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ORIGINAL RESEARCH

Henagliflozin Increases Serum and Salivary Levels of High-Molecular-Weight Adiponectin in Patients with Type 2 Diabetes in the Community

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Purpose: To investigate Henagliflozin's effect on high-molecular-weight (HMW) adiponectin in serum and saliva of type 2 diabetes mellitus (T2DM) patients.

Patients and Methods: This study included 66 patients with T2DM consecutively recruited from two community health service stations in southeastern Shanxi Province between December 2023 and November 2024, along with 66 healthy individuals as the normal control group. T2DM patients with glycated hemoglobin A1c (HbA1c) >7% and without drug treatment received henagliflozin (10 mg once daily) for 12 weeks. The general data of the two groups before and after treatment were collected and the clinical indicators were detected, including body mass index (BMI), waist circumference, fasting plasma glucose (FPG), total cholesterol (TC), triglyceride (TG), high density lipoprotein cholesterol (HDL-C), etc. At the same time, the blood and salivary samples of the two groups were collected before and after treatment, and the levels of HMW adiponectin in serum and saliva were detected by ELISA. Statistical comparisons were performed using paired or unpaired t-tests for normally distributed variables and the Mann-Whitney U test for non-normally distributed ones. The correlation between serum and saliva HMW adiponectin levels was assessed using Spearman's rank correlation. Furthermore, stepwise linear regression was employed to identify factors affecting HMW adiponectin levels in serum and saliva.

Results: Compared with the healthy control group, the serum and salivary levels of HMW adiponectin were decreased in T2DM patients (4.10 (2.30,6.80) VS 3.70 (1.55,5.65), 2.35 (0.87,5.80) VS 1.80 (0.72,4.53), $P < 0.05$). T2DM patients treated with henggliflozin for 12 weeks exhibited significant increases in both serum and salivary HMW adiponectin levels (3.70 (1.55,5.65) VS 4.70 (2.65,8.60), 1.80 (0.72,4.53) VS 3.85 (1.88,10.33), $p < 0.05$). Furthermore, significant improvements were observed in multiple metabolic parameters, including reductions in DBP, BMI, TC and TG ($p < 0.05$). A weak but statistically significant correlation was found between serum and salivary adiponectin levels ($r = 0.210$, $R^2 = 0.044$; $p < 0.05$). In order to reveal the influence factors of adiponectin in serum and saliva, linear stepwise regression analysis showed that waist circumference was an independent risk factor for adiponectin in serum (95% CI: −0.087, −0.015; $P < 0.05$), and gender was an independent risk factor for adiponectin in saliva (95% CI: −4.663, −0.529; $P < 0.05$).

Conclusion: In our study, serum and salivary HMW adiponectin levels were decreased in patients with T2DM, and Sodium-glucose co-transporter-2 (SGLT2) inhibitors could improve serum and salivary HMW adiponectin levels after treatment, which is expected to be a major target for diabetes treatment.

Keywords: serum, saliva, high-molecular-weight adiponectin, HMW adiponectin, type 2 diabetes mellitus, sodium-glucose co-transporter-2 inhibitors

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Introduction

Type 2 diabetes mellitus (T2DM) is one of the common chronic complications, often accompanied by cardiovascular disease, obesity, dyslipidemia, etc.,[1] which brings a heavy burden to global human health and social development.[2] As of 2019, over 463 million people are estimated to be living with diabetes globally, and this is projected to reach 700.2 million by 2045.[3] Cellular dysfunction or increased hepatic glucose output and insulin resistance are important pathophysiological features of T2DM.[4] Persistent hyperglycemia can cause harmful complications.

