ORIGINAL RESEARCH

Liraglutide Plus Dapagliflozin for High Uric Acid and Microalbuminuria in Diabetes Mellitus Complicated With Metabolic Syndrome

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ABSTRACT

Context • Diabetes mellitus (DM) represents an emerging epidemic, poses serious threats to human health, and can seriously compromise patients' quality of life (QoL). Currently, no cure exists for DM. Some studies have found that both liraglutide and dapagliflozin have great therapeutic potential in preventing and treating DM and its complications.

Objective • The study aimed to examine the impact of liraglutide plus dapagliflozin on high uric acid (UA) and microalbuminuria (MAU) in patients with diabetes mellitus (DM) complicated with metabolic syndrome (MS).

Design • The research team designed a randomized controlled trial.

Setting • The study took place at the Second Affiliated Hospital of Nanjing Medical University in Nanjing, Jiangsu, China.

Participants • Participants were 125 patients with DM complicated with MS who were treated in the outpatient clinic of the endocrinology department at the hospital between January 1, 2020 and December 31, 2021, with 68 in the intervention group and 57 in the control group.

Intervention • The intervention and control groups both received 0.6 mg of liraglutide. The intervention group also received 5 mg of dapagliflozin once a day. The dosages were increased at one week after baseline based on the participant's condition.

Outcome Measures • Therapeutic effects, glycolipid metabolism, inflammation, uric acid (UA), microalbuminuria (MAU), cardiac function, and quality of life (QoL) were compared between the two groups.

Results • Postintervention, the clinical efficacy was significantly higher in the intervention group than in the control group. The intervention group had significantly lower glycolipid metabolism and inflammatory-factor levels than the control group UA and MAU had declined in both groups but were significantly lower in the intervention group. The left ventricular ejection fraction (LVEF) increased and the left ventricular end diastolic diameter (LVEDd) decreased in both groups, but the intervention group had significantly greater changes as compared with those in the control group. The intervention group was also superior to the control group in patients' QoL.

Conclusions • Liraglutide plus dapagliflozin has highly therapeutic effect for patients with DM complicated with MS and can effectively reduce UA and MAU levels. The current research team will launch a more comprehensive analysis as soon as possible to obtain the most accurate results. (*Altern Ther Health Med.* 2022;28(6):14-21)

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Diabetes mellitus (DM) is a commonly seen, chronic endocrine disease with a high prevalence. Widely regarded as a metabolic disease, DM represents an emerging epidemic, poses serious threats to human health, and can seriously compromise patients' quality of life (QoL).[1,2]

DM's incidence is extremely high and is still growing, with cumulative effects on almost every country, age group and economy in the world.[3] According to the a survey on the incidence of DM, the global prevalence of DM was 9.3% in 2019 and is expected to rise to 10.2% by 2030.[4]

Type 2 diabetes mellitus (T2DM), which accounts for over 90% of the DM population in China, is the dominant type of DM.[5] Since no obvious symptoms of discomfort or clinical manifestations are evident in T2DM's early stage, most patients have little awareness that they have the disease and are found to be ill through a physical examination and blood-glucose test.[6]

Consequently, complications caused by DM can further aggravate patients' health.[7] Although DM itself doesn't immediately threaten patients' lives, its combination with other diseases is an important cause of death of diabetic patients.[8]

Metabolic syndrome (MS), also known as insulin resistance syndrome and syndrome X, includes a group of conditions known as the deadly quartet—obesity, non-insulin-dependent DM, hypertension, and dyslipidemia—that can seriously impact the body's health.[9] MS is a syndrome resulting from obesity, has elevated blood sugar and dyslipidemia as clinical reactions, is strongly associated with insulin resistance, and is an important risk factor for T2DM.[10]

These factors can accelerate the progression of cardiovascular diseases, posing a grave threat to patients' physical and mental health.[11] Currently, no cure exists for DM, and instead, interventions include drugs to control blood sugar or comprehensive treatment to help patients stabilize their illnesses.[12] However, due to the individual differences in patients, and adverse drug reactions, the overall effects of clinical treatment are far from satisfactory.[13] Therefore, DM complicated with MS is clinically difficult to treat.

Liraglutide, a human glucagon-like peptide-1 (GLP-1) analogue, is the main hypoglycemic drug for T2DM patients in clinical practice and is commonly used for controlling blood sugar in T2DM patients.[14,15] Its advantages are different from traditional, oral hypoglycemic drugs and insulin; it promotes insulin secretion by pancreatic β cells and is able to lower blood sugar while protecting pancreatic β-cells.[16,17] In addition, liraglutide exerts certain advantages in reducing the risk of cardiovascular disease.[18]

Dapagliflozin is another drug used in treatment of T2DM and has significant hypoglycemic and metabolic effects.[19] It's a new class of hypoglycemic agents, also called sodium-glucose cotransporter inhibitors,[20] that help reduce blood sugar in a non-insulin-dependent manner by excreting sugar in the urine.[21] Dapagliflozin can be used to reduce the glucose content absorbed by the kidney to a certain extent, maintain the stability of blood sugar, and reduce the urinary protein content.[22] It also has a positive effect on cardio-cerebrovascular diseases or diseases, such as renal-function damage and cardiac insufficiency.[23]

Some studies have found that both liraglutide and dapagliflozin have great therapeutic potential in preventing and treating DM and its complications.[24,25] The current research team speculates that liraglutide plus dapagliflozin may also have positive clinical effects in the treatment of patients with DM complicated with MS and may provide a new treatment option for such patients in the future. At present, the employment of liraglutide plus dapagliflozin for DM complicated with MS is hard to track in the existing literature.

