

Full Length Research Paper

Comparison between the clinical efficacy of linagliptin and sitagliptin

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After the introduction of dipeptidylpeptidase-4 (DPP-4) inhibitors into the treatment for diabetes, these drugs have been widely used because of their capability and safety. Therefore, the clinical efficacy of linagliptin to sitagliptin was compared. Patients with type 2 diabetes, in whom pharmacological treatment was recently started, were randomly assigned to two separate groups, namely sitagliptin (50 mg/day) group and linagliptin (5 mg/day) group. A total of 42 patients (21 patients in each group), who received a single dose of their respective pharmacological agents, were evaluated in this study. The study primarily focused on changes in HbA1c levels before and 24 weeks after drug administration and effects of these drugs on renal function, liver function, and fat. Significant improvement in HbA1c levels (%) was found in both linagliptin and sitagliptin groups. Significant improvements were observed in low density lipoprotein-cholesterol (LDL-C) levels in patients in the linagliptin group. Linagliptin offers a great potential in terms of improving effect on blood glucose and lipid profile. This study has demonstrated that linagliptin can be a valuable option in the treatment of patients with type 2 diabetes.

Key words: Linagliptin, dipeptidylpeptidase-4 (DPP-4) inhibitors, type 2 diabetes, glycated hemoglobin (HbA1c), low-density lipoprotein cholesterol (LDL-C).

INTRODUCTION

Dipeptidylpeptidase-4 (DPP-4) inhibitors were recently introduced as new oral antidiabetic drugs and have quickly come into use in clinical practice. DPP-4 inhibitors are noteworthy pharmacological agents, with new components being consecutively developed. DPP-4 inhibitors result in an increase in blood concentrations of glucagon-like peptide-1 (GLP-1) by inhibiting the DPP-4 effects *in vivo*. They result in an increase in blood levels of insulin by promoting insulin secretion from pancreatic β cells. In patients with type 2 diabetes, if the glucagon concentration is decreased, DPP-4 inhibitors also inhibit the increase in

blood glucose levels (Drucker and Nauck, 2006). A number of DPP-4 inhibitors are currently being used in clinical practice. Among the DPP-4 inhibitors, linagliptin is excreted through biliary tract, and because of its characteristic route of excretion, it may potentially be useful for patients with type 2 diabetes who are at a high risk of reduced renal function (Heise et al., 2009). Therefore, this study compared the clinical efficacy of linagliptin to the first DPP-4 inhibitor, sitagliptin. A prospective comparative study was conducted on the clinical effects of linagliptin and sitagliptin.

Table 1. Patient characteristics at the beginning of the study.

Characteristic	Linagliptin group	Sitagliptin group
Age (years)	50.8 ± 14.9	51.4 ± 13.8
Gender (human: male/female)	12/9	7/14
HbA1c (%) (mmol/mol)	6.9 ± 0.8 (52 ± 9)	7.3 ± 0.9 (56 ± 10)
Fasting blood glucose level (mg/dl)	145.1 ± 50.6	146.8 ± 43.6
HDL-C (mg/dl)	55.5 ± 16.1	57.8 ± 12.9
LDL-C (mg/dl)	148.1 ± 48.5	128.7 ± 36.8
Creatinine (mg/dl)	0.65 ± 0.2	0.57 ± 0.1
eGFR	101.7 ± 47.1	102.6 ± 26.6
AST (IU/L)	29.8 ± 19.7	34.2 ± 16.3
ALT (IU/L)	42.8 ± 35.4	45.5 ± 29.5

Mean ± SD (except for gender).

MATERIALS AND METHODS

Patients with type 2 diabetes, in whom pharmacological treatment was recently initiated at our hospital, were randomly assigned to two separate groups, namely sitagliptin (50 mg/day) and linagliptin (5 mg/day) groups. A total of 42 patients (21 patients in each group), who received a single dose of their respective pharmacological agents, were evaluated in this study. The study primarily focused on changes in HbA1c (HbA1c was measured in National Glycohemoglobin Standardization Program (NGSP) values. It was measured in Toyota Kosei Hospital Japan with a measuring instrument of TohSoh Inc. The calculated regression equation is $NGSP = 0.09148 (IFCC) + 2.152 (David, 2012)$, which is the levels before and 24 weeks after drug administration and the influence of drug administration on renal function, liver function, and fat. Patient characteristics in sitagliptin and linagliptin groups were as follows: age (mean ± standard deviation (SD)): 51.4 ± 13.8 and 50.8 ± 14.9; gender (male:female): 7 males:14 females and 12 males:9 females; baseline HbA1c: 7.3 ± 0.9 and 6.9 ± 0.8 (%); 56 ± 10 and 52 ± 9 (mmol/mol) and baseline fasting blood glucose levels (mg/dl): 146.8 ± 43.6 and 145.1 ± 50.6 (Table 1). For statistical evaluations, paired Student's t-test was used to evaluate the therapeutic efficacy of the drugs.

