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Effect of semaglutide combined with metformin on type 2 diabetes mellitus and its regulation of IL-6/JAK2/STAT3 signaling axis

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Abstract: Objective To investigate the efficacy of semaglutide combined with metformin in the treatment of type 2 diabetes mellitus (T2DM) , and to analyze its regulatory effect on the interleukin-6 (IL-6) /Janus kinase 2 (JAK2) / signal transducer and activator of transcription 3 (STAT3) signaling axis. **Methods** A total of 103 patients with T2DM admitted to Cangzhou Hospital of Integrated Traditional Chinese and Western Medicine in Hebei Province from August 2022 to August 2024 were prospectively selected as research subjects. They were divided into control group (n=51, metformin) and observation group (n=52, metformin + semaglutide) using random number table. The levels of glucose metabolism indexes [fasting plasma glucose (FPG) , 2 - hour postprandial plasma glucose (2hPG) , glycosylated hemoglobin (HbA1c) , Homeostasis Model Assessment Insulin Resistance Index (HOMA - IR)] , serum adipokines [serine protease inhibitor (Vaspin) , Chemerin, Apelin] and the expression of IL-6/JAK2/STAT3 signal axis related mRNA [tumor necrosis factor alpha (TNF-α) , IL-6, STAT3, JAK2] in peripheral blood mononuclear cells of two groups before and after treatment were observed. **Results** After 3 months of treatment, FPG, 2hPG, HbA1C and HOMA- IR in the observation group were (6.56 ± 0.66) mmol/L, (8.50 ± 1.01) mmol/L, (6.45 ± 0.41) % and 1.88 ± 0.31, respectively, which were lower than (7.12±0.69) mmol/L, (9.36±1.11) mmol/L, (6.92±0.43) % and 2.24±0.33 in the control group (P<0.05) ; the mRNA expression levels of TNF-α, IL-6, STAT3 and JAK2 in the observation group were 2.23±0.62, 2.35±0.68, 1.56±0.41 and 1.05±0.30 respectively, which were lower than 3.40±0.74, 3.05±0.87, 2.13± 0.58 and 1.59±0.40 in the control group (P<0.05) ; Vaspin, Chemerin, Apelin levels in the observation group were also lower than those in the control group (P<0.05) . **Conclusion** Semaglutide combined with metformin has a significant therapeutic effect in the treatment of T2DM patients, which can improve insulin resistance and regulate the level of adipokines, possibly by inhibiting the activation of IL-6/JAK2/STAT3 signaling axis.

Keywords: Type 2 diabetes mellitus; Metformin; Semaglutide; Interleukin-6; Janus kinase 2; Phosphorylated signal transducer and activator of transcription 3; Insulin resistance; Adipokines
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Type 2 diabetes mellitus (T2DM) is clinically characterized by chronic hyperglycemia. The prevalence of T2DM in China is approximately 11.2%, and the development and progression of T2DM may be related to insulin resistance; as the disease advances, glycemic control becomes increasingly difficult [1]. Metformin tablets are commonly used in clinical practice for the treatment of T2DM, which can control blood glucose levels and promote the proliferation and differentiation of pancreatic β-cells [2]. Semaglutide possesses the advantages of rapid onset of action and a favorable adverse-effect profile, effectively controlling blood glucose levels and improving pancreatic β-cell function [3-4]. Metformin reduces the sources of glucose, whereas semaglutide primarily optimizes glucose utilization and promotes insulin secretion. Their mechanisms of action are complementary, covering multiple key pathophysiological processes including islet functional defects, excessive hepatic glucose output, and insulin resistance, thereby achieving potent synergistic glucose-lowering effects [2]. For patients whose blood glucose remains inadequately controlled on metformin monotherapy, the addition of semaglutide represents a superior option compared with traditional sulfonylureas or insulin, as it not only provides potent glycemic reduction but also confers cardiovascular and renal protective effects [4]. Previous studies have demonstrated that activation of the interleukin-6 (IL-6)/Janus kinase 2 (JAK2)/signal transducer and activator of transcription 3 (STAT3) signaling axis can induce inflammatory responses and insulin resistance, participating in the pathogenesis and progression of various diseases including T2DM [5]. However, whether semaglutide can modulate the IL-6/JAK2/STAT3 signaling axis remains incompletely elucidated. The present study was designed to investigate the therapeutic efficacy of semaglutide combined with conventional treatment in patients with T2DM, and to analyze its effects on glucose metabolism, adipokines, and the IL-6/JAK2/STAT3 signaling axis, thereby providing a reference for the exploration of its mechanisms of action and for rational clinical drug use.

1 Subjects and Methods

1.1 General Data

The present study was reviewed and approved by the

Ethics Committee of Cangzhou Integrated Traditional Chinese and Western Medicine Hospital of Hebei Province [project number: CZX2022093 (Shen)]. A prospective selection was conducted among patients with T2DM admitted to Cangzhou Integrated Traditional Chinese and Western Medicine Hospital of Hebei Province from August 2022 to August 2024 as the screening population.

(1) **Inclusion criteria:**

① meeting the diagnostic criteria for T2DM [6], namely fasting plasma glucose (FPG) ≥7.0 mmol/L, or 2-hour postprandial plasma glucose (2hPG) ≥11.1 mmol/L;

② meeting the indications for semaglutide treatment;

③ tolerating the therapeutic agents;

④ aged ≥45 years;

⑤ voluntary participation in the study and signing of the informed consent form.

(2) **Exclusion criteria:**

① complicated by urinary tract infection or malignant tumors;

② history of glucocorticoid use;

③ use of lipid-lowering agents within 3 months prior to consultation;

④ psychiatric disorders or cognitive impairment;

⑤ serum creatinine exceeding the upper limit of normal;

⑥ history of gastrointestinal surgery;

⑦ concomitant primary cardiovascular disease.

(3) **Withdrawal criteria:**

① loss to follow-up;

② failure to complete the full course of treatment.