The study aimed to examine the impact of liraglutide plus dapagliflozin on high uric acid (UA) and microalbuminuria (MAU) in patients with diabetes mellitus (DM) complicated with metabolic syndrome (MS).

METHODS

Participants

The research team designed a randomized controlled trial. The study took place at the Second Affiliated Hospital of Nanjing Medical University in Nanjing, Jiangsu, China. Potential participants were patients with DM complicated with MS were treated in the outpatient clinic of the endocrinology department at the hospital between January 1, 2020 and December 31, 2021. We took all patients with DM and MS admitted during the study period as potential study objects, screened the final study objects according to the inclusion and exclusion criteria, and then grouped the patients according to their treatment methods. The data and examination results of each subject were collected by Ting Ou and Yuntao Li for experimental analysis.

Potential participants were included in the study if: (1) their records provided complete case data, (2) they met the clinical symptoms and diagnostic criteria of DM complicated with MS, and (3) they agreed to take part in the study.

Potential participants were excluded from the study if they: (1) had a severe infection, (2) had malignant tumor(s); (3) had serious heart, liver, or kidney insufficiency; (4) had a severe endocrine or autoimmune disease; (5) had a drug allergy; or (6) were pregnant or lactating women.

This study was conducted in strict compliance with the Declaration of Helsinki and was approved by the Ethics Committee of our hospital. All research participants signed an informed-consent form.

Procedures

Drugs. The research team purchased the liraglutide from Novo Nordisk (Copenhagen, Denmark), SFDA Approval No. J20160037, and the dapagliflozin from AstraZeneca Pharmaceutical, London, UK), SFDA Approval No. J20170040.

Grouping. The patients were divided into groups according to the mode of medication, and the patients treated with liraglutide combined with dapagliflozin served as the intervention group, and the patients treated with liraglutide served as the control group. Both groups were treated continuously for 3 months.

Medical staff. During the study, general practitioners at the hospital were responsible for regular observation of and guidance to participants. General practitioners are health-

service providers and physicians who provide individuals, families, and communities with quality, convenient, cost-effective and integrated healthcare services for the responsible management of life, health, and disease.[26] For chronic diseases such as diabetes and hypertension that are difficult to cure and have a long treatment cycle, general practitioners can provide patients with sufficient rehabilitation, allowing them to get professional and accurate medical services in nonmedical environments while reducing clinical medical resources and treatment costs for patients.[27]

Electronic case files. The general practitioners at the hospital established the electronic case files for each participant. These case files recorded each participant's age, gender, course of disease, degree of illness, and other pertinent information in detail.

WeChat applet. A WeChat applet for doctor-patient communications was set up to remind all participants, using daily push messages, to monitor their blood glucose. The uploaded results were archived and sorted by the general practitioners to allow them to check for changes in participants' conditions.

Phone checks. The general practitioners communicated directly with all participants by phone at least once a week, instructing them about precautions to take during treatment, inquiring about disease development, and providing timely feedback to and communication with the clinical attending physicians as summarized information related to a patient's condition.

Patients with aggravated conditions. The general practitioners paid special attention to these participants, and if necessary, visited them or asked them to return to the hospital for better medical services. At the same time, the general practitioners promoted a positive and optimistic attitude toward treatment for participants and their families, so as to help them build confidence about overcoming the disease.

Outcome measures. At baseline and postintervention, the study measured: (1) therapeutic efficacy,[28] (2) glucolipid metabolism, (3) inflammatory factors (IFs), (4) metabolic function, and (5) alterations in cardiac function. Postintervention, the team also measured QoL.

Intervention

The control and interventions groups received 0.6 mg of liraglutide, which was injected subcutaneously every day, and the dosage was increased at one week after baseline according to the participant's condition.

The intervention group was additionally given 5 mg of dapagliflozin once a day, and the dosage was increased at one week after baseline based on the participant's condition.

Outcome Measures

Therapeutic efficacy. Markedly effective: After treatment, clinical symptoms disappeared, blood sugar was basically stable, and there was no major fluctuation within 2 months. Effective: Clinical symptoms improved after treatment, blood sugar was significantly reduced, and there was no repeated increase within 2 months. Ineffective: No obvious change or even aggravation after treatment. Total effective rate = (Markedly effective+Effective)/total × 100%.

