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Original Article

Effects of SGLT2 inhibitors and GLP-1 receptor agonists on glycemic variability, islet cell function, and insulin resistance in patients with type 2 diabetes mellitus and renal cell carcinoma

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Abstract: This study evaluated the effects of sodium-glucose co-transporter 2 inhibitors (SGLT2i) and glucagon-like peptide-1 receptor agonists (GLP-1RA) on glycemic control, islet cell function, and insulin resistance in type 2 diabetes mellitus (T2DM) patients with T1-stage renal cell carcinoma (RCC). A retrospective cohort of 175 patients was divided into a control group receiving SGLT2i monotherapy (n = 84) and an observation group receiving combination therapy with SGLT2i and GLP-1RA (n = 91). Propensity score matching (PSM) was employed to balance baseline characteristics, resulting in 35 patients per group. After treatment, the observation group showed significant improvements in fasting plasma glucose (FPG), 2-hour postprandial glucose (2hPG), and glycated hemoglobin (HbA1c) compared to the control group ($P < 0.001$). Islet cell function markers, including fasting insulin and HOMA-IR, also improved significantly ($P < 0.001$). Renal function markers, such as serum creatinine, blood urea nitrogen, and urinary albumin excretion rate, were better in the observation group ($P < 0.05$). Multivariate analysis identified older age (OR = 7.434, P = 0.025), higher BMI (OR = 6.812, P = 0.003), and high-fat diet (OR = 0.044, P = 0.005) as independent risk factors for insulin resistance. The combined use of SGLT2i and GLP-1RA demonstrated superior efficacy in improving glycemic variability, insulin sensitivity, and renal function, highlighting its potential as an effective strategy for managing patients with T2DM and RCC.

Keywords: Type 2 diabetes mellitus, SGLT2 inhibitors, GLP-1 receptor agonists, insulin resistance, renal cell carcinoma

Introduction

Type 2 diabetes mellitus (T2DM), one of the most prevalent chronic metabolic diseases worldwide, poses a significant challenge to global health [1, 2]. According to data from the International Diabetes Federation (IDF), the number of diabetes patients reached 392 million by 2015, with T2DM accounting for the vast majority of cases [3]. The pathophysiology of T2DM primarily involves insulin resistance and the progressive decline in β-cell function [4]. Poor glycemic control is the most common clinical issue in T2DM patients. As the disease progresses, patients are subjected to higher risk of severe complications, such as cardiovascular disease, diabetic nephropathy, retinopathy, and neuropathy, profoundly impacting their quality of life and survival [5].

In recent years, the association between T2DM and renal cell carcinoma (RCC) has garnered considerable attention [6]. Diabetic patients, particularly those with long-standing poor glycemic control, have a significantly higher risk of developing RCC compared to the general population [7]. RCC, especially clear cell renal cell carcinoma (ccRCC), is the most common malignant kidney tumor with a high mortality rate [8]. According to the 2022 Global Cancer Statistics, there were approximately 430,000 new cases of RCC and 180,000 related deaths worldwide,

with ccRCC accounting for 70-80% of all RCC cases [9]. The relationship between diabetes and RCC is likely mediated by multiple mechanisms, including metabolic abnormalities caused by insulin resistance, direct renal damage from chronic hyperglycemia, and diabetes-related inflammation and oxidative stress [10]. Furthermore, recent studies suggest that T2DM may increase the risk of RCC by influencing endocrine regulation and promoting tumor growth and metastasis. These findings highlight the urgent need for effective diabetes management to prevent or delay diabetes-related complications.

Among the pharmacological options for T2DM, sodium-glucose co-transporter 2 inhibitors (SGLT2i) and glucagon-like peptide-1 receptor agonists (GLP-1RA) represent significant advances in recent years [11]. These two classes of drugs have demonstrated remarkable efficacy in glycemic control and metabolic improvements, showing potential in preventing diabetes-related complications [12]. SGLT2i can lower blood glucose by inhibiting SGLT2 proteins in the proximal renal tubules, reducing glucose reabsorption, and promoting glucose excretion [13]. Additionally, SGLT2i have been shown to provide benefits such as weight reduction, cardiovascular health improvement, and renal protection, particularly in the management of diabetic nephropathy [14, 15]. These effects make SGLT2i a vital treatment option, especially for diabetic patients with renal impairment [14, 15]. On the other hand, GLP-1RA mimic the action of GLP-1, enhancing insulin secretion and suppressing glucose production, thereby achieving glycemic control [16]. Moreover, GLP-1RA promote satiety, reduce food intake, and aid in weight management while also showing potential in cardiovascular health improvement [6]. Despite their distinct mechanisms of action, both drug classes have shown therapeutic benefits for T2DM patients and may impact diabetes-related complications, including RCC [10]. As research into their mechanisms and clinical effects continues to evolve, these drugs are likely to play a prominent role in diabetes management, particularly in reducing complications and improving patients' quality of life.

This study aimed to evaluate the clinical efficacy of SGLT2i and GLP-1RA in T2DM patients, focusing on their effects on glycemic variability, islet cell function, and insulin resistance. By conducting a retrospective analysis of clinical data, this study seeks to compare pre- and post-treatment glycemic control, insulin resistance levels, and clinical outcomes in RCC patients, providing valuable evidence for clinical practice and further validating the efficacy and safety of these two drug classes.

Materials and methods

Study population

This retrospective cohort study was conducted at First Hospital of Hebei Medical University, with patient data collected from February 2020 to March 2024. The study protocol was approved by the institutional ethics committee of First Hospital of Hebei Medical University. A total of 244 patients who met the inclusion criteria were initially identified, and after screening, 175 patients were included in the study (control group: 84; observation group: 91) (**Figure 1**).

Inclusion and exclusion criteria

Inclusion criteria: 1. Diagnosis of T2DM according to the criteria of the IDF [17]. 2. Concurrent diagnosis of T1-stage RCC (ccRCC or other subtypes), confirmed by imaging (CT, MRI) and/or pathological examination. 3. Age between 18 and 80 years. 4. Complete clinical data available. 5. Life expectancy > 12 months.

Exclusion criteria: 1. Severe comorbidities such as advanced cardiovascular disease or hepatic/renal failure. 2. Pregnant or lactating women. 3. History of severe allergic reactions or intolerance to study medications. 4. Concurrent use of other medications affecting glucose metabolism during the study period. 5. Other serious endocrine or metabolic disorders.

Treatment protocols

Preoperative glycemic control: One week before surgery, patients were prescribed with preoperative blood glucose control regimen. The control group received oral dapagliflozin tablets (National Drug Approval Number: HJ20170119, 10 mg per tablet), a SGLT2i, at a dosage of 10 mg, once every morning, along with dietary adjustments and exercise interventions. These

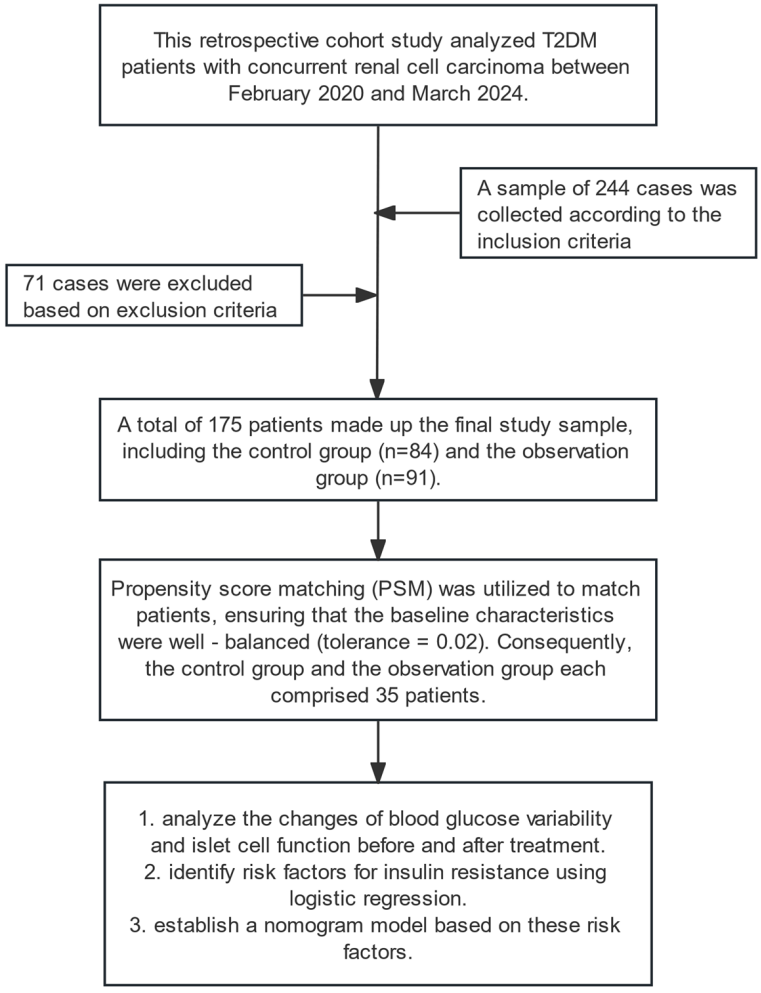

Figure 1. Study flow chart.

interventions were continue for 1 week until the day of surgery. The observation group received additional liraglutide injection (National Drug Approval Number: SJ20190022, 1.5 mg/0.5 mL), a GLP-1RA, at a dosage of 1.5 mg, administered subcutaneously once a week.

Laparoscopic surgery: The surgery was performed under general anesthesia with endotracheal intubation. The patients were placed in a lateral position on the healthy side, with the waist elevated to facilitate the surgical procedure. The first operative port was located 2 cm above the iliac crest along the mid-axillary line. The lumbar fascia and muscle layers were separated bluntly, and after carbon dioxide was insufflated to establish pneumoperitoneum, a laparoscope was inserted. The second and third operative ports were placed 1-2 cm below the 12th rib at the junction of the posterior axillary line and anterior axillary line to facilitate the use of surgical instruments. Under laparoscopic guidance, an ultrasonic scalpel was used to separate and clamp the proximal and distal ends of the ureter before cutting it. Subsequently, the renal vein, renal artery, and renal hilum were dissected, and the associated blood vessels were severed with an ultrasonic scalpel. The incision was then enlarged to 5-6 cm to remove the kidney through the first operative port. Postoperatively, the patients were transferred to the recovery room, where their closely monitored for vital signs, administered pain management and infection prevention treatments, and regularly checked for renal function.