A total of 103 patients with T2DM were enrolled and randomly allocated using a random number table method into a control group (51 patients) and an observation group (52 patients). No statistically significant differences were observed in baseline general characteristics between the two groups (P>0.05). See **Table 1**.

Tab.1 Comparison of general information between two groups [case(%)]

Item	Observation group (n=52)	Control group (n=51)	t/χ^2 value	P value
Gender				
Male	28(53.85)	30(58.82)	0.259	0.611
Female	24(46.15)	21(41.18)		
Age(year, $\bar{x} \pm s$)	57.54±6.58	58.44±5.03	0.779	0.438
BMI(kg/m^2, $\bar{x} \pm s$)	24.83±1.04	25.18±1.23	1.561	0.122
Duration of diabetes (year, $\bar{x} \pm s$)	3.24±0.63	3.18±0.52	0.527	0.600
Basic disease				
Hypertension	10(19.23)	15(29.41)	1.452	0.228
Hyperlipidemia	11(21.15)	13(25.49)	0.271	0.603
Coronary heart disease	9(17.31)	7(13.73)	0.252	0.616

1.2 Treatment Protocol

Both groups received individualized diabetic diet and exercise interventions. The control group was treated with metformin (Hebei Tiancheng Pharmaceutical Co., Ltd., National Drug Approval Number H13021647, specification: 0.25 g/tablet) at a dose of 0.5 g per administration, three times daily, orally, for a continuous treatment period of 3 months. The observation group received the same dose of metformin as the control group, with the addition of subcutaneous injection of semaglutide (Novo Nordisk Pharmaceutical, National Drug Approval Number SJ20210014, specification: 1.34 mg/mL). The initial dose was 0.25 mg per administration, once weekly; after 4 weeks of continuous treatment, the dose was adjusted to 0.5 mg per administration, once weekly; after an additional 4 weeks of treatment, the dose could be increased to 1.0 mg per administration, once weekly. The total treatment duration was 3 months.

1.3 Observational Indices

1.3.1 Assessment of Glycemic Metabolic Parameters

Glycemic metabolic parameters were measured in both groups before and after treatment. On the evening prior to blood sampling, patients fasted for 8 hours. On the following morning, 5 mL of fasting peripheral venous blood was collected. Glycosylated hemoglobin (HbA1c) levels were determined using a high-performance liquid chromatography system (AUPOS SCIENTIFIC, Germany). FPG and fasting insulin levels were measured using a 7600 automatic biochemical analyzer (Hitachi, Japan). At 2 hours after meal consumption, 5 mL of peripheral venous blood was collected, and 2hPG levels were measured using the same automatic biochemical analyzer. The Homeostasis Model Assessment of Insulin Resistance (HOMA-IR) index was calculated accordingly.

1.3.2 Determination of mRNA Expression Levels of IL-6/JAK2/STAT3 Signaling Axis Components

Before and after treatment, 5 mL of fasting peripheral venous blood was collected from each group and placed into centrifuge tubes. An appropriate volume of Ficoll separation solution was added, and the diluted blood was carefully layered over the Ficoll solution along the tube wall. After centrifugation at 1,500 r/min (centrifugal radius 10 cm) for 30 minutes at -20 °C, the liquid was clearly separated into four layers. The uppermost plasma layer was carefully aspirated and discarded using a sterile pipette. The buffy coat layer (appearing as a white foggy layer) along with approximately 1 mm thickness of the surrounding liquid was gently aspirated along the tube wall and transferred to a new centrifuge tube. At least 3 volumes of pre-cooled phosphate-buffered saline were added, and the pellet was gently resuspended. The washed cell pellet was resuspended in an appropriate volume of culture medium or buffer, yielding isolated peripheral blood mononuclear cells (flow cytometry analysis revealed that CD45+ cells accounted for 80%–90% of total events, with granulocyte contamination <10%). Total RNA was extracted from mononuclear cells using Trizol reagent (Invitrogen, USA). cDNA was synthesized according to the instructions of the reverse transcription kit. Quantitative reverse transcription polymerase chain reaction was performed to determine the relative mRNA expression levels of tumor necrosis factor α (TNF-α), IL-6, STAT3, and JAK2. The reaction system consisted of 2 μL of cDNA, 10 μL of Real-Time Master Mix, 1 μL each of forward and reverse primers, and RNase-Free ddH_2O to a

final volume of 20 μL. The reaction conditions were as follows: 95 °C for 2 minutes, followed by 40 cycles of 95 °C for 15 seconds, 60 °C for 1 minute, and 72 °C for 30 seconds. All related kits were purchased from Tiangen Biotech (Beijing) Co., Ltd.

1.3.3 Determination of Adipokine Levels

Before and after treatment, 3 mL of fasting peripheral venous blood was collected from each group, and serum was separated by centrifugation at 3,000 r/min (centrifugal radius 10 cm) for 8 minutes at 4 °C. Serum levels of Vaspin, Chemerin, and Apelin were determined using enzyme-linked immunosorbent assay. Vaspin and Chemerin detection kits were provided by Shanghai Yiyan Biotechnology Co., Ltd., and the Apelin detection kit was provided by Shanghai Saipaisen Biotechnology Co., Ltd.

1.4 Statistical Methods

Data analysis was performed using SPSS 26.0 software. Continuous variables conforming to a normal distribution were expressed as $\bar{x} \pm s$ Comparisons between groups were conducted using independent-sample t-tests. Comparisons of indices measured at multiple time points were performed using repeated-measures analysis of variance, with pairwise comparisons conducted using the LSD-*t* test. Categorical data were expressed as cases (percentages) and compared using the chi-square test. A *P*-value <0.05 was considered statistically significant.

2 Results

2.1 Comparison of FPG, 2hPG, HbA1c, and HOMA-IR Levels Between the Two Groups

Compared with baseline values, both groups exhibited a decreasing trend in FPG, 2hPG, HbA1c, and HOMA-IR levels at 1 month and 3 months of treatment (P<0.05). At both 1 month and 3 months, the levels of FPG, 2hPG, HbA1c, and HOMA-IR in the observation group were significantly lower than those in the control group (*P*<0.05). See **Table 2**.