Glucolipid metabolism. Glucolipid metabolism is the most important indicator in DM, which directly determines the degree of disease progression of the patient. Decreased levels of Glucolipid metabolism indicated that DM was effectively controlled. These levels included: (1) homeostatic model assessment for insulin resistance (HOMA-IR), (2) serum total cholesterol (TC), (3) triglycerides (TG), (4) apolipoprotein-B (ApoB), (5) fasting blood glucose (FPG), and (6) glycosylated hemoglobin (HbA_{1c}), as detected by an automatic biochemical analyzer (Mindray BS-220, Shenzhen, Guangdong, China). ApoB is a protein in plasma lipoproteins with the primary function of carrying lipids.

IFs. TNF-α, IL-6 and hs-CRP are vital IFs that can reflect the inflammatory state of the body.[27] The tested IFs included: (1) tumor necrosis factor alpha (TNF-α), (2) interleukin-6 (IL-6), and (3) high sensitivity C-reactive protein (hs-CRP), determined by enzyme-linked immunoassay (ELISA).

Metabolic function. MS can reduce UA and MAU levels. The tests measured changes in uric acid (UA) and microalbuminuria (MAU). They are important indicators of metabolic function with extremely high sensitivity.

UA is the metabolic product of purine nucleotides in the body. The change in UA level can fully reflect the metabolism and immune function of human body, and abnormal levels can directly affect the glomerular filtration function.[28] When the glomerular filtration rate increases, the leakage of albumin in urine increases, which increases the MAU level.[29] Therefore, reducing UA and MAU is very important for diabetic patients complicated with MS. Lower UA and MAU indicate better metabolic capacity of the patient.

Alterations in cardiac function. These alterations included: (1) left ventricular ejection fraction (LVEF) and (2) left ventricular end diastolic diameter (LVEDd). They were measured by a cardiac function instrument (Ruibo PM-9000A, Changsha, Hunan, China). Cardiovascular disease is the most common complication of DM, so paying attention to the patient's cardiac function can effectively prevent the occurrence of cardiovascular disease. The higher the LVEF, the lower the LVEDd, the better the cardiac function.

QoL.[30] QoL was assessed from the dimensions of physical function, mental function, social function, and independence, higher scores for each item indicate better quality of life.

Statistical Analysis

Data analysis was performed using SPSS, vs 22.0 (IBM, Armonk, New York, USA). The calculated average values of the results were described as means ± standard deviations (SDs). The independent sample *t* test was used for between-group comparisons; one-way analysis of variance (ANOVA) and least significant difference (LSD) post-hoc test for between-group comparisons, and repeated measures ANOVA and Bonferroni post-hoc test for multipoint comparisons. The level of significance was set at $P < .05$.

Table 1. Demographic Data (N=125)

	Intervention Group n = 68 Mean ± SD	Control Group n = 57) Mean ± SD	*t* or χ^2	*P* Value
Age, y	56.7 ± 5.6	57.2 ± 5.3	0.509	.611
	n (%)	n (%)		
Gender			0.348	.556
Male	36 (54.41)	28 (49.12)		
Female	31 (45.59)	29 (50.88)		
Living Environment			0.568	.451
Urban	45 (66.18)	34 (59.65)		
Rural	23 (33.82)	23 (40.35)		
Educational Level			0.901	.343
<High school	38 (55.88)	27 (47.37)		
≥High school	30 (44.12)	30 (52.63)		
Exercise Habits			0.426	.514
Yes	35 (51.47)	26 (45.61)		
No	33 (48.53)	31 (54.39)		
Eating Habits			0.069	.793
Regular	48 (70.59)	39 (68.42)		
Irregular	20 (29.41)	18 (31.58)		
Ethnicity			0.068	.796
Han	64 (94.12)	53 (92.98)		
Ethnic minorities	4 (5.88)	4 (7.02)		
Family Medical History			0.447	.504
Yes	9 (13.24)	10 (17.54)		
No	59 (86.76)	47 (82.46)		

Table 2. Therapeutic Effects for the Groups

	Intervention Group n = 68 n (%)	Control Group n = 57 n (%)	χ^2	*P* Value
Markedly effective	28 (41.18)	19 (33.33)		
Effective	35 (51.47)	26 (45.61)		
Ineffective	5 (7.35)	12 (21.05)		
Total effective rate	63 (92.65)	45 (78.95)	4.953	.026[a]

[a]$P < .05$, indicating a significantly higher efficacy for the intervention group compared to that of the control group

RESULTS

Participants

The study included 125 participants, 68 in the intervention group and 57 in the control group (Table 1). No significant differences existed at baseline between the groups in age, gender, living environment, educational level, exercise habits, eating habits, ethnicity, family medical history, with $P > .05$, suggesting clinical comparability.

Clinical Efficacy

The clinical efficacy was compared between the two groups. The total effective rate postintervention for the intervention group was 92.65%, which was significantly higher than that of the control group's at 78.95%, with $P < .05$ (Table 2). The clinical efficacy for both groups was at the effective level, at 51.47% in the intervention group and 45.61% in the control group. However, the treatment for only 7.35% of participants in the intervention group was rated as ineffective compared with 21.05% for the control group.

