中国临床研究 Chin J Clin Res, January 2026, Vol.39, No.1

Cite as: Liu C, Zhu L, Guo YW, Zhu ML, He L. Research on the correlation of serum lipid with serum Adropin and 25-hydroxylvitamin D3 levels in patients with type 2 diabetes mellitus of different body mass indexes [J]. Chin J Clin Res, 2026, 39(1):57-62.

DOI: 10.13429/j.cnki.cjcr.2026.01.011

Research on the correlation of serum lipid with serum Adropin and 25-hydroxylvitamin D_3 levels in patients with type 2 diabetes mellitus of different body mass indexes

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Abstract: Objective To explore the correlation of serum Adropin, 25- hydroxylvitamin D3 [25 (OH)D3] levels with serum lipids in patients with type 2 diabetes mellitus (T2DM)stratified by different body mass indexes (BMI), and to provide new ideas for the prevention and treatment of lipid metabolism-related issues in T2DM. **Methods** A total of 199 T2DM patients hospitalized in Zhengzhou Central Hospital from May 2023 to July 2024 were selected as research subjects. They were divided into three groups according to BMI: normal weight group (18.5 kg/m2 ≤BMI<24 kg/m^2 , n=50), overweight group (24 kg/m2 ≤BMI<28 kg/m2 , n=60), and obesity group (BMI≥28 kg/m^2 , n=89). General clinical data, and laboratory indicators including fasting plasma glucose (FPG), glycated hemoglobin (HbA1c), four blood lipid indicators [total cholesterol (TC), triglycerides (TG), high-density lipoprotein cholesterol (HDL-C), low- density lipoprotein cholesterol (LDL-C)], and 25 (OH)D3 were collected and measured. Serum Adropin levels in each group were detected by ELISA. The changes of Adropin, 25 (OH)D3, blood lipids and other indicators among groups and their correlations were analyzed. **Results** FPG, HbA1c, TC, TG, LDL-C, and fasting insulin in the obesity group were significantly higher than those in the normal weight group and overweight group (P<0.05), while HDL-C and serum 25 (OH)D3 in the obesity group were significantly lower than those in the other two groups (P<0.05). Adropin decreased sequentially in the normal weight group, overweight group, and obesity group (P<0.05). The proportion of patients with hyperlipidemia was 44.00% in the normal weight group, 56.67% in the overweight group, and as high as 69.66% in the obesity group, with a statistically significant difference (P<0.05). In each group, T2DM patients complicated with hyperlipidemia had significantly lower serum Adropin and 25 (OH)D3 levels. The correlation of Adropin and 25 (OH)D3 with TC, TG, and LDL-C were negative, while those with HDL-C were positive (P<0.05). **Conclusion** The decrease of serum Adropin and 25 (OH)D3 is closely related to the increased risk of hyperlipidemia in T2DM patients across different BMI strata. They have potential significance for the prevention and treatment of obesity and hyperlipidemia in T2DM patients.

Keywords: Type 2 diabetes mellitus; Adropin; 25-hydroxylvitamin D3; Hyperlipidemia ; Body mass index

Fund program: Science and Technology Research Project of Henan Province (182102310089)

Type 2 diabetes mellitus (T2DM) is one of the major chronic diseases threatening human health. Its typical clinical manifestations include polydipsia, polyphagia, polyuria, and weight loss, which are caused by persistent hyperglycemia. The core pathological mechanisms involve insulin resistance and insulin deficiency. T2DM is closely associated with body mass index (BMI); as BMI increases, the risk of developing T2DM significantly rises. Studies have indicated that obesity and the onset of T2DM may be linked to insulin resistance, immune-inflammatory responses, abnormal microRNA expression, and dyslipidemia [1]. The underlying mechanism may be that insulin promotes fat synthesis and storage while inhibiting lipolysis, thereby disrupting glucose and lipid metabolism in T2DM patients, triggering dyslipidemia, exacerbating the elevation of the homeostasis model assessment of insulin resistance (HOMA-IR) index, and increasing the risk of hyperlipidemia simultaneously. Epidemiological surveys show that the prevalence of dyslipidemia in the general population ranges from 20% to 40%, whereas in T2DM patients, the prevalence is as high as 60%, and there is a strong positive correlation between BMI and the development of dyslipidemia [2].

Adropin is a secretory protein discovered by Kumar *et al.* [3] in 2008, which is regulated by energy balance-related genes. It is closely associated with obesity and T2DM, suggesting that Adropin can enhance insulin sensitivity and correct lipid metabolism disorders. In addition, vitamin D_3 is another critical factor influencing the development of T2DM. 25-hydroxyvitamin D_3 [25(OH)D_3] is the hydroxylated product of vitamin D_3 in the liver, which exists in a stable form in the body and is therefore commonly used as an indicator to assess vitamin D levels in vivo. 1,25-dihydroxyvitamin D_3 [1,25$(OH)_2D_3$] is the active form of vitamin D, which can bind to vitamin D receptors in the body and play a role in insulin synthesis and secretion [4].