Data collection

Data were retrospectively extracted from the electronic medical records. Collected clinical and demographic data included:

Basic characteristics: age, sex (male/female), body mass index (BMI, categorized as 18-22.9, 23-24.9, and ≥ 25 kg/m^2), history of hypertension (yes/no), family history of diabetes (yes/no), average monthly income (< 3000, 3000-4499, ≥ 4500), marital status (married/unmarried/other), educational level (up to high school/college/postgraduate or higher), smoking history (yes/no), alcohol consumption (yes/no), regular physical activity (yes/no), high-fat diet (yes/no), and cancer type (ccRCC/papillary RCC/other).

Laboratory indices: systolic blood pressure (SBP), diastolic blood pressure (DBP), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), fasting plasma glucose (FPG), 2-hour postprandial glucose (2hPG), glycated hemoglobin (HbA1c), fasting

insulin (FI), and homeostasis model assessment of insulin resistance (HOMA-IR).

Laboratory measurements

1. FPG and 2hPG were measured using a Roche Cobas c311 glucose analyzer (Roche Diagnostics, Switzerland) following international standard enzymatic methods. 2. HbA1c was determined using a Bio-Rad D-10 high-performance liquid chromatography system (Bio-Rad, USA) based on ion-exchange chromatography. 3. FI was measured using the Abcam Human Insulin ELISA Kit (Abcam, USA). 4. HOMA-IR was calculated using FI and FPG values based on the standard formula. 5. Renal function indicators, including serum creatinine (Scr), blood urea nitrogen (BUN), and urinary albumin excretion rate (UAER), were monitored using a fully automated biochemical analyzer (Beckman Coulter AU5800). These parameters were assessed at three time points: before treatment, preoperatively, and 1 week postoperatively.

Follow-up

Patients were followed up periodically for six months after treatment initiation, and all participants underwent in-clinic assessments at the six-month follow-up visit.

Propensity score matching (PSM)

To minimize baseline differences between the control and observation groups, PSM was employed. PSM reduced potential confounding factors and improved the reliability and comparability of the study results. Patients in the observation and control groups with similar demographic and clinical characteristics were matched with a tolerance of 0.02 for propensity scores. After matching, 35 patients from each group were included in the final analysis, ensuring balanced baseline characteristics.

Outcome measures

1. Comparison of baseline characteristics before and after PSM. 2. Analysis of changes in glycemic variability and islet cell function before and after treatment (pre- and post-PSM). 3. Identification of risk factors for insulin resistance (defined as HOMA-IR ≥ 2.7) using logistic regression analysis [18]. 4. Development of a nomogram model based on identified risk factors.

Statistical analysis

Data analysis was conducted using SPSS 26.0 and R 4.3.3 software.

Normality assessment: The Shapiro-Wilk test was used to evaluate the normality of continuous variables.

Continuous variables: Normally distributed variables were presented as mean ± standard deviation (SD) and compared using an independent-samples t-test. Non-normally distributed variables were expressed as median (interquartile range) and compared using the Mann-Whitney U test.

Categorical variables: Categorical variables were presented as frequencies and percentages, and compared using the Chi-square test.

Repeated Measures Analysis: For repeated measures, repeated measures analysis of variance (ANOVA) was conducted, followed by post hoc Bonferroni correction to adjust for multiple comparisons.

PSM analysis: PSM analysis was performed using R packages MatchIt, optmatch, and cobalt.

Logistic regression: Multivariate logistic regression was used to identify factors associated with insulin resistance.

Nomogram development: A nomogram model was constructed and visualized using the rms package in R.

Significance threshold: All statistical tests were two-sided, with $P < 0.05$ considered statistically significant.

Results

Comparison of baseline characteristics

We first compared the baseline characteristics of patients in the control group (n = 84) and the observation group (n = 91). The results showed certain differences between the two groups. The mean age of the observation group was significantly lower than that of the control group (P

= 0.002). However, there were no significant differences in the distribution of variables such as sex, BMI, history of hypertension, family history of diabetes, average monthly income, marital status, education level, smoking history, alcohol consumption, and high-fat diet, with *P*-values all greater than 0.05. Additionally, regular physical activity showed significant differences between the groups (P = 0.004), with a higher proportion of patients in the observation group engaging in regular exercise. In summary, most variables showed no significant differences, and only age and regular physical activity reached statistical significance (**Table 1**).

Comparison of blood glucose changes

We compared the changes in blood glucose levels between the control and observation groups at three time points: before treatment, 1 day before surgery, and 1 week postoperatively. Before treatment, there were no significant differences in FPG, 2hPG, or HbA1c between the two groups (P = 0.625, 0.204 and 0.925, respectively). However, 1 day before surgery and 1 week after surgery, the observation group showed significantly better improvement in FPG and 2hPG compared to the control group. The FPG and 2hPG levels in the observation group were significantly lower than those in the control group (P < 0.001 for both). Additionally, the post-treatment HbA1c levels in the observation group were significantly lower than those in the control group (P < 0.001) (**Figure 2**).

Changes in islet cell function

This study compared the changes in islet cell function of patients before medication, 1 day before surgery, and 1 week after surgery. Before treatment, there was no statistically significant difference in FI and HOMA-IR values between the control and observation groups (P = 0.124 and P = 0.583, respectively). However, 1 day before surgery and 1 week after surgery, the observation group showed significantly greater improvement in FI levels and HOMA-IR values compared to the control group. Specifically, 1 day before surgery and 1 week after surgery, the FI levels in the observation group were significantly higher than those in the control group (P < 0.001), while HOMA-IR values were significantly lower than those in the control group (P < 0.001) (**Figure 3**).

Changes in kidney function

This study compared the changes in kidney function levels between the control and observation groups before medication, 1 day before surgery, and 1 week after surgery. Before treatment, there were no significant differences in Scr, BUN, and UAER between the two groups (*P* values were 0.939, 0.426, and 0.568, respectively). However, 1 day before surgery and 1 week after surgery, the observation group showed significantly better improvements in Scr, BUN, and UAER. Scr, BUN, and UAER were significantly lower in the observation group than in the control group (P < 0.001) (**Figure 4**).

Comparison of blood glucose, islet cell function, and kidney function in postoperative insulin resistance patients

One week after surgery, 2hPG, HOMA-IR, Scr, and BUN showed significant differences between the insulin resistance group and the non-resistance group. Specifically, 2hPG was significantly higher in the insulin resistance group than in the non-resistance group (P = 0.014). HOMA-IR was significantly higher in the insulin resistance group (P < 0.001). Scr and BUN levels were significantly higher in the insulin resistance group (P < 0.001). These results indicate that insulin resistance is closely related to blood glucose regulation, insulin signaling pathways, and changes in kidney function. However, there were no significant differences in FPG, HbA1c, FIns, and UAER between the two groups (P > 0.05) (**Table 2**).

Comparison of baseline data between postoperative insulin resistance and non-resistance patients

This study compared the baseline data between insulin resistance and non-resistance groups. In terms of treatment regimen, the proportion of patients in the observation group with insulin resistance was significantly higher than that in the non-resistance group (P = 0.009). The average age of the insulin resistance group was significantly higher than that of the non-resistance group (P < 0.001). BMI distribution differed significantly between the two groups (P < 0.001), with the insulin resistance group having a significantly higher proportion of patients with BMI ≥ 25, while the non-resistance group had a higher proportion of patients in the BMI range

Table 1. Baseline characteristics of patients

Variables	Total	Control Group (n = 84)	Observation Group (n = 91)	Statistic	*P*-Value
Age (years)	62.32±7.55	64.18±7.01	60.60±7.67	-3.209	0.002
Sex				2.768	0.096
Male	107	46	61		
Female	68	38	30		
BMI (kg/m^2)				1.656	0.437
18-22.9	47	26	21		
23-24.9	74	35	39		
≥ 25	54	23	31		
History of Hypertension				0.079	0.778
Yes	37	17	20		
No	138	67	71		
Family History of Diabetes				0.051	0.821
Yes	64	30	34		
No	111	54	57		
Average Monthly Income				0.25	0.882
≤ 2999	84	39	45		
3000-4499	54	26	28		
≥ 4500	37	19	18		
Marital Status				3.573	0.168
Married	148	67	81		
Single	16	9	7		
Other	11	8	3		
Education Level				5.053	0.08
≤ High School	60	35	25		
College	79	31	48		
≥ Postgraduate	36	18	18		
Smoking History				0.012	0.913
Yes	93	45	48		
No	82	39	43		
Alcohol Consumption				3.331	0.068
Yes	55	32	23		
No	120	52	68		
Regular Physical Activity				8.484	0.004
Yes	63	21	42		
No	112	63	49		
High-Fat Diet				1.008	0.315
Yes	127	58	69		
No	48	26	22		
Cancer Type				0.334	0.846
Clear Cell Renal Carcinoma	143	70	73		
Papillary Renal Carcinoma	19	8	11		
Other	13	6	7		
SBP (mmHg)	136.79±14.87	138.20±14.20	135.48±15.43	-1.21	0.228
DBP (mmHg)	80.60±8.46	79.40±7.56	81.70±9.12	1.808	0.072
HDL (mmol/L)	1.026±0.267	1.011±0.215	1.041±0.307	0.741	0.46
LDL (mmol/L)	3.251±0.702	3.299±0.702	3.207±0.702	-0.873	0.384