Glucolipid Metabolism

No significant difference in the HOMA-IR level was found between the groups at baseline, but postintervention, the HOMA-IR levels had decreased to 4.16 ± 0.74 and 5.31 ± 0.85 in the intervention group and the control group, respectively. The decrease was significantly greater in the intervention group than in the control group, with $P < .05$ (Figure 1A).

The TC and TG levels showed no significant differences between the groups at baseline, but both levels had decreased postintervention for both groups, with significant greater reductions in the intervention group than in the control group, with $P < .05$ (Figures 1B and 1C).

No significant difference existed between the groups in the ApoB at baseline, but the level was significantly lower in the intervention group than in the control group postintervention, with $P < .05$ (Figure 1D).

Finally, the levels of FPG and HbA_{1c} showed no significant differences between the groups at baseline, and the levels of FPG (Figure 1E) and HbA_{1c} (Figure 1F) postintervention in the intervention group were 6.05 ± 0.52 and 4.12 ± 1.52, respectively, both significantly lower than those in the control group, with $P < .05$.

All the glucose metabolism indices decreased in both groups postintervention, with more significant reductions in the intervention group, indicating that liraglutide combined with dapagliflozin has a better glycemic-control effect.

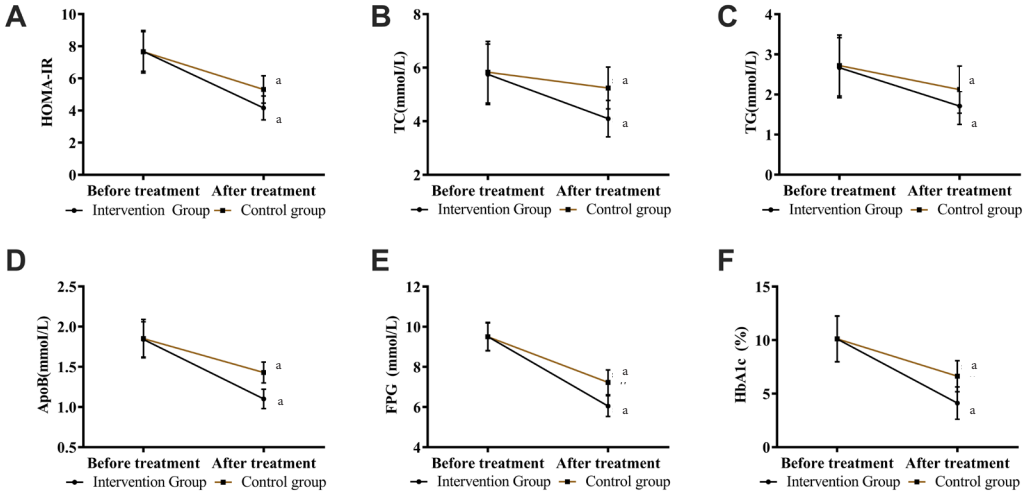
IFs

No significant differences existed in the levels of TNF-α (Figure 2A), IL-6 (Figure 2B), and hs-CRP (Figure 2C) between the groups at baseline ($P > .05$). Postintervention, the levels of the three inflammatory factors in the intervention group were all significantly lower than those in the control group ($P < .05$). In addition, the levels in both groups had decreased significantly postintervention compared with baseline ($P < .05$), which also indicated that the inflammatory response in both groups had been significantly alleviated postintervention, with more significant effects in the intervention group.

UA and MAU

The UA levels at baseline and postintervention in the intervention group were 609.56 ± 89.47 μmol/L and 164.21 ± 65.99 μmol/L, respectively, while those in the control group were 611.62 ± 88.17 μmol/L and 289.36 ± 76.55 μmol/L, respectively. No differences in UA existed between the groups at baseline. Postintervention, the UA levels had decreased in both groups but were significantly lower in the intervention group compared with the control group, with $P < .05$ (Figure 3A).

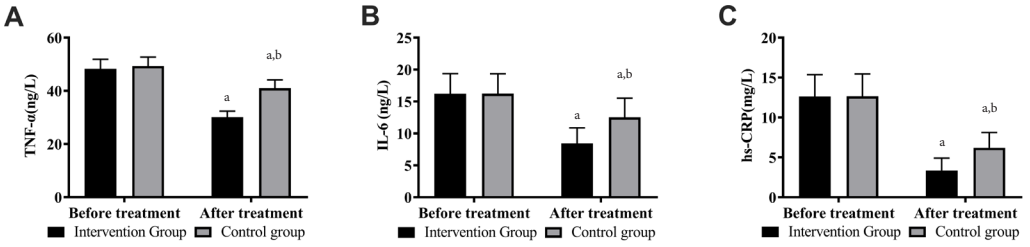
Figure 1. Glucolipid Metabolism. Figure 1A shows the HOMA-IR level, Figure 1B the TC level, Figure 1C the TG level, Figure 1D the ApoB level, Figure 1E the FPG level, and Figure 1F the HbA_{1c} level.