This study is the first to conduct a joint analysis of two indicators, 25(OH)D_3 and Adropin, to explore their effects on lipid metabolism in T2DM patients stratified by BMI and their potential role in the context of dyslipidemia. It expands the research perspective on lipid metabolism in T2DM and provides new insights for the individualized prevention and treatment of lipid metabolism disorders in T2DM. This study is reported as follows.

1 Subjects and Methods

1.1 Study Subjects

A total of 199 patients with T2DM hospitalized at Zhengzhou Central Hospital from May 2023 to July 2024 were enrolled as study subjects. **Inclusion criteria:** (1) Diagnosed with T2DM in accordance with the 1999 WHO etiological classification system for diabetes mellitus; (2) Body mass index (BMI) ≥ 18.5 kg/m²; (3) Aged 18 to 75 years. **Exclusion criteria:**(1) Complicated with various acute complications of diabetes, including hyperosmolar hyperglycemic state, diabetic ketoacidosis, lactic acidosis, and hypoglycemia; (2) Complicated with acute or chronic infections; (3) Complicated with autoimmune diseases, hepatic or renal insufficiency, or malignant tumors; (4) Suffering from other endocrine system diseases such as hyperadrenocorticism or hyperthyroidism; (5) Having taken statins, hormones, vitamin D, or other drugs that may affect blood lipid or 25(OH)D_3 levels within the past 3 months. Eligible patients were grouped by BMI according to the standards of the National Health Commission of the People's Republic of China: normal weight group (18.5 kg/m² ≤ BMI < 24 kg/m²), overweight group (24 kg/m² ≤ BMI < 28 kg/m²), and obese group (BMI ≥ 28 kg/m²). This study was conducted in compliance with the Declaration of Helsinki and approved by the Medical Ethics Committee of Zhengzhou Central Hospital (Approval No.: ZXYY2024147). All patients were informed of the study procedures and signed informed consent forms, and all data were anonymized.

1.2 Study Methods

General data including age, gender, height, body weight, blood pressure, and disease duration were collected from patients. Clinical and laboratory indicators such as liver and kidney function, and C-reactive protein were measured and collected. Serum Adropin levels in each group were detected using the enzyme-linked immunosorbent assay (ELISA) method. Fasting plasma glucose (FPG), glycated hemoglobin (HbA1c), serum 25-hydroxyvitamin D_3 [25(OH)D_3], and blood lipid indicators including total cholesterol (TC), triglyceride (TG), high-density lipoprotein cholesterol (HDL-C), and low-density lipoprotein cholesterol (LDL-C) were measured using an automatic biochemical analyzer. Patients were divided into hyperlipidemia and non-hyperlipidemia groups according to the definition of hyperlipidemia in the 2023 Chinese guideline for lipid management [2]. Changes and correlations of serum Adropin, 25(OH)D_3 with hyperlipidemia status and other indicators were analyzed across groups.

Height and body weight of all subjects were measured by fixed personnel, and BMI was calculated accordingly. Physical examinations included measurements of height, BMI, waist-to-hip ratio, and blood pressure. Fasting venous blood samples (defined as 8–10 hours of overnight fasting) were collected, and blood analyses were performed in the Clinical Laboratory of Zhengzhou Central Hospital to measure biochemical indicators such as FPG, HbA1c, fasting C-peptide, insulin, liver and kidney function, serum 25(OH)D_3, blood lipid indicators, and HOMA-IR.

1.3 Statistical Methods

All data were processed using SPSS 27.0 statistical software. Continuous variables conforming to a normal distribution were expressed as $\bar{x}$ ±s, and comparisons of clinical data between different groups were performed using one-way analysis of variance (ANOVA). Variables not conforming to a normal distribution were expressed as $M(Q_1, Q_3)$, and comparisons were conducted using non-parametric tests. Categorical variables were expressed as n (%), and comparisons were performed using the χ^2 test. The relationship between Adropin, 25(OH)D_3 and hyperlipidemia was analyzed using logistic regression analysis. The correlation between Adropin, 25(OH)D_3 and blood lipid indicators was examined using Spearman's rank correlation analysis. A P value < 0.05 was considered statistically significant.