Note: BMI, Body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

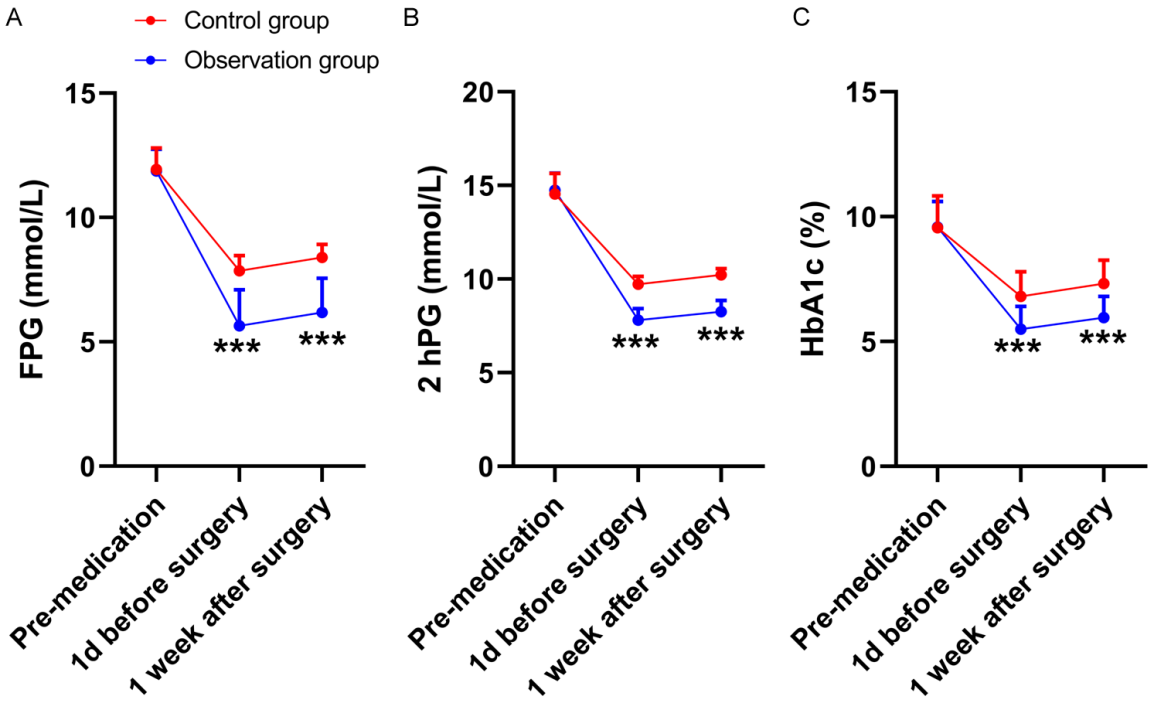

Figure 2. Blood glucose level changes before treatment, 1 day before surgery, and 1 week after surgery. A. Changes in FPG levels. B. Changes in 2hPG levels. C. Changes in HbA1c levels. Note: FPG, Fasting plasma glucose; 2Hpg, 2-hour postprandial glucose; HbA1c, glycated hemoglobin. ***P < 0.001.

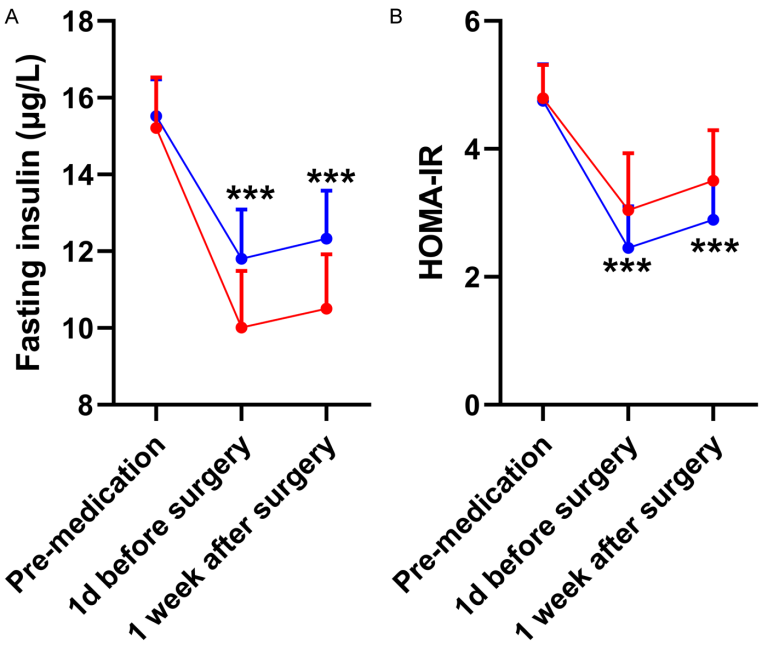

Figure 3. Beta-cell function changes. A. Changes in fasting insulin levels. B. Changes in HOMA-IR values. Note: HOMA-IR. Homeostasis model assessment of insulin resistance. ***P < 0.001.

of 18-22.9. There were also significant differences in the proportions of patients engaging in regular exercise (P < 0.001) and consuming a high-heat diet (P < 0.001). Regarding laboratory indicators, only the 2hPG (P = 0.022) and FI (P = 0.036) showed significant differences. Other factors such as gender, hypertension history, family history of diabetes, income level, marital status, education level, smoking history, drinking history, and other test indicators showed no significant differences (P > 0.05) (**Table 3**).

Independent risk factors for insulin resistance

Multivariate logistic regression analysis was used to assess the independent risk factors for insulin resistance. The results showed that treatment regimen, age, pre-treatment 2hPG, BMI, regular exercise, and high-heat diet were significant influencing factors for

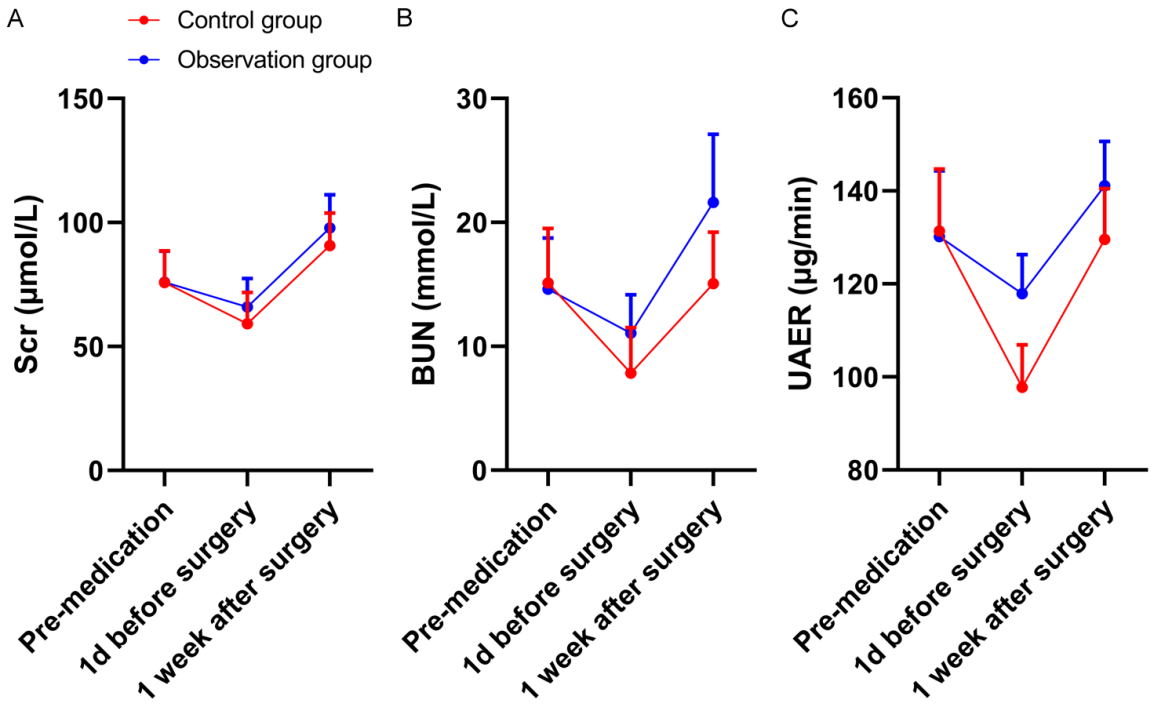

Figure 4. Kidney function changes. A. Changes in Scr levels. B. Changes in BUN levels. C. Changes in UAER levels. Note: Scr, Serum creatinine; BUN, blood urea nitrogen; UAER, urinary albumin excretion rate.

Table 2. Comparison of blood glucose, islet cell function and renal function measures between patients with or without insulin resistance

Index	Total	Resistant Group (n = 135)	Non-Resistant Group (n = 40)	Statistic	*P*-Value
FPG 1 week after surgery	7.74 [6.09, 8.47]	7.88 [6.25, 8.50]	7.00±1.48	1.473	0.141
2hPG 1 week after surgery	9.15 [8.34, 10.19]	9.78 [8.41, 10.25]	8.61 [8.29, 9.84]	2.459	0.014
HbA1c 1 week after surgery	6.61±1.12	6.65±1.08	6.48±1.24	0.763	0.448
Fasting insulin 1 week after surgery	11.45±1.61	11.51±1.64	11.24±1.52	0.97	0.336
HOMA-IR 1 week after surgery	3.18±0.76	3.38 [3.02, 3.87]	2.34 [1.99, 2.55]	9.594	< 0.001
Src 1 week after surgery	94.07±13.75	96.31±13.58	86.54±11.59	4.495	< 0.001
BUN 1 week after surgery	18.20±5.85	19.14±5.77	15.02±4.98	4.429	< 0.001
UAER 1 week after surgery	136.33±10.87	137.00±10.78	134.04±10.98	1.504	0.137

Note: FPG, Fasting plasma glucose; 2hPG, 2-hour postprandial glucose; HbA1c, glycated hemoglobin; HOMA-IR, homeostasis model assessment of insulin resistance; Scr, serum creatinine; BUN, blood urea nitrogen; UAER, urinary albumin excretion rate.

Table 3. Comparison of baseline characteristics between insulin-resistant and non-resistant groups

Factor	Total	Resistant Group (n = 135)	Non-Resistant Group (n = 40)	Statistic	*P*-Value
Treatment Regimen				6.731	0.009
Observation Group	91 (52.00%)	63 (46.67%)	28 (70.00%)		
Control Group	84 (48.00%)	72 (53.33%)	12 (30.00%)		
Age (years)	62.32±7.55	63.81±7.58	57.30±4.88	-5.12	< 0.001
Sex				0.325	0.569
Male	107 (61.14%)	81 (60.00%)	26 (65.00%)		
Female	68 (38.86%)	54 (40.00%)	14 (35.00%)		