[a]$P < .05$, indicating significantly greater decreases postintervention in the intervention group compared to those in the control group

Abbreviations: HOMA-IR, homeostatic model assessment for insulin resistance; TC, serum total cholesterol; TG, triglycerides; ApoB, apolipoprotein-B; FPG, fasting blood glucose; HbA_{1c}, glycosylated hemoglobin.

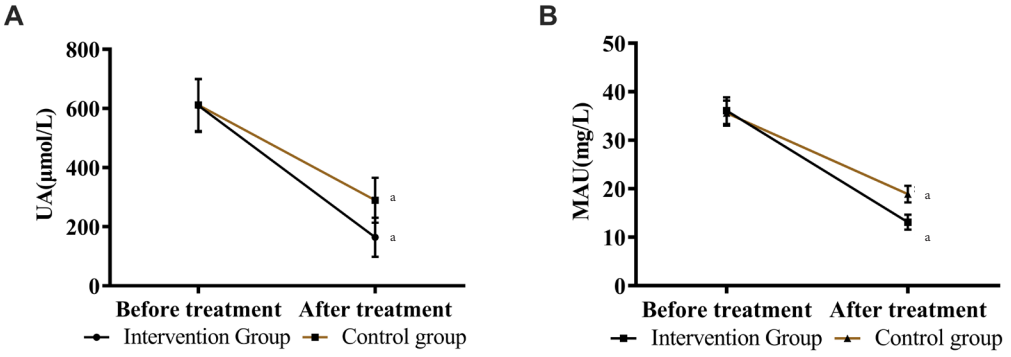
Figure 2. Levels of Inflammatory Factors. Figure 2A shows the TNF-α level, Figure 2B the IL-6 level, and Figure 2C the hs-CRP level.



[a]$P < .05$, indicating significantly lower levels postintervention as compared to baseline levels
[b]$P < .05$ indicating significantly lower levels postintervention in the intervention group as compared to those in the control group

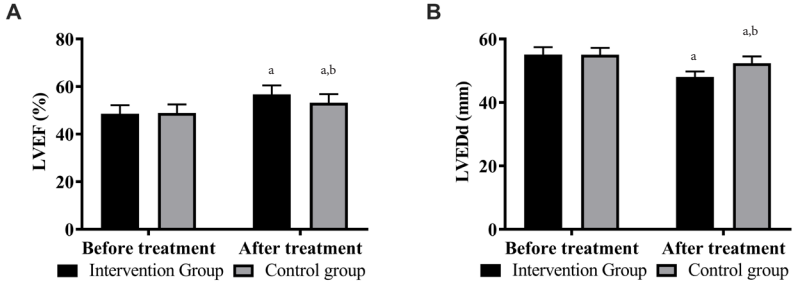
Abbreviations: TNF-α, tumor necrosis factor alpha; IL-6, interleukin-6; hs-CRP, high sensitivity C-reactive protein

Figure 3. Changes in Uric Acid (UA) and Microalbuminuria (MAU). Figure 3A shows the uric acid-level, and Figure 3B shows the microalbuminuria level.



[a]$P < .05$, indicating significantly lower levels postintervention in the intervention group as compared to the control group

Figure 4. LVEF and LVEDd Changes. Figure 4A shows the changes in LVEF, and Figure 4B shows the changes of LVEDd.

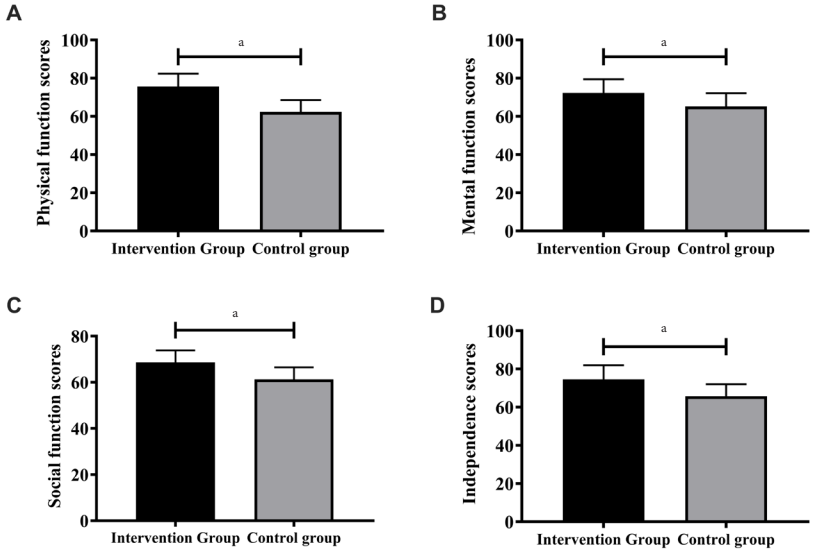


[a]$P < .05$, indicating significantly higher levels postintervention as compared to baseline levels

[b]$P < .05$ indicating significantly higher LVEF levels and lower LVEDd levels postintervention in the intervention group as compared to those of the control group

Abbreviations: LVEF, left ventricular ejection fraction; LVEDd, left ventricular end diastolic diameter.

