Effect of antihyperglycemic drug monotherapy to prevent the progression of mild hyperglycemia in early type 2 diabetic patients: the Japan Early Diabetes Intervention Study (JEDIS)

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Received: 2 October 2016 / Accepted: 27 March 2017 / Published online: 18 April 2017
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Abstract To effectively prevent the worsening of hyperglycemia in type 2 diabetes mellitus, it is of interest to see the clinical efficacy of early introduction of pharmacotherapy in addition to lifestyle intervention which is not always easy to continue throughout life. This is a randomized unblinded comparative clinical study on suppressive effects of lifestyle intervention alone and additional monotherapies for mild hyperglycemia at an early stage of treatment-naïve type 2 diabetic patients, whose fasting plasma glucose (FPG) and glycosylated hemoglobin (HbA1c) are less than 140 mg/dl and 7.4%, respectively. The control group (group N = arm N) received conventional lifestyle intervention assisted by routine facilities, while the pharmacological intervention group (group D composed of 4 arms) was additionally treated by monotherapy with one of four kinds of oral antihyperglycemic agents i.e., sulfonylurea (SU), α -glucosidase inhibitor, biguanide and dipeptidyl peptidase-4

inhibitor. The participants were scheduled to follow up for 3 years to maintain glycemic control below primary endpoint which was defined as the first occurrence of FPG ≥ 140 mg/dl and HbA1c $\geq 7.4\%$ simultaneously even by increasing doses of oral drug in group D, if necessary. The outcomes of occurrences of primary endpoint were not different between group N and group D composed of 4 arms during 3 years by Kaplan–Meyer plots ($p = 0.405$). On the other hand, Δ FPG (Δ : incremental change from baseline) and Δ HbA1c in group D significantly decreased when compared to those of group N during 3 years ($p < 0.05$ and $p < 0.01$ respectively). Significant reductions of Δ BMI were seen similarly in both groups throughout the study ($p < 0.05$), but did not differ between two groups. Among these 5 arms, significant decreases of Δ HbA1c were observed in three monotherapy arms of group D compared to arm N for 3 years ($p < 0.05$ or $p < 0.01$), except for arm SU in which Δ BMI and Δ HbA1c tended to increase at the latter half of the study. The final achievement rates of target HbA1c less than 7.4, 7.0 and 6.5% in all the participants tended to be higher in group D than in group N ($p < 0.047$ for 7.4%, but not significant for others). In conclusion, the early introduction of pharmacological monotherapy in addition to lifestyle intervention seem to suppress mild hyperglycemia with small doses of antihyperglycemic agents for 3 years, except for the use of SU drug. Although a larger scale of trial will be necessary to conclude, the early treatment with suitable monotherapy could be effective to bring and keep “safe level of glycemia”.

Members of the JEDIS (Japan Early Diabetes Intervention Study) Research Group are listed in “Acknowledgement”.

In 2012, HbA1c values which were standardized by JDS (Japan Diabetes Society) were officially revised to use NGSP (National Glycohemoglobin Standardization Program) values, the latter being approximately 0.4% higher than old JDS values. So, HbA1c values which appear in this report are all expressed as NGSP values [1, 2].

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Keywords Type 2 diabetes mellitus (T2DM) · Lifestyle modification · Oral antihyperglycemic agent (AHA) · Glycated hemoglobin (HbA1c) · Fasting plasma glucose (FPG) · Body mass index (BMI)

Background and aims

The prevalence of type 2 diabetes mellitus (T2DM) has been increasing, both nationwide in Japan and worldwide [3–6]. At present (2014), about 422 million people are estimated to have diabetes in the world by NCD Risk Factor Collaboration [7]. In Japan, about 10 million people are estimated to be suffering from diabetes, of which more than 90% are T2DM [8]. It continues to be a growing concern, probably due to the rise in prevalence of obesity, especially in young adults [4, 5, 9] and the dramatically increased aging people of societies [10, 11].

Despite efforts taken by various health screening providers or organizations supported by government, certain delays in diagnosis and initiation of its treatment inevitably lead to specific organ damage due to diabetic micro- and macro-angiopathies [8, 12–14], the reduction of which would bring ultimately both desirable quality of life (QOL) and socioeconomic benefits [6, 14].

Needless to say, it has already been reported from many countries including Japan that lifestyle modification is effective in the primary and secondary prevention of T2DM [15–19]. Moreover, if glycemic control is kept within a certain limit from an early stage of the disease, prevention of diabetic vascular complications, particularly of microangiopathies such as retinopathy, might be possible, as indicated by clinical experiences [20, 21] and epidemiological surveys [22], and more recently as evidenced by several large-scale clinical trials in type 1 and 2 diabetes mellitus [23–27].

These available evidences indicate that it will be possible to prevent or slow the development of diabetic microvascular complications by suppressing the level of fasting plasma glucose (FPG) under 140 mg/dl and 2-h plasma glucose (2-h PG) during 75 g oral glucose tolerance test (OGTT) under 200 mg/dl, or HbA1c under 7.0%. More recently, evidence has emerged that macrovascular complications in diabetes may also be related to hyperglycemia nearly in the same level, even though the sharp distinction of glycemia at risk for macroangiopathy is difficult [12, 28]. Thus, the sooner the better in glycemic control to prevent complications, as is known as “legacy effect” by “metabolic memory” [27].

Accordingly, even in diabetic patients diagnosed by current criteria (FPG ≥ 126 mg/dl and HbA1c $\geq 6.5\%$), those whose glycemic control are kept within FPG < 140 mg/dl and/or HbA1c $< 7.0\%$, could mostly escape from the risks of diabetic complications, if they could start treatment timely at an early stage of T2DM. Thus, it is reasonable to take measures to cope with diabetes a little earlier than the stage where the risk of vascular complications definitely increase, by suppressing the progression

to harmful hyperglycemia (FPG and HbA1c more than 140 mg/dl and 7.0%, respectively). For these reasons, in addition to diabetes education and care on diet and physical activity, the effect of early initiation of pharmacological treatment using oral antihyperglycemic agents (AHAs) seems to deserve consideration in order to avoid reaching excessive hyperglycemia.