2.2 Comparison of mRNA Expression Levels of IL-6/JAK2/STAT3 Signaling Axis Components Between the Two Groups

Compared with baseline values, the mRNA expression levels of TNF-α, IL-6, STAT3, and JAK2 in both groups showed a decreasing trend at 1 month and 3 months of treatment (*P*<0.05). At both time points, the mRNA expression levels of TNF-α, IL-6, STAT3, and JAK2 in the observation group were significantly lower than those in the control group (*P*<0.05). See **Table 3**.

2.3 Comparison of Adipokine Levels Between the Two Groups

Compared with baseline, the levels of Vaspin, Chemerin, and Apelin in both groups showed a decreasing trend at 1 month and 3 months after treatment (*P*<0.05). At both 1 month and 3 months, the levels of Vaspin, Chemerin, and Apelin in the observation group were significantly lower than those in the control group (*P*<0.05). See **Table 4**.

Tab. 2 Comparison of FPG, 2hPG, HbA1C and HOMA-IR levels between two groups ($\bar{x} \pm s$)

Time-point	HbA_{1C}(%)		FPG(mmol/L)		2hPG(mmol/L)		HOMA-IR	
	Observation group (*n*=52)	Control group (*n*=51)	Observation group (*n*=52)	Control group (*n*=51)	Observation group (*n*=52)	Control group (*n*=51)	Observation group (*n*=52)	Control group (*n*=51)
Before treatment	8.60±0.66	8.51±0.72	9.50±0.78	9.38±0.85	11.65±1.23	11.73±1.30	3.02±0.42	3.15±0.35
1 month after treatment	7.36±0.53^{ac}	7.89±0.60^{a}	8.19±0.75^{ac}	8.73±0.80^{a}	10.02±1.15^{ac}	10.78±1.24^{a}	2.53±0.35^{ac}	2.71±0.34^{a}
3 months after treatment	6.45±0.41^{abc}	6.92±0.43^{ab}	6.56±0.66^{abc}	7.12±0.69^{ab}	8.50±1.01^{abc}	9.36±1.11^{ab}	1.88±0.31^{abc}	2.24±0.33^{ab}
$F_{group/time/interaction}$ **value**	56.352/35.285/16.396		68.544/36.956/20.085		74.162/46.245/22.357		63.396/40.175/21.193	
$P_{group/time/interaction}$ **value**	<0.001/<0.001/<0.001		<0.001/<0.001/<0.001		<0.001/<0.001/<0.001		<0.001/<0.001/<0.001	

Note: Compared with before treatment, ^{a}P<0.05; Compared with 1 month after treatment, ^{b}P<0.05; Compared with control group, ^{c}P<0.05.

Tab. 3 Comparison of expression levels of IL-6/JAK2/STAT3 signal axis related mRNA between two groups ($\bar{x} \pm s$)

Time-point	TNF-α		IL-6		p-STAT3		JAK2	
	Observation group (*n*=52)	Control group (*n*=51)	Observation group (*n*=52)	Control group (*n*=51)	Observation group (*n*=52)	Control group (*n*=51)	Observation group (*n*=52)	Control group (*n*=51)
Before treatment	6.64±1.73	7.18±1.29	7.11±1.46	6.87±1.59	6.00±1.38	5.74±1.53	5.52±1.23	5.74±1.01
1 month after treatment	4.12±0.95^{ac}	5.23±1.01^{a}	4.35±1.12^{ac}	5.38±1.20^{a}	3.56±0.73^{ac}	3.91±0.68^{a}	3.88±0.87^{ac}	4.26±0.95^{ac}
3 months after treatment	2.23±0.62^{abc}	3.40±0.74^{ab}	2.35±0.68^{abc}	3.05±0.87^{ab}	1.56±0.41^{abc}	2.13±0.58^{ab}	1.05±0.30^{abc}	1.59±0.40^{ab}
$F_{group/time/interaction}$ **value**	74.152/52.326/33.219		75.442/50.036/36.247		75.214/46.396/30.112		63.587/41.031/26.359	
$P_{group/time/interaction}$ **value**	<0.001/<0.001/<0.001		<0.001/<0.001/<0.001		<0.001/<0.001/<0.001		<0.001/<0.001/<0.001	

Note: Compared with before treatment, ^{a}P<0.05; Compared with 1 month after treatment, ^{b}P<0.05; Compared with control group, ^{c}P<0.05.

Tab.4 Comparison of expression levels of adipokines between two groups ($\bar{x} \pm s$)

Time-point	Vaspin(ng/mL)		Chemerin(ng/mL)		Apelin(pg/mL)	
	Observation group (*n*=52)	Control group (*n*=51)	Observation group (*n*=52)	Control group (*n*=51)	Observation group (*n*=52)	Control group (*n*=51)
Before treatment	2.35±0.44	2.46±0.40	105.12±15.56	103.98±16.63	815.52±211.18	817.99±208.99
1 month after treatment	1.58±0.36^{ac}	1.89±0.37^{a}	84.38±10.04^{ac}	93.67±11.12^{a}	679.95±145.53^{ac}	755.61±166.81^{a}
3 months after treatment	0.91±0.31^{abc}	1.34±0.33^{ab}	72.74±8.81^{abc}	80.85±9.66^{ab}	526.63±100.24^{abc}	601.12±120.84^{ab}
$F_{group/time/interaction}$ **value**	56.396/32.241/18.574		77.416/50.129/29.637		92.357/70.142/55.136	
$P_{group/time/interaction}$ **value**	<0.001/<0.001/<0.001		<0.001/<0.001/<0.001		<0.001/<0.001/<0.001	

Note: Compared with before treatment, ^{a}P<0.05; Compared with 1 month after treatment, ^{b}P<0.05; Compared with control group, ^{c}P<0.05.