Figure 5. Quality of Life Score.



[a]$P < .05$, indicating significantly higher levels postintervention in the intervention group as compared to those in the control group

The same change was observed in the MAU levels. No differences existed in the MAU between the groups at baseline. It had decreased in both groups postintervention and was significantly lower in the intervention group then that in the control group, with $P < .05$ (Figure 3B). These results suggest that the combination therapy of liraglutide and dapagliflozin may be better at improving the metabolic function of patients.

Cardiac Function

The LVEF of the intervention and control groups postintervention were 56.68 ± 3.81% and 53.21 ± 3.63%, respectively. Both were significantly higher than at baseline, but the LVEF level was significantly higher postintervention in the intervention group than that in the control group, with $P < .05$ (Figure 4A).

Similarly, no differences existed between the groups in the LVEDd at baseline. Postintervention, the LVEDd had decreased significantly in both groups, and the value in the intervention group, at 48.08 ± 1.67 mm, was significantly lower than that in the control group, at 52.38 ± 2.14 mm, with $P < .05$ (Figure 4B).

QoL

Postintervention, the scores for physical function, mental function, social function, and independence in the intervention group were 75.6 ± 6.8 (Figure 5A), 72.3 ± 7.1 (Figure 5B), 68.6 ± 5.2 (Figure 5C), and 74.61 ± 7.33 (Figure 5D), respectively. All were significantly higher than those in the control group ($P < .05$). Therefore, patients had a better prognosis for a higher QoL after therapy with liraglutide plus dapagliflozin.

DISCUSSION

The comparison of therapeutic efficacy in the current study revealed a statistically higher overall response rate in the intervention group (92.65%) compared with the control group (78.95%), and these results are supported by those of two previous studies.[31,32] The current research team suggests that liraglutide plus dapagliflozin for DM complicated with MS can achieve significant and exact, clinical therapeutic effects.

The indices for glycolipid metabolism, all decreased postintervention, with significantly lower levels in the intervention group. These results suggest that liraglutide plus dapagliflozin can improve glucolipid metabolism in patients by stimulating insulin secretion.

The current study showed no distinct differences in IFs between the groups at baseline, but the levels all decreased in both groups postintervention, with significantly lower levels in the intervention group. This suggests that liraglutide plus dapagliflozin has positive clinical-application value, because the combination therapy can reduce the release of IFs, alleviate patients' inflammatory reactions, and help to decrease the vascular endothelial function, with remarkably curative effects. At present, liraglutide and dapagliflozin have been widely used in clinical practice, and both have achieved remarkable results in the treatment of DM and related

complications.[33,34] The results of this study once again confirmed the excellent application value of liraglutide and dapagliflozin.

In the current study, the UA and MAU were both found to decrease in both groups postintervention, especially in the intervention group. This demonstrates that liraglutide plus dapagliflozin has great therapeutic potential in treating DM complicated with MS and has a positive effect on improving renal function of patients. We think it's dapagliflozin that played his role.The effect of SGLT2 is to reabsorb glucose in the renal tubules and urine into the blood.[35] Dapagliflozin is an SGLT2 inhibitor, which can hinder the occurrence of this process and promote the metabolism of glucose through the kidneys and urine.[36] However, previous studies have pointed out that the use of dapagliflozin may increase the possibility of urinary tract infections in patients, so it is necessary to pay attention to the dosage in practical application.[37]

Comparing the changes of heart function in the current study, the LVEF increased and LVEDd decreased in both groups postintervention, with greater changes in the intervention group. This indicates that liraglutide plus dapagliflozin can not only alleviate patients' clinical symptoms but also effectively improve their cardiac function, which further verifies the above results.

Finally, QoL was found to be obviously better in the intervention group postintervention, which reflects the clinical-application value of liraglutide plus dapagliflozin for DM complicated with MS.

The current study had some limitations. The exact mechanism of action of liraglutide plus dapagliflozin hasn't been determined, and because of the short period of the study, the current research team couldn't evaluate the effects of liraglutide plus dapagliflozin on patients' long-term prognosis.

CONCLUSIONS

Liraglutide plus dapagliflozin has highly therapeutic effect for patients with DM complicated with MS and can effectively reduce UA and MAU levels. The current research team will launch a more comprehensive analysis as soon as possible to obtain the most accurate results.

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AUTHORS' DISCLOSURE STATEMENT

The research team has no conflicts of interest associated with the study.