Adiponectin is a secreted protein encoded by apM1 gene, which is specifically expressed in adipocytes. Its monomer is composed of 244 amino acid residues, and its molecular weight is 28kDa. Adiponectin has attracted wide attention due to its important protective physiological functions such as improving insulin sensitivity, anti-diabetes, anti-atherosclerosis, anti-inflammation and anti-cancer.[5] Adiponectin is secreted into the blood as a homotrimer, a disulfide bond dependent hexamer, and a high polymer in the form of 12–18 or higher aggregates. Among them the trimer 65kDa is low-molecular-weight (LMW) adiponectin, the hexamer 150kDa is middle-molecular-weight (MMW) adiponectin, and the 12–18 and higher polymeric forms are high-molecular-weight (HMW, 280–420kDa or higher) adiponectin, mainly in the form of HMW.[6] Studies have shown that adiponectin in the form of high molecular form has a protective effect in the process of cell metabolism. It is known that the effect of adiponectin on improving insulin sensitivity mainly depends on the form of HMW, and the improvement of insulin sensitivity caused by weight loss is mainly related to the increase of HMW adiponectin level.[7] The improvement of insulin resistance by thiazolidinedione derivatives is closely related to the increase of HMW,[8,9] the cardiovascular protective effect of adiponectin is also mainly dependent on the HMW form, only HMW can activate the NF-κB transcription factor, and the reduction of HMW is more relevant to the onset of coronary heart disease.[10] The imbalance of adiponectin secretion caused by visceral fat accumulation, especially the reduction of HMW, is the molecular basis connecting obesity with the occurrence and development of T2DM, metabolic syndrome and cardiovascular disease. Increasing HMW adiponectin levels has also become a new target for the development of drugs related to type 2 diabetes.

Sodium-glucose co-transporter-2 (SGLT2) inhibitor is a new type of hypoglycemic drug, which selectively acts on SGLT2 in the proximal renal tubule to inhibit glucose reabsorption and promote urinary glucose excretion.[11] SGLT2 inhibitors have significant advantages in improving glycated hemoglobin A1c (HbA1c) and fasting plasma glucose (FPG).[12] In addition, SGLT2 inhibitors have been shown to have weight loss[13] and cardiovascular protection.[14] It has some unique mechanisms that may affect the levels of adipocytokines in patients with T2DM.[15,16] Henagliflozin is the first novel SGLT2 inhibitor independently developed in China. Its molecular structure has been optimized through the introduction of an L-proline moiety and a fluorine atom, enhancing the drug's selectivity and stability toward the SGLT2 receptor. Saliva testing, as a non-invasive method, offers advantages such as simple collection, low cost, and good patient compliance, and has demonstrated significant potential in the long-term monitoring of diabetes in recent years. Current research on henagliflozin and adipokines has largely been confined to serum levels, and its effect on salivary adiponectin remains insufficiently explored. Therefore, we evaluated the changes of serum and salivary levels of HMW adiponectin in community T2DM patients after receiving henagliflozin, which may help to explain the relationship between type 2 diabetes and HMW adiponectin, reveal new drug targets, early prediction of related diseases, long-term efficacy monitoring and prognosis.

Materials and Methods

A total of 66 healthy volunteers, 66 newly diagnosed or diagnosed T2DM patients without drug treatment who underwent physical examination at two community health service centers from December 2023 to November 2024 were selected to participate in this study. (Figure 1) Henagliflozin treatment was initiated in patients with T2DM at a dose of 10 mg/day and continued for 3 months. Inclusion criteria for patients with T2DM: (1) All patients were diagnosed in accordance with the 1999 WHO diagnostic criteria for T2DM,[17] (2) the patients had complete clinical data and could cooperate to complete the study, (3) The patient's HbA1c was greater than 7%. Exclusion criteria for patients with T2DM: (1) patients with type 1 diabetes mellitus and other types of diabetes mellitus; (2) patients with diabetic ketoacidosis and diabetic hyperosmolar coma; (3) patients with urinary tract infection; (4) patients with severe organ dysfunction, severe infection and malignant tumor; (5) those with mental illness and other communication disorders; (6) patients who were unable to cooperate with the study. This study was approved by the Ethics Committee of the authors' affiliated hospital, and all patients signed informed consent.