BMI (kg/m^2)				37.247	< 0.001
18-22.9	44 (25.14%)	20 (14.81%)	24 (60.00%)		
23-24.9	77 (44.00%)	63 (46.67%)	14 (35.00%)		
≥ 25	54 (30.86%)	52 (38.52%)	2 (5.00%)		
History of Hypertension				1.174	0.279
Yes	37 (21.14%)	31 (22.96%)	6 (15.00%)		
No	138 (78.86%)	104 (77.04%)	34 (85.00%)		
Family History of Diabetes				2.993	0.084
Yes	64 (36.57%)	54 (40.00%)	10 (25.00%)		
No	111 (63.43%)	81 (60.00%)	30 (75.00%)		
Average Monthly Income				1.19	0.552
≤ 2999	84 (48.00%)	63 (46.67%)	21 (52.50%)		
3000-4499	54 (30.86%)	41 (30.37%)	13 (32.50%)		
≥ 4500	37 (21.14%)	31 (22.96%)	6 (15.00%)		
Marital Status				1.148	0.563
Married	148 (84.57%)	113 (83.70%)	35 (87.50%)		
Single	16 (9.14%)	14 (10.37%)	2 (5.00%)		
Other	11 (6.29%)	8 (5.93%)	3 (7.50%)		
Education Level				1.568	0.457
≤ High School	60 (34.29%)	48 (35.56%)	12 (30.00%)		
College	79 (45.14%)	62 (45.93%)	17 (42.50%)		
≥ Postgraduate	36 (20.57%)	25 (18.52%)	11 (27.50%)		
Smoking History				0.072	0.789
Yes	93 (53.14%)	71 (52.59%)	22 (55.00%)		
No	82 (46.86%)	64 (47.41%)	18 (45.00%)		
Alcohol Consumption				0.049	0.825
Yes	55 (31.43%)	43 (31.85%)	12 (30.00%)		
No	120 (68.57%)	92 (68.15%)	28 (70.00%)		
Regular Physical Activity				15.804	< 0.001
Yes	63 (36.00%)	38 (28.15%)	25 (62.50%)		
No	112 (64.00%)	97 (71.85%)	15 (37.50%)		
High-Fat Diet				27.636	< 0.001
Yes	127 (72.57%)	111 (82.22%)	16 (40.00%)		
No	48 (27.43%)	24 (17.78%)	24 (60.00%)		
Cancer Type				2.632	0.268
Clear Cell Renal Carcinoma	143 (81.71%)	112 (82.96%)	31 (77.50%)		
Papillary Renal Carcinoma	19 (10.86%)	12 (8.89%)	7 (17.50%)		
Other	13 (7.43%)	11 (8.15%)	2 (5.00%)		
SBP (mmHg)	136.79±14.87	137.89±14.53	133.08±15.59	-1.81	0.072
DBP (mmHg)	80.60±8.46	80.48±8.41	81.00±8.71	0.34	0.735
HDL (mmol/L)	1.03±0.27	1.03±0.27	1.03±0.25	0.012	0.99
LDL (mmol/L)	3.25±0.70	3.28±0.68	3.14±0.76	-1.115	0.266
Pre-treatment FPG (mmol/L)	11.90±0.87	11.94±0.85	11.75±0.94	-1.198	0.233
Pre-treatment 2hPG (mmol/L)	14.65±1.01	14.55±1.00	14.97±0.99	2.328	0.021
Pre-treatment HbA1c (%)	9.57±1.15	9.64±1.18	9.34±0.99	-1.469	0.144
Pre-treatment Fasting Insulin (μg/L)	15.49 [14.73, 16.07]	15.59 [14.81, 16.16]	15.20 [14.57, 15.78]	2.102	0.036
Pre-treatment HOMA-IR	4.77±0.55	4.74±0.55	4.88±0.51	1.415	0.159

Note: BMI, Body mass index; FPG, fasting plasma glucose; 2hPG, 2-hour postprandial glucose; HbA1c, glycated hemoglobin; HOMA-IR, homeostasis model assessment of insulin resistance; SBP, systolic blood pressure; DBP, diastolic blood pressure; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

insulin resistance. Specifically, compared to the control group, the risk of insulin resistance was significantly increased in the observation group (OR = 3.362, P = 0.048). With each additional year of age, the risk of insulin resistance increased by approximately 5.869 times (P =

Table 4. Variable assignment

Variable	Assignment
Treatment Regimen	Control group = 1, Observation group = 2
Age	≤ 60.5 = 1, > 60.5 = 2
Pre-treatment 2hPG	≤ 15.205 = 1, > 15.205 = 2
Pre-treatment Fasting Insulin	≤ 15.94 = 1, > 15.94 = 2
BMI	18-22.9 = 1, 23-24.9 = 2, ≥ 25 = 3
Regular Physical Activity	Yes = 1, No = 2
High-Fat Diet	Yes = 1, No = 2
Insulin Resistance	Yes = 1, No = 2

Note: BMI, Body mass index; 2hPG, 2-hour postprandial glucose.

Table 5. Multivariate logistic regression analysis

Variable	Estimate	SE	*P* Value	OR	Lower	Upper
Treatment Regimen	1.213	0.612	0.048	3.362	1.052	11.94
Age	1.770	0.584	0.002	5.869	1.949	19.781
Pre-treatment 2hPG	-1.446	0.608	0.017	0.235	0.067	0.755
Pre-treatment Fasting Insulin	0.650	0.762	0.394	1.915	0.460	9.676
BMI	2.114	0.478	< 0.001	8.284	3.522	23.461
Regular Physical Activity	1.555	0.593	0.009	4.736	1.542	16.257
High-Fat Diet	-2.671	0.651	< 0.001	0.069	0.017	0.230

Note: BMI, Body mass index; OR, odds ratio; SE, standard error.

0.002). For each unit increase in pre-treatment 2hPG, the risk of insulin resistance significantly decreased (OR = 0.235, P = 0.017). For each unit increase in BMI, the risk of insulin resistance significantly increased (OR = 8.284, P < 0.001), especially in patients with BMI ≥ 25. Regular exercise significantly reduced the risk of insulin resistance (OR = 4.736, P = 0.009), while a high-heat diet significantly increased the risk (OR = 0.069, P < 0.001) (see **Tables 4**, **5**).

Comparison of baseline data after PSM

This study used PSM to adjust the baseline data between the control and observation groups, with the goal of eliminating potential differences between the two groups. After applying a tolerance value of 0.02, 70 patients (35 per group) were successfully matched. After PSM matching, the baseline characteristics of the two groups were comparable, and the potential bias due to differences between the groups was eliminated. The major clinical features (such as age, BMI, pre-treatment blood glucose levels, etc.) were effectively controlled, providing a reliable basis for further analysis (**Figure 5**). Further analysis of the matched baseline data found no statistical differences between the groups (P > 0.05) (Table S1).

Comparison of blood glucose changes after PSM matching

This study compared the changes in blood glucose levels in the control and observation groups before medication, 1 day before surgery, and 1 week after surgery after PSM matching. Before treatment, there were no significant differences in FPG, 2hPG, and HbA1c between the two groups (*P* values were 0.535, 0.859 and 0.166, respectively). However, after treatment, the observation group showed significantly greater improvement in FPG, 2hPG, and HbA1c compared to the control group. Specifically, 1 day before surgery and 1 week after surgery, FPG levels were significantly lower in the observation group than in the control group (P < 0.001). 2hPG levels were also significantly lower in the observation group (P < 0.001). The HbA1c level was significantly lower in the observation group after treatment (P < 0.001) (**Figure 6**).

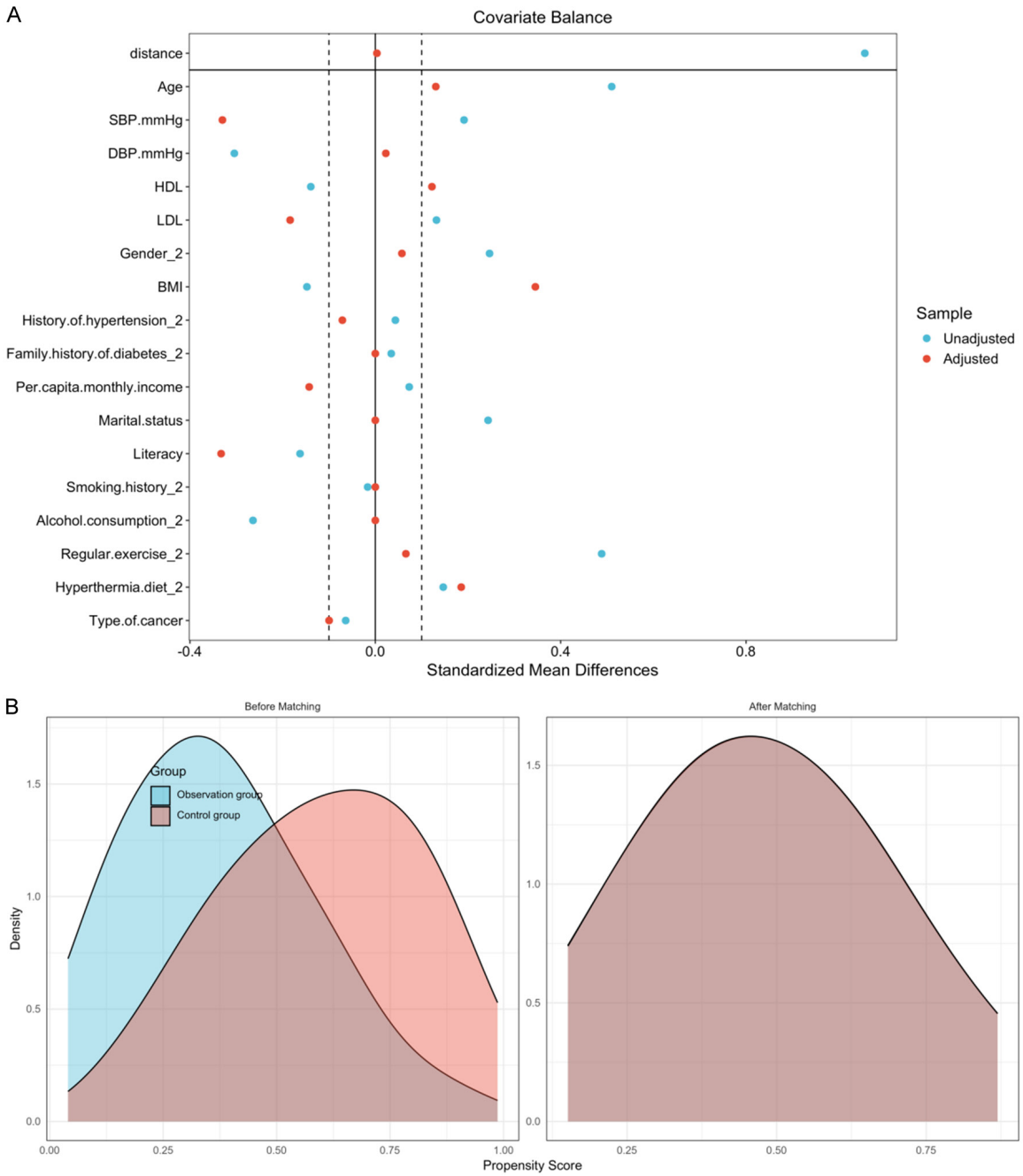

Figure 5. Baseline characteristics of matched patients in the control and observation groups after PSM. A. Differences in major clinical characteristics between the control and observation groups before PSM. B. Comparison of clinical characteristics between the two groups after PSM, showing no significant differences across variables post-matching. Note: PSM, Propensity score matching; SBP, Systolic blood pressure; DBP, diastolic blood pressure; HDL, high-density lipoprotein; LDL, low-density lipoprotein; BMI, body mass index; hyperthermia diet indicator (Hyperthermia diet_2). PSM was employed to adjust for baseline covariates between the control and observation groups. Standardized mean differences (SMDs) were used to assess the balance of covariates before and after matching.