REFERENCES

1. Faselis C, Katsimardou A, Imprialos K, Deligkaris P, Kallistratos M, Dimitriadis K. Microvascular complications of type 2 diabetes mellitus. *Curr Vasc Pharmacol*. 2020;18(2):117-124. doi:10.2174/1570161117666190502103733
2. Zheng Y, Ley SH, Hu FB. Global aetiology and epidemiology of type 2 diabetes mellitus and its complications. *Nat Rev Endocrinol*. 2018;14(2):88-98. doi:10.1038/nrendo.2017.151
3. Shepard BD. Sex differences in diabetes and kidney disease: mechanisms and consequences. *Am J Physiol Renal Physiol*. 2019;317(2):F456-F462. doi:10.1152/ajprenal.00249.2019
4. Bonora E, Cataudella S, Marchesini G, et al; under the mandate of the Italian Diabetes Society. Incidence of diabetes mellitus in Italy in year 2018. A nationwide population-based study of the ARNO Diabetes Observatory. *Nutr Metab Cardiovasc Dis*. 2021;31(8):2338-2344. doi:10.1016/j.numecd.2021.04.017
5. Lehrke M, Marx N. Diabetes mellitus and heart failure. *Am J Med*. 2017;130(6S):S40-S50. doi:10.1016/j.amjmed.2017.04.010
6. Biondi B, Kahaly GJ, Robertson RP. Thyroid dysfunction and diabetes mellitus: two closely associated disorders. *Endocr Rev*. 2019;40(3):789-824. doi:10.1210/er.2018-00163
7. Cole JB, Florez JC. Genetics of diabetes mellitus and diabetes complications. *Nat Rev Nephrol*. 2020;16(7):377-390. doi:10.1038/s41581-020-0278-5
8. Harreiter J, Roden M. [Diabetes mellitus-Definition, classification, diagnosis, screening and prevention (Update 2019)]. *Wien Klin Wochenschr*. 2019;131(S1)(suppl 1):6-15. doi:10.1007/s00508-019-1450-4
9. Ansarimoghaddam A, Adineh HA, Zareban I, Iranpour S, HosseinZadeh A, Kh F. Prevalence of metabolic syndrome in Middle-East countries: meta-analysis of cross-sectional studies. *Diabetes Metab Syndr*. 2018;12(2):195-201. doi:10.1016/j.dsx.2017.11.004
10. Myers J, Kokkinos P, Nyelin E. Physical activity, cardiorespiratory fitness, and the metabolic syndrome. *Nutrients*. 2019;11(7):E1652. doi:10.3390/nu11071652
11. Di Pino A, DeFronzo RA. Insulin resistance and atherosclerosis: implications for insulin-sensitizing agents. *Endocr Rev*. 2019;40(6):1447-1467. doi:10.1210/er.2018-00141
12. Johnson L, Rayner B. A cross-sectional cohort study with microvascular complications in patients with type 2 diabetes with and without hypothyroidism. *Cardiovasc J Afr*. Jan/Feb 23 2020; 31(1):5-8.
13. Petersmann A, Muller-Wieland D, Muller UA, et al. Definition, classification, and diagnosis of diabetes mellitus. *Exp Clin Endocrinol Diabetes*. Dec 2019; 127(S 01):S1-S7. doi:10.1055/a-1018-9078
14. Kelly AS, Auerbach P, Barrientos-Perez M, et al; NN8022-4180 Trial Investigators. A randomized, controlled trial of liraglutide for adolescents with obesity. *N Engl J Med*. 2020;382(22):2117-2128. doi:10.1056/NEJMoa1916038
15. Li M, Yang Y, Jiang D, Ying M, Wang Y, Zhao R. Efficacy and safety of liraglutide versus sitagliptin both in combination with metformin in patients with type 2 diabetes: A systematic review and meta-analysis. *Medicine (Baltimore)*. 2017;96(39):e8161. doi:10.1097/MD.0000000000008161
16. Lin CH, Shao L, Zhang YM, et al. An evaluation of liraglutide including its efficacy and safety for the treatment of obesity. *Expert Opin Pharmacother*. 2020;21(3):275-285. doi:10.1080/14656566.2019.1695779
17. Capehorn MS, Catarig AM, Furberg JK, et al. Efficacy and safety of once-weekly semaglutide 1.0mg vs once-daily liraglutide 1.2mg as add-on to 1-3 oral antidiabetic drugs in subjects with type 2 diabetes (SUSTAIN 10). *Diabetes Metab*. 2020;46(2):100-109. doi:10.1016/j.diabet.2019.101117
18. O'Neil PM, Birkenfeld AL, McGowan B, et al. Efficacy and safety of semaglutide compared with liraglutide and placebo for weight loss in patients with obesity: a randomised, double-blind, placebo and active controlled, dose-ranging, phase 2 trial. *Lancet*. 2018;392(10148):637-649. doi:10.1016/S0140-6736(18)31773-2
19. Johnston R, Uthman O, Cummins E, et al. Canagliflozin, dapagliflozin and empagliflozin monotherapy for treating type 2 diabetes: systematic review and economic evaluation. *Health Technol Assess*. 2017;21(2):1-218. doi:10.3310/hta21020
20. Dhillon S. Dapagliflozin: A review in type 2 diabetes. *Drugs*. 2019;79(10):1135-1146. doi:10.1007/s40265-019-01148-3
21. Heerspink HJL, Stefánsson BV, Correa-Rotter R, et al; DAPA-CKD Trial Committees and Investigators. dapagliflozin in patients with chronic kidney disease. *N Engl J Med*. 2020;383(15):1436-1446. doi:10.1056/NEJMoa2024816
22. Heerspink HJL, Stefansson BV, Chertow GM, et al; DAPA-CKD Investigators. Rationale and protocol of the Dapagliflozin And Prevention of Adverse outcomes in Chronic Kidney Disease (DAPA-CKD) randomized controlled trial. *Nephrol Dial Transplant*. 2020;35(2):274-282. doi:10.1093/ndt/gfz290
23. Petrie MC, Verma S, Docherty KF, et al. Effect of dapagliflozin on worsening heart failure and cardiovascular death in patients with heart failure with and without diabetes. *JAMA*. 2020;323(14):1353-1368. doi:10.1001/jama.2020.1906
24. Wheeler DC, Stefánsson BV, Jongs N, et al; DAPA-CKD Trial Committees and Investigators. Effects of dapagliflozin on major adverse kidney and cardiovascular events in patients with diabetic and non-diabetic chronic kidney disease: a prespecified analysis from the DAPA-CKD trial. *Lancet Diabetes Endocrinol*. 2021;9(1):22-31. doi:10.1016/S2213-8587(20)30369-7
25. le Roux CW, Astrup A, Fujioka K, et al; SCALE Obesity Prediabetes NN8022-1839 Study Group. 3 years of liraglutide versus placebo for type 2 diabetes risk reduction and weight management in individuals with prediabetes: a randomised, double-blind trial. *Lancet*. 2017;389(10077):1399-1409. doi:10.1016/S0140-6736(17)30069-7
26. Green A, Callaway L, McIntyre HD, Mitchell B. Diagnosing and providing initial management for patients with Gestational Diabetes: what is the General Practitioner's experience? *Diabetes Res Clin Pract*. 2020;166:108290. doi:10.1016/j.diabres.2020.108290

