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Lipids Behavior and Adverse Effects for Oral Antidiabetic Agents in Patients with Type2 Diabetes Treated with Sulfonylureas Alone Based on Systematic Review

Junichi MUKAI,[a,b] Hitoshi TADA,[*,a,c] Yuka WATANABE,[c] Masatomo MIURA,[a] Sou KATSUYAMA,[c] Tohru SHOJI,[c] Kiminori MOURI,[b] Masaaki ETO,[d,e] and Toshio SUZUKI[a]

[a]*Department of Pharmacy, Akita University Hospital, 1–1–1 Hondo Akita, Akita 010–8543, Japan,* [b]*Department of Clinical Pharmacy, Meiji Pharmaceutical University, 2–522–1 Noshio Kiyose 204–8588, Japan,* [c]*Department of Clinical Pharmacy, School of Pharmaceutical Science, Ohu University, 31–1 Misumido, Tomita-Machi, Koriyama City 963–8611, Japan,* [d]*Department of Internal Medicine, Ohu University Hospital, 31–1 Misumido, Tomita-Machi, Koriyama City 963–8611, Japan,* [e]*Department of Medicine, School of Pharmaceutical Science, Ohu University, 31–1 Misumido, Tomita-Machi, Koriyama City 963–8611, Japan*

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The secondary and adverse effects when biguanides, alpha-glycosidase inhibitor or thiazolidine derivative was used with sulphonylurea agent (SU) as compared with those with SU alone in Type 2 diabetes patients by using Systematic Review. Two-agent concurrent treatment groups, taken from studies in which subjects were assigned to a group given only a sulfonylurea agent and a group given a sulfonylurea agent with the other glycemic control agent (combination of a sulfonylurea agent and a biguanide agent (I), combination of a sulfonylurea agent and an α-glucosidase inhibitor (II), and combination of a sulfonylurea agent and thiazolidinedione (III)), were studied in a randomized controlled trial. The secondary efficacy outcome measures were total cholesterol (TC), triglyceride (TG), HDL-C, LDL-C, and change in body weight. The incidence of hypoglycemia, feeling of fullness, diarrhea, liver dysfunction, and edema was investigated as a safety outcome measure, and the clinical significance of concurrent treatment with a sulfonylurea agent in addition to the other glycemic control agent was investigated. With respect to (II), an antidiabetic effect was showed. As for (III), it had the disadvantage of increased body weight. Furthermore, increase of HDL-C levels, in particular, was observed. The improving effect of (III) on serum lipids may be clinically effective for considering the pathologic condition of diabetes, which is often complicated by hyperlipidemia.

Key word——meta-analysis; sulfonylurea; diabetes; cholesterol; triglyceride

INTRODUCTION

The chief goal of diabetes treatment is prevention of complications. Strict long-term glycemic control is key to achieving that goal. There are currently five types of oral antidiabetic agent available in Japan. In detail, biguanides (BG), which are used in obese diabetic patients, and sulphonylurea drugs (SU) are known to improve the long-term prognosis. SU, in particular, have been used in a clinical setting for many years, and the evidence supporting their effectiveness is clear. Moreover, it was reported that improvement in glycemic control resulted in a reduction in the risk of microvascular complications in the United Kingdom Prospective Diabetes Study (UKPDS).[1)2)] It has been reported that the risk of onset of diabetes increases in proportion to the duration of hyperglycemia, and that the lower the blood glucose level is, the lower the risk of onset will be.[3)]

If glycemic control is sufficiently improved with oral antidiabetic agent, suggesting that concomitant therapy with such agents as the α-glycosidase inhibitor (AGI) have a potential to reduce the progression of diabetes as well as macro- and microvasucular complicatrions.[4)] Many combinations of oral antidiabetic agents with different mechanisms of action have been reported to improve serum glucose, including the following eight: (1) SU+BG, (2) SU+AGI, (3) BG+AGI, (4) SU+thiazolidine derivative (TZD), (5) BG+TZD, (6) AGI+TZD (not covered by insurance), (7) AGI+phenylalanine derivative, and (8) BG+phenylalanine derivative (not covered by insurance).[5)] However, with regard to selection of a second drug in patients using SU, the Evidence-based practice guideline for the treatment of diabetes in Japan[5)] only states that patients should be started on