Comparison of islet cell function after PSM matching

This study compared the changes in islet cell function (FI and HOMA-IR values) before medication, 1 day before surgery, and 1 week after surgery between the control and observation groups after PSM matching. Before treatment, there were no statistically significant differences in FI and HOMA-IR values (*P* values were 1

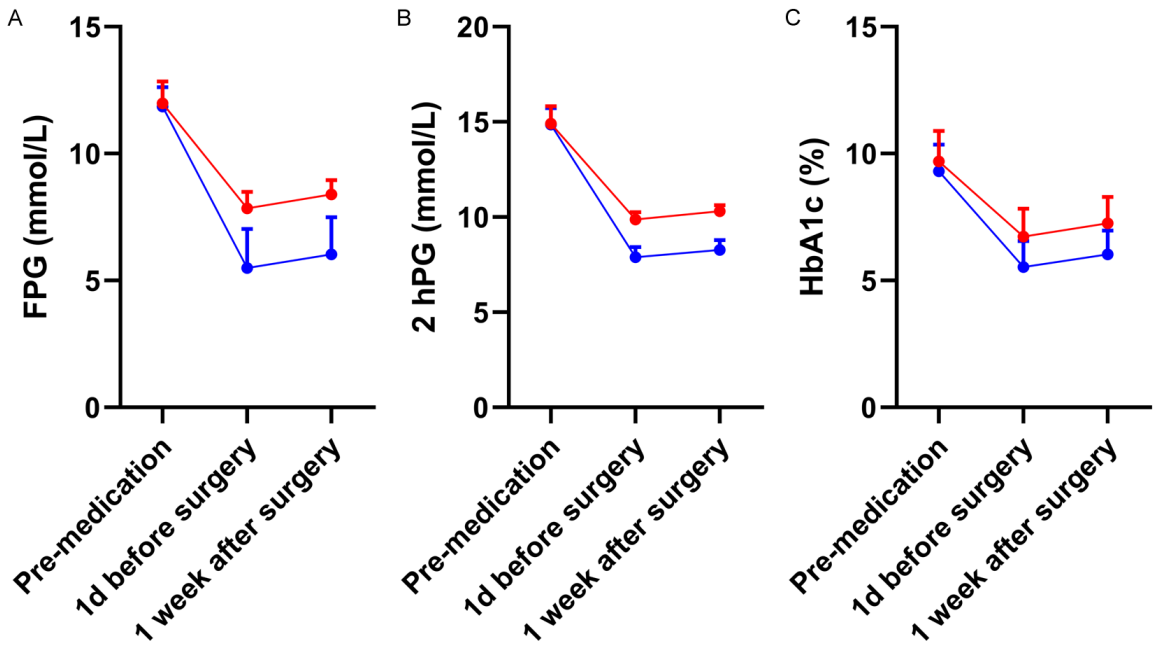

Figure 6. Changes in blood glucose levels (after PSM). A. Changes in FPG levels (after PSM). B. Changes in 2hPG levels (after PSM). C. Changes in HbA1c levels (after PSM). Note: FPG, Fasting plasma glucose; 2hPG, 2-hour postprandial glucose; HbA1c, glycated hemoglobin; PSM, propensity score matching.

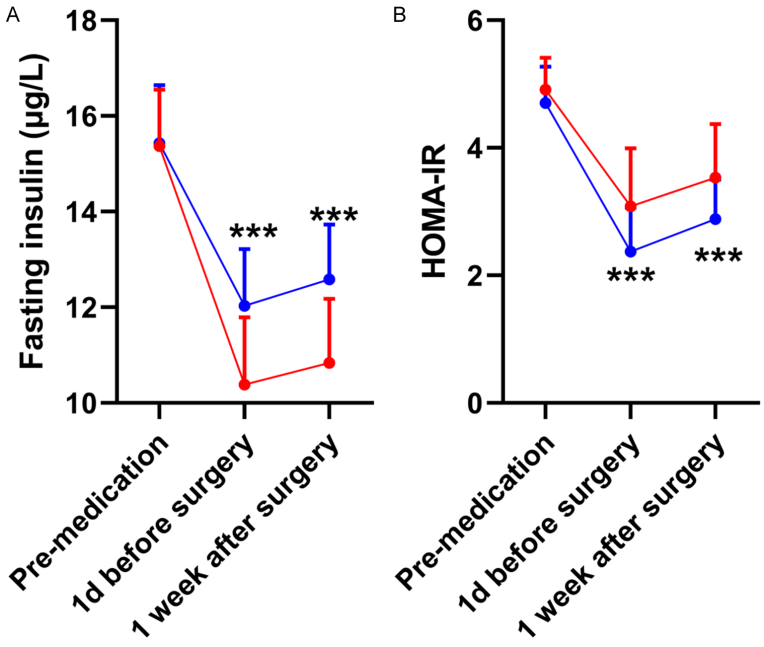

Figure 7. Changes in islet cell function (after PSM). A. Changes in fasting insulin levels (after PSM). B. Changes in HOMA-IR values (after PSM). Note: HOMA-IR, homeostasis model assessment of insulin resistance; PSM, propensity score matching. ***P < 0.001.

and 0.096, respectively). However, 1 day before surgery and 1 week after surgery, the observation group showed significantly greater improvements in FI levels and HOMA-IR values compared to the control group. Specifically, 1 day before surgery and 1 week after surgery, FI levels in the observation group were significantly higher than those in the control group (P < 0.001). HOMA-IR values were significantly lower in the observation group (P < 0.001) (**Figure 7**).

Comparison of kidney function after PSM matching

This study compared the changes in kidney function (Scr, BUN, and UAER) before medication, 1 day before surgery, and 1 week after surgery between the control and observation groups after PSM matching. Before treatment, there were no significant differences in Scr, BUN, and UAER between the two groups (*P* values were 0.766, 0.921 and

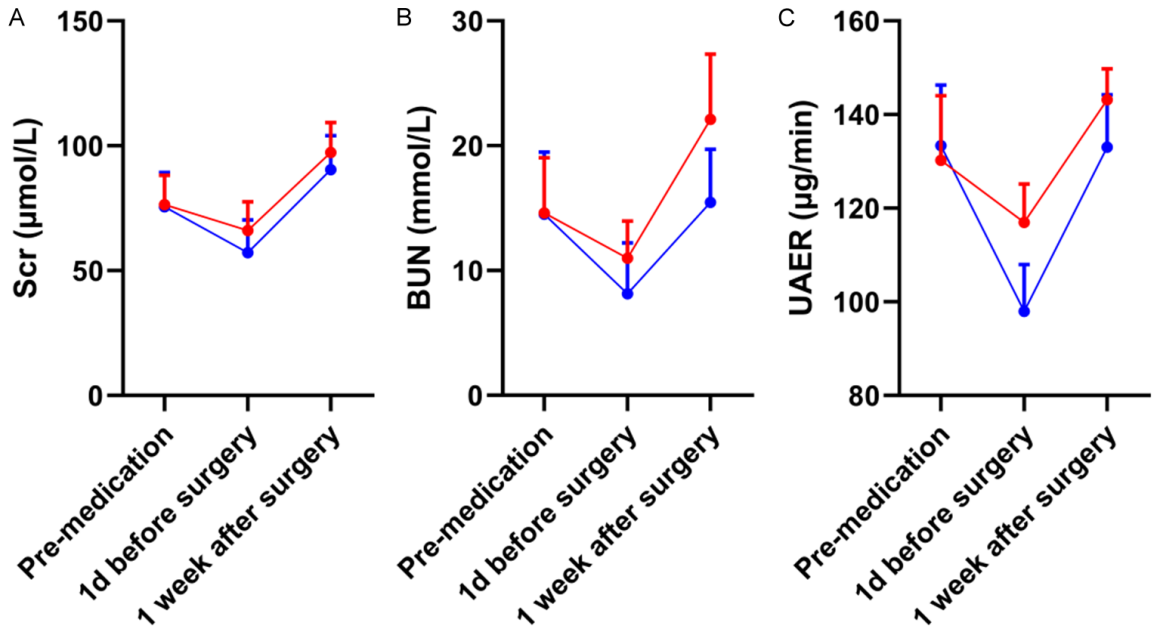

Figure 8. Kidney function changes (after PSM). A. Changes in Scr levels (after PSM). B. Changes in BUN levels (after PSM). C. Changes in UAER levels (after PSM). Note: Scr, Serum creatinine; BUN, blood urea nitrogen; UAER, urinary albumin excretion rate; PSM, propensity score matching.

Table 6. Comparison of postoperative blood glucose, islet cell function and renal function indexes in patients with insulin resistance after PSM

Index	Total	Resistant Group (n = 45)	Non-Resistant Group (n = 15)	Statistic	*P*-Value
FPG 1 week after surgery	7.85 [6.14, 8.51]	7.86 [6.00, 8.50]	7.33±1.48	-0.286	0.78
2hPG 1 week after surgery	9.54 [8.31, 10.32]	9.83 [8.32, 10.34]	8.89±1.16	1.31	0.193
HbA1c 1 week after surgery	6.65±1.16	6.61±1.11	6.77±1.38	-0.412	0.685
Fasting insulin 1 week after surgery	11.71±1.52	11.67±1.62	11.86±1.10	-0.523	0.605
HOMA-IR 1 week after surgery	3.21±0.80	3.38 [3.01, 3.80]	2.15±0.45	5.904	< 0.001
Src 1 week after surgery	96.06 [87.23, 103.84]	100.42 [90.53, 105.08]	83.54±10.11	3.664	< 0.001
BUN 1 week after surgery	18.79±5.79	19.64±6.03	15.64±3.42	3.335	0.002
UAER 1 week after surgery	138.31 [130.93, 145.01]	140.87±8.85	130.18 [125.68, 133.88]	4.215	< 0.001

Note: FPG, Fasting plasma glucose; 2hPG, 2-hour postprandial glucose; HbA1c, glycated hemoglobin; HOMA-IR, homeostasis model assessment of insulin resistance; Scr, serum creatinine; BUN, blood urea nitrogen; UAER, urinary albumin excretion rate; PSM, propensity score matching.