27. Ha NT, Harris M, Preen D, Moorin R. Time protective effect of contact with a general practitioner and its association with diabetes-related hospitalisations: a cohort study using the 45 and Up Study data in Australia. *BMJ Open*. 2020;10(4):e032790. doi:10.1136/bmjopen-2019-032790
28. Santilli F, D'Ardes D, Guagnano MT, Davi G. Metabolic Syndrome: sex-related cardiovascular risk and therapeutic approach. *Curr Med Chem*. 2017;24(24):2602-2627. doi:10.2174/0929867324666170710121145
29. Ng A, Tam WW, Zhang MW, et al. IL-1beta, IL-6, TNF-alpha and CRP in elderly patients with depression or Alzheimer's disease: systematic review and meta-analysis. *Sci Rep*. 2018;8(1):12050. doi:10.1038/s41598-018-30487-6
30. Haraldstad K, Wahl A, Andenæs R, et al; LIVSFORSK network. A systematic review of quality of life research in medicine and health sciences. *Qual Life Res*. 2019;28(10):2641-2650. doi:10.1007/s11136-019-02214-9
31. Cicerello E. Uric acid nephrolithiasis: an update. *Urologia*. 2018;85(3):93-98. doi:10.1177/0391560318766823
32. Chen L, Dai L, Liu Y, Li X, Wang H. Yiqi Huoxue recipe regulates autophagy through degradation of advanced glycation end products via mTOR/S6K1/LC3 pathway in diabetic nephropathy. *Evid Based Complement Alternat Med*. 2021;2021:9942678. doi:10.1155/2021/9942678
33. Jain AB, Kanters S, Khurana R, Kissock J, Severin N, Stafford SG. Real-World Effectiveness Analysis of Switching From Liraglutide or Dulaglutide to Semaglutide in Patients With Type 2 Diabetes Mellitus: The Retrospective REALISE-DM Study. *Diabetes Ther*. 2021;12(2):527-536. doi:10.1007/s13300-020-00984-x
34. Nicholson MK, Ghazal Asswad R, Wilding JP. Dapagliflozin for the treatment of type 2 diabetes mellitus - an update. *Expert Opin Pharmacother*. 2021;22(17):2303-2310. doi:10.1080/14656566.2021.1953471
35. Jongs N, Greene T, Chertow GM, et al; DAPA-CKD Trial Committees and Investigators. Effect of dapagliflozin on urinary albumin excretion in patients with chronic kidney disease with and without type 2 diabetes: a prespecified analysis from the DAPA-CKD trial. *Lancet Diabetes Endocrinol*. 2021;9(11):755-766. doi:10.1016/S2213-8587(21)00243-6
36. Chertow GM, Vart P, Jongs N, et al; DAPA-CKD Trial Committees and Investigators. Effects of Dapagliflozin in Stage 4 Chronic Kidney Disease. *J Am Soc Nephrol*. 2021;32(9):2352-2361. doi:10.1681/ASN.2021020167
37. Inzucchi SE, Docherty KF, Køber L, et al; DAPA-HF Investigators and Committees. Dapagliflozin and the Incidence of Type 2 Diabetes in Patients With Heart Failure and Reduced Ejection Fraction: An Exploratory Analysis From DAPA-HF. *Diabetes Care*. 2021;44(2):586-594. doi:10.2337/dc20-1675