*e-mail: h-tada@pha.ohu-u.ac.jp

a small dose of a single oral antidiabetic agent and that an agent with a different mechanism of action should be administered when satisfactory control cannot be achieved with an increased dose. It is well known that combination therapy intensifies a decrease in blood glucose. However, little attention has been given to the behavior of serum lipids and side effects when selecting a second agent. It is important to note that combination therapy affects the behavior of serum lipids in Type 2 diabetes patients.

In the present study, we systematically examined by means of systematic review the secondary effects when BG, AGI or TZD was used with SU as compared with those with SU alone in Type 2 diabetes patients.

METHOD

Randomized controlled trials (RCT) in patients with Type 2 diabetes in which subjects were assigned to a group given only SU and a group given SU plus another agent (combination of SU and BG (I), combination of SU and AGI (II), and combination of SU and TZD (III)) were systematically searched. The efficacy outcome measure was HbA1c. Secondary efficacies were evaluated by total cholesterol (TC), triglyceride (TG), HDL-C, LDL-C, and change in body weight. For safety outcome measures, the incidence of hypoglycemia, feeling of fullness, diarrhea, edema, and liver damage was investigated as adverse reactions of (I) to (III) specified in the Evidence-based practice guideline for the treatment of diabetes in Japan,[5] and the clinical significance of concurrent treatment with SU plus another agent was investigated.

For one endpoint, the results were integrated using meta-analysis, and efficacy and safety were evaluated.

Article Extraction Method Using PubMed (1966-November 2004) and Issue 4 of the 2004 Cochrane Library (CCTR/CENTRAL was used) as databases, RCT (articles in English) that investigated the efficacy of concomitant use of two oral antidiabetic agents in patients with Type 2 diabetes were systematically searched separately for (I) to (III). Articles in Japanese were extracted using the same search method as that used for English articles, using Japana Centra Revuo Medicina (January 1981-November 2004) as a database.

Article Adoption Criteria

Study Design RCT with a parallel or crossover design were used. In the case of trials with a crossover design, only the results of the first half of the trial were used.

Subjects Trials in which subjects had been diagnosed with Type 2 diabetes and underwent two-agent treatment with SU and AGI, TZD or BG were used.

Intervention Placebo-controlled RCT were used.

Endpoints In terms of the primary endpoint, articles that included HbA1c as indicator used for evaluation of drug main efficacy were used. Secondary endpoints were change in body weight, TC, TG, LDL-C, and HDL-C.

Observation Period Trials with an observation period of at least 4 weeks and that measured the above-mentioned primary endpoints were used.

Language Articles written in a language other than Japanese or English were excluded from the analysis in the present study since they could not be understood by the investigators.

Data Collection

Method-related Parameters Extracted

Clinical study design
Patient background
Doses of oral antidiabetic agents
Duration of administration of oral antidiabetic agents
Number of concomitant oral antidiabetic agents

Result-related Parameters Extracted

Number of patients at time of analysis
Mean difference and standard deviation for HbA1c, change in body weight, TC, TG, LDL-C, and HDL-C at completion of observation
Incidence of adverse reactions at completion of observation

Evaluation of Article Quality Using the scale of Jadad et al.,[6] extracted articles were scored (maximum of 5 points) in terms of randomization, masking, and handling of dropouts in each clinical study, and the quality of articles was evaluated based on the total score.

Statistical Analysis (Meta-Analysis) Extracted articles underwent meta-analysis after they were classified from the viewpoint of endpoints and duration of treatment, *etc.*, and they were statistically evaluated based on the results.