0.337, respectively). However, 1 day before surgery and 1 week after surgery, the observation group showed significantly better improvements in Scr, BUN, and UAER compared to the control group. Furthermore, the Scr, BUN, and UAER were significantly lower in the observation group ($P < 0.05$) (**Figure 8**).

Comparison of blood glucose, islet function, and kidney function in insulin resistance patients after PSM

Following PSM, we compared the blood glucose, islet cell function, and kidney function between insulin resistance and non-resistance patients 1 week after surgery. The results showed that there were no statistically significant differences in FPG ($P = 0.780$), 2hPG ($P = 0.193$), or HbA1c ($P = 0.685$) between the insulin resistance and non-resistance groups. Similarly, FI levels showed no significant differences between the two groups ($P = 0.605$). However, Scr, BUN, and UAER were significantly higher in the insulin resistance group compared to the non-resistance group ($P < 0.01$), indicating a potential association between insulin resistance and kidney function decline (**Table 6**).

Comparison of baseline data between insulin resistance and non-insulin resistance groups after PSM matching

After PSM, this study compared the baseline data between the patients with insulin resistance and those without. The results showed that the average age of the insulin resistance group was significantly higher than that of the non-resistance group (P = 0.031). There was a significant difference in BMI distribution between the two groups, with a higher proportion of patients in the insulin resistance group having a BMI ≥ 25, while the non-resistance group had a higher proportion in the lower BMI category (BMI 18-22.9) (P < 0.001). Additionally, there were statistical differences between the groups regarding regular exercise (P = 0.012) and high-calorie diet (P = 0.003). Regarding laboratory indicators, only the 2hPG before treatment showed a significant difference between the groups (P = 0.011). Other factors, such as gender, history of hypertension, family history of diabetes, income level, marital status, education level, smoking history, alcohol consumption, and other relevant indicators, did not show significant differences between the two groups (all *P* values > 0.05) (**Table 7**).

Risk factors for insulin resistance after PSM

Multivariate logistic regression analysis of PSM-matched data identified age and BMI as independent risk factors for insulin resistance. Each additional year of age increased the risk of insulin resistance by approximately 7.4 times (OR = 7.434, P = 0.025), and each unit increase in BMI raised the risk by approximately 6.8 times (OR = 6.812, P = 0.003). Regular physical activity (P = 0.053) and high-fat diet (P = 0.005) were also associated with insulin resistance, with regular physical activity showing a trend toward significance and high-fat diet significantly increasing the risk (OR = 0.044, P = 0.005) (**Table 8**).

Nomogram model for predicting insulin resistance

Based on significant risk factors identified in the multivariate analysis, a nomogram model was constructed to predict the risk of insulin resistance. The model incorporated age, BMI, and high-fat diet as predictors, assigning risk scores to each variable to calculate a total score for individual patients. For example, a high-risk patient had a total score of 117.2, reflecting high age, BMI, and high-fat diet scores, while a low-risk patient had a total score of 32, indicating lower scores for all variables. This model provides a practical tool for assessing the risk of insulin resistance in clinical settings (**Figure 9**).

Discussion

T2DM is a globally prevalent chronic metabolic disorder, and its incidence continues to rise with socioeconomic development and lifestyle changes, posing a significant threat to public health [19, 20]. The findings of this study highlight the significant benefits of combination therapy of SGLT2i and GLP-1RA in improving glycemic control and insulin sensitivity. Specifically, the observation group demonstrated significantly lower FPG, 2hPG, and HbA1c levels post-treatment, alongside marked improvements in the HOMA-IR, suggesting a protective effect on islet function. Furthermore, renal function in the observation group was notably superior compared to the control group, both 1 day and 1 week after treatment. PSM analysis further confirmed the advantages of the combination therapy, particularly in patients with severe insulin resistance.

Comparison with previous studies

The positive outcomes observed in our study are consistent with the findings of previous research. Kristensen et al. [21] reported a meta-analysis showing that GLP-1RA therapy reduces the incidence of MACE, including cardiovascular death, stroke, myocardial infarction, renal events, and overall mortality, which parallels our results of improved cardiovascular outcomes in the observation group. Additionally, Gourdy et al. [22] highlighted the synergistic protective effects of GLP-1RA and SGLT2i in cardiovascular, renal, and metabolic diseases, which aligns with the results of this study. It is suggested that combination therapy not only improves glycemic control but also provides significant renal protection, improving both kidney and heart health in T2DM patients.

During the initial analysis, significant differences in age and regular physical activity were noted between the observation and control groups, which could influence the reliability of

Table 7. Comparison of baseline data between insulin resistance and non-insulin resistance patients after PSM

Factor	Total	Resistant Group (n = 55)	Non-Resistant Group (n = 15)	Statistic	*P*-Value
Treatment Regimen				6.731	0.009
Observation Group	35 (50.00%)	30 (54.55%)	5 (33.33%)	2.121	0.145
Control Group	35 (50.00%)	25 (45.45%)	10 (66.67%)		
Age (years)	62.06±7.18	58.53±5.15	63.02±7.39	-2.203	0.031
Sex					
Male	45 (64.29%)	37 (67.27%)	8 (53.33%)	0.997	0.318
Female	25 (35.71%)	18 (32.73%)	7 (46.67%)		
BMI (kg/m^2)					
18-22.9	17 (24.29%)	8 (14.55%)	9 (60.00%)	14.268	< 0.001
23-24.9	31 (44.29%)	26 (47.27%)	5 (33.33%)		
≥ 25	22 (31.43%)	21 (38.18%)	1 (6.67%)		
History of Hypertension					
Yes	15 (21.43%)	14 (25.45%)	1 (6.67%)	2.471	0.116
No	55 (78.57%)	41 (74.55%)	14 (93.33%)		
Family History of Diabetes					
Yes	22 (31.43%)	19 (34.55%)	3 (20.00%)	1.157	0.282
No	48 (68.57%)	36 (65.45%)	12 (80.00%)		
Average Monthly Income					
≤ 2999	36 (51.43%)	27 (49.09%)	9 (60.00%)	1.157	0.561
3000-4499	22 (31.43%)	19 (34.55%)	3 (20.00%)		
≥ 4500	12 (17.14%)	9 (16.36%)	3 (20.00%)		
Marital Status					
Married	63 (90.00%)	50 (90.91%)	13 (86.67%)	4.761	0.093
Single	4 (5.71%)	4 (7.27%)	0 (0.00%)		
Other	3 (4.29%)	1 (1.82%)	2 (13.33%)		
Education Level					
≤ High School	26 (37.14%)	20 (36.36%)	6 (40.00%)	0.752	0.687
College	29 (41.43%)	22 (40.00%)	7 (46.67%)		
≥ Postgraduate	15 (21.43%)	13 (23.64%)	2 (13.33%)		
Smoking History					
Yes	46 (65.71%)	35 (63.64%)	11 (73.33%)	0.492	0.483
No	24 (34.29%)	20 (36.36%)	4 (26.67%)		
Alcohol Consumption					
Yes	26 (37.14%)	21 (38.18%)	5 (33.33%)	0.119	0.730
No	44 (62.86%)	34 (61.82%)	10 (66.67%)		
Regular Physical Activity					
Yes	27 (38.57%)	17 (30.91%)	10 (66.67%)	6.360	0.012
No	43 (61.43%)	38 (69.09%)	5 (33.33%)		
High-Fat Diet					
Yes	53 (75.71%)	46 (83.64%)	7 (46.67%)	8.760	0.003
No	17 (24.29%)	9 (16.36%)	8 (53.33%)		
Cancer Type					
Clear Cell Renal Carcinoma	58 (82.86%)	45 (81.82%)	13 (86.67%)	2.175	0.337
Papillary Renal Carcinoma	6 (8.57%)	4 (7.27%)	2 (13.33%)		
Other	6 (8.57%)	6 (10.91%)	0 (0.00%)		

SBP (mmHg)	137.86±13.88	138.00±16.10	137.82±13.37	0.045	0.965
DBP (mmHg)	79.80±8.53	78.13±7.86	80.26±8.72	-0.852	0.397
HDL (mmol/L)	1.00±0.25	1.02±0.20	0.99±0.26	0.342	0.734
LDL (mmol/L)	3.27±0.75	3.14±0.90	3.30±0.71	-0.761	0.449
Pre-treatment FPG (mmol/L)	11.92±0.81	11.56±0.70	12.02±0.81	-2.023	0.047
Pre-treatment 2hPG (mmol/L)	14.88±0.90	15.07±0.89	14.83±0.90	0.905	0.368
Pre-treatment HbA1c (%)	9.50±1.14	9.25±1.12	9.57±1.14	-0.963	0.339
Pre-treatment Fasting Insulin (μg/L)	15.40±1.19	15.56±0.74	15.36±1.28	0.597	0.552
Pre-treatment HOMA-IR	4.80±0.54	4.79±0.56	4.81±0.55	-0.126	0.900

Note: BMI, Body mass index; FPG, fasting plasma glucose; 2hPG, 2-hour postprandial glucose; HbA1c, glycated hemoglobin; HOMA-IR, homeostasis model assessment of insulin resistance; SBP, systolic blood pressure; DBP, diastolic blood pressure; HDL, high-density lipoprotein; LDL, low-density lipoprotein; PSM, propensity score matching.

Table 8. Analysis of the risk factors for insulin resistance after PSM

Variable	Estimate	SE	*P* Value	OR	Lower	Upper
Age	2.006	0.893	0.025	7.434	1.444	53.133
BMI	1.919	0.638	0.003	6.812	2.215	28.715
Regular Physical Activity	1.790	0.926	0.053	5.989	1.095	46.431
High-Fat Diet	-3.119	1.114	0.005	0.044	0.003	0.309

Note: BMI, Body mass index; OR, odds ratio; SE, standard error; PSM, propensity score matching.