2 Results

2.1 Comparison of General Data

FPG, HbA1c, TC, LDL-C, TG, fasting C-peptide, and fasting insulin were significantly elevated in the obese group compared with the normal weight and overweight groups (P<0.05), whereas HDL-C and serum 25-hydroxyvitamin D_3 [25(OH)D_3] in the obese group were significantly lower than those in the other two

groups (P<0.05). Diastolic blood pressure in the obese group was significantly higher than that in the normal weight group (P<0.05), and systolic blood pressure in both the overweight and obese groups was significantly higher than that in the normal weight group (P<0.05). Adropin levels decreased sequentially from the normal weight group to the overweight group and then to the obese group, while the homeostasis model assessment of insulin resistance index (HOMA-IR) increased progressively across these groups (P<0.05). **[Table 1]**

2.2 Association Between Different BMI Groups and Complicated Hyperlipidemia

The prevalence of complicated hyperlipidemia was 44.00% in the normal weight group, 56.67% in the overweight group, and as high as 69.66% in the obese group, with a statistically significant difference among the three groups (P<0.05). **[Table 2]**

2.3 Relationship Between Complicated Hyperlipidemia and Serum Adropin, 25(OH)D₃ in Different BMI Groups

In all three groups, serum Adropin and 25(OH)D₃ levels in patients with complicated hyperlipidemia were significantly lower than those in patients without hyperlipidemia, with statistically significant differences (P<0.05). **[Table 3]**

2.4 Logistic Regression Analysis of the Effects of Adropin and 25(OH)D₃ on Hyperlipidemia in Different BMI Groups

Logistic regression analysis was conducted with hyperlipidemia as the dependent variable in each BMI group. After adjusting for confounding factors such as age and disease duration, the results showed that decreased Adropin and 25(OH)D₃ levels were independent risk factors for hyperlipidemia (P<0.05). Specifically, for each 1-unit increase in Adropin and 25(OH)D₃ in the normal weight group, the risk of hyperlipidemia decreased by 18.6% and 14.4%, respectively; in the overweight group, each 1-unit increase was associated with a 24.6% and 43.1% reduction in hyperlipidemia risk, respectively; in the obese group, each 1-unit increase correlated with a 57.4% and 58.1% decrease in hyperlipidemia risk, respectively. **[Table 4]**

2.5 Correlation Between Adropin, 25(OH)D₃ and Blood Lipids in Different BMI Groups

In all BMI subgroups, Adropin and 25(OH)D₃ were significantly negatively correlated with TC, TG, and LDL-C, and significantly positively correlated with HDL-C (P<0.05). **[Table 5]**

Tab.1 Comparison of general data of subjects ($\bar{x} \pm s$)

Item	Normal weight group (n=50)	Overweight group (n=60)	Obese group (n=89)	F/H value	P value
Duration of disease (years)	6.10±2.34	6.87±3.34	5.81±2.71	2.540	0.081
Age (years)	52.92±11.18	53.62±9.60	51.28±12.42	0.834	0.436
Systolic blood pressure (mmHg)	127.58±13.00	133.93±13.79[b]	135.38±16.38[b]	4.605	0.011
Diastolic blood pressure (mmHg)	77.94±7.30	79.60±6.34	82.64±14.47[b]	3.282	0.040
FPG (mmol/L)	6.33±1.66	6.86±1.24	7.57±2.27[bc]	7.484	0.001
HbA1c (%)	7.38±1.51	7.89±1.65	8.70±2.24[bc]	8.320	<0.001
TC (mmol/L)	4.17±1.12	4.39±1.23	4.72±1.56[bc]	3.075	0.048
TG (mmol/L)[a]	1.19(0.87, 1.66)	1.44(1.05, 2.02)	1.85(1.30, 2.87)[bc]	26.184	<0.001
HDL-C (mmol/L)	1.20±0.38	1.10±0.46	0.74±0.35[bc]	27.359	<0.001
LDL-C (mmol/L)	2.15±0.96	2.29±0.85	2.70±0.96[bc]	6.687	0.002
Creatinine (μmol/L)	61.69±17.65	69.09±15.44	67.00±21.31	2.228	0.111
Fasting insulin (μIU/mL)	5.42±2.93	7.93±5.43	10.65±8.82[bc]	9.807	<0.001
FCP (μg/mL)[a]	1.74(1.17, 2.45)	2.12(1.41, 2.69)	2.56(1.20, 3.42)[bc]	7.531	0.023
25-(OH)D₃ (ng/mL)	22.20±8.06	20.64±8.06	14.50±5.41[bc]	24.282	<0.001
Adropin (ng/mL)	21.76±9.93	17.19±7.69[b]	14.38±7.71[bc]	12.599	<0.001
HOMA-IR[a]	1.40(0.81, 2.04)	1.83(1.32, 3.47)[b]	2.62(1.42, 4.74)[bc]	27.927	<0.001

Note:[a] Data are expressed as $M(Q_1, Q_3)$;[b] P < 0.05 compared with the normal weight group;[c] P < 0.05 compared with the overweight group.