When multiple articles were merged, the heterogeneity of articles to be analyzed was first evaluated using the Q-test (with degree of freedom of chi-

square distribution of -1 of number of articles, $p<0.10$). When the heterogeneity was rejected, a fixed-effect model (Mantel-Haenszel test) was used. Although the heterogeneity was not rejected but it was believed to be possible to merge articles, a random-effect model (DerSimonian-Laird test) was used. The statistical analysis software used was Cochrane Review Manager 4.2.3. For meta-analysis related to evaluation of primary and secondary endpoints, calculations were expressed as the weighted mean difference (WMD) by weighting the mean difference between groups using more than one antidiabetic drug and groups using SU alone with the inverse distribution, using the WMD method.

With regard to evaluation of safety, the frequency (incidence) of adverse reactions was calculated as an odds ratio. Statistical superiority was evaluated based on WMD or odds ratios and their 95% confidence interval. The statistical analysis software used was Cochrane Review Manager 4.2.3 (Revman 4.2.3: The Cochrane Collaboration).

RESULTS

Search and Extraction Results A MEDLINE search of English-language articles yielded 238 reports (I), 55 reports (II), and 54 reports (III). Excluding duplications, the Cochrane Library (CCTR/CENTRAL) yielded 8 reports (I). Of these, the number of articles that satisfied the adoption criteria was 11 reports (I), 7 reports (II), and 11 reports (III). Articles excluded were those that compared two two-agent concomitant therapies, those that compared three-agent concomitant therapies, and those with a different study design. Three reports (I), 5 reports (II), and 5 reports (III) were included in the analysis after evaluation of the quality of each article by means of scoring using the scale of Jadad *et al*.[6]

A Japana Centra Revuo Medicina search of Japanese-language articles yielded 19, 24, and 14 reports for (I), (I), and (III), respectively (same order hereafter), but the number of those that satisfied the adoption criteria was 0, 0, and 3, respectively. Articles excluded included those that were collections of commentaries, those that were records of proceedings, and those with a different study design. Consequently, in the case of (III), a total of 8 reports were of a high quality of 3 points or higher according to the scoring of Jadad *et al*.[6]

The characteristics of the articles in (I), (II), and (III) included in the analysis are shown in Table 1.

Meta-analysis Results

Main Effect

1) Improvement in HbA1c Level after Concomitant Use The number of articles with HbA1c level at completion of observation as an outcome measure was 3, 5, and 8 for (I), (II), and (III), respectively. Meta-analysis of HbA1c level was performed using the WMD method. In the case of (III), since the heterogeneity was not rejected by Q-test when articles were merged, a random-effect model (DerSimonian-Laird test) was used. In the case of (I) and (II), since the heterogeneity was rejected by Q-test, a fixed-effect model (Mantel-Haenszel test) was used. The results of analysis showed that WMD and its 95% confidence interval in concomitant therapy groups (I), (II), and (III) did not include 0, and a significant ($P<0.00001$, $P<0.00001$, $P<0.00001$) improvement was found in HbA1c level compared with groups given SU alone (Table 2).

Secondary Effects

1) Change in Body Weight after Concomitant Use The number of articles with change in body weight at completion of observation as an outcome measure was 3, 1, and 3 for (I), (II), and (III), respectively. Meta-analysis of change in body weight was performed using the WMD method. For (III), since the heterogeneity was not rejected by Q-test when articles were merged, a random-effect model (DerSimonian-Laird test) was used. As for the result, 0 was included in merged WMD and its confidence interval range. Results of analysis of (I) and (III) showed a significant ($P=0.01$, $P=0.00001$) decrease in body weight in the groups given SU alone compared with the concomitant therapy groups (Table 5).

2) Change in TC Level after Concomitant Use Total cholesterol level as an outcome measure was 1, 1, and 7 for (I), (II), and (III), respectively. For study (III), since the heterogeneity was not rejected by Q-test, a random-effect model (DerSimonian-Laird test) was used. As shown in Table 6, the value of total cholesterol did not show a significant decrease ($P=0.45$).