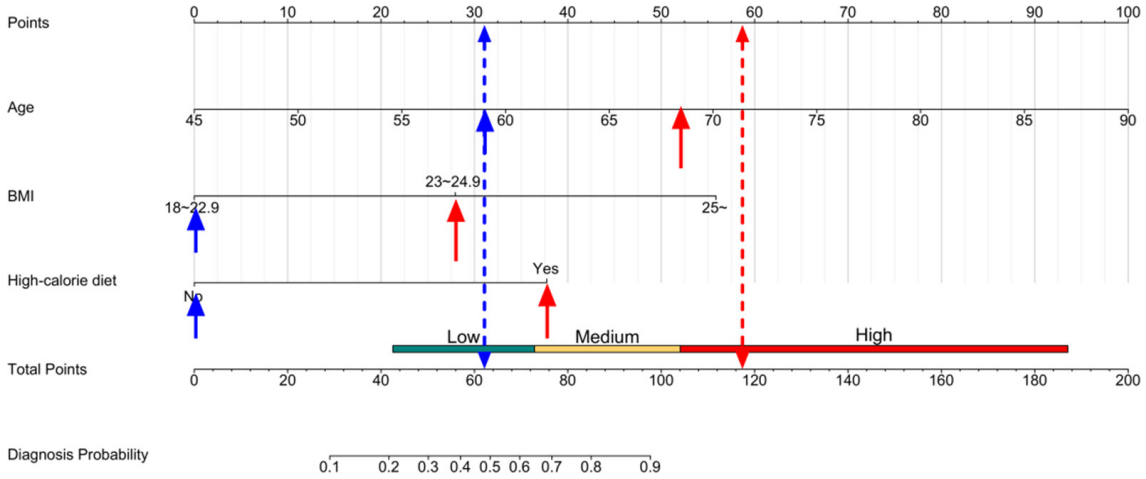

Figure 9. Nomogram model for predicting the risk of insulin resistance. A nomogram model incorporating key risk factors (age, BMI, and high-fat dietary habits) for predicting the risk of insulin resistance, showing patient-specific total risk scores and corresponding probabilities of insulin resistance. Note: BMI, Body mass index; OR, odds ratio.

the results. To address potential confounding factors and balance baseline characteristics, PSM was employed [23]. By calculating the propensity score for each patient, PSM ensured comparability between the groups, minimizing selection bias. Mittman et al. [24] emphasized that PSM is widely applied in retrospective studies to optimize baseline balance, thereby enhancing the credibility of the findings. Following PSM adjustment, the clinical characteristics between the groups were well-matched, providing a solid basis for comparing treatment outcomes.

Mechanisms of the combined therapy

Following treatment, the observation group receiving the SGLT2i and GLP-1RA combination demonstrated superior blood glucose control compared to the control group. Notably, the

observation group exhibited significant reductions in FPG, 2hPG, and HbA1c, coupled with improvements in HOMA-IR, suggesting a beneficial effect on blood glucose fluctuations and insulin sensitivity. Furthermore, insulin function improved significantly in the observation group, reflecting protection of pancreatic β-cells. In contrast, no significant changes were observed in the control group, confirming the superiority of the combination therapy. Riley et al. [25] conducted a study showing that the combination of SGLT2i and GLP-1RA reduced all-cause mortality and hospitalization risk over a 5-year follow-up, providing further support for its long-term efficacy and safety.

SGLT2i reduces blood glucose by promoting urinary glucose excretion while also aiding in weight reduction and protecting renal and cardiac functions [26]. This mechanism is consistent with previous studies showing that SGLT2i significantly mitigate renal function decline, particularly in patients with elevated albuminuria [27]. GLP-1RA helps control blood glucose by stimulating insulin secretion, delaying gastric emptying, enhancing satiety, and reducing body weight [28]. D'Marco et al. [29] showed that both SGLT2i and GLP-1RA exhibited significant anti-inflammatory and antioxidant effects, helping alleviate oxidative stress, improve chronic inflammation, and enhance insulin sensitivity, which may further reduce cardiovascular and metabolic risks. The complementary actions of the two drugs suggest that their combined use could result in more significant improvements in blood glucose regulation and pancreatic cell function.

In addition, the observation group showed better renal function improvement compared to the control group, with significant reductions in Scr, BUN, and UAER both 1 day before surgery and 1 week after treatment. These findings indicate that the combination therapy not only offers excellent blood glucose control but also provides potential renal protection. This is consistent with Edmonston et al.'s [30] findings, where SGLT2i significantly reduced the risk of estimated glomerular filtration rate (eGFR) decline compared to other treatments. SGLT2i reduces renal glucose reabsorption, alleviating the metabolic burden on the kidneys, while also reducing hypertension and proteinuria, which helps protect renal function. GLP-1RA may protect the kidneys by enhancing insulin sensitivity and reducing systemic inflammation. The combined action of these two drugs provides superior renal protection by mitigating oxidative stress, improving vascular function, and reducing chronic inflammation.

Influence of risk factors

The study identified age, BMI, and high-fat dietary habits as key factors influencing glycemic control and insulin sensitivity. These factors, closely linked to patients' metabolic states, are important in optimizing treatment strategies. Age emerged as a significant risk factor, with each additional year increasing the risk of insulin resistance by 7.4 times (OR = 7.434, P = 0.025). This is likely due to age-related metabolic decline, reduced insulin secretion capacity, and an increased prevalence of comorbidities. Duan et al. [31] reported that age-related metabolic abnormalities were strongly associated with cardiovascular and all-cause mortality, particularly in individuals under 65 years. Older patients may also have reduced drug tolerance, increasing the risk of treatment-related adverse events such as hypoglycemia or weight loss, which may affect the sustainability of therapeutic outcomes.

BMI was another critical factor, with each unit increase significantly raising the risk of insulin resistance by 6.812 times (P = 0.003). High BMI is strongly associated with insulin resistance due to increased inflammation and impaired insulin signaling caused by excess adipose tissue. Wu et al. [32] found that high BMI not only correlated with insulin resistance but may also exacerbated metabolic dysfunction by increasing β-cell dysfunction risk. Moreover, high BMI patients are at a significantly higher risk of insulin resistance and metabolic disorders, highlighting the importance of targeting BMI reduction in treatment strategies [33]. Nikrad et al. [34] emphasized that optimizing carbohydrate quality in the diet could significantly reduce insulin resistance risk in high-BMI patients and improve cardiometabolic health. For patients with high BMI, combination therapy with SGLT2i and GLP-1RA can alleviate insulin resistance by reducing weight and improving metabolic status. However, lifestyle modifications, including dietary management and exercise, are essential to optimizing treatment outcomes.

The study also found that avoiding high-fat dietary habits was protective. Patients who did not frequently consume high-fat diets had a significantly lower risk of insulin resistance (OR = 0.044, P = 0.005), consistent with research linking high-calorie intake to insulin resistance. High-fat diets can lead to excess energy intake and fat accumulation, worsening insulin resistance. González-González et al. [35] found that high-calorie diets significantly increased insulin resistance and metabolic disorders through chronic inflammation and lipotoxicity. Reducing high-fat diets and limiting excessive calorie consumption are critical for improving insulin resistance and metabolic health.

Based on these findings, individualized treatment strategies should be adopted in clinical practice. For older patients, enhanced monitoring of comorbidities and appropriate adjustments to medication doses are crucial. For patients with high BMI, SGLT2i and GLP-1RA combination therapy should be prioritized alongside weight management. For those with high-fat dietary habits, nutritional counseling to reduce calorie intake and optimize dietary composition should be integrated into the treatment plan to enhance metabolic outcomes.

A nomogram model based on the identified risk factors was developed to provide a more intuitive assessment of insulin resistance risk and treatment response. Although the model was constructed with post-PSM data, it utilized pre-PSM data to ensure sufficient sample size and robustness. Validation of the model in two randomly selected patients demonstrated that age, BMI, and high-fat dietary habits were effective predictors of treatment response and insulin sensitivity improvements. The consistency of risk scores with actual treatment outcomes further validated the model's reliability and clinical applicability.

This study provides valuable insights into the combined use of SGLT2i and GLP-1RA for diabetes treatment. However, its limitations include the small sample size and single-center design, which may limit the generalizability of the findings. The short follow-up period also leaves the long-term efficacy and safety unverified. Future studies should include larger sample size, multi-center design, extended follow-up periods, and additional metabolic indicators, such as body weight and lipid profiles, for a comprehensive evaluation. Moreover, further research is needed to explore individualized treatment strategies for different diabetes subtypes, such as obese or insulin-deficient types.

Conclusion

Combination therapy with SGLT2i and GLP-1RA significantly improves glycemic control, insulin sensitivity, and renal function in patients with diabetes, and this combination therapy is particularly effective in patients with severe insulin resistance. Furthermore, risk factor analysis identified age, BMI, and lack of a healthy diet as key factors influencing treatment outcomes.

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Disclosure of conflict of interest

None.

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References

[1] GRADE Study Research Group; Nathan DM, Lachin JM, Balasubramanyam A, Burch HB, Buse JB, Butera NM, Cohen RM, Crandall JP, Kahn SE, Krause-Steinrauf H, Larkin ME, Rasouli N, Tiktin M, Wexler DJ and Younes N. Glycemia reduction in type 2 diabetes - glycemic outcomes. N Engl J Med 2022; 387: 1063-1074.

[2] Abel ED, Ingelfinger JR, Linhales Barker S, Peek M, Reusch JEB and Rosen CJ. Type 2 diabetes - controlling the epidemic, episode 4: understanding old and new therapies for diabetes. N Engl J Med 2023; 389: e31.

[3] GBD 2015 Disease and Injury Incidence and Prevalence Collaborators. Global, regional, and national incidence, prevalence, and years lived with disability for 310 diseases and injuries, 1990-2015: a systematic analysis for the Global Burden of Disease Study 2015. Lancet 2016; 388: 1545-1602.