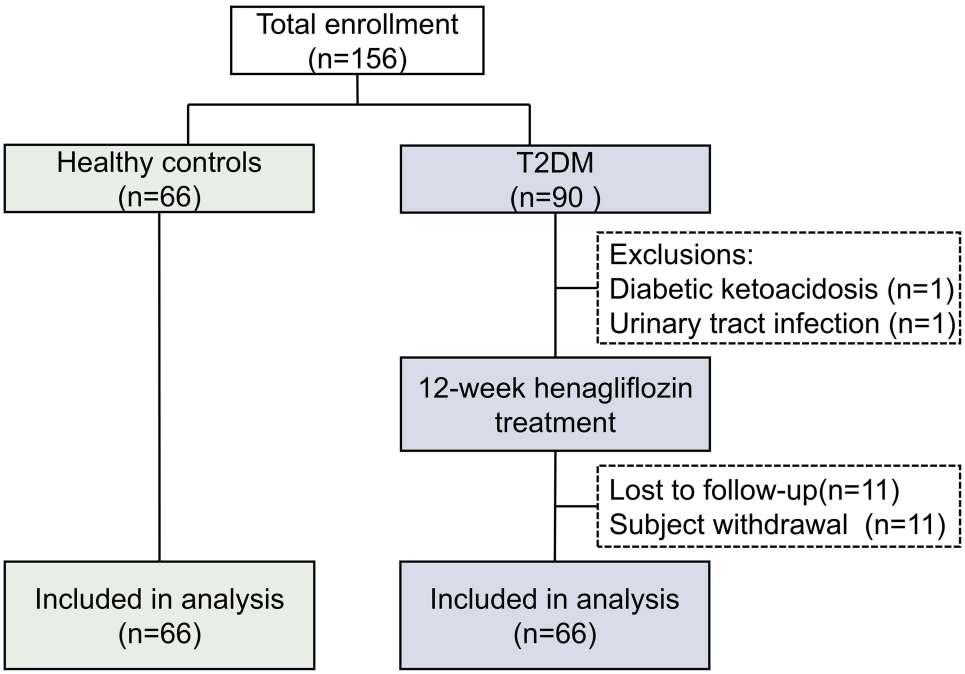

Figure 1 Flowchart of participant recruitment, screening, and follow-up.

Research Methods

The height, weight, abdominal circumference and blood pressure of the patients were measured on the day of examination, and the body mass index (BMI)= weight/height2(kg/m^2) was calculated. Salivette was used to collect fasting saliva. The Salivette filler was put into the mouth to chew for 2 minutes, centrifuged at 3000rbm for 15 minutes, and saliva was aspirated for the determination of HMW adiponectin. Fasting blood samples were obtained for the measurement of triglyceride (TG), total cholesterol (TC), and high-density lipoprotein cholesterol (HDL-C) (Beckman Automatic Biochemical analyzer, BK-200, USA), glycated hemoglobin A1c (HbA1c) was measured by High pressure liquid phase method. (Roche 501, Switzerland). All serum and saliva samples were stored at −80°C.

HMW Adiponectin Assay

After the samples were collected, the serum and salivary adiponectin concentrations were measured at one time by adipokines ELISA (The intra-assay CV was 5.6% and the inter-assay CV was 8.7%).

Statistical Treatment

SPSS 22.0 (IBM Corp., Armonk, NY, USA) was used for data analysis. The Q-Q plots were employed for normality testing. Measurement data with normal distribution were represented as $\bar{x} \pm s$, and comparison between groups was analyzed using the *t* test. Non-normal distribution measurement data were represented as M (Q1, Q3), and Mann Whitney *U*-test was used for comparison between the two groups. Categorical variables of count data were expressed as the number of cases (percentage), and χ^2-test was used for component comparison. Spearman's Rho correlation coefficients were calculated to examine relationships between serum and salivary HMW adiponectin. Stepwise linear logistic regression analysis controlling for the effect of covariates was further performed to ascertain the independent predictive value and impact of variables significantly correlated with serum and salivary HMW adiponectin levels. p value < 0.05 was considered to be statistically significant.

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Results

Baseline Characteristics

Compared with the healthy control group, although there was no statistical difference, the average age of T2DM patients had an increasing trend ($p > 0.05$), the levels of SBP, DBP, BMI, waist circumference, FPG, TC and TG were increased ($P < 0.05$), and the levels of HDL-C, serum adiponectin and salivary adiponectin were significantly decreased ($P < 0.05$). In the patients with T2DM, after Henagliflozin treatment for three months, DBP, BMI, waist circumference, FPG, TC and TG levels were improved compared with those before treatment ($P < 0.05$).