3 Discussion

The pathogenesis of T2DM is relatively complex and may be associated with an imbalance between oxidation and antioxidation, as well as between pro-inflammatory and anti-inflammatory factors [7]. T2DM is characterized not only by chronic hyperglycemia but also by profound adipose tissue dysfunction; alterations in adipose tissue play a critical role in the development of systemic insulin resistance, ectopic lipid accumulation, and metabolic complications [8].

Metformin primarily lowers blood glucose by inhibiting hepatic gluconeogenesis, an effect mediated through modulation of the mitochondrial respiratory chain complex, changes in cellular energy charge, and activation of adenosine monophosphate-activated protein kinase (AMPK) [9-10]. Semaglutide, as a glucagon-like peptide-1 receptor agonist, promotes insulin synthesis and secretion from pancreatic β-cells and suppresses glucagon secretion and release from pancreatic α-cells in a glucose-dependent manner, thereby exerting its glucose-lowering effects. Its clinical application can reduce FPG, 2hPG, and HbA1c levels [11], and it is more effective than existing therapeutic modalities in lowering HbA1c [12]. Semaglutide promotes the functional transition of adipose tissue from a pro-inflammatory lipid-storing phenotype toward a more oxidative, insulin-sensitive, and metabolically flexible state; these adipose-centric adaptations may contribute to improved systemic insulin sensitivity, regulation of adipokine levels, reduction of ectopic fat deposition, and mitigation of metabolic risk in patients with T2DM [8].

Zhang *et al.* [13] demonstrated that semaglutide combined with metformin effectively improves glycolipid metabolism in patients with T2DM, although some patients did not derive benefit from this combination. A meta-analysis showed that semaglutide plus metformin significantly improved glycemic control, insulin resistance, body weight, body mass index, and lipid profiles in overweight or obese patients with T2DM [11]. Another study indicated that in patients with T2DM whose blood glucose remained inadequately controlled on metformin, the addition of oral semaglutide for 52 weeks resulted in more pronounced reductions in HbA1c and body weight compared with the addition of empagliflozin [14]. Moreover, no safety or tolerability issues were identified with the combined use of metformin and semaglutide [15]. In terms of adipokines, elevated Apelin levels are associated with decreased insulin sensitivity [16]; Chemerin is a pro-inflammatory adipokine whose increased levels are closely related to insulin resistance [17]; Vaspin regulates glucose and lipid metabolism, induces vascular dysfunction, and participates in the pathogenesis and progression of T2DM [18]. In the present study, the combination therapy group (metformin plus semaglutide) exhibited significantly lower levels of FPG, 2hPG, HbA1c, HOMA-IR, Vaspin, Chemerin, and Apelin compared with the metformin monotherapy group, supporting the aforementioned findings.

The IL-6/JAK2/STAT3 axis serves as a core signaling pathway mediating chronic inflammation and insulin resistance. TNF-α promotes the secretion of IL-6, which in turn activates the downstream JAK2/STAT3 signaling pathway, suppresses regulatory T-cell differentiation, potentiates inflammatory immune responses, amplifies the inflammatory cascade, and induces vascular endothelial dysfunction, thereby contributing to the pathogenesis of T2DM [5]. JAK2 activation promotes STAT3 phosphorylation and nuclear translocation; activated STAT3 further regulates the expression of downstream target genes, promotes adipocyte deposition, induces pancreatic β-cell apoptosis, exacerbates oxidative stress, and aggravates the severity of T2DM [19]. Deng et al. [20] demonstrated that semaglutide inhibits STAT3 expression. Martins et al. [21] showed that semaglutide suppresses TNF-α and IL-6 expression and attenuates visceral adipocyte inflammation and endoplasmic reticulum stress in mice. Metformin, on the other hand, can inhibit the JAK/STAT3 pathway via AMPK activation, reduce p-STAT3 levels, and synergistically attenuate inflammation, thereby alleviating insulin resistance [22]. Therefore, the combination of these two agents may exert dual inhibition of this axis, both upstream (suppression of TNF-α and IL-6) and downstream (blockade of p-STAT3), with a synergistic effect stronger than that of either agent alone. In the present study, after treatment with semaglutide plus metformin, the levels of FPG, 2hPG, HbA1c, HOMA-IR, and the mRNA expression of TNF-α, IL-6, STAT3, and JAK2 were all significantly lower than those in the metformin-alone group, supporting the above hypothesis. The combined therapy may modulate the IL-6/JAK2/STAT3 signaling pathway, inhibit JAK2 and STAT3 activation, alleviate oxidative stress injury to pancreatic β-cells, improve β-cell function, and thereby enhance therapeutic efficacy and control the progression of T2DM. Moreover, in vitro cell experiments have confirmed that semaglutide plus metformin synergistically suppresses high-glucose and high-lipid-induced release of TNF-α and IL-6, downregulates p-STAT3, and protects β-cell function [23], suggesting a potential mechanism underlying the combination therapy for T2DM.

In summary, semaglutide combined with metformin in the treatment of patients with T2DM can more effectively control blood glucose levels and reduce adipokine levels, and the mechanism may be related to the inhibition of IL-6/JAK2/STAT3 signaling axis activation. However, the present study did not include a semaglutide monotherapy group, and therefore it cannot be asserted that the observed therapeutic improvement is due to a genuine synergistic interaction between semaglutide and metformin. Future studies should expand the sample size and incorporate a semaglutide-alone treatment group to clarify whether the effect is additive or synergistic, thereby providing robust evidence-based support for the rational treatment of T2DM. In addition, the present study did not investigate the adverse effects of the two agents, which constitutes a limitation that warrants further exploration in subsequent research.