3) Change in TG Level during Concomitant Use The number of articles included in the analysis was 1, 1, and 7 for (I), (II), and (III), respectively. Therefore, meta-analysis was performed for (III), the heterogeneity was not rejected by Q-test for (III), and a

Table 1. Summary of Clinical Study for the Outcome between Combination Therapy with Sulfonylurea and Sulfonylurea Alone in Patient with Diabtes

Reference	Study design	Masking	Number of entry patient Combination /SU alone	Study drug		Mean baseline		Duration (weeks)	Jadad's score	End point							
				SU	Concomitant drug	HbA1c (%)	FPG (mmol/l)			HbA1c	FPG	PPG	BW	TC	TG	LDL	HDL
Willms B[7]	P	double	27/29	77% glibenclamide	met 1700 mg	10.6	11.9	12	5	+	−	+	+	+	+	−	−
Erle G[8]	C	double	20/20	glyburide<10 mg	met 1600 mg	7.37 (g) /7.67 (met)	12.3 (g) /11.4 (met)	12	5	+	+	−	+	+	+	−	+
DeFronzo RA[9]	P	open	213/209	glyburide	met 2500 mg	8.5 (g) /8.8 (met)	13.7 (g) /13.9 (met) *a)*	29	3	+	+	−	+	+	+	+	+
Lin BJ[10]	P	double	32/32	unknown	acarbose 300 mg	9.0	9.95	24	5	+	+	+	−	−	−	−	−
Willms B[7]	P	double	31/29	77% glibenclamide	acarbose 300 mg	10.6	11.6	12	5	+	−	+	+	+	+	−	−
Johnston PS[11]	P	double	91/43	glyburide/glipizide	mig 150–300 mg	8.7	10.3	28	5	+	−	−	−	−	−	−	−
Costa B[12]	P	double	36/29	glibenclamide<10 mg	acarbose 300 mg	9.0	10	24	5	+	+	+	−	+	+	−	+
Chiasson JL[13]	P	double	52/51	glyburide/tolbutamide/ chlorpropamide	acarbose 150–600 mg	8.0	12.1 (p) /11.7 (ac)	52	5	+	+	+	+	+	+	+	+
Kerenyi Z[14]	P	double	165/170	glibenclamide<7.5 mg	rosiglitazone 8 mg	8.1 (gb) /7.9 (ro)	9.6 (gb) /9.4 (ro)	26	5	+	+	−	−	+	+	+	+
Zhu XX[15]	P	double	215/105	glibenclamide/gliclazide	rosiglitazone 4 mg	9.8	10.2 *a)*	24	5	+	+	−	−	−	−	−	−
Kipnes MS[16]	P	double	189/187	glyburide/glipizide	pioglitazone 30 mg	9.9	13.1/13.7 *a)*	16	5	+	+	−	+	+	+	+	+
Miyazaki Y[17]	P	double	12/11	unknown	pioglitazone 45 mg	8.9	10.2 *a)*	16	4	+	+	−	+	+	+	+	+
Wolffenbuttel BHR[18]	P	double	183/192	glibenclamide/gliclazide/glipizide	rosiglitazone 4 mg	9.2	11.4	26	5	+	+	−	+	+	+	+	+
Kaneko T_a[19]	P	double	76/73	glibenclamide/gliclazide etc.	pioglitazone 30 mg	9.8	10.8 *a)*	12	5	+	+	−	+	+	+	−	+
Kaneko T_b[20]	P	single	68/66	unknown	pioglitazone 30 mg	9.9	11.5 *a)*	12	3	+	+	−	+	+	+	−	+
Kosaka K[21]	P	double	145/146	glibenclamide/gliclazide	troglitazone 400 mg	9.1 (t)	10.3 (t) *a)*	12	5	+	+	−	+	+	+	−	+

P: parallel, C: cross-over, double: double-blind, single: single-blind, (met): metformin, (mig): miglitol, (g): glyburide, (p): placebo, (ac): acarbose, (gb): glibenclamide, (ro): rosiglitazone, (t): troglitazone. *a)* Fasting plasma glucose level (FPG, mmol/l) was converted from glucose level (mg/dl).

Table 2. Meta-analysis for HbA1c between Combination Therapy with Sulfonylurea and Sulfonylurea Alone Therapy

Study (I)

Reference	Combination N	SU alone N	← Combination better	SU alone better →	WMD (95% CI)
Erle G 1999	15	18			−1.36 (−2.45 ; −0.27)
Willms B 1999	27	29			−1.20 (−1.94 ; −0.46)
DeFronzo RA 1995	213	209			−1.90 (−2.18 ; −1.62)
Total	255	256			−1.79 (−2.04 ; −1.54)

−3 0 3 (%)

Study (II)

Reference	Combination N	SU alone N	← Combination better	SU alone better →	WMD (95% CI)
Willms B 1999	31	29			−1.00 (−1.91 ; −0.09)
Lin BJ Wu 2003	32	32			−1.05 (−1.76 ; −0.34)
Chiasson JL 1994	49	47			−0.80 (−1.35 ; −0.25)
Johnson PS 1998	91	43			−1.41 (−1.85 ; −0.97)
Costa B 1997	36	29			−0.80 (−1.08 ; −0.52)
Total	239	180			−0.99 (−1.26 ; −0.72)

−2 0 2 (%)

Study (III)

Reference	Combination N	SU alone N	← Combination better	SU alone better →	WMD (95% CI)
Wolffenbuttel BHR 2000	183	192			−1.23 (−34.08 ; 31.62)
Miyazaki Y 2001	12	11			−1.70 (−2.41 ; −0.99)
Kaneko T 1997_a	56	49			−1.16 (−1.64 ; −0.68)
Kipnes MS 2001	182	181			−1.30 (−1.82 ; −0.78)
Kaneko T 1997_b	52	59			−1.62 (−2.01 ; −1.23)
Zhu XX 2003	215	105			−1.00 (−1.32 ; −0.68)
Kosaka K 1993	117	117			−0.85 (−1.08 ; −0.62)
Kerenyi Z 2004	160	154			−0.77 (−0.99 ; −0.55)
Total	977	868			−1.13 (−1.37 ; −0.88)

−4 0 4 (%)

N: Number of total patients. ■: Weighted mean difference (WMD) for HbA1c, the size represents weight degree. ◆: Estimated value of WMD in the total, the size shows the number of objective patients relatively. ← or →: The value for 95% CI to exceed value (±4) of x-axis.

random-effect model (DerSimonian-Laird test) was used. There was a significant difference in TG level between SU alone and the concomitant therapy (P=0.01). The concomitant therapy decreased TG level compared with SU alone (Table 5).

4) Change in HDL-C Level during Concomitant Use The number of articles was 2, 1, and 7 for (I), (II), and (III), respectively. In the case of (I) and (III), since the heterogeneity was rejected by Q-test, a fixed-effect model (Mantel-Haenszel test) was used. The results showed no significant decrease in (I) (P=0.73) and a significant (P=0.00001) decrease in (III) in the groups given SU alone compared with the concomitant therapy groups (Table 6).

5) Change in LDL-C Level during Concomitant Use The number of articles that satisfied the criteria was 1, 0, and 3 for (I), (II), and (III), respectively. For (III), since the heterogeneity was not rejected by Q-test, a random-effect model (DerSimonian-Laird test) was used. (III) straddled 0 and did not show a significant decrease (P=0.650) (Table 7).

Risk of Onset of Adverse Reactions during Concomitant Therapy

1) Investigation of Bloating Sensation in (II)

Table 3. Meta-analysis for Body Weight between Combination Therapy with Sulfonylurea and Sulfonylurea Alone Therapy

Study (I)

Reference	Combination N	SU alone N	← Combination better	SU alone better →	WMD (95%CI)
Erle G 1999	15	18			−0.20 (−9.18 ; 8.78)
Willms B 1999	27	29			0.80 (−1.81 ; 3.41)
DeFronzo RA 1995	213	209			0.70 (0.15 ; 1.25)
Total	255	256			0.70 (0.16 ; 1.24)

−10 0 10 (Kg)

Study (III)

Reference	Combination N	SU alone N	← Combination better	SU alone better →	WMD (95%CI)
Kosaka K 1993	112	117			0.90 (−1.55 ; 3.35)
Miyazaki Y 2001	12	11			3.30 (0.45 ; 6.15)
Kaneko T 1997_b	49	59			1.19 (0.60 ; 1.78)
Total	173	187			1.26 (0.69 ; 1.82)

−10 0 10 (Kg)

N: Number of total patients. ■: Weighted mean difference (WMD) for body weight, the size represents weight degree. ◆: Estimated value of WMD in the total, the size shows the number of objective patients relatively.

Table 4. Meta-analysis for TC between Combination Therapy with Sulfonylurea and Sulfonylurea Alone Therapy

Study (III)

Reference	Combination N	SU alone N	← Combination better	SU alone better →	WMD (95%CI)
Miyazaki Y 2001	12	11			−6.00 (−21.30 ; 9.30)
Kaneko T 1997_a	49	46			0.90 (−13.70 ; 15.50)
Kosaka K 1993	116	121			2.79 (−6.78 ; 12.36)
Zsuzsa K 2004	144	139			19.64 (10.74 ; 28.54)
Kaneko T 1997_b	49	59			0.88 (−8.07 ; 9.83)
Wolffenbuttel BHR 2000	183	192			11.55 (3.59 ; 19.51)
Kipnes MS 2001	181	180			−7.00 (−9.10 ; −4.90)
Total	734	748			3.42 (−5.39 ; 12.24)

−30 0 30 (mg/dl)

N: Number of total patients. ■: Weighted mean difference (WMD) for TC, the size represents weight degree. ◆: Estimated value of WMD in the total, the size shows the number of objective patients relatively.

Two articles from (II) satisfied the criteria. Since the heterogeneity was rejected by Q-test, a fixed-effect model (Mantel-Haenszel test) was used. The results showed that a significant ($P=0.0008$) increase in bloating sensation was seen in the concomitant therapy groups (Table 8).

2) Investigation of Incidence of Diarrhea in (II) Two articles satisfied the criteria. Since the heterogeneity was rejected by Q-test, a fixed-effect model (Mantel-Haenszel test) was used. The results showed that a significant ($P=0.01$) increase in onset of diarrhea was seen in the concomitant therapy groups (Table 9).

3) Investigation of Incidence of Hypoglycemia in (III) Six articles satisfied the criteria. Since the heterogeneity was not rejected by Q-test, a random-effect model (DerSimonian-Laird test) was used. The results showed that a significant ($P=0.00001$) increase in onset of hypoglycemia was seen in the concomitant therapy groups (Table 10).

4) Investigation of Edema in (III) Five articles satisfied the criteria. Since the heterogeneity was

Table 5. Meta-analysis for TG between Combination Therapy with Sulfonylurea and Sulfonylurea Alone Therapy

Study (III)

Reference	Combination N	SU alone N	← Combination better	SU alone better →	WMD (95% CI)
Miyazaki Y 2001	12	11			−34.00 (−64.49 ; −3.51)
Kaneko T 1997_a	50	45			−31.40 (−73.16 ; 10.36)
Kipnes MS 2001	181	180			−70.00 (−95.83 ; −44.17)
Kaneko T 1997_b	49	59			−27.90 (−53.69 ; −2.11)
Wolffenbuttel BHR 2000	183	192			8.75 (−16.45 ; 33.95)
Kosaka K 1993	114	120			−22.27 (−41.93 ; −2.61)
Kerenyi Z 2004	144	139			−1.75 (−11.80 ; 8.30)
Total	733	746			−24.12 (−43.51 ; −4.73)

−100 0 100 (mg/dl)

N: Number of total patients. ■: Weighted mean difference (WMD) for TG, the size represents weight degree. ◆: Estimated value of WMD in the total, the size shows the number of objective patients relatively.

Table 6. Meta-analysis for HDL-C between Combination Therapy with Sulfonylurea and Sulfonylurea Alone Therapy

Study (I)

Reference	Combination N	SU alone N	← Combination better	SU alone better →	WMD (95% CI)
Erle G 1999	15	18			4.00 (−3.76 ; 11.76)
DeFronzo RA 1995	213	209			0.00 (−2.77 ; 2.77)
Total	228	227			0.45 (−2.16 ; 3.06)

−10 0 10 (mg/dl)

Study (III)

Reference	Combination N	SU alone N	← Combination better	SU alone better →	WMD (95% CI)
Kaneko T 1997_a	46	45			3.40 (−3.01 ; 9.81)
Kipnes MS 2001	179	175			6.00 (0.32 ; 11.68)
Miyazaki Y 2001	12	11			2.00 (−2.38 ; 6.38)
Kosaka K 1993	72	84			1.48 (−2.78 ; 5.74)
Kaneko T 1997_b	47	56			2.78 (−0.60 ; 6.16)
Wolffenbuttel BHR 2000	183	192			3.85 (1.27 ; 6.43)
Kerenyi Z 2004	143	138			5.87 (4.87 ; 6.87)
Total	682	701			5.10 (4.26 ; 5.95)

−10 0 10 (mg/dl)

N: Number of total patients. ■: Weighted mean difference (WMD) for HDL-C, the size represents weight degree. ◆: Estimated value of WMD in the total, the size shows the number of objective patients relatively. ← or →: The value for 95% CI to exceed value (+10) of x-axis.

rejected by Q-test, a fixed-effect model (Mantel-Haenszel test) was used. The results showed that a significant (P=0.0001) increase in onset of edema was seen in the concomitant therapy groups (Table 11).

5) Investigation of Risk of Hepatic Dysfunction in (III) Three articles satisfied the criteria. Since the heterogeneity was rejected by Q-test, a fixed-effect model (Mantel-Haenszel test) was used. The results showed that no increase in onset of hepatic dysfunction was seen in the concomitant therapy groups (P=0.83) (Table 12).

DISCUSSION

The results of the present meta-analysis showed that, in the case of (I), a antidiabetic action was seen,

Table 7. Meta-analysis for LDL-C between Combination Therapy with Sulfonylurea and Sulfonylurea Alone Therapy Study (III)

Reference	Combination N	SU alone N	← Combination better	SU alone better →	WMD (95%CI)
Miyazaki Y 2001	12	11			−2.00(−16.13 ; 12.13)
Kerenyi Z 2004	132	130			19.25(4.09 ; 34.41)
Kipnes MS 2001	155	151			−4.00(−7.72 ; −0.28)
Total	299	292			3.05(−9.99 ; 16.09)
			−50	0 50 (mg/dl)	

N: Number of total patients. ■: Weighted mean difference (WMD) for LDL-C, the size represents weight degree. ◆: Estimated value of WMD in the total, the size shows the number of objective patients relatively.

Table 8. The Odds Ratio for Feeling of Abdominal Distension between Combined αGI with Sulfonylurea Therapy and Sulfonylurea Therapy

Reference	Combination n/N	SU alone n/N	← Combination better	SU alone better →	OR (95%CI)
Lin BJ Wu 2003	11/33	2/32			7.50(1.51 ; 37.29)
Costa B 1997	13/36	3/29			4.90(1.24 ; 19.38)
Total	24/69	5/61			5.91(2.09 ; 16.74)
			0.01	1 100	

N: Number of total patients: n: number of harmful event. ■: Odds ratio (OR). ◆: Total clinical outcome.

Table 9. The Difference for Diarrhea between Combined αGI with Sulfonylurea Therapy and Sulfonylurea Therapy

Reference	Combination n/N	SU alone n/N	← Combination better	SU alone better →	WMD (95%CI)
Costa B 1997	10/36	0/29			23.38(1.31 ; 418.59)
Lin BJ Wu 2003	3/33	0/32			7.46(0.37 ; 150.43)
Total	13/69	0/61			14.86(1.91 ; 115.48)
			0.001	1 1000	

N: Number of total patients, n: number of harmful event. ■: Weighted mean difference (WMD) for body weight, the size represents weight degree. ◆: Estimated value of WMD in the total, the size shows the number of objective patients relatively.