Effects of SGLT2 Inhibitors on the Levels of Serum and Salivary HMW Adiponectin Levels

At 12 weeks, the levels of serum and saliva HMW adiponectin levels were significantly increased in the Henagliflozin group ($p<0.05$) (Table 1). Serum HMW adiponectin levels are measured respectively in the healthy control group patients, during the identification of patients with type 2 diabetes and after 12 weeks of treatment as 4.10 (2.30, 6.80), 3.70 (1.55, 5.65), 4.70 (2.65,8.60)μg/mL (Table 1 and Figure 2). Salivary HMW adiponectin levels are measured respectively in the healthy control group patients, during the identification of patients with T2DM and after 12 weeks of treatment as 2.35 (0.87, 5.80), 1.80 (0.72, 4.53), 3.85 (1.88, 10.33)ng/mL (Table 1 and Figure 2).

Table 1 Comparison of the Clinical Characteristics of Patients

	Control (n=66)	T2DM (0.week) (n=66)	T2DM (12.weeks) (n=66)	P^a	P^b
Age (y)	34.64±10.95	53.51±8.88	53.51±8.88	0.262	
SBP (mmHg)	106.17±9.76	123.3±18.32	119.27±16.12	0.000	0.067
DBP (mmHg)	72.71±8.21	80.10±10.35	75.19±11.27	0.043	0.001
BMI (kg/m^2)	21.55±1.89	26.71±4.28	26.0±3.67	0.001	0.004
Waist (cm)	75.57±9.16	93.05±9.65	88.02±9.63	0.000	0.000
AST* (IU/L)	22.25(15.38,27.90)	37.73(29.9,45.0)	22.20(13.30,28.58)	0.000	0.000
ALT* (IU/L)	14.75(10.28,20.85)	22.90(15.15,33.50)	20.70(15.25,32.65)	0.000	0.406
TC (mmol/L)	3.58±6.31	6.31±1.59	4.16±0.97	0.000	0.000
TG*(mmol/L)	0.63(0.50,0.97)	1.65(1.03,2.46)	1.14(0.77,1.94)	0.000	0.049
HDL-C (mmol/L)	0.75±0.34	0.89±0.19	1.52±2.99	0.005	0.096
FPG (mmol/L)	4.98±0.62	7.36±2.04	7.22±1.84	0.000	0.000
Serum HMW adiponectin*(μg/mL)	4.10(2.30,6.80)	3.70(1.55,5.65)	4.70(2.65,8.60)	0.009	0.000
Saliva HMW adiponectin* (ng/mL)	2.35(0.87,5.80)	1.80(0.72,4.53)	3.85(1.88,10.33)	0.005	0.000

Notes: Data are presented as mean ± standard deviation (SD) or median (interquartile range). Control: Healthy control group. T2DM (0 week): Patients with type 2 diabetes at baseline, before Henagliflozin treatment. T2DM (12 weeks): The same cohort of T2DM patients after 12 weeks of Henagliflozin treatment. Statistical comparisons: * was determined using the Mann–Whitney *U*-test; all other significances were determined using paired or unpaired *t*-test. P^a: p-value for the comparison between the Control group and T2DM (0 week). P^b: p-value for the comparison between the T2DM (0 week) and T2DM (12 weeks).

Abbreviations: BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; AST, aspartate aminotransferase; ALT, alanine aminotransferase; TG, triglycerides; TC, total cholesterol; HDL-C, high-density lipoprotein cholesterol; FPG, fasting plasma glucose; HMW, High molecular weight.

