HbA1c level. Thus, we considered that patient education might also influence the decrease in HbA1c level. Zhao et al. also reported that ignorance about drug effects or misunderstanding of the insulin injection technique could be corrected by pharmacist education, and that education led to a decrease of HbA1c level. Seven out of 10 patients used insulin in the HbA1c ≥ 8% group (Table 3), which is significantly more than in the other two groups (p = 0.03). The pharmacist confirmed their injection technique as one of the items assessed, and found that all of the patients had some problems with technique. In 4 of 7 patients who injected insulin, HbA1c level decreased by from 0.3% to 3%. They didn’t understand appropriate injection site and the rule that keep the needle stuck at their abdomens more than 6 s after injection. Because the pharmacist provided education on the correct technique, this might be the reason why HbA1c level decreased. In the other 3 patients, HbA1c level only increased slightly by 0.2 to 0.3%. They had hypoglycemia before patient education. Thus we mainly educated the timing of insulin use and how to deal with hypoglycemia. In addition, we proposed the decrease of insulin dosage for one patient to physician. HbA1c level did not change in the 7% ≤ HbA1c < 8% group. According to the guideline, HbA1c level should be maintained between 7 to 8% if stricter treatment is difficult because of old age or other factors. In our study, the HbA1c values of the patients remained within this range. In the HbA1c < 7% group, HbA1c level showed a significant increased at 6 months after the start of patient education.

According to “Evidence-based Practice Guideline for the Treatment for Diabetes in Japan 2013”, it needed to pay attention to a lower limit value of HbA1c taking into account the risk of hypoglycemia. In this study, there were three, three, and seven 75 years of age and older in the each groups of HbA1c ≤ 7%, 7% ≤ HbA1c < 8%, and HbA1c ≥ 8%. However, there were no high risk patients who are frail and cog-
hypoglycemia for the patients in the HbA1c guide line. The pharmacists considered the risk of hypoglycemia for the patients in the HbA1c <7% group, and suggested cessation or decrease of dose for antidiabetic drugs to physicians as needed. Therefore, the prescriptions of three of seven 75 years of age and older in the group were changed, and these might contribute the increasing of HbA1c level at 6 months after the start of patient education.

Physicians and nurses in the hospital, and pharmacists out of the hospital pharmacy also involved to patient education. We think that two reasons which the HbA1c levels after the education of hospital pharmacist were improved. Pharmacist could make adequate time for about 20 min, which patients were waiting for the doctor, to determine adherence and understanding of medications, as well as to explain the insulin injection procedure. Moreover, the pharmacist could share information with the doctor about the patient’s problem. In some cases, the doctor was informed about the frequency of hypoglycemia and medications dosages were changed. The doctor sometimes asked the pharmacist to perform education about insulin injection. We consider that while patient education by other medical staffs including community pharmacist contribute to HbA1c control, our approach may provide additive effect.

Because this study was carried out in a small medium hospital, the number of patients enrolled was low, various antidiabetic drugs were used, and the dosages were not fixed. Some patients received treatment at other hospitals before they visited our hospital, so we could not determine how long these patients had diabetes. However, we selected the patients who had been on drug treatment for more than 3 months. There might be differences with the history of diabetes among the each group. In the future, a multicenter study should be conducted in more patients.

We found a decrease of HbA1c level in outpatients with poorly controlled diabetes (HbA1c ≥8%) who received patient education from the hospital pharmacist. These findings indicate that patient education by a hospital pharmacist could be important for the improvement of glycemic control in Japan.

**Conflicts of Interest** The authors declare no conflict of interest.

**REFERENCES**

1) The Diabetes Control and Complications Trial Research Group, *N. Engl. J. Med.*, **329**, 977-986 (1993).
2) UK Prospective Diabetes Study (UKPDS) Group, *Lancet*, **352**, 837-853 (1998).
3) Shichiri M., Kishikawa H., Ohkubo Y., Wake N., *Diabetes Care*, **23**, B21-B29 (2000).
4) Ferrannini E., DeFronzo R. A., *Eur. Heart J.*, **36**, 2288-2296 (2015).
5) American Diabetes Association, *Diabetes Care*, **38** (Suppl. 1), S1-S94 (2015).
6) Japan Diabetes Society, “Treatment Guide for Diabetes 2012-2013,” Bunkodo, Tokyo, 2013, pp. 13-14.
7) Rubin R. R., *Am. J. Med.*, **118** (Suppl.), 27S-34S (2005).
8) Ip E. J., Shah B. M., Yu J., Chan J., Nguyen L. T., Bhatt D. C., *Am. J. Health Syst. Pharm.*, **70**, 877-886 (2013).
9) Spence M. M., Makarem A. F., Reyes S. L., Rosa L. L., Nguyen C., Oyekan E. A., Kiyohara A. T., *J. Manag. Care Spec. Pharm.*, **20**, 1036-1045 (2014).
10) Xin C., Xia Z., Jiang C., Lin M., Li G., *Patient Prefer. Adherence*, **9**, 797-802 (2015).
11) Jarab A. S., Alqudah S. G., Mukattash T. L., Shattat G., Al-Qirim T., *J. Manag. Care Pharm.*, **18**, 516-526 (2012).
12) Chen G. D., Huang C. N., Yang Y. S., Lew-Ting C. Y., *BMC Public Health*, **14**, 683 (2014).
13) Souza J. G., Apolinario D., Magaldi R. M., Busse A. L., Campora F. Jacob-Filho W., *BMJ Open*, **4**, e004180 (2014).
14) Rothman R. L., Malone R., Bryant B., Shintani A. K., Crigler B., Dewalt D. A., Dittus R. S., Weinberger M., Pignone M. P., *Am. J. Med.*, **118**, 276-284 (2005).
15) Edelman D., Fredrickson S. K., Melnyk S. D., Coffman C. J., Jeffreys A. S., Datta S., Jackson G. L., Harris A. C., Hamilton N. S., Stewart H., Stein J., Weinberger M., *Ann. Intern. Med.*, **152**, 689-696 (2010).
16) Taveira T. H., Friedmann P. D., Cohen L. B., Dooley A. G., Khatanah S. A., Pirraglia P. A., Wu W. C., *Diabetes Educ.*, **36**, 109-117 (2010).
17) Choe H. M., Mitrovich S., Dubay D., Hayward R. A., Krein S. L., Vijan S., *Am. J. Manag. Care*, **11**, 253–260 (2005).

18) Zhao R. Y., He X. W., Shan Y. M., Zhu L. L., Zhou Q., *Clin. Interv. Aging*, **10**, 1201–1212 (2015).

19) The Japan Diabetes Society, “Evidence-based Practice Guideline for the Treatment for Diabetes in Japan 2013,” 2013, pp. 245–261.