This study has been reviewed and approved by the ethical review committee of Toyota Kosei Hospital. And this trial was registered with UMIN (no. 000010998).

RESULTS

Significant improvement in HbA1c levels was found in both linagliptin and sitagliptin groups (Figure 1), namely in patients in the sitagliptin group, in whom HbA1c levels changed from 7.29 ± 0.9% (56 ± 10 mmol/mol) (before administration of sitagliptin) to 6.72 ± 0.8 (%) (50 ± 9 mmol/mol) (24 weeks after administration) and in patients in the linagliptin group, in whom levels changed from 6.94 ± 0.8% (52 ± 9 mmol/mol) (before administration of linagliptin) to 6.32 ± 0.5% (45 ± 6 mmol/mol) (24 weeks after administration). Renal function was evaluated on the basis of the eGFR (ml/min/1.73 m²) and blood creatinine levels (mg/dl). The eGFR (ml/min/1.73 m²) changed from 102.6 ± 26.6 to 99.0 ± 28.9 in patients in the sitagliptin group and from 101.7 ± 47.0 to 102.0 ± 43.8 in patients in

the linagliptin group. Blood creatinine levels (mg/dl) changed from 0.57 ± 0.1 to 0.60 ± 0.2 in patients in the sitagliptin group and from 0.65 ± 0.2 to 0.64 ± 0.2 in patients in the linagliptin group. No marked changes in renal function for eGFR and creatinine levels were found in patients in the two groups. Liver function was evaluated on the basis of aspartate transaminase (AST) and alanine aminotransferase (ALT) levels (IU/l). AST level (IU/l) ranged from 34.2 ± 16.3 to 26.5 ± 11.8 in patients in the sitagliptin group and from 29.8 ± 19.7 to 23.3 ± 9.8 in patients in the linagliptin group. Significant improvements were observed in AST and ALT levels in patients in the sitagliptin group; these levels also improved in patients in the linagliptin group. Fat was evaluated on the basis of the high density lipoprotein-cholesterol (HDL-C) (mg/dl) and low density lipoprotein-cholesterol (LDL-C) levels (mg/dl). HDL-C level (mg/dl) changed from 57.8 ± 12.9 to 59.0 ± 13.3 in patients in the sitagliptin group and from 55.5 ± 16.1 to 58.4 ± 14.9 in patients in the linagliptin group, whereas LDL-C level (mg/dl) changed from 128.7 ± 36.8 to 121.0 ± 25.4 in patients in the sitagliptin group and from 148.1 ± 48.5 to 106.2 ± 23.8 in patients in the linagliptin group, showing a significant improvement (Figure 2).

DISCUSSION

Results of a recent meta-analysis have shown that the effects of sitagliptin 100 mg and linagliptin 5 mg were comparable (Gross et al., 2013). In the present study, a comparison between the actual clinical use of linagliptin 5 mg and long-term use of sitagliptin 50 mg demonstrated that their effect on glycemic control was virtually the same. In addition, the tests conducted in our hospital on eGFR and creatinine suggested that there was a marginal effect on renal function. However, at the 72nd annual meeting of the American Diabetes Association (ADA) held in 2012, the administration of linagliptin was reported to result in an improvement in albuminuria (Groop et al., 2012), and more detailed studies are expected to be conducted in the

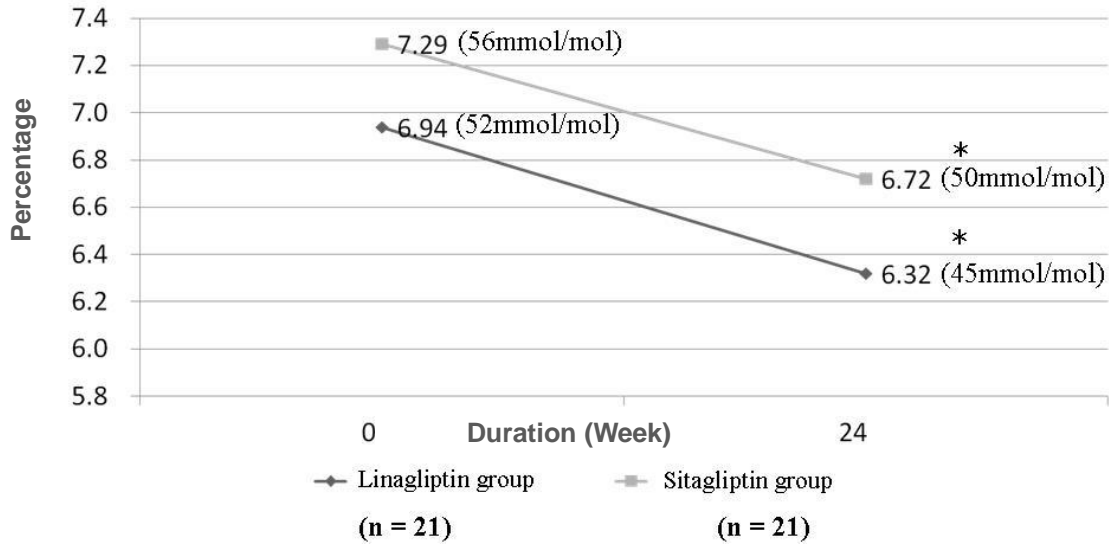


Figure 1. Study of changes in HbA1c levels, *P<0.05.