Tab.2 Relationship between different BMI groups and hyperlipidemia

Group	n	Non-hyperlipidemia	Complicated hyperlipidemia	χ^2 value	P value
Normal weight group	50	28 (56.00)	22 (44.00)	8.982	0.011
Overweight group	60	26 (43.33)	34 (56.67)		
Obese group	89	27 (30.34)	62 (69.66)		

Tab.3 Relationship between hyperlipidemia and Adropin and 25-(OH)D3 in different BMI groups (ng/mL)

Group	Index	Non-hyperlipidemia	Complicated hyperlipidemia	*t* value	P value
Normal weight group (n=50)	25-(OH)D_3	27.07±6.27	16.01±5.39	6.580	<0.001
	Adropin	27.54±7.75	14.40±7.19	6.144	<0.001
Overweight group (n=60)	25-(OH)D_3	26.86±7.29	15.89±4.69	7.075	<0.001
	Adropin	23.49±6.16	12.38±4.69	7.938	<0.001
Obese group (n=89)	25-(OH)D_3	19.38±4.18	11.49±3.56	9.504	<0.001
	Adropin	21.91±5.35	9.73±4.64	11.34	<0.001

Tab.4 Binary logistic regression of hyperlipidemia with Adropin and 25-(OH)D_3 in different BMI groups

Variable	Grouping	*β*	*SE*	*Wald*	*OR*	95% *CI*	*P* value
25-(OH)D_3	Normal weight group (*n*=50)	-0.265	0.106	6.305	0.856	0.657 ~ 0.989	0.012
	Overweight group (*n*=60)	-0.517	0.234	4.951	0.569	0.328 ~ 0.971	0.026
Adropin	Obese group (*n*=89)	-0.894	0.363	6.079	0.419	0.215 ~ 0.695	0.014
	Normal weight group (*n*=50)	-0.187	0.076	5.997	0.814	0.614 ~ 0.956	0.014
	Overweight group (*n*=60)	-0.285	0.119	5.783	0.754	0.511 ~ 0.968	0.016
	Obese group (*n*=89)	-0.745	0.236	9.937	0.426	0.228 ~ 0.798	0.001

Note: The dependent variable was hyperlipidemia; adjusted covariates included age, disease duration, blood pressure, and HOMA-IR.

Tab.5 Correlation of Adropin and 25（OH）D_3 with blood lipids in different BMI groups

Variable	Grouping	TC		TG		HDL-C		LDL-C	
		r	*P* value	*r*	*P* value	*r*	*P* value	*r*	*P* value
25-(OH)D_3	Normal weight group (*n*=50)	-0.369	0.007	-0.368	0.008	0.585	<0.001	-0.615	<0.001
	Overweight group (*n*=60)	-0.062	<0.001	-0.416	0.003	0.356	0.007	-0.627	<0.001
	Obese group (*n*=89)	-0.377	<0.001	-0.311	0.003	0.654	<0.001	-0.350	0.001
Adropin	Normal weight group (*n*=50)	-0.461	0.002	-0.404	0.003	0.426	0.002	-0.498	<0.001
	Overweight group (*n*=60)	-0.482	<0.001	-0.531	<0.001	0.462	<0.001	-0.448	<0.001
	Obese group (*n*=89)	-0.403	<0.001	-0.325	0.002	0.64	<0.001	-0.368	<0.001

3 Discussion

Recent studies have revealed that Adropin and 25(OH)D_3 influence glucose and lipid metabolism, offering novel insights and therapeutic targets for the prevention and management of obesity and hyperlipidemia in patients with T2DM. This cross-sectional study aimed to explore the correlations between serum Adropin and 25(OH)D_3 levels and blood lipid profiles in T2DM patients stratified by BMI.

Adropin is a newly identified energy-regulating protein involved in multiple physiological processes such as glucose and lipid metabolism, and it is closely associated with obesity, diabetes, and cardiovascular diseases [5]. In this study, serum Adropin levels decreased in a stepwise manner with increasing BMI, suggesting that low Adropin levels may be linked to metabolic disorders. This finding aligns with conclusions from animal experiments demonstrating Adropin's metabolic-improving effects [6]. Additionally, consistent with previous studies reporting significantly reduced Adropin levels in obese populations [7], our results further support this association. Adropin may regulate metabolism through multiple mechanisms. White adipose tissue (WAT) and brown adipose tissue (BAT) are the primary adipose subtypes: excessive WAