

The efficacy of saxagliptin in T2DM patients with non-alcoholic fatty liver disease: preliminary data

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SUMMARY

OBJECTIVE: To investigate the clinical efficacy and the possible mechanisms of saxagliptin in the treatment of type 2 diabetes mellitus (T2DM) combined with non-alcoholic fatty liver disease (NAFLD).

METHODS: A total of 95 T2DM and NAFLD patients were randomly divided into group A (saxagliptin group), group B (glimepiride group), and group C (glimepiride combined with polyene phosphatidylcholine group).

RESULTS: After intervention treatment for 24 w, body mass index (BMI), waist-to-hip ratio (WHR), glycated haemoglobin (HbA1c), fasting plasma glucose (FPG), fasting insulin (FINS), homeostatic model assessment of insulin resistance (HOMA-IR), interleukin-6 (IL-6), triglyceride (TG), total cholesterol (TC), alanine aminotransferase (ALT), aspartate aminotransferase (AST), γ -glutamyltransferase (γ -GT), and quantitative detection of liver steatosis of study subjects were observed, the action of liver steatosis in subjects of groups A and C were significantly different from those of group B; however, there were no differences between groups A and C. The FINS, HOMA-IR, and IL-6 of subjects in group A was lower than those in groups B and C; however, there were no significant differences between the latter two groups.

CONCLUSION: For T2DM combined with NAFLD patients, the saxagliptin treatment could not only effectively control blood glucose but also attenuate insulin resistance and inflammatory injury of the liver to improve fatty liver further.

KEYWORDS: Dipeptidyl-peptidase IV inhibitors/therapeutic use. Diabetes mellitus, type 2. Interleukin-6. Fatty liver. Non-alcoholic fatty liver disease.

INTRODUCTION

Non-alcoholic fatty acid disease (NAFLD) refers to one type of metabolic stress-induced liver injury syndrome that is closely associated with insulin resistance and genetic susceptibility resulting from factors other than alcohol and other clear liver injury factors¹. Epidemiological survey results have shown

that the prevalence of NAFLD in the world reaches 30%, the prevalence of combined NAFLDs among type 2 diabetes mellitus (T2DM) patients reaches 34%-74%, and NAFLD is present in almost all T2DM combined with obesity patients². Insulin resistance is even more evident in T2DM combined with NAFLD

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TABLE 1. COMPARISON OF BASELINE CLINICAL INFORMATION OF SUBJECTS AMONG ALL GROUPS

Group	Number of cases (male/female)	Age (year)	Disease history (month)	BMI (kg/m ²)	WHR (cm/cm)	HbA1c (%)	FPG (mmol/L)	FINS (μIU/ml)	HOMA-IR	IL-6 (pg/ml)
Group A	31 (15/16)	46.58±8.15	11.32±6.64	27.20±4.06	0.89±0.06	7.79±0.52	7.86±1.25	10.63±2.25	3.72±0.98	10.60±8.20
Group B	33 (17/16)	47.36±9.40	10.15±7.55	26.46±3.23	0.89±0.05	7.82±0.61	7.57±1.24	9.97±2.45	3.37±0.99	10.05±7.57
Group C	31 (16/15)	49.26±8.94	9.55±5.37	26.02±2.91	0.88±0.05	7.85±0.57	7.54±0.98	10.57±2.61	3.55±1.02	11.36±9.10
F	0.084	0.908	2.448	2.544	0.218	1.659	0.230	0.639	0.148	0.270
p	0.959	0.407	0.092	0.084	0.805	0.196	0.795	0.530	0.863	0.764

Group	Number of cases (male/female)	Age (year)	Disease history (month)	TC (mmol/L)	TG (mmol/L)	ALT (U/L)	AST (U/L)	γ-GT (U/L)	Quantitative detection of liver steatosis (%)
Group A	31 (15/16)	46.58±8.15	11.32±6.64	5.35±0.94	1.98±1.08	31.74±18.99	32.48±20.33	51.19±27.01	20.50±8.96
Group B	33 (17/16)	47.36±9.40	10.15±7.55	5.55±0.79	2.13±0.84	28.36±14.55	28.88±14.08	46.61±20.26	21.11±8.85
Group C	31 (16/15)	49.26±8.94	9.55±5.37	5.57±1.20	2.06±1.02	30.26±13.05	27.13±12.17	45.00±21.37	22.03±9.19
F	0.084	0.908	2.448	1.816	0.164	1.643	2.314	2.436	0.229
p	0.959	0.407	0.092	0.169	0.849	0.199	0.105	0.093	0.796

patients, and the risk of cardio-cerebrovascular diseases increases in these patients. Therefore, during the control of blood glucose compliance, it would be more beneficial also to improve fatty liver at the same time. Studies in recent years have suggested that the development and progression of various chronic liver diseases are associated with dipeptidyl peptidase-4 (DPP-4). NAFLD patients have higher levels of serum DPP-4, and administration of DPP-4 inhibitor treatment can improve liver functions and hepatocyte degeneration levels in these patients^{3,4}; however, its possible mechanisms are still not completely elucidated. This study aimed to observe the efficacy of saxagliptin in the reduction of glucose and the improvement of fatty liver in newly diagnosed T2DM patients combined with NAFLD and to investigate the possible mechanisms underlying the improvement of fatty liver.

INVESTIGATIONS AND RESULTS

A total of 95 subjects were enrolled in this study. Group A had 31 cases, and 1 case was lost during follow-up; group B had 33 cases, and no case was lost during follow-up, and group C had 31 cases, and 2 cases were lost during follow-up. A total of 92 subjects completed this study.

Comparison of baseline clinical information among all groups

Age, gender, DM history, BMI, WHR, HbA1c, FPG, FINS, IL-6, TG, TC, ALT, AST, γ-GT, and quan-

titative detection of liver steatosis of subjects among the three groups before enrolment were not significantly different ($p>0.05$) (Table 1) and had comparability.

Comparison of the control of BMI, WHR, blood glucose, and blood lipids after 24 w of treatment among all groups

BMI, WHR, HbA1c, FPG, TC, and TG of subjects among the three groups were not significantly different at the observation endpoint ($p>0.05$) (Table 2), suggesting that the hypoglycemic efficacy in the saxagliptin treatment group was equivalent to that in the glimepiride group.

Comparison of liver functions, quantitative detection of liver steatosis, FINS, HOMA-IR, and IL-6 among all groups after 24 w of treatment

ALT, AST, γ-GT, and quantitative detection of liver steatosis of subjects in groups A and C were all lower than that in group B, and the differences were significant ($p<0.05$); in contrast, there were no differences between groups A and C. FINS, HOMA-IR, and IL-6 of subjects in group A was lower than those in groups B and C ($p<0.05$); however, there was no significant difference between the latter 2 groups (Table 3).

DISCUSSION

Dipeptidyl peptidase-4 (DPP-4) inhibitors can stimulate pancreatic islet β cells to secrete insulin and

can also inhibit abnormal secretion of glucagon by α cells, functioning on the α,β -double-channel glucose-dependent blood glucose regulation mechanism⁵. Based on metformin administration, the comparison of blood glucose control compliance rates between combined saxagliptin treatment and combined glimepiride treatment did not have a significant difference in elderly T2DM patients⁶. This study observed that the treatment of newly diagnosed DM patients using saxagliptin or glimepiride alone did not have a significant difference in the control of FPG and HbA1c, suggesting that the blood glucose control effects between these two treatments were equivalent. In addition, the results in this study showed that the HOMA-IR indicator in the saxagliptin treatment group was lower than that in the glimepiride group, suggesting that saxagliptin could improve insulin resistance in newly diagnosed T2DM combined with NAFLD patients. Previous study results mainly suggested that saxagliptin could stimulate insulin secretion and improve β cell functions but did not have apparent functions on insulin resistance^{7,8}. Some studies have suggested that saxagliptin could also improve insulin resistance in DM patients⁹. The differences in the study results might be associated with characteristics of the populations enrolled in the different studies. Therefore, large-scale clinical trials are still needed for further studies and observations.

NAFLD is characterized by hepatocyte steatosis, and fat deposition includes simple fatty liver, steatohepatitis, and fatty liver fibrosis and cirrhosis. Currently, its pathogenetic mechanisms have not been completely elucidated. The “second hit” theory is currently the most recognized viewpoint by most scholars. In the first hit, fat accumulation in the liver causes hepatocyte apoptosis and induces insulin resistance. Insulin resistance, directly and indirectly,

participates in the second hit to cause inflammatory responses, hepatocyte injury, and fibrosis¹⁰. Studies on NAFLD-associated chronic inflammation have received extensive attention in recent years, and cytokines and inflammatory factors have become research hot spots^{11,12}. IL-6 is mainly produced by immune cells, including macrophages, T cells, and B cells; it is an important pro-inflammatory cytokine, and the deregulation of its expression is closely associated with various diseases. The functions of IL-6 in hepatocyte steatosis are very complicated. It has been shown that IL-6 plays a role in liver protection through the inhibition of oxidative stress and the prevention of mitochondrial dysfunction in the early stage of fatty liver. However, during the pathological changes in the late stage of fatty liver, IL-6 can induce hepatocyte apoptosis, produce insulin resistance, participate in NAFLD development and progression, and cause hepatocyte injury^{13,14}. This study showed that the blood glucose control, BMI, and WHR of subjects in the saxagliptin group were not significantly different compared to the glimepiride group. However, the IL-6 and HOMA-IR levels were both lower than those in the glimepiride group and the glimepiride combined with polyene phosphatidylcholine group. In addition, the level of liver steatosis quantitation of subjects in the saxagliptin group was significantly lower than that in the glimepiride group and was equivalent to that in the glimepiride combined with polyene phosphatidylcholine group. These results suggested that based on the same levels of blood glucose control and body weight management, the administration of saxagliptin treatment could improve insulin resistance and reduce the levels of inflammatory factors such as IL-6 to improve hepatocyte steatosis and protect hepatocytes in newly diagnosed patients with T2DM combined with NAFLD.

TABLE 2. COMPARISON OF THE CONTROL CONDITIONS OF BMI, WHR, HBA1C, FBG, TC, AND TG AMONG ALL GROUPS

Group	Number of cases (male/female)	BMI (kg/m ²)	WHR (cm/cm)	HbA1c (%)	FPG (mmol/L)	TC (mmol/L)	TG (mmol/L)
Group A	30 (14/16)	26.69±4.16	0.88±0.06	6.91±0.48	6.46±0.44	5.12±0.78	1.58±0.85
Group B	33 (17/16)	25.65±3.03	0.88±0.05	6.92±0.58	6.42±0.57	5.40±0.62	1.65±0.77
Group C	29 (14/15)	25.52±2.79	0.87±0.05	6.85±0.47	6.42±0.48	5.28±1.08	1.74±1.12
F	0.155	1.132	0.477	0.197	0.080	0.898	0.245
p	0.926	0.327	0.622	0.821	0.923	0.411	0.784

In summary, the administration of saxagliptin treatment could effectively control blood glucose in patients newly diagnosed with T2DM combined with NAFLD, and its efficacy was no worse than that of glimepiride. In addition, saxagliptin treatment could improve insulin resistance, reduce IL-6 levels, and attenuate inflammatory responses to improve hepatocyte steatosis, protect hepatocytes, and obtain extra benefits other than the hypoglycemic effect in NAFLD patients. However, whether the treatment effect of saxagliptin on the fatty liver is independent of the hypoglycemic effect still requires further studies for investigation.

EXPERIMENTAL

Patients

A total of 95 T2DM patients (48 male and 47 female) who were treated in the Department of Endocrinology of our hospital between July 2014 and December 2016 were selected. All subjects signed an informed consent form. This study was approved by the Research Ethics Committee of Qilu Hospital of Shandong University.

Case inclusion and exclusion criteria

Inclusion criteria: (1) patients who met the World Health Organisation (WHO) 1999 T2DM diagnostic criteria; (2) patients who were newly diagnosed with T2DM or had a disease history of less than 2 years and did not receive hypoglycaemic drug treatment; (3) patients with ages between 30-60 years, body mass index (BMI) between 23-30 kg/m² and glycosylated haemoglobin (HbA1c) between 7%-9%; and (4) patients who met the relevant diagnostic criteria of the *Guidelines for the Management of Non-alcoholic Fatty Liver Disease (2010 revised edition)* by the Chinese Society of Hepatology, Chinese Medical Association and did not receive drug treatment for liver protec-

tion. Exclusion criteria: (1) patients with acute complications and severe chronic complications of DM; (2) patients with viral hepatitis, drug hepatitis, autoimmune liver disease, other liver diseases caused by clear damage factors, hepatolenticular degeneration, and total parenteral nutrition; and (3) patients with liver cirrhosis, severe liver and kidney insufficiency, cardio-cerebrovascular diseases, acute infection, and genetic diseases.

Patient grouping and treatment

Subjects were randomly divided into groups A, B, and C according to a computer-generated random number table. Group A received oral saxagliptin at 5 mg once a day (QD), group B received oral glimepiride at 2 mg QD, and group C received oral glimepiride at 2 mg QD and polyene phosphatidylcholine at 456 mg orally three times a day (PO TID) based on providing diet and exercise therapy guidance. The doses of glimepiride for subjects in groups B and C were adjusted based on blood glucose. Patients were observed for 24 w.

Observation indicators

Body weight, height, waist circumference, hip circumference, HbA1c, fasting plasma glucose (FPG), fasting insulin (FINS), interleukin-6 (IL-6), triglyceride (TG), total cholesterol (TC), alanine aminotransferase (ALT), aspartate aminotransferase (AST), γ -glutamyltransferase (γ -GT), and quantitative detection of liver steatosis of study subjects were observed before enrolment and after 12 and 24 w of treatment. In addition, BMI, waist-to-hip ratio (WHR), and homeostatic model assessment of insulin resistance (HOMA-IR) were calculated. Fingertip FPG and two h postprandial blood glucose were measured every two w. Patients with liver fat contents between 5%-10% were considered to have

TABLE 3. COMPARISON OF FINS, HOMA-IR, IL-6, ALT, AST, γ -GT, AND QUANTITATIVE DETECTION OF LIVER STEATOSIS AMONG ALL GROUPS

Group	Number of cases (male/female)	FINS (μ IU/ml)	HOMA-IR	IL-6 (pg/ml)	ALT (U/L)	AST (U/L)	γ -GT (U/L)	Quantitative detection of liver steatosis (%)
Group A	30 (14/16)	7.82 \pm 2.14*#	2.25 \pm 0.63*#	6.04 \pm 4.01*#	22.10 \pm 9.25*	16.94 \pm 6.43*	30.84 \pm 21.30*	14.57 \pm 7.78*
Group B	33 (17/16)	9.75 \pm 2.34	2.79 \pm 0.75	9.84 \pm 6.81	29.00 \pm 14.62	22.03 \pm 10.27	44.21 \pm 12.42	20.13 \pm 8.18
Group C	29 (14/15)	10.29 \pm 2.40	2.94 \pm 0.76	10.46 \pm 7.56	19.32 \pm 9.50*	17.68 \pm 5.60*	31.48 \pm 28.12*	15.09 \pm 9.09*
F	0.155	9.940	8.229	4.470	6.072	3.600	3.999	4.733
p	0.926	0.000	0.001	0.014	0.003	0.031	0.022	0.011

Note: * compared with group B, p<0.05; # compared with group C, p<0.05.

mildly fatty livers, between 11%-30%, were considered to have moderately fatty livers, and above 30% were considered to have severely fatty livers.

STATISTICAL ANALYSES

Analyses were performed using SPSS 21.0 software. Continuous variables conformed to the normal distribution and were expressed as $\bar{x} \pm s$. Based on the distribution features of clinical information

among all groups, the comparison of measurement data that conformed to the normal distribution and had homogenous variances was performed using the analysis of variance (ANOVA). The comparison inside a group was performed using the least significant difference (LSD) method. $P < 0.05$ indicated that the difference had statistical significance.

Declaration of conflict of interest

None.

RESUMO

OBJETIVO: Investigar a eficácia clínica e os possíveis mecanismos da saxagliptina no tratamento do diabetes mellitus tipo 2 (DM2) associado à doença hepática gordurosa não alcoólica (DHGNA).

MÉTODOS: Um total de 95 DM2 combinados com pacientes com DHGNA foram aleatoriamente divididos em grupo A (grupo saxagliptina), grupo B (grupo glimepirida) e grupo C (glimepirida combinado com grupo fosfatidilcolina polienizada).

RESULTADOS: Após a intervenção tratamento por 24 w, índice de massa corporal (IMC), relação cintura-quadril (RCQ), hemoglobina glicada (HbA1c), glicemia de jejum (FPG), insulina de jejum (Fins), avaliação do modelo homeostático de insulina resistência (Homa-IR), interleucina-6 (IL-6), triglicérides (TG), colesterol total (CT), alanina aminotransferase (ALT), aspartato aminotransferase (AST), γ -glutamiltansferase (γ -GT) e detecção de esteatose hepática dos sujeitos do estudo foram observados. Ação de esteatose hepática de indivíduos nos grupos A e C foram significativamente diferentes do grupo B; no entanto, não houve diferenças entre os grupos A e C. Os grupos Fins, Homa-IR e IL-6 dos participantes do grupo A foram menores que os dos grupos B e C; no entanto, não houve diferenças significativas entre os dois últimos grupos.