While diet and exercise therapies important as the basis of diabetes treatment [12, 14, 17], especially in prediabetes and T2DM, it is not easy to sustain ideal lifestyle long enough to live out the allotted span of life. Accordingly, it should be elucidated whether the use of pharmacological treatment including new classes of AHAs is really beneficial in combination with conventional lifestyle interventions to prevent or delay the occurrence of harmful hyperglycemia.

In Japan, three large-scale clinical trials supported by the Ministry of Health, Labor and Welfare are underway, i.e., Diabetes Outcome Intervention Trial (DOIT)-1, 2 and 3, the underlying rationales of which are the primary, secondary and tertiary preventions of T2DM [29, 30]. This study, Japan Early Diabetes Intervention Study (JEDIS), complements these DOITs by comparing the effect on hyperglycemia of standard education and care for diabetes, i.e., lifestyle interventions, to that of additional administration of AHAs in patients with T2DM at its early stage without any complication.

The American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) had published the guidelines for the management of hyperglycemia and the treatment algorithm of T2DM [31, 32]. They involve lifestyle intervention and pharmacological therapy to be commenced at an early stage of diabetes, recommending metformin as the first line of drugs. As stated in the publications, however, the algorithm is mostly based on clinical experiences and economic backgrounds with little evidence for the true benefit of respective drug use for a long time. It is unknown whether guidelines of ADA and EASD are directly applicable to Japanese patients who are comparatively lower in BMI [4, 5, 8] and more insulinopenic than in Caucasians [4, 33–36]. The guidelines also point out that there are need for international clinical reports of empirical studies based on the guideline and its algorithm. Thus, to prevent the worsening to harmful hyperglycemia efficiently, the clinical evaluation of applying AHAs in comparison with the education and care for lifestyle modification alone is to be established [31, 32, 37]. Still, need for intensive, early glycemic control in patients with type 2 diabetes remained to be solved [38].

The main aim of JEDIS is to compare the clinical durable effect of conventional standard lifestyle intervention

assisted by routine facilities to that of combined additional monotherapy with commercially available AHAs, in treatment-naïve patients at an early stage of T2DM without any complication.

Materials and methods

Study design and participants of JEDIS (JEDIS-1 and JEDIS-2)

The study, JEDIS (JEDIS-1), was started in July, 2007 as a prospective, randomized, open-label and blinded endpoints (PROBE) study primarily to compare the standard intervention group of lifestyle modification (group N/arm N) to additional pharmacologic intervention group (group D), which is composed of three monotherapy arms: gliclazide (sulfonylurea: SU), acarbose or miglitol (α -glucosidase inhibitor: α -GI) and metformin (biguanide: BG), commercially available in Japan. As stated below in detail, the study was revised later as JEDIS-2, because of two reasons. One was the difficulty of collecting enough numbers of eligible applicants due to decreased use of 75 g OGTT at screening since the introduction of HbA1c as a diagnostics parameter, and the other one was the new approval of DPP-4i drugs in Japan at the end of 2009. Accordingly, JEDIS is finally composed of JEDIS-1 (2007–2009) and JEDIS-2 (2009–2014), as shown in Fig. 1.

In JEDIS-1, subjects without previous history of diabetes were identified as being potentially eligible from individuals who had undergone health screening tests including 75 g OGTT within the previous 6 months and who met the screening criteria as shown in Fig. 1. Namely, they were for the first time diagnosed as T2DM by the criteria of Japan Diabetes Society (JDS) [2, 39] but FPG and HbA1c were less than 126 mg/dl and 7.4%, respectively. Thereafter, 75 g OGTT and HbA1c measurements were repeated again within 3 months, after obtaining informed consent in document. Thus, the subjects who had an isolated postprandial hyperglycemia (IPH) pattern, i.e., FPG <126 mg/dl and 2-h PG $\geq$ 200 mg/dl, and a simultaneously measured HbA1c <7.4%, in two occasions, were registered on JEDIS website by in-office doctor's own personal computer. In Japanese population, IPH pattern during 75 g OGTT is reported to be more frequently found at an early period of T2DM, compared to that in Caucasian people [40]. Moreover, 2-h PG is reported to be a more important risk factor for cardiovascular diseases [41, 42].

The patients aged 30–69 years old with body mass index (BMI) ranged between 18.5–35.0 were eligible in the study, excluding those who were already suffering from other severe diseases such as cerebro- or cardio-vascular and kidney diseases. The candidate patients were also

confirmed not to suffer from diabetic microangiopathies, i.e. retinopathy, proteinuria and neuropathy, by internist and ophthalmologist in charge. The patients with hypertension, biochemical dyslipidemia and hyperuricemia under appropriate medications were allowed to be included.

In JEDIS-1, the screened and registered patients were randomly assigned into 4 arms; control standard arm N (group N) or one of three pharmacological intervention (monotherapy) arms, i.e., arm SU, arm α -GI and arm BG, of which group D is composed. The doctor in charge was free to choose either acarbose or miglitol when assigned to α -GI arm. The randomization method employed in this study randomly assigned subjects by means of a permuted block design with the test site as the stratification factor.

All the participants in both groups (all arms) were equally provided with a sphygmomanometer for home use, a scale for body weight measurement which is capable of body fat estimation, a pedometer with calorie counter and a platform scale for cooking, in addition to patient education booklets [43] for improving health literacy, namely, balanced diet intake and exercise performance of themselves. They were instructed and empowered to check and record everyday the results of body weight, home blood pressure taken in the morning before breakfast, the number of walking steps taken a day and daily energy consumption in notebooks especially prepared for their personal health record. Daily plans for physical exercise and diet therapy were individually noticed in advance by nurses and dietitians under doctor's prescription. Food Exchange List was provided to each participant [44].

They were requested to visit his or her clinic every 2 months to check body weight, abdominal circumference (if possible), blood pressure, FPG, HbA1c, plasma lipids, uric acid, creatinine and other biochemical parameters as well as urinary examinations. In every visit, they could be instructed and advised face to face by his or her doctor and medical staffs including dietitians when necessary. They were also monitored regularly by electrocardiogram (ECG) and by ophthalmologic examination at least once a year. Plasma insulin was also measured once a year. The Guideline for the Treatment of Diabetes Mellitus in Japan (Japanese Standard Maneuvers: JSM) edited by JDS were used and referenced in the process of clinical observations [45].

In the pharmacological intervention arms of group D, patients were prescribed with one of the following drugs starting from minimal daily doses, i.e., 10 mg/day of gliclazide (allowed maximal dose 120 mg/day in Japan), 150 mg/day of acarbose (max. 300 mg/day), 75 mg/day of miglitol (max. 225 mg/day), or 250 mg/day of metformin (max. 2250 mg/day). The doses of drugs were recommended to augment gradually up to maximal doses officially allowed in Japan as mentioned above, if FPG

Fig. 1 Recruitment and assignment of patients in JEDIS-1 and JEDIS-2. **a** screening criteria for, 2-h PG (75 g OGTT) and HbA1c: FPG 100-125 mg/dl, 2-h PG ≥ 200 mg/dl and HbA1c 5.9–7.3%, **b** second time 75 g OGTT, **c** the diagnosis of T2DM depends on JDS criteria in 2002 (ref. 38), **d** final valid included numbers of group

N (=arm N) and group D composed of arm SU, BG, α-GI and DPP-4i are sum of those in JEDIS-1 and JEDIS-2. Numbers of patients excluded are indicated by dotted lines with arrows, **e** numbers and percentages of patients dropped out in the middle of 3 years in the study

exceeded continuously an alarm level (126 mg/dl or more), which was timely notified from JEDIS center to the doctor in charge by e-mail. Hypoglycemia defined as FPG less than 70 mg/dl or its self-awareness was also alarmed incidentally to recover by taking 10 g of glucose or more, if necessary.

After 2 years from the start of JEDIS-1, the protocol was revised to JEDIS-2 in October, 2009, as shown in Fig. 1, because of above explained reasons. In JEDIS-2, drug naive patients with T2DM already diagnosed by JDS criteria whose FPG and HbA1c are less than 140 mg/dl and 7.4%, respectively and whose estimated duration of diabetes is less than 5 years could be also enrolled. The patients suffering from any diabetic complications were excluded, as done in JEDIS-1. At the same time, in JEDIS-2, DPP-4 is i.e., sitagliptin and vildagliptin were additionally adopted as an another arm of pharmacologic treatment (DPP-4i arm as group D), as they became commercially available and getting popular in Japan at the end of 2009. In this occasion, gliclazide drug (arm SU) was omitted out of JEDIS-2, because its risk to induce severe hypoglycemia or weight gain was seriously concerned in practice, as often discussed in some articles [46, 47].

The different inclusion criteria in JEDIS-1 and -2 also reflected the newly proposed diagnostic criteria which adopted HbA1c as a diagnostic parameter. Thus, the small differences of inclusion criteria in FPG, the level of HbA1c being the same, were thought to be acceptable (2, 39).

In JEDIS-2, the eligible patients were equally randomized into two groups; group N and D. The participants of the latter group were assigned to be treated with anyone of adopted AHAs according to his or her doctor's own choice. In the case of DPP-4i, 25 mg/day of sitagliptin or 50 mg/day of vildagliptin was used at the beginning, increasing the dose up to maximal 100 mg/day respectively, if necessary, as the same manner as the other drugs already mentioned above. The other methods of interventions employed in JEDIS-1 including routine facilities for healthy life were all similarly taken over to JEDIS-2.

Thus, JEDIS was composed of JEDIS-1 and JEDIS-2, being finally combined and analyzed together. For this reason, the numbers of patients enrolled in the individual arm and group were different, as shown in Table 1 and Fig. 1. Finally, 108 patients from 27 clinical sites in Japan, all of whom were uneventfully observed more than 12 months, could be used for statistical analyses. Fundamental data of participants were all registered and pooled in the management center of JEDIS via JEDIS website using personal computer. The communications with clinical sites about the information on diabetes education and care and on the warnings of excessive hyperglycemia or hypoglycemia were appropriately notified, being linked each other by e-mail.

In the study of JEDIS-1 and JEDIS-2, additional secondary intervention study applying self-monitoring of blood glucose (SMBG) was also tried in a part of participants in all the groups (arms), when they hoped to join this program with their own will. The equipment and materials needed to perform SMBG were given free of charge. The results of SMBG were used solely for his or her doctor's reference.

Primary and secondary outcomes

Primary endpoint (PE) was defined as follows; the first occurrence of both FPG ≥ 140 mg/dl and HbA1c $\geq 7.4\%$, and it should be confirmed by repeated tests, in pharmacological intervention arms even after the increase up to maximal doses of AHAs. Final judgements of worsening to primary end points were confirmed independently by the Committee for Data and Safety Monitoring (CDSM). The data from SMBG were not used for this purpose.

Secondary endpoints were as follows; (1) the appearance of diabetic retinopathy, diagnosed by ophthalmologist by a direct retinal examination or by photographs taken by a non-mydratic retinal camera, (2) diabetic nephropathy, diagnosed by continuous proteinuria $\geq \pm$ or by measuring albuminuria ≥ 30 mg/g creatinine, and (3) macrovascular events such as cerebral and myocardial infarctions. These outcomes were also principally independently judged by CDMS including special experts such as ophthalmologist, nephrologist and cardiologist.

Clinical measurements and data collections on daily lifestyle

Height (cm), body weight (BW) (kg), abdominal circumference at the level of navel (cm) (if possible) and blood pressures (systolic and diastolic) (mmHg) were measured at every visit (at least every 6 months, obligatorily) at individual clinical site. BMI was calculated as $[BW(kg)]/[height(m)]^2$ (kg/m^2). Patients were requested to bring carbon copies of patients' own notebooks where BW, blood pressures, numbers of walking steps a day, dietary energy consumption (calorie/day) and SMBG data (when performed) and so on were recorded.

Questionnaire surveys were also done at every visit to contribute to medical treatments. They include self-reported physical activities such as estimated walking steps/day (more or less than approximately 10,000 casual walking steps/day), daily energy intake (estimated Calorie/day) (more or less than prescribed dietary plan) and the notes of compliance for regular taking medicines, and so on. Although the education of diet therapy by dietitian was done beforehand, it could be repeated when the need arose depending on the answer to questionnaire and also on his or

Table 1 Baseline characteristics of the study groups

	Group N	Group D	<i>p</i> value
Demography			
Number of patients	45	63	—
Age (years old)	59.04 ± 8.88	59.60 ± 8.57	0.729
Sex (male/female)	28/17	42/21	0.633*
Accompanied disorders			
Hypertension (%)	40%	42.9%	0.767*
Dyslipidemia (%)	48.9%	55.6%	0.494*
Hyperuricemia (%)	11.1%	9.5%	0.788*
Clinical and metabolic status			
BMI (Kg/m ²)	23.7 ± 3.2	23.8 ± 3.5	0.824
SBP (mmHg)	126.3 ± 13.9	128.2 ± 16.3	0.541
DBP (mmHg)	75.9 ± 9.4	76.9 ± 10.8	0.617
TC (mg/dl)	202.3 ± 33.2 (<i>n</i> = 35)	201.7 ± 30.0 (<i>n</i> = 46)	0.934
HDL-C (mg/dl)	59.0 ± 15.1 (<i>n</i> = 40)	57.7 ± 14.9 (<i>n</i> = 60)	0.672
LDL-C (mg/dl)	118.0 ± 30.7 (<i>n</i> = 34)	114.5 ± 25.7 (<i>n</i> = 46)	0.581
TG (mg/dl)	114.7 ± 51.5 (<i>n</i> = 39)	148.4 ± 123.9 (<i>n</i> = 58)	0.111
Uric acid (mg/dl)	5.5 ± 1.0 (<i>n</i> = 39)	5.6 ± 1.4 (<i>n</i> = 56)	0.757
Creatinine (mg/dl)	0.76 ± 0.18 (<i>n</i> = 39)	0.74 ± 0.13 (<i>n</i> = 58)	0.571
UAE (mg/g.Cr)	9.3 ± 5.5 (<i>n</i> = 40)	11.1 ± 5.4 (<i>n</i> = 48)	0.129
Glycemia related status			
FPG (mg/dl)	116.2 ± 13.7	125.7 ± 18.5	0.004
HbA1c (%)	6.5 ± 0.4	6.7 ± 0.4	0.089
IRI	5.75 ± 3.77 (<i>n</i> = 32)	7.10 ± 5.92 (<i>n</i> = 43)	0.236
HOMA-IR	2.12 ± 1.87 (<i>n</i> = 32)	1.73 ± 1.15 (<i>n</i> = 43)	0.264
HOMA-βF	45.38 ± 34.86 (<i>n</i> = 32)	37.62 ± 25.98 (<i>n</i> = 43)	0.272

Data are expressed as mean ± SD, *P* values by unpaired Student's *t* test

BMI body mass index, *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *TC* total cholesterol, *HDL-C* high-density lipoprotein cholesterol, *LDL-C* low-density lipoprotein cholesterol (calculated), *TG* triglyceride, *UAE* urinary albumin excretion rate corrected by creatinine, *FPG* fasting plasma glucose, *HbA1c* glycosylated hemoglobin as NGSP value, *IRI* immunoreactive insulin, *HOMA-IR* homeostasis model assessment for insulin resistance, *HOMA-βF* homeostasis model assessment for β-cell function

* *P* values by χ^2 test

her doctor's view. In this connection, the adherence rates of dietary performances were clinically rather acceptable in most of participants.

The average numbers of walking steps recommended by the Ministry of Health, Labor and Welfare in Japan were roughly 8000 and 7000 steps/day in male and female adults respectively in Japan [48]. Accordingly, those whose self-reported mean number of walking steps/day written in their notebooks was over these numbers were defined as active patients for exercise. Meanwhile, a questionnaire survey was also done at every visit inquiring on the performance of daily exercise whether more than 10,000 steps/day was regularly counted or not, as mentioned above. Those who answered as Yes at more than a half times of visits were also accepted and considered as active patients for exercise.

The doctors in charge at clinical sites were requested to report the data of all the clinical and biochemical

measurements including the results of questionnaires day by day via JEDIS website, as possible as quickly.

Measurements of biochemical parameters

Patients' venous blood samples at fasting in the morning were collected in each clinical site every two months and sent to central or own laboratory (if well equipped) to measure FPG and HbA1c. Biochemical parameters such as total cholesterol (TC), high-density lipoprotein-cholesterol (HDL-C), triglyceride (TG), uric acid and creatinine (Cr) were also measured every six months, including liver function tests (transaminases). Counts of blood cells were also done every 6 months. HbA1c measured in central and local own laboratories were compared beforehand and they were confirmed to be closely correlated each other (data are not shown).

Data of HbA1c were all obtained by the method of high-performance liquid chromatography (HPLC). Other biochemical parameters were all measured by enzyme method. Low-density lipoprotein-cholesterol (LDL-C) was calculated by Friedewald's formula ($\text{LDL-C} = \text{TC} - \text{HDL-C} - \text{TG}/5$). Immunoreactive insulin (IRI) was measured by enzyme immunoassay method once a year. HOMA-IR (insulin resistance) and HOMA- β F (β -cell function) were calculated by the methods derived from homeostasis model assessment [49].

Statistical analyses

Numerical data were expressed as mean (m) $\pm$ standard deviation (SD). Baseline data between the two groups (N and D) were compared by Student's unpaired *t* test or Pearson's Chi square test according to the type of data. The change data from baseline at 2, 4, 6, 12, 18, 24, 30 and 36 months were compared by Student's unpaired *t* test or Fisher's analysis of variance for changes from baseline, two-group or multi-arm comparisons. No statistical adjustments for multiple comparisons were applied. Kaplan–Meier plots were drawn for the time to event data followed by Mantel–Haenszel log-rank test.

P values less than 0.05 were considered statistically significant. Statistical software used was the JMPTM version 11 (Cary, N.C., USA).

Results

Clinical and metabolic characteristics at baseline

As shown in Table 1, the accompanying morbidities at baseline [0 month (M)], i.e. hypertension, dyslipidemia and hyperuricemia, mostly treated already with some medications, were similarly prevalent both in group N and D, being not significantly different between 2 groups. These disorders did not significantly worsen during 3 years, almost maintaining the same levels. Except for FPG, all the clinical and metabolic parameters at baseline (0 M) were not significantly different between group N and D. Because of this difference of FPG ($p = 0.004$), the incremental change from baseline value at 0 M of each parameter (Δ) such as BMI, FPG and HbA1c was adopted for further analyses, as shown next in Fig. 2.

BMI, FPG and HbA1c of all 5 arms at baseline, 12 M and final observations are shown in Table 2. Data at final observations include the results of these parameters of all the patients who reached the primary endpoint and dropped out after more than 12 M. Fortunately, all the participants passed through 12 M without any event until last visit. Mean observation period until last visit in each arm did not differ, but it tended to be longer in arm DPP-4i

(35.2 ± 2.1 M, $n = 15$) than in arm SU (30.6 ± 7.9 M, $n = 10$) and others, but not significant. There were no significant differences of the parameters (BMI, FPG and HbA1c) among these 5 arms at baseline, 12 M and final observations. There were also no changes of these 3 parameters during observation period, except significantly increased HbA1c in arm N at final ($6.7 \pm 0.6\%$, $n = 45$) vs baseline observation ($6.5 \pm 0.4\%$, $n = 45$) ($p = 0.049$).

Mean final doses of each drug used at last visit in 4 arms of group D are individually shown in Table 2, indicating rather a small amount of each drug was needed.

Incremental changes of BMI, FPG and HbA1c in time course during 3 years

As shown in Fig. 2 (left panel), the reductions from baseline of Δ FPG and Δ HbA1c in group D became significant immediately after starting the study ($p = 0.023$ and $p = 0.000$ at 2 M, respectively), and sustained significant reductions throughout 6 M to 3 years ($p < 0.05$ or < 0.01). In contrast, in group N, there were no significant changes of Δ FPG and Δ HbA1c from baseline until 36 M. Thus, there were significant differences of Δ FPG and Δ HbA1c between group N and D during the study ($p < 0.05$ or < 0.01). These significances of differences were more clear and consistent in Δ HbA1c than in Δ FPG. On the other hand, gradual but significant decreases of Δ BMI during 3 years ($p < 0.05$ or < 0.01) were observed in both groups almost in the same manner, without significant differences between two groups.

As shown in Fig. 2 (right panel), these tendencies of decreases of Δ HbA1c were almost similarly seen in three monotherapy arms, i.e. α -GI, BG and DPP-4i arms of group D, being significantly different from control arm N (group N) ($p < 0.05$ or < 0.01). On the contrary, in arm SU, Δ HbA1c decreased at 4 M and 6 M ($p < 0.05$), but thereafter increased or even exceeded the baseline level just as seen in arm N. Significant reductions of Δ FPG in time course were also observed in arm BG and DPP-4i ($p < 0.05$ or $p < 0.01$), but not in arm SU and α -GI as well as in arm N. Δ BMI remained unchanged in arm SU and DPP-4i, but somewhat decreased in arm α -GI and BG, as well as in arm N ($p < 0.05$ or $p < 0.01$). As described in Table 2, small doses of drugs seemed to be sufficient to suppress mild hyperglycemia to a certain extent during 3 years, except for SU drug.

Primary and secondary outcomes

The outcomes of primary and secondary endpoints in group N and D until 1,000 days (approximately 3 years) were analysed by Kaplan Meyer plots, as shown in Fig. 3. The number of patients who reached primary endpoint (FPG ≥ 140 mg/dl and HbA1c $\geq 7.4\%$) was 6 and 5 in group N

GroupN	45	41	39	45	45	45	41	38	36
GroupD	63	57	60	63	63	59	56	56	49

GroupN	45	41	39	45	45	45	41	38	36
GroupD	63	57	60	63	63	59	56	56	49

Fig. 2 Time courses of Δ BMI, Δ FPG and Δ HbA1c in group N and D (left panel), and in arm N and each arm of group D (right panel). Comparisons of incremental changes of BMI, FPG and HbA1c between group N and group D (left panel) and among arms N, BG, SU, α -GI and DPP-4i. Data were analysed by Student's unpaired *t* test. Significances defined $p < 0.05$ are shown as follows by colored marks: left panel $^{\dagger}p < 0.05$, $^{\dagger\dagger}p < 0.01$ vs 0 M in each group and $^*p < 0.05$, $^{**}p < 0.01$ vs group N, and right panel; $^{\ddagger}p < 0.05$, $^{\ddagger\ddagger}p < 0.01$ vs 0 M in each arm, $^{\star}p < 0.05$, $^{\star\star}p < 0.01$ vs arm N and $^{\S}p < 0.05$ vs arm SU

and D, respectively, but the difference by log-rank test was not significant ($p = 0.406$) (Fig. 3, upper panel). Meanwhile, the mean periods until reaching primary endpoints in both groups were also not different (28.0 ± 9.1 M, $n = 6$ vs 22.0 ± 7.5 M, $n = 5$ in group N and D, respectively).

The patients who developed adverse vascular complications as secondary endpoint in group N and D were 2 and 6 respectively, and there was also no significant difference between two groups by Kaplan–Meyer plots followed by log-rank test ($p = 0.483$) (Fig. 3, lower panel).

There were no patients who suffered from severe adverse or hypoglycemic event due to pharmacological treatment.

Achievement rates of target HbA1c

As shown in Fig. 4, the achievement rates of glycemic control in all the patients of group N and D at final observations were compared by means of 3 target HbA1c levels. In this analysis, there include all the patients who reached PE and dropped out over 12 M [mean observation periods were 32.5 ± 5.6 M ($n = 45$) and 33.0 ± 6.7 M ($n = 63$), in group N and D respectively, but not significant]. The percentage of patients whose HbA1c was kept less than 7.4% was ultimately 86.7 and 96.8% in group N and D respectively with significance ($p = 0.047$). The percentages of patients whose HbA1c were kept less than 7.0 and 6.5% respectively, were not significantly different between two groups.

As shown in Fig. 5, the resulted percentages within each HbA1c range at baseline and final observations in group D seemed to be shifted toward lower value, while HbA1c values tended to increase in group N, indicating the suppressive effects of drugs on harmful hyperglycemia to a certain extent. Namely, the mean of HbA1c in group N significantly augmented from 6.5% at baseline to 6.7% at final observation ($p = 0.049$), but they did not differ in group D ($p = 0.149$).

Table 2 BMI, FPG and HbA1c in each arm at baseline, 12 months and final observations

	Arm N/group N	Arm SU	Arm α -GI	Arm BG	Arm DPP4i	Group D
BMI (Kg/m ²)						
Baseline (<i>n</i>)	23.7 $\pm$ 3.2 (45)	23.5 $\pm$ 4.6 (10)	22.9 $\pm$ 3.3 (13)	24.1 $\pm$ 3.7 (25)	24.5 $\pm$ 2.4 (15)	23.8 $\pm$ 3.5 (63)
12 months (<i>n</i>)	23.5 $\pm$ 3.5 (45)	23.5 $\pm$ 4.5 (10)	22.4 $\pm$ 2.9 (13)	23.9 $\pm$ 3.7 (25)	24.6 $\pm$ 2.5 (15)	23.7 $\pm$ 3.4 (63)
Final (<i>n</i>)	23.4 $\pm$ 3.4 (45)	23.5 $\pm$ 4.6 (10)	22.2 $\pm$ 2.9 (13)	23.8 $\pm$ 3.7 (25)	24.1 $\pm$ 1.9 (15)	23.5 $\pm$ 3.4 (63)
FPG (mg/dl)						
Baseline (<i>n</i>)	116.2 $\pm$ 13.7 (45)	123.2 $\pm$ 15.3 (10)	122.6 $\pm$ 12.2 (13)	127.8 $\pm$ 18.1 (25)	126.7 $\pm$ 25.7 (15)	125.7 $\pm$ 18.5 (63)
12 months (<i>n</i>)	116.4 $\pm$ 15.5 (45)	123.1 $\pm$ 20.8 (10)	118.8 $\pm$ 17.3 (13)	120.6 $\pm$ 17.3 (25)	124.1 $\pm$ 16.8 (15)	121.5 $\pm$ 17.4 (63)
Final (<i>n</i>)	120.9 $\pm$ 18.1 (45)	122.3 $\pm$ 19.7 (10)	121.9 $\pm$ 16.7 (13)	123.3 $\pm$ 18.9 (25)	123.3 $\pm$ 24.7 (15)	122.9 $\pm$ 19.7 (63)
HbA1c (%)						
Baseline (<i>n</i>)	6.5 $\pm$ 0.4 (45)	6.5 $\pm$ 0.5 (10)	6.8 $\pm$ 0.4 (13)	6.6 $\pm$ 0.4 (25)	6.7 $\pm$ 0.3 (15)	6.7 $\pm$ 0.4 (63)
12 months (<i>n</i>)	6.5 $\pm$ 0.5 (45)	6.5 $\pm$ 0.6 (10)	6.5 $\pm$ 0.4 (13)	6.4 $\pm$ 0.5 (25)	6.5 $\pm$ 0.4 (15)	6.5 $\pm$ 0.5 (63)
Final (<i>n</i>)	6.7 $\pm$ 0.6 (45)*	6.6 $\pm$ 0.5 (10)	6.5 $\pm$ 0.4 (13)	6.6 $\pm$ 0.4 (25)	6.5 $\pm$ 0.5 (15)	6.6 $\pm$ 0.5 (63)
Final observation periods (months)	32.5 $\pm$ 5.6 (45)	30.6 $\pm$ 7.9 (10)	31.8 $\pm$ 9.0 (13)	33.4 $\pm$ 6.7 (25)	35.2 $\pm$ 2.1 (15)	33.0 $\pm$ 6.7 (63)
Means of final doses of each drug used (mg/day) (<i>n</i>)		21 $\pm$ 20 (10) ^a	156 $\pm$ 92 (9) ^b	420 $\pm$ 286 (25) ^d	50 $\pm$ 27 (12) ^e	67 $\pm$ 29 (3) ^f
			100 $\pm$ 41 (4) ^c			

Data at final observations include all the results of patients who reached primary endpoint and dropped out after more than 12 months. Data are expressed as mean $\pm$ SD (*n*) number of patients