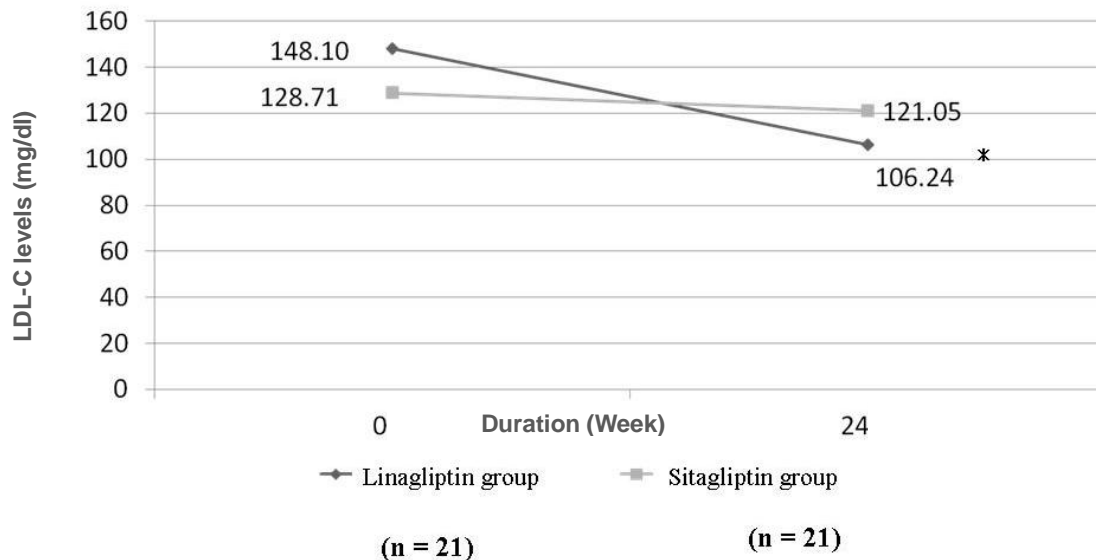


Figure 2. Study of the changes in LDL-C levels, *P<0.05.

future. Improvement in LDL-C level has been reported from experiments conducted on mice (Thomas et al., 2008). In addition, the presence of GLP-1 receptors on the surface of human hepatocytes was confirmed in 2010 (Gupta et al., 2010), and stimulation of either GLP-1 or GLP-1 receptor agonists promoted phosphorylation of PDK-1, PKC ζ , and AKT, which are important for transduction of signals from intracellular insulin receptors. Previous studies have suggested that signals from GLP-1 receptors may promote stimulation and activation of the insulin signaling pathway; this mediates an inhibitory effect on hepatic steatosis by exerting a direct action on

hepatocytes (Ono et al., 2011). Unlike any other DPP-4 inhibitor, linagliptin has a unique structure composed of a xanthine skeleton, and some compounds containing this xanthine skeleton have been found to possess an antioxidant effect, suggesting that linagliptin may also possess similar antioxidant properties (Kröller-Schön et al., 2012; Ishibashi et al., 2013). Thus, linagliptin may potentially have improving effects on fatty liver, thereby improving effects on fat. This study also suggested that serum levels of LDL-C were significantly improved in patients in the linagliptin group.

Further studies are required in a large number of patients.

Linagliptin, which is the first DPP-4 inhibitor that can be eliminated through biliary excretion, offers a great potential in terms of improving effect on blood glucose and lipid profile.

This study has demonstrated that the effect of newly developed DPP-4 inhibitor, linagliptin, was almost similar to that of other DPP-4 inhibitors, which have been used in clinical practice. In addition, because of its unique property of being eliminated through biliary excretion, it is believed to have marginal impact on renal or hepatic functions. In the future, linagliptin can be a valuable option in the treatment of patients with type 2 diabetes.

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ABBREVIATIONS

DPP-4, Dipeptidylpeptidase-4; **GLP-1**, glucagon-like peptide-1; **HbA1c**, glycated hemoglobin; **eGFR**, estimated glomerular filtrating ratio; **AST**, aspartate aminotransferase; **ALT**, alanine aminotransferase; **HDL-C**, high-density lipoprotein cholesterol; **LDL-C**, low-density lipoprotein cholesterol.

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