Conflict of Interest None

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·论　著·

司美格鲁肽联合二甲双胍治疗2型糖尿病及对IL-6/JAK2/STAT3信号轴的调控

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摘要：目的　探讨司美格鲁肽联合二甲双胍治疗2型糖尿病（T2DM）的效果，分析其对白细胞介素-6（IL-6）/Janus激酶2（JAK2）/信号转导和转录活化因子-3（STAT3）信号轴的调控作用，以及对脂肪因子水平的影响。**方法**　前瞻性选取2022年8月至2024年8月河北省沧州中西医结合医院收治的103例T2DM患者作为研究对象。采用随机数字表法分为对照组（治疗采用二甲双胍，n=51）和观察组（治疗采用二甲双胍+司美格鲁肽，n=52）。观察两组治疗前后糖代谢指标[空腹血糖（FPG）、餐后2小时血糖（2hPG）、糖化血红蛋白（HbA_{1C}）、稳态模型评估胰岛素抵抗指数（HOMA-IR）]、血清脂肪因子[丝氨酸蛋白酶抑制蛋白（Vaspin）、趋化素（Chemerin）、爱帕琳肽（Apelin）]水平，及外周血单核细胞IL-6/JAK2/STAT3信号轴相关mRNA[肿瘤坏死因子α（TNF-α）、IL-6、STAT3、JAK2]表达量。**结果**　治疗3个月后，观察组FPG、2hPG、HbA_{1C}、HOMA-IR分别为（6.56±0.66）mmol/L、（8.50±1.01）mmol/L、（6.45±0.41）%、1.88±0.31，低于对照组的（7.12±0.69）mmol/L、（9.36±1.11）mmol/L、（6.92±0.43）%、2.24±0.33（P<0.05）；观察组TNF-α、IL-6、STAT3、JAK2 mRNA相对表达量分别为2.23±0.62、2.35±0.68、1.56±0.41、1.05±0.30，低于对照组的3.40±0.74、3.05±0.87、2.13±0.58、1.59±0.40（P<0.05）；Vaspin、Chemerin、Apelin水平也低于对照组（P<0.05）。**结论**　司美格鲁肽联合二甲双胍治疗T2DM患者的治疗效果显著，可改善胰岛素抵抗，调节脂肪因子水平，可能通过抑制IL-6/JAK2/STAT3信号轴的活化发挥作用。

关键词：2型糖尿病；二甲双胍；司美格鲁肽；白细胞介素-6；Janus相关激酶2；磷酸化信号转导和转录活化因子-3；胰岛素抵抗；脂肪因子
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Effect of semaglutide combined with metformin on type 2 diabetes mellitus and its regulation of IL-6/JAK2/STAT3 signaling axis

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Abstract: Objective　To investigate the efficacy of semaglutide combined with metformin in the treatment of type 2 diabetes mellitus (T2DM), and to analyze its regulatory effect on the interleukin-6 (IL-6)/Janus kinase 2 (JAK2)/signal transducer and activator of transcription 3 (STAT3) signaling axis. **Methods**　A total of 103 patients with T2DM admitted to Cangzhou Hospital of Integrated Traditional Chinese and Western Medicine in Hebei Province from August 2022 to August 2024 were prospectively selected as research subjects. They were divided into control group (n=51, metformin) and observation group (n=52, metformin + semaglutide) using random number table. The levels of glucose metabolism indexes [fasting plasma glucose (FPG), 2-hour postprandial plasma glucose (2hPG), glycosylated hemoglobin (HbA_{1C}), Homeostasis Model Assessment Insulin Resistance Index (HOMA-IR)], serum adipokines [serine protease inhibitor (Vaspin), Chemerin, Apelin] and the expression of IL-6/JAK2/STAT3 signal axis related

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mRNA [tumor necrosis factor alpha (TNF-α), IL-6, STAT3, JAK2] in peripheral blood mononuclear cells of two groups before and after treatment were observed. **Results** After 3 months of treatment, FPG, 2hPG, HbA_{1c} and HOMA-IR in the observation group were (6.56±0.66) mmol/L, (8.50±1.01) mmol/L, (6.45±0.41) % and 1.88±0.31, respectively, which were lower than (7.12±0.69) mmol/L, (9.36±1.11) mmol/L, (6.92±0.43) % and 2.24±0.33 in the control group (P<0.05); the mRNA expression levels of TNF-α, IL-6, STAT3 and JAK2 in the observation group were 2.23±0.62, 2.35±0.68, 1.56±0.41 and 1.05±0.30 respectively, which were lower than 3.40±0.74, 3.05±0.87, 2.13±0.58 and 1.59±0.40 in the control group (P<0.05); Vaspin, Chemerin, Apelin levels in the observation group were also lower than those in the control group (P<0.05). **Conclusion** Semaglutide combined with metformin has a significant therapeutic effect in the treatment of T2DM patients, which can improve insulin resistance and regulate the level of adipokines, possibly by inhibiting the activation of IL-6/JAK2/STAT3 signaling axis.

Keywords: Type 2 diabetes mellitus; Metformin; Semaglutide; Interleukin-6; Janus kinase 2; Phosphorylated signal transducer and activator of transcription 3; Insulin resistance; Adipokines

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2型糖尿病(type 2 diabetes mellitus,T2DM)临床表现为慢性血糖升高,我国T2DM发病率约为11.2%,T2DM的发生发展可能与胰岛素抵抗有关,随着疾病进展,血糖控制难度增加[1]。临床常采用二甲双胍片治疗T2DM,可控制血糖水平,促进胰岛β细胞增殖、分化[2]。司美格鲁肽具有起效迅速、不良反应少等优点,可有效控制血糖水平,改善胰岛β细胞功能[3-4]。二甲双胍可减少糖的来源,而司美格鲁肽主要优化糖的利用,促进胰岛素分泌。二者作用机制互补,可覆盖胰岛功能缺陷、肝糖输出过多、胰岛素抵抗等多个关键环节,从而强效协同地降低血糖[2]。对于使用二甲双胍单药治疗血糖仍不达标的患者,加用司美格鲁肽是比传统磺脲类或胰岛素更优的选择,因为它不仅能强效降糖,还对心血管和肾脏具有保护作用[4]。既往研究表明白细胞介素-6(interleukin-6, IL-6)/Janus相关激酶2(Janus kinase 2,JAK2)/信号转导和转录活化因子-3(signal transducer and activator of transcription 3, STAT3)信号轴活化可引起炎性反应、胰岛素抵抗,参与T2DM等多种疾病发生发展过程[5]。但司美格鲁肽是否可调控IL-6/JAK2/STAT3信号轴尚不十分清晰。本研究主要探讨司美格鲁肽联合常规治疗T2DM患者的治疗效果,并分析其对糖代谢、脂肪因子及IL-6/JAK2/STAT3信号轴的影响,为其作用机制探讨和临床合理用药提供参考。