CONCLUSÃO: Para o DM2 combinado com pacientes com DHGNA, o tratamento com saxagliptina pode não apenas controlar efetivamente a glicemia, mas também atenuar a resistência à insulina e a lesão inflamatória do fígado para melhorar ainda mais o fígado gorduroso.

PALAVRAS-CHAVE: Inibidores da dipeptidil peptidase IV/uso terapêutico. Diabetes mellitus tipo 2. Interleucina-6. Fígado gorduroso. Hepatopatia gordurosa não alcoólica.

REFERENCES

- Gastaldelli A. Insulin resistance and reduced metabolic flexibility: cause or consequence of NAFLD? *Clin Sci*. 2017;131(22):2701-4.
- Dai W, Ye L, Liu A, Wen SW, Deng J, Wu X, et al. Prevalence of nonalcoholic fatty liver disease in patients with type 2 diabetes mellitus: a meta-analysis. *Medicine (Baltimore)*. 2017;96(39):e8179.
- Dixon LJ, Berk M, Thapaliya S, Papouchado BG, Feldstein AE. Caspase-1-mediated regulation of fibrogenesis in diet-induced steatohepatitis. *Lab Invest*. 2012;92(5):713-23.
- Sugino H, Kumagai N, Watanabe S, Toda K, Takeuchi O, Tsunematsu S, et al. Polaprezinc attenuates liver fibrosis in a mouse model of non-alcoholic steatohepatitis. *J Gastroenterol Hepatol*. 2008;23(12):1909-16.
- Irons BK, Weis JM, Stapleton MR, Edwards KL. An update in incretin-based therapy: a focus on dipeptidyl peptidase: 4 inhibitors. *Curr Diabetes Rev*. 2012;8(3):169-82.
- Scherthner G, Durán-García S, Hanefeld M, Langslet G, Niskanen L, Östgren CJ, et al. Efficacy and tolerability of saxagliptin compared with glimepiride in elderly patients with type 2 diabetes: a randomized, controlled study (GENERATION). *Diabetes Obes Metab*. 2015;17(7):630-8.
- Bugliani M, Syed F, Paula FMM, Omar BA, Suleiman M, Mossuto S, et al. DPP-4 is expressed in human pancreatic beta cells, and its direct inhibition improves beta cell function and survival in type 2 diabetes. *Mol Cell Endocrinol*. 2018;473:186-93.
- Henry RR, Smith SR, Schwartz SL, Mudaliar SR, Deacon CF, Holst JJ, et al. Effects of saxagliptin on beta-cell stimulation and insulin secretion in patients with type 2 diabetes. *Diabetes Obes Metab*. 2011;13(9):850-8.
- Kenawy S, Hegazy R, Hassan A, El-Shenawy S, Gomaa N, Zaki H, et al. Involvement of insulin resistance in D-galactose-induced age-related dementia in rats: protective role of metformin and saxagliptin. *PLoS One*. 2017;12(8):e0183565.
- Hajjighees A, Farzanegi P, Mazaheri Z. Effects of combined therapy with resveratrol, continuous and interval exercises on apoptosis, oxidative stress, and inflammatory biomarkers in the liver of old rats with non-alcoholic fatty liver disease. *Arch Physiol Biochem*. 2018;1-8.
- Qu HJ, Wang L, Jin PH, Gao Q, Zhou JX, Song Y, et al. Value of hydrogen proton magnetic resonance spectroscopy in the determination of liver triglyceride in patients with fatty liver disease and its influencing factors. *Zhonghua Gan Zang Bing Za Zhi*. 2017;25(11):858-63.
- Younossi ZM, Stepanova M, Rafiq N, Henry L, Loomba R, Makhlof H, et al. Nonalcoholic steatofibrosis independently predicts mortality in nonalcoholic fatty liver disease. *Hepatol Commun*. 2017;1(5):421-8.
- Dembek A, Laggai S, Kessler SM, Czepukojc B, Simon Y, Kiemer AK, et al. Hepatic interleukin-6 production is maintained during endotoxin tolerance and facilitates lipid accumulation. *Immunobiology*. 2017;222(6):786-96.
- Mohammadi S, Karimzadeh Bardei L, Hojati V, Ghorbani AG, Nabiuni M. Anti-inflammatory effects of curcumin on insulin resistance index, levels of interleukin-6, C-reactive protein, and liver histology in polycystic ovary syndrome-induced rats. *Cell J*. 2017;19(3):425-33.