* $P = 0.049$ vs baseline

^a Gliclazide

^b Acarbose

^c Miglitol

^d Metformin

^e Sitagliptin

^f Vildagliptin

Fig. 3 Kaplan–Meier plots for primary (*upper panel*) and secondary (*lower panel*) endpoints. Kaplan–Meier plots were drawn for the time to event data followed by Mantel–haenszel log-rank test as significance is shown in each *panel*

Fig. 4 Cumulative achievement rates of target HbA1c. Numbers and percentages of patients whose HbA1c were kept less than 6.5, 7.0 and 7.4% at final observations were shown in each column. Statistical analyses were done by Pearson's Chi square test

Effect of physical activity on BMI and target HbA1c

Performance rates of daily active exercise, which were defined as above, tended to be higher in patients in group N than in group D, but the difference was not significant (17/45, 37.8 vs 15/63, 23.8%) ($p = 0.117$). BMI and glycemic control did not seem to be influenced directly by performing light intensity walking in this study (data are not shown). Interestingly, when looked at all the participants together, the percentage of patients estimated to be active for exercise was tended to be more frequent in non-overweight (BMI < 24.0) participants (23/63, 36.5%) than in overweight (BMI $\geq$ 24.0) participants (9/45, 20.0%) at baseline ($p = 0.064$), indicating that overweight participants were rather sedentary in their lifestyle. Overweight patients were equally prevalent in group N and D (each about 38%) without difference, and this tendency did not change at all during the study. As discussed in background and aims, Japanese are thinner in general than western Caucasians even in type 2 diabetic patients [4, 8]. This is why the cut-off of BMI = 24.0 was adopted to specify overweight. In fact, the mean BMI in groups N and D was 23.7 and 23.8, respectively, close to 24.0.

Other biochemical and physiological parameters

There were also no significant changes and differences of blood pressure (systolic and diastolic) or biochemical parameters, i.e., TC, HDL-C, LDL-C, TG, uric acid and Cr in two groups before and after 3 years (data are not shown), as shown in Fig. 6.

Fig. 5 Distributions of patients in each range of HbA1c at baseline and final visits in group N and D. Percentages of numbers of patients within the limits of HbA1c are individually shown in each column. HbA1c data at baseline and final visits in group N and D were expressed as mean $\pm$ SD (*n*). Significant increase of mean of HbA1c at final visit compared to that at baseline ($p = 0.049$) was seen solely in group N

In relation to the changes of insulin sensitivity and secretion, fasting plasma insulin (F-IRI), HOMA-IR and HOMA- β F were assessed in control arm N (group N) and respective drug arm, separately, as they may be probably reflected by each of oral AHAs different in action mechanisms. There were no significant changes of these parameters among these arms during 3 years, and also no differences in the effects of these drugs were detected in time course (data are not shown).

Discussion

Many studies indicate that microangiopathy can be largely prevented, if HbA1c is kept under 7.0% and FPG under 140 mg/dl [23–27, 31, 32].

Several epidemiological surveys also showed that the prevalence of microangiopathy in deciles stratified by HbA1c and FPG levels increased rather sharply above the glycemic threshold levels of HbA1c about 7.0% and of FPG about 140 mg/dl [2, 38, 50]. These values are a little higher than the current diagnostic criteria of diabetes, i.e., FPG ≥ 126 mg/dl and/or HbA1c $\geq 6.5\%$, suggesting that there is a range of mild diabetes, in which the risk of developing microangiopathy is small.

In an early stage of type 2 diabetic patients with only mild hyperglycemia, lifestyle intervention consisting of educations for diet and physical exercise is usually

recommended to start at first [31, 32, 45]. If conducted properly, lifestyle modification could be effective to prevent the worsening of diabetes, but it is usually not easy to continue an ideal lifestyle throughout life [12]. Furthermore, hyperglycemia in T2DM could generally aggravate with time passing as natural history [37, 51]. So, it seems to be reasonable to introduce AHA at an earlier stage not to overlook the occurrence of harmful hyperglycemia [38]. This is one of the reasons why we started JEDIS.

Recently, numerous AHAs with different mechanisms of action have been developed for the management of type 2 diabetes. As a general rule, when lifestyle modification failed, any monotherapy, usually with metformin at first, is recommended to follow thereafter [31, 32]. Recently, a large scale of trial named GRADE in US are going on, which is designed as metformin-based intervention with another plus one (SU, DPP-4i, GLP-1 analog or insulin), aiming target HbA1c $<7.0\%$ for about 5 years [52]. It is expected to know which an effective and preferable one it is to add on metformin therapy to keep target HbA1c in medical practice for a long time.

In Japan, biguanide drug is not always considered as a first line of choice for newly diagnosed patients with T2DM [45]. We thought the administration of small dose of anyone of these drugs properly early after diagnosis may help to prevent the progression to the stage of “harmful hyperglycemia”. The question is whether AHA monotherapy is useful enough to keep HbA1c and FPG at

Fig. 6 Time courses of blood pressure (systolic and diastolic), or TC, LDL-C(calculated), HDL-C, TG, uric acid and creatinine in sera of participants in group N and D. Data were expressed as means of parameters. There were no significant changes of these parameters for 3 years

“safe level” more easily and surely than the management by lifestyle intervention alone. Furthermore, one of our main interests is which medication should be the best for the long-life maintenance of glycemic control among many optional possibilities of pharmacotherapies, including newly approved DPP-4i and in these several years. Facing reality, it will be reasonable to start treatment by oral pharmacological monotherapy choosing anyone of these medications from the standpoints of life-long, medical and economic considerations.

In this JEDIS study, we compared the 3-year course of glycemia at an early stage of T2DM, with and without pharmacological monotherapy. Comparison of group N and D revealed that the addition of AHA resulted significantly in prompt and sustained reduction of hyperglycemia throughout the observation period for 3 years, with almost the same declining changes of BMI in both groups (Fig. 2, left panel). But, the rate of reaching the primary endpoint (PE) (i.e., FPG ≥ 140 mg/dl and HbA1c $\geq 7.4\%$) analysed by Kaplan Meyer plots did not differ between group N and D (Fig. 3, upper panel). Incidences of the secondary endpoints also did not differ between group N and D (Fig. 3, lower panel), and no severe adverse events were observed including hypoglycemia.