1　资料与方法

1.1　一般资料　本研究经河北省沧州中西医结合医院伦理委员会审核批准[项目编号:CZX2022093(申)]。前瞻性选取2022年8月至2024年8月河北省沧州中西医结合医院收治的T2DM患者作为筛选人群。(1) 纳入标准:①符合T2DM诊断标准[6],即空腹血糖(fasting plasma glucose, FPG)≥7.0 mmol/L,或餐后2 h血糖(2-hour postprandial plasma glucose, 2hPG)≥11.1 mmol/L;②符合司美格鲁肽治疗适应证;③对治疗药物耐受;④年龄≥45岁;⑤自愿参加本次研究并签署知情同意书。(2) 排除标准:①合并尿路感染、恶性肿瘤;②既往有糖皮质激素使用史;③就诊前3个月内使用降脂药物;④患有精神疾病或认知功能障碍;⑤血肌酐>正常值上限;⑥既往有胃肠手术史;⑦伴有原发性心血管疾病。(3)脱落标准:①自然失访;②未完成周期治疗。共纳入103例T2DM患者,采用随机数字表法将其分为对照组51例和观察组52例,两组一般资料差异无统计学意义(P>0.05)。见表1。

1.2　治疗方法　两组均采取个体化糖尿病饮食、运动干预。对照组治疗采用二甲双胍(河北天成药业,国药准字H13021647,规格:0.25 g/片),0.5 g/次,3次/d,口服,持续治疗3个月。观察组二甲双胍剂量同对照组,加以皮下注射司美格鲁肽(诺和诺德制药,国药准字SJ20210014,规格:1.34 mg/mL),首剂0.25 mg/次,1次/周,连续治疗4周后更改为0.5 mg/次,1次/周,继续治疗4周后,剂量可增加至1.0 mg/次,1次/周,共治疗3个月。

1.3　观察指标

1.3.1　检测血糖代谢指标　两组治疗前后检测血糖代谢指标。检测前一晚禁食8 h,次日清晨采集空腹外周静脉血5 mL,采用高效液相色谱仪(德国AUPOS SCIENTIFIC公司)检测糖化血红蛋白(glycosylated hemoglobin,HbA_{1c})水平,采用7600型全自动生化分析仪(日本日立)检测FPG、空腹胰岛素水平。进食后2 h采集外周静脉血5 mL,采用7600型全自动生化分析仪检测2hPG水平,计算稳态模型评估胰岛

素抵抗指数(Homeostasis Model Assessment of Insulin Resistance,HOMA-IR)。

1.3.2　检测 IL-6/JAK2/STAT3 信号轴相关 mRNA 表达水平　两组治疗前后分别采集空腹外周静脉血 5 mL 置于离心管内,先加入适量 Ficoll 分离液,吸取稀释后的血液,沿管壁缓慢叠加到 Ficoll 液面上方,放入离心机(-20 ℃, 1 500 r/min, 离心半径 10 cm)离心 30 min 后,液体将清晰分为 4 层,用无菌吸管小心吸弃最上层的血浆,然后沿着管壁,将白膜层(呈白雾状)及周边约 1 mm 厚度的液体轻轻吸出,转移至新的离心管中,加入至少 3 倍体积的预冷磷酸盐缓冲液,轻柔重悬,用适量培养基或缓冲液重悬洗涤后的细胞沉淀,即为分离好的外周血单核细胞(经流式细胞术检查显示 $CD45^+$ 细胞占总事件数的 80%~90%、粒细胞污染<10%)。采用 Trizol 试剂(美国 Invitrogen 公司)提取单核细胞总 RNA,参照反转录试剂盒说明书合成 cDNA,定量逆转录聚合酶链反应法检测肿瘤坏死因子α(tumor necrosis factor α,TNF-α)、IL-6、STAT3、JAK2 等的 mRNA 相对表达量:cDNA 2 μL,Real-Time Master Mix 10 μL,正反向引物各 1 μL,RNase-Free ddH_2O 补足体系至 20 μL;反应条件:95 ℃ 2 min,95 ℃ 15 s,60 ℃ 1 min,72 ℃ 30 s(循环 40 次)。相关试剂盒均购自北京天根生化公司。

1.3.3　检测脂肪因子水平　两组治疗前后分别采集空腹外周静脉血 3 mL 并分离血清(4 ℃,3 000 r/min,离心半径 10 cm,离心 8 min),血清丝氨酸蛋白酶抑制剂(Vaspin)、趋化素(Chemerin)、爱帕琳肽(Apelin)水采用以酶联免疫吸附测定法测定,上海一研生物公司提供 Vaspin、Chemerin 检测试剂盒,上海赛培森生物公司提供 Apelin 检测试剂盒。

1.4　统计学方法　采用 SPSS 26.0 软件分析数据。符合正态分布的计量资料采用 $\bar{x}\pm s$ 表示,组间比较采用独立样本 t 检验,多时间点指标比较采用重复测量方差分析,两两比较采用 LSD-t 检验。计数资料以例(%)表示,比较采用 χ^2 检验。P<0.05 为差异有统计学意义。

2　结　果

2.1　两组一般资料比较　两组一般资料比较差异无统计学意义(P>0.05)。见表 1。

2.2　两组 FPG、2hPG、HbA_{1C} 及 HOMA-IR 水平比较　相较于治疗前,治疗 1 个月和 3 个月时,两组 FPG、2hPG、HbA_{1C} 及 HOMA-IR 水平呈降低趋势(P<0.05);治疗 1 个月和 3 个月时,观察组 FPG、2hPG、HbA_{1C}、HOMA-IR 水平均显著低于对照组(P<0.05)。见表 2。