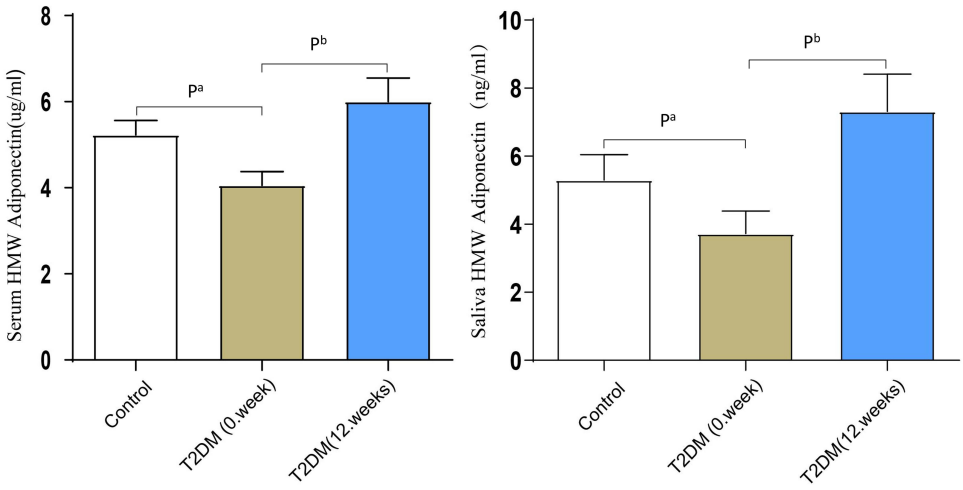

Figure 2 Serum HMW adiponectin levels and Salivary HMW adiponectin levels in the three groups. P^a: p-value for the comparison between the Control group and T2DM (0 week). P^b: p-value for the comparison between the T2DM (0 week) and T2DM (12 weeks).

Scatter Plot Demonstrating the Association Between Serum and Salivary HMW Adiponectin Levels

Spearman's Rho correlation between serum and salivary HMW adiponectin levels showed significant association (r = 0.210, p=0.018) (Figure 3).

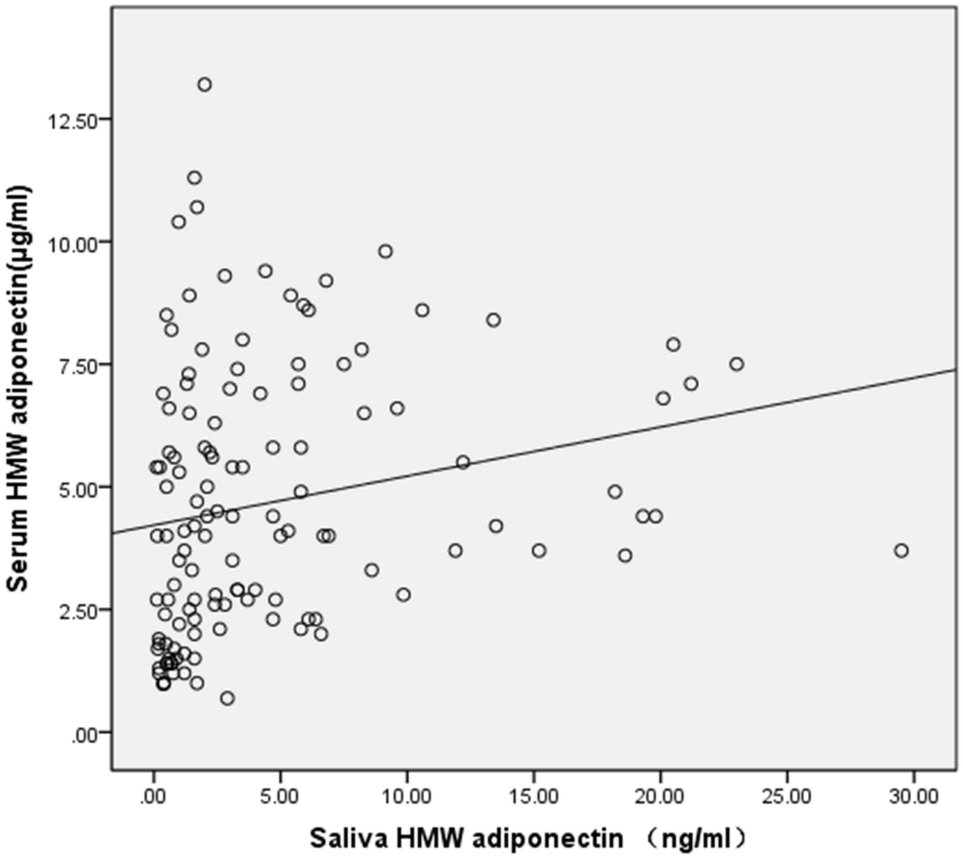

Figure 3 Scatter plot demonstrating the association between salivary and serum HMW adiponectin levels (R2=0.044).