The rates of PE in group N and D from where SU arm was deleted were also not different, despite different features of Δ BMI, Δ FPG and Δ HbA1c in SU arm when compared with those in other arms (Fig. 2, right panel).

The distributions of HbA1c at last visits were compared before and after the follow up, including all the participants who reached PE and who dropped out after more than 12 M (Table 2; Fig. 4). The rates of maintaining HbA1c below 6.5, 7.0 and 7.4% all tended to be higher in group D than in group N, but the difference was significant only for HbA1c below 7.4% ($p = 0.047$) (Fig. 4). In turn, as shown in Fig. 5, in group N, the prevalence of those with HbA1c $\geq 7.0\%$ were increased from 17.8 to 31.1% and those with HbA1c $< 6.5\%$ were decreased from 46.7 to 33.3%, while in group D, those with HbA1c $\geq 7.0\%$ decreased from 27.0 to 20.7% and those with HbA1c $< 6.5\%$ increased from 25.4 to 34.9%, respectively. Taken all together, these results seem to indicate the efficacy of an early introduction of monotherapy to obtain “safe level of glycemia” under conventional lifestyle modification, at least for 3 years. By the way, the results of incremental changes of BMI, FPG and HbA1c were almost similar when SU arm was excluded.

In this study, body weight long decreased and remained lower enough during the study with and without medication, in contrast to the results of other studies from Caucasian countries in which rebound increase in body weight

has been observed frequently [25, 26, 51]. It is of interest whether it comes from genetic trait or environmental factors of customs including the rapid global changes of dietary habits and daily works which could be disadvantageous for T2DM. In any case, of course, the important roles of the education and care supported by routine facilities might be also stressed [32, 45, 53].

Thus, the administration of only small dose of AHA seemed to be effective to introduce better glycemic control in newly diagnosed patients at an early stage of T2DM, and it was also shown that small dose of drug was sufficient to keep the glycemic level below the harmful hyperglycemia, at least for 3 years. In the process of this study, there were no cases of severe hypoglycemia or adverse event at all. This means that the proper use of any oral medication, probably except for SU drug, could be preferable approach from an earlier stage to obtain and keep “safe glycemia” in diabetic patients, giving consideration to its natural time course [37] as well as diabetic complications.

It was also of interest which medication would be the best for longtime maintenance of glycemic control among classes of drugs with different mechanism of action. At present, many evidences seem to support metformin as first-line agent to treat T2DM [54, 55]. The data in Fig. 2 (right panel) suggest that metformin, α -GIs and DPP-4is were similarly effective to keep HbA1c. α -GIs seem to be somewhat weaker than metformin and DPP-4i to suppress FPG. The latter two drugs, metformin and DPP-4i, seem to be more preferable than the others, but it is necessary to check for a longer period to confirm their true efficacy also on the fate of T2DM [56]. It is possible that α -GI primarily inhibits post-prandial blood glucose and their effect on FPG may be rather indirect. The time course in arm SU was somewhat different from other drug arms. After the start of glizlazide (SU), HbA1c decreased temporarily but after 6 M it returned to the baseline level and increased further thereafter. The decrease of BW was minimal in arm SU as compared to other arms, suggesting a distinct effect of SU on body weight [28, 46, 47]. There was also the concern on hypoglycemia to use drugs in an early stage of T2DM, especially for SU drug [54], and we thought that physicians in charge may have hesitated to dose up glizlazide sufficiently [47]. Anyhow, we think that available many kinds of AHAs could be potential candidates to delay the occurrence of harmful hyperglycemia.

There are several limitations in this study. First, the number of participants was rather small to demonstrate difference in the rate of primary endpoint. Particularly, each arm in group D was too small to draw definite features of each drug. Second, the revision of protocol from JEDIS-1 to JEDIS-2 complicated the study and brought about

uneven number of cases assigned to treatment arms. Third, there was a difference in baseline FPG between group N and D, necessitating the comparison by incremental changes from baseline values rather than by absolute values of BMI, FPG and HbA1c in time course analyses.

In conclusion, early introduction of small dose AHA monotherapy, except for SU, in addition to lifestyle intervention, seems to be effective to prevent the progression of hyperglycemia. Although a larger scale of trial is necessary to conclude, the early commencement of suitable AHA monotherapy could bring better result to individual diabetic patient to maintain “safe glycemia” not only for diabetic complications but also for less “glucotoxicity” on T2DM itself.

Acknowledgement This study was supported by the grant from Japan Diabetes Foundation. We want to express sincere thanks to all the members joined in this study, including medical doctors and staffs in practice, listed in Investigators’ list as shown below. Especially, the late Professor Emeritus of Tokyo University Kinori Kosaka who strongly pushed to start and progress this study is greatly appreciated. We also want to express deep thanks to Professors Emeritus Hideto Sakai (Tokai University) and Kazuyuki Shimada (Jichi Medical University) and Professor Hidetoshi Yamashita (Yamagata University) who steadily supported us in the study as medical specialist in the field of nephrology, cardiology and ophthalmology, respectively. Professor Mitsuhiko Noda (Saitama Medical University) and Professor Emeritus of Washington University Wilfred Y Fujimoto are also appreciated for their valuable advice and suggestions when we prepare the protocol of this study JEDIS.

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Compliance with ethical standards

Conflict of interest statements All the authors declare that they have no conflict of interest.

Human rights statement and informed consent All procedures followed were in accordance with the ethical standards of the

responsible committee on institutional human experimentation and with the Helsinki Declaration of 1964 and later versions. Informed consent was obtained from all patients for being included in the study.

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