2.3　两组 IL-6/JAK2/STAT3 信号轴相关 mRNA 表达水平比较　相较于治疗前,治疗 1 个月和 3 个月时两组 TNF-α、IL-6、STAT3、JAK2 mRNA 表达水平呈降低趋势(P<0.05);治疗 1 个月、3 个月观察组 TNF-α、IL-6、STAT3、JAK2 mRNA 表达水平显著低于对照组(P<0.05)。见表 3。

2.4　两组脂肪因子水平比较　相较于治疗前,治疗 1 个月和 3 个月时,两组 Vaspin、Chemerin、Apelin 水平呈降低趋势(P<0.05);治疗 1 个月、3 个月观察组 Vaspin、Chemerin、Apelin 水平低于对照组(P<0.05)。见表 4。

表 1　两组一般资料比较

Tab.1　Comparison of general information between two groups

项目	观察组(n=52)	对照组(n=51)	χ^2/t 值	P 值
性别[例(%)]				
男	28(53.85)	30(58.82)	0.259	0.611
女	24(46.15)	21(41.18)		
年龄(岁,$\bar{x}\pm s$)	57.54±6.58	58.44±5.03	0.779	0.438
身体质量指数(kg/m²,$\bar{x}\pm s$)	24.83±1.04	25.18±1.23	1.561	0.122
糖尿病病程(年,$\bar{x}\pm s$)	3.24±0.63	3.18±0.52	0.527	0.600
基础疾病[例(%)]				
高血压	10(19.23)	15(29.41)	1.452	0.228
高脂血症	11(21.15)	13(25.49)	0.271	0.603
冠心病	9(17.31)	7(13.73)	0.252	0.616

注:冠心病为冠状动脉粥样硬化性心脏病。

表 2　两组 FPG、2hPG、HbA_{1C} 及 HOMA-IR 水平比较　($\bar{x}\pm s$)

Tab.2　Comparison of FPG, 2hPG, HbA_{1C} and HOMA-IR levels between two groups　($\bar{x}\pm s$)

时间点	HbA_{1C}(%)		FPG(mmol/L)		2hPG(mmol/L)		HOMA-IR	
	观察组(n=52)	对照组(n=51)	观察组(n=52)	对照组(n=51)	观察组(n=52)	对照组(n=51)	观察组(n=52)	对照组(n=51)
治疗前	8.60±0.66	8.51±0.72	9.50±0.78	9.38±0.85	11.65±1.23	11.73±1.30	3.02±0.42	3.15±0.35
治疗 1 个月	7.36±0.53^{ac}	7.89±0.60^{a}	8.19±0.75^{ac}	8.73±0.80^{a}	10.02±1.15^{ac}	10.78±1.24^{a}	2.53±0.35^{ac}	2.71±0.34^{a}
治疗 3 个月	6.45±0.41^{abc}	6.92±0.43^{ab}	6.56±0.66^{abc}	7.12±0.69^{ab}	8.50±1.01^{abc}	9.36±1.11^{ab}	1.88±0.31^{abc}	2.24±0.33^{ab}
$F_{组间/时间/交互}$值	56.352/35.285/16.396		68.544/36.956/20.085		74.162/46.245/22.357		63.396/40.175/21.193	
$P_{组间/时间/交互}$值	<0.001/<0.001/<0.001		<0.001/<0.001/<0.001		<0.001/<0.001/<0.001		<0.001/<0.001/<0.001	

注:与本组治疗前比较,^{a}P<0.05;与本组治疗 1 个月比较,^{b}P<0.05;与对照组同期比较,^{c}P<0.05。

表3　两组IL-6/JAK2/STAT3信号轴相关mRNA表达水平比较　($\bar{x}\pm s$)

Tab.3　Comparison of expression levels of IL-6/JAK2/STAT3 signal axis related mRNA between two groups　($\bar{x}\pm s$)

时间点	TNF-α		IL-6		STAT3		JAK2	
	观察组(n=52)	对照组(n=51)	观察组(n=52)	对照组(n=51)	观察组(n=52)	对照组(n=51)	观察组(n=52)	对照组(n=51)
治疗前	6.64±1.73	7.18±1.29	7.11±1.46	6.87±1.59	6.00±1.38	5.74±1.53	5.52±1.23	5.74±1.01
治疗1个月	4.12±0.95^{ac}	5.23±1.01^{a}	4.35±1.12^{ac}	5.38±1.20^{a}	3.56±0.73^{ac}	3.91±0.68^{a}	3.88±0.87^{ac}	4.26±0.95^{ac}
治疗3个月	2.23±0.62^{abc}	3.40±0.74^{ab}	2.35±0.68^{abc}	3.05±0.87^{ab}	1.56±0.41^{abc}	2.13±0.58^{ab}	1.05±0.30^{abc}	1.59±0.40^{ab}
$F_{组间/时间/交互}$值	74.152/52.326/33.219		75.442/50.036/36.247		75.214/46.396/30.112		63.587/41.031/26.359	
$P_{组间/时间/交互}$值	<0.001/<0.001/<0.001		<0.001/<0.001/<0.001		<0.001/<0.001/<0.001		<0.001/<0.001/<0.001	

注：与本组治疗前比较，^{a}P<0.05；与本组治疗1个月比较，^{b}P<0.05；与对照组同期比较，^{c}P<0.05。

表4　两组脂肪因子水平比较　($\bar{x}\pm s$)

Tab.4　Comparison of expression levels of adipokines between two groups　($\bar{x}\pm s$)

时间点	Vaspin(ng/mL)		Chemerin(ng/mL)		Apelin(pg/mL)	
	观察组(n=52)	对照组(n=51)	观察组(n=52)	对照组(n=51)	观察组(n=52)	对照组(n=51)
治疗前	2.35±0.44	2.46±0.40	105.12±15.56	103.98±16.63	815.52±211.18	817.99±208.99
治疗1个月	1.58±0.36^{ac}	1.89±0.37^{a}	84.38±10.04^{ac}	93.67±11.12^{a}	679.95±145.53^{ac}	755.61±166.81^{a}
治疗3个月	0.91±0.31^{abc}	1.34±0.33^{ab}	72.74±8.81^{abc}	80.85±9.66^{ab}	526.63±100.24^{abc}	601.12±120.84^{ab}
$F_{组间/时间/交互}$值	56.396/32.241/18.574		77.416/50.129/29.637		92.357/70.142/55.136	
$P_{组间/时间/交互}$值	<0.001/<0.001/<0.001		<0.001/<0.001/<0.001		<0.001/<0.001/<0.001	