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Table 2 Stepwise Linear Regression Analysis Identifying Independent Factors Associated with Serum HMW Adiponectin Levels

Variable	Regression Coefficient (β)	Standard Regression Coefficient (β')	t	P value	95% CI	
Intercept	8.955		5.772	<0.001	5.884	12.026
Waistline	−0.051	−0.244	−2.783	0.006	−0.087	−0.015

Notes: The dependent variable was serum HMW adiponectin. The initial independent variables included gender, age, SBP, DBP, TG, TC, waist circumference, BMI and FPG. Only variables retained in the final model at $p < 0.05$ are shown.

Table 3 Stepwise Linear Regression Analysis Identifying Independent Factors Associated with Salivary HMW Adiponectin Levels

Variable	Regression Coefficient (β)	Standard Regression Coefficient (β')	t	P value	95% CI	
Intercept	5.585		8.702	<0.001	4.314	6.857
Gender	−2.596	−0.224	−2.487	0.014	−4.663	−0.529

Notes: The dependent variable was serum HMW adiponectin. The initial independent variables included gender, age, SBP, DBP, TG, TC, waist circumference, BMI and FPG. Only variables retained in the final model at $p < 0.05$ are shown.

Multiple Linear Regression Analysis of Serum and Saliva Levels of HMW Adiponectin and Related Indicators

To identify factors influencing HMW adiponectin concentrations in serum and saliva, we performed stepwise linear regression analysis with serum HMW adiponectin as the dependent variable and gender, age, SBP, DBP, TG, TC, waist circumference, BMI and FPG as independent variables. The stepwise linear regression analysis revealed that waist circumference emerged as an independent risk factor for serum HMW adiponectin (95% CI: −0.087, −0.015; $P < 0.05$) (Table 2). With salivary high polymer adiponectin as the dependent variable and gender, age, SBP, DBP, TG, TC, waist circumference, BMI and FPG as independent variables, the results of stepwise linear regression showed that gender was an independent risk factor for salivary HMW adiponectin ((95% CI: −4.663, −0.529; $P < 0.05$) (Table 3).

Discussion

In recent years, the prevalence of T2DM has been increasing year by year, which seriously affects the quality of life of patients. It is imperative to detect diabetes early so that appropriate treatment can be started early. Therefore, by changing lifestyle on the one hand and exploring the relationship between serum and salivary biomarkers and type 2 diabetes on the other hand, to minimize the incidence and early mortality of T2DM. Decreased serum adiponectin level is one of the characteristic markers of T2DM. Obesity and insulin resistance are important factors leading to T2DM, and chronic metabolic diseases characterized by increased number or volume of adipocytes, or both.[18] The present study found that BMI, waist circumference, and insulin levels were higher in T2DM patients than in normal controls. The results were consistent with those of Gozel.[19]

Adipose tissue can secrete a variety of hormones or cytokines and participate in the process of lipid metabolism.[20] Adiponectin is an endogenous bioactive polypeptide or protein secreted by adipocytes, and it is also one of the most abundant protein products in adipose tissue gene expression. It is composed of four parts: carboxy-terminal globular domain, collagen fiber domain, amino-terminal non-helical domain and amino-terminal signal sequence. The globular domain is the active site of adiponectin. When adiponectin circulates in vivo, it exists in the form of full-length protein and C-terminal globular domains formed by proteolysis. The latter may have enhanced biological activity than the former. There are trimer, hexamer, multimer and other forms in plasma, most of which are high molecular mass multimers.[6] Studies have shown that adiponectin, as a specific polypeptide, is different from other adipocytokines