Table 10. The Odds Ratio for Hypoglycemia between Combined TZD with Sulfonylurea Therapy and Sulfonylurea Therapy Study (III)

Reference	Combination n/N	SU alone n/N	← Combination better	SU alone better →	OR (95%CI)
Kaneko T 1997_a	3/76	0/73			7.00(0.36 ; 137.92)
Kosaka 1993	5/138	0/142			11.74(0.64 ; 214.39)
Zhu XX 2003	20/221	0/112			22.89(1.37 ; 382.07)
Kipnes MS 2001	7/182	1/181			7.20(0.88 ; 59.13)
Wolffenbuttel BHR 2000	10/183	4/192			2.72(0.84 ; 8.82)
Kerenyi Z 2004	31/170	7/165			5.03(2.15 ; 11.79)
Total	76/970	11/865			5.73(3.14 ; 10.46)
			0.01	1 100	

N: Number of total patients: n: number of harmful event. ■: Odds ratio (OR). ◆: Total clinical outcome. ← or →: The value for 95%CI to exceed value (+100) of x-axis.

Table 11. The Difference for Edema between Combined TZD with Sulfonylurea Therapy and Sulfonylurea Therapy

Reference	Combination n/N	SU alone n/N	← Combination better	SU alone better →	WMD (95%CI)
kaneko T 1997_a	2/67	0/65			5.00 (0.24 ; 106.17)
Zhu XX 2003	30/221	0/115			36.79 (2.23 ; 607.42)
Kosaka K 1993	0/138	1/142			0.34 (0.01 ; 8.43)
kaneko T 1997_b	3/76	2/73			1.46 (0.24 ; 8.99)
Kerenyi Z 2004	16/170	5/165			3.32 (1.19 ; 9.30)
Total	51/672	8/560			4.62 (2.24 ; 9.49)

0.1 1 10

N: Number of total patients, n: number of harmful event. ■: Weighted mean difference (WMD) for body weight, the size represents weight degree. ◆: Estimated value of WMD in the total, the size shows the number of objective patients relatively. ← or →: The value for 95%CI to exceed value (0.1～10) of x-axis.

Table 12. The Odds Ratio for Liver Dysfunction between Combined TZD with Sulfonylurea Therapy and Sulfonylurea Therapy

Reference	Combination n/N	SU alone n/N	← Combination better	SU alone better →	OR (95%CI)
Kaneko T 1997_a	2/76	2/73			0.96 (0.13 ; 7.00)
Kaneko T 1997_b	3/67	3/65			0.97 (0.19 ; 4.98)
Kosaka K 1993	9/138	8/142			1.17 (0.44 ; 3.12)
Total	14/281	13/280			1.09 (0.50 ; 2.36)

0.1 1 10

N: Number of total patients: n: number of harmful event. ■: Odds ratio (OR). ◆: Total clinical outcome.

but an increase in body weight was noted. In addition, it had a beneficial effect on serum lipid levels; in particular, a lowering effect on LDL-C was noted. In the case of (II), a decrease in HbA1c was seen. On the other hand, only one article investigated the effect on weight change and TG level, so it was not included in the meta-analysis. As for (III), a antidiabetic action greater than that with SU used alone was found, but it had the disadvantage of increased body weight. Furthermore, in terms of serum lipids, increased HDL-C levels were observed. This action of (III) to increase HDL-C may be clinically effective considering the pathologic condition of diabetes, which is often complicated by hyperlipidemia.

We investigated adverse effects associated with concomitant therapy with each agent (BG, AGI, TZD) given in the Evidence-based practice guideline for the treatment of diabetes in Japan.[5] In the case of (III), the risk of hypoglycemia increased significantly as a result of concomitant use. A significant difference was not seen in terms of the risk of onset of hepatic impairment. However, a significant increase in the risk of developing edema was seen as a result of concomitant use.

It was shown that (I) caused weight gain, but it was believed to be because about 80 percent of the subjects in the articles included in the present analysis used glibenclamide as the SU. In general, use of BG is said to cause weight loss, but the opposite result was seen in this study. Therefore, attention should be paid to weight gain in the case of concomitant use with glibenclamide.

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