注：与本组治疗前比较，^{a}P<0.05；与本组治疗1个月比较，^{b}P<0.05；与对照组同期比较，^{c}P<0.05。

3　讨　论

T2DM发病机制较为复杂，可能与氧化-抗氧化失衡、促炎因子-抗炎因子失衡等有关[7]。T2DM的特征不仅在于慢性高血糖，还在于深度脂肪组织功能障碍，脂肪组织的改变在全身性胰岛素抵抗、异位脂质积聚和代谢并发症的发展中起着重要作用[8]。

二甲双胍主要通过抑制肝脏糖异生来降低血糖，这种作用是通过调节线粒体呼吸链复合物、细胞能量电荷的变化和腺苷酸活化蛋白激酶(adenosine monophosphate-activated protein kinase，AMPK)的激活来介导[9-10]。作为胰高血糖素样肽-1受体激动剂的司美格鲁肽，则是以葡萄糖依赖性的方式促进胰岛β细胞合成与分泌胰岛素、抑制胰岛α细胞分泌与释放胰高血糖素，起到降血糖的作用，其临床应用可降低FPG、2hPG、HbA_{1C}水平[11]，而且在降低HbA_{1C}方面比现有的治疗手段更为有效[12]。司美格鲁肽促进脂肪组织从促炎性脂质储存表型向更具氧化性、胰岛素敏感性和代谢灵活状态的功能转变，这些以脂肪为中心的适应可能有助于改善全身胰岛素敏感性，调节脂肪因子水平，减少异位脂肪沉积，降低T2DM患者的代谢风险[8]。

张凤丽等[13]研究表明司美格鲁肽联合二甲双胍治疗T2DM患者可有效改善糖脂代谢，但有部分患者未从中获益。一篇荟萃分析显示，司美格鲁肽联合二甲双胍治疗显著改善了超重或肥胖T2DM患者的血糖控制、胰岛素抵抗、体质量、身体质量指数和血脂水平[11]。一项研究显示，在二甲双胍治疗仍无法控制血糖的T2DM患者中，联合口服司美格鲁肽52周时，较联合恩格列净能更显著地降低HbA_{1C}水平并减轻体质量[14]。且二甲双胍和司美格鲁肽合用时未发现安全性或耐受性问题[15]。另外，在脂肪因子方面，Apelin水平升高可降低胰岛素敏感性[16]；Chemerin为促炎性脂肪因子，其水平升高与胰岛素抵抗密切相关[17]；Vaspin可调节糖脂代谢，引起血管功能损伤，参与T2DM发生发展过程[18]。本研究二甲双胍联合司美格鲁肽治疗组FPG、2hPG、HbA_{1C}、HOMA-IR以及Vaspin、Chemerin、Apelin水平均显著低于单用二甲双胍的对照组，支持了上述研究结论。

IL-6/JAK2/STAT3是介导慢性炎症与胰岛素抵抗的核心信号轴。TNF-α可促进IL-6分泌，IL-6则通过激活下游JAK2/STAT3信号通路，抑制调节性T细胞分化、促进炎症免疫反应，并放大炎性级联反应，引发血管内皮细胞功能障碍，进而参与T2DM的发生发展[5]。JAK2活化可促进STAT3磷酸化与核转位，激活的STAT3进一步调控下游靶基因表达，促使脂肪细胞沉积，促进胰岛β细胞凋亡，并可加剧氧化应激反应，加重T2DM病情严重程度[19]。Deng等[20]研究表明司美格鲁肽可抑制STAT3表达。Martins等[21]研究表明司美格鲁肽可抑制TNF-α、IL-6表达，并可减

轻小鼠内脏脂肪细胞炎症-内质网应激反应。而二甲双胍则可通过 AMPK 抑制 JAK/STAT3 通路，降低 p-STAT3，协同减轻炎症，进而减轻胰岛素抵抗[22]。因此，二者联合可能从上游（抑制 TNF-α、IL-6）与下游（阻断 p-STAT3）双重抑制该轴，协同效应强于单药。

本研究中司美格鲁肽联合二甲双胍治疗后，FPG、2hPG、HbA_{1c}、HOMA-IR，以及 TNF-α、IL-6、STAT3、JAK2 的 mRNA 表达水平均显著低于单纯二甲双胍治疗，支持了以上推测，二者联合应用或可能通过调控 IL-6/JAK2/STAT3 信号通路，抑制 JAK2 及 STAT3 活化，减轻胰岛β细胞氧化应激损伤，改善胰岛β细胞功能，进而提高疗效，控制 T2DM 病情进展。且目前已有体外细胞实验证实，司美格鲁肽+二甲双胍协同抑制高糖高脂诱导的 TNF-α、IL-6 释放，并下调 p-STAT3，保护β细胞功能[23]，这可能是二者联合治疗 T2DM 的潜在机制。

综上所述，司美格鲁肽联合二甲双胍治疗 T2DM 患者，可更有效地控制血糖水平，降低脂肪因子水平，其机制可能与抑制 IL-6/JAK2/STAT3 信号轴活化有关。然而本研究并未设置单独的司美格鲁肽治疗组，无法断言观察到的疗效提升是由于司美格鲁肽与二甲双胍之间存在真正的协同作用。后续研究中应扩大样本量，增设单纯司美格鲁肽治疗组，明确两者间是叠加效应还是协同效应，为 T2DM 治疗提供合理的循证依据。另外，本研究未探讨两药治疗的不良反应，是一大不足，有待后续研究进一步完善。

利益冲突　无

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