such as leptin, and the serum concentration of adiponectin in patients with T2DM is significantly lower than that in the control population.[21] However, HMW adiponectin is the more active form of the protein, and it has been found in population surveys that plasma levels of HMW adiponectin are associated with parameters of glucose homeostasis in the body.[22] Notably, the ratio of HMW adiponectin to total adiponectin in plasma correlates much more with blood glucose and insulin levels than with total adiponectin, suggesting that changes in plasma HMW adiponectin levels are more associated with insulin resistance than changes in plasma total adiponectin levels. Studies have reported that HMW adiponectin and HMW/ total adiponectin ratio are more advantageous in the prediction of T2DM and MS.[23] Our results showed that the level of adiponectin in saliva was lower than its corresponding level in serum, indicating that there is a clear difference between adiponectin in saliva and serum circulation. Compared with the normal control group, the levels of HMW adiponectin in serum and saliva were decreased in the T2DM group. The reason is that in the diabetes group, the BMI and waist circumference of obese people increased. Therefore, it is considered that the correlation between serum adiponectin level and obesity is mainly manifested in visceral adipose tissue rather than subcutaneous adipose tissue. The reduction of adiponectin levels in the systemic circulation through genetic mutations or environmental factors has been shown to contribute to the development of diabetes. Meanwhile, in vitro studies have shown that cultured visceral adipocytes secrete more adiponectin than subcutaneous adipocytes.[24]

SGLT2 inhibitors can increase the utilization of white adipose tissue and enhance the consumption of adipose tissue, thereby promoting the synthesis and release of adiponectin by adipose tissue.[25] In this study, we found that SGLT2 inhibitor treatment increased the level of HMW adiponectin in serum and saliva. At the same time, waist circumference, BMI and blood glucose were decreased compared with those before treatment. Our study also found a statistically significant correlation between salivary HMW adiponectin and serum HMW adiponectin levels ($p < 0.05$), suggesting that the increase in both serum and salivary HMW adiponectin following 12 weeks of henagliflozin treatment may contribute to the improvement of type 2 diabetes.[22] However, the strength of the association between serum and salivary HMW adiponectin levels was limited ($R^2 = 0.044$), which may be attributed to the fact that salivary adiponectin levels are influenced not only by circulating adiponectin concentrations but also by other factors such as salivary flow rate and the local oral immune environment. Therefore, salivary measurement cannot currently fully replace serum measurement for clinical decision-making. Associations of serum and salivary adiponectin with age, waist circumference, and BMI have been reported, but no correlation between salivary adiponectin and BMI has been found.[26,27] Similar to our study, serum adiponectin was associated with waist circumference, and salivary adiponectin was not significantly associated with either age or BMI.

Little is known about the origin of adiponectin in saliva. Murrah VA et al[28] found that the permeability of salivary gland basement membrane increased in diabetic patients, which made the protein molecules in serum ultrafiltration into saliva secretion. Marchetti P et al[29] used physicochemical and radioimmunoassay techniques to confirm that insulin was transferred from blood to saliva by accumulation ultrafiltration. Carda et al[30] found that the parotid gland acini of patients with T2DM were rich in small lipid droplets, and there were also lipids in the interstitium, suggesting that adipocytokines in saliva may be secreted by adipocytes in the salivary glands. The present study found that salivary adiponectin levels were lower than the corresponding serum levels, indicating a distinct distribution pattern between the salivary and systemic circulatory systems. Although a certain correlation was observed between salivary and serum HMW adiponectin, supporting the possibility that salivary adiponectin may be derived partially from blood ultrafiltration and/or local synthesis, further fundamental research is warranted to conclusively elucidate the precise origin of adiponectin in saliva.

This study has several limitations. First, the relatively small sample size and short study duration (12 weeks), while sufficient to observe improvements in adiponectin levels and metabolic parameters following short-term Henagliflozin treatment in T2DM patients, are inadequate to evaluate the long-term sustainability of these effects. Second, the lack of a placebo or active comparator control group limits our ability to definitively attribute the observed metabolic improvements and changes in adiponectin levels solely to Henagliflozin treatment. Third, research on the detection of salivary adipocytokines is still in its early stages; methods for its measurement and its correlation with established standards require further refinement. Future studies should incorporate additional clinical parameters to better elucidate the mechanism of action of serum high-molecular-weight adiponectin.

Conclusions

Serum and salivary HMW adiponectin levels were decreased in patients with T2DM. Henagliflozin could increase these levels, suggesting that this pathway is expected to be a major target for diabetes treatment.

Ethics Statement

Approval of the research protocol: The research protocol is applicable by the ethics committee of the First Hospital of Shanxi Medical University (approval number: N.KYLL-2023-207).

Informed consent: All study participants provided informed written consent. The study kept patient data confidential and complied with the Declaration of Helsinki.

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Disclosure

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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