[4] Harris E. Meta-analysis: faster walking linked with lower type 2 diabetes risk. JAMA 2024; 331: 16.
[5] Numsang P, Oumtanee A, Kurat S, Sananok R, Kraichan S and Sarapoke P. "Failure to control blood sugar" experiences of persons with type 2 diabetes mellitus. Int J Nurs Sci 2023; 10: 527-532.
[6] Zhang YB, Pan XF, Lu Q, Wang YX, Geng TT, Zhou YF, Liao LM, Tu ZZ, Chen JX, Xia PF, Wang Y, Wan ZZ, Guo KQ, Yang K, Yang HD, Chen SH, Wang GD, Han X, Wang YX, Yu D, He MA, Zhang XM, Liu LG, Wu T, Wu SL, Liu G and Pan A. Associations of combined healthy lifestyles with cancer morbidity and mortality among individuals with diabetes: results from five cohort studies in the USA, the UK and China. Diabetologia 2022; 65: 2044-2055.
[7] Yeh HC, Golozar A and Brancati FL. Cancer and Diabetes. In: Cowie CC, Casagrande SS, Menke A, Cissell MA, Eberhardt MS, Meigs JB, Gregg EW, Knowler WC, Barrett-Connor E, Becker DJ, Brancati FL, Boyko EJ, Herman WH, Howard BV, Narayan KMV, Rewers M, Fradkin JE, editors. Diabetes in America. Bethesda (MD) interest.: National Institute of Diabetes and Digestive and Kidney Diseases (US); 2018.
[8] Stewart GD, Klatte T, Cosmai L, Bex A, Lamb BW, Moch H, Sala E, Siva S, Porta C and Gallieni M. The multispeciality approach to the management of localised kidney cancer. Lancet 2022; 400: 523-534.
[9] Bray F, Laversanne M, Sung H, Ferlay J, Siegel RL, Soerjomataram I and Jemal A. Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2024; 74: 229-263.
[10] Bhargava P, Jena R and Giri RK. Stereotactic ablative radiotherapy for primary kidney cancer. Lancet Oncol 2024; 25: e228.
[11] Escobar Cervantes C. SGLT2 inhibitors and GLP-1 receptor agonists: the definitive combination? Lancet Diabetes Endocrinol 2024; 12: 507-508.
[12] Emanuel EJ, Dellgren JL, McCoy MS and Persad G. Fair allocation of GLP-1 and dual GLP-1-GIP receptor agonists. N Engl J Med 2024; 390: 1839-1842.
[13] Rydén L and Norhammar A. SGLT2 inhibitors in clinical practice. Lancet Diabetes Endocrinol 2024; 12: 434-435.
[14] Keener AB. SGLT2 inhibitors breathe life into kidney-disease care. Nature 2023; 615: S2-S4.
[15] Hegland TA, Fang Z and Bucher K. GLP-1 medication use for type 2 diabetes has soared. JAMA 2024; 332: 952-953.
[16] Watts G. Jens Juul Holst: physician-scientist and co-discoverer of GLP-1. Lancet 2024; 404: 1186.
[17] Chinese Elderly Type 2 Diabetes Prevention and Treatment of Clinical Guidelines Writing Group; Geriatric Endocrinology and Metabolism Branch of Chinese Geriatric Society; Geriatric Endocrinology and Metabolism Branch of Chinese Geriatric Health Care Society; Geriatric Professional Committee of Beijing Medical Award Foundation; National Clinical Medical Research Center for Geriatric Diseases (PLA General Hospital). Clinical guidelines for prevention and treatment of type 2 diabetes mellitus in the elderly in China (2022 edition). Zhonghua Nei Ke Za Zhi 2022; 61: 12-50.
[18] Podlipskyte A, Kazukauskiene N, Varoneckas G and Mickuviene N. Association of insulin resistance with cardiovascular risk factors and sleep complaints: a 10-year follow-up. Front Public Health 2022; 10: 848284.
[19] Ahmad E, Lim S, Lamptey R, Webb DR and Davies MJ. Type 2 diabetes. Lancet 2022; 400: 1803-1820.
[20] Abel ED, Giffin J, Ingelfinger JR, Peek M, Reusch JEB, Rosen CJ, Sagendorf A and Thomas E Sr. Type 2 diabetes - controlling the epidemic, episode 1: understanding and preventing type 2 diabetes. N Engl J Med 2023; 389: e18.
[21] Kristensen SL, Rørth R, Jhund PS, Docherty KF, Sattar N, Preiss D, Køber L, Petrie MC and McMurray JJV. Cardiovascular, mortality, and kidney outcomes with GLP-1 receptor agonists in patients with type 2 diabetes: a systematic review and meta-analysis of cardiovascular outcome trials. Lancet Diabetes Endocrinol 2019; 7: 776-785.
[22] Gourdy P, Darmon P, Dievart F, Halimi JM and Guerci B. Combining glucagon-like peptide-1 receptor agonists (GLP-1RAs) and sodium-glucose cotransporter-2 inhibitors (SGLT2is) in patients with type 2 diabetes mellitus (T2DM). Cardiovasc Diabetol 2023; 22: 79.
[23] Kurz CF, Krzywinski M and Altman N. Propensity score matching. Nat Methods 2024; 21: 1770-1772.
[24] Mittman BG, Le P, Payne JY, Ayers G and Rothberg MB. Sociodemographic disparities in GLP-1RA and SGLT2i use among US adults with type 2 diabetes: NHANES 2005-March 2020. Curr Med Res Opin 2024; 40: 377-383.
[25] Riley DR, Essa H, Austin P, Preston F, Kargbo I, Ibarburu GH, Ghuman R, Cuthbertson DJ, Lip GYH and Alam U. All-cause mortality and cardiovascular outcomes with sodium-glucose Cotransporter 2 inhibitors, glucagon-like peptide-1 receptor agonists and with combination therapy in people with type 2 diabetes. Diabetes Obes Metab 2023; 25: 2897-2909.

[26] Anson M, Zhao SS, Austin P, Ibarburu GH, Malik RA and Alam U. SGLT2i and GLP-1 RA therapy in type 1 diabetes and reno-vascular outcomes: a real-world study. Diabetologia 2023; 66: 1869-1881.

[27] Neuen BL, Heerspink HJL, Vart P, Claggett BL, Fletcher RA, Arnott C, de Oliveira Costa J, Falster MO, Pearson SA, Mahaffey KW, Neal B, Agarwal R, Bakris G, Perkovic V, Solomon SD and Vaduganathan M. Estimated lifetime cardiovascular, kidney, and mortality benefits of combination treatment with SGLT2 inhibitors, GLP-1 receptor agonists, and nonsteroidal MRA compared with conventional care in patients with type 2 diabetes and albuminuria. Circulation 2024; 149: 450-462.

[28] Nelson AJ, Pagidipati NJ, Aroda VR, Cavender MA, Green JB, Lopes RD, Al-Khalidi H, Gaynor T, Kaltenbach LA, Kirk JK, Lingvay I, Magwire ML, O'Brien EC, Pak J, Pop-Busui R, Richardson CR, Reed M, Senyucel C, Webb L, McGuire DK and Granger CB. Incorporating SGLT2i and GLP-1RA for cardiovascular and kidney disease risk reduction: call for action to the cardiology community. Circulation 2021; 144: 74-84.

[29] D'Marco L, Morillo V, Gorriz JL, Suarez MK, Nava M, Ortega Á, Parra H, Villasmil N, Rojas-Quintero J and Bermúdez V. SGLT2i and GLP-1RA in cardiometabolic and renal diseases: from glycemic control to adipose tissue inflammation and senescence. J Diabetes Res 2021; 2021: 9032378.

[30] Edmonston D, Mulder H, Lydon E, Chiswell K, Lampron Z, Shay C, Marsolo K, Shah RC, Jones WS, Gordon H, Hwang W, Ayoub I, Ford D, Chamberlain A, Rao A, Fonseca V, Chang A, Ahmad F, Hung A, Hunt K, Butler J, Bosworth HB and Pagidipati N. Kidney and cardiovascular effectiveness of SGLT2 inhibitors vs GLP-1 receptor agonists in type 2 diabetes. J Am Coll Cardiol 2024; 84: 696-708.

[31] Duan M, Zhao X, Li S, Miao G, Bai L, Zhang Q, Yang W and Zhao X. Metabolic score for insulin resistance (METS-IR) predicts all-cause and cardiovascular mortality in the general population: evidence from NHANES 2001-2018. Cardiovasc Diabetol 2024; 23: 243.

[32] Wu X, Wang Y, Jia Y, Liu J and Wang G. Risk factors for nonalcoholic fatty liver disease with different insulin resistance in a nonobese chinese population. J Diabetes Res 2022; 2022: 9060405.

[33] Wright AK, Carr MJ, Kontopantelis E, Leelarathna L, Thabit H, Emsley R, Buchan I, Mamas MA, van Staa TP, Sattar N, Ashcroft DM and Rutter MK. Primary prevention of cardiovascular and heart failure events with SGLT2 inhibitors, GLP-1 receptor agonists, and their combination in type 2 diabetes. Diabetes Care 2022; 45: 909-918.

[34] Nikrad N, Hosseini B, Pakmehr A, Tousi AZ, Ardekani AM, Farhangi MA and Akhavan-Sigari R. Dietary carbohydrate quality index (CQI), cardio-metabolic risk factors and insulin resistance among adults with obesity. BMC Endocr Disord 2023; 23: 171.

[35] González-González JG, Violante-Cumpa JR, Zambrano-Lucio M, Burciaga-Jimenez E, Castillo-Morales PL, Garcia-Campa M, Solis RC, González-Colmenero AD and Rodríguez-Gutiérrez R. HOMA-IR as a predictor of health outcomes in patients with metabolic risk factors: a systematic review and meta-analysis. High Blood Press Cardiovasc Prev 2022; 29: 547-564.

Table S1. Comparison of baseline patient data after PSM

Factor	Total	Control Group (n=35)	Observation Group (n=35)	Statistic	*P*-Value
Age (years)	62.00 [58.00, 66.00]	62.00 [59.50, 65.50]	60.00 [57.00, 66.00]	0.494	0.621
Sex					
Male	45	22	23	0.062	0.803
Female	25	13	12		
BMI (kg/m^2)					
18-22.9	17	6	11	2.230	0.328
23-24.9	31	16	15		
≥25	22	13	9		
History of Hypertension					
Yes	15	8	7	0.085	0.771
No	55	27	28		
Family History of Diabetes					
Yes	22	11	11	0.000	1.000
No	48	24	24		
Average Monthly Income					
≤2999	36	19	17	0.444	0.801
3000-4499	22	11	11		
≥4500	12	5	7		
Marital Status					
Married	63	31	32	1.349	0.509
Single	4	3	1		
Other	3	1	2		
Education Level					
≤High School	26	16	10	2.295	0.317
College	29	13	16		
≥Postgraduate	15	6	9		
Smoking History					
Yes	46	23	23	0.000	1.000
No	24	12	12		
Alcohol Consumption					
Yes	26	13	13	0.000	1.000
No	44	22	22		
Regular Physical Activity					
Yes	27	13	14	0.060	0.806
No	43	22	21		
High-Fat Diet					
Yes	53	25	28	0.699	0.403
No	17	10	7		
Cancer Type					
Clear Cell Renal Carcinoma	58	30	28	0.736	0.692
Papillary Renal Carcinoma	6	2	4		
Other	6	3	3		
SBP (mmHg)	137.857±13.876	135.514±13.502	140.200±14.039	1.423	0.159
DBP (mmHg)	79.800±8.529	79.886±7.387	79.714±9.645	-0.083	0.934
HDL (mmol/L)	1.000±0.249	1.013±0.197	0.987±0.295	-0.438	0.663
LDL (mmol/L)	3.266±0.750	3.201±0.749	3.330±0.757	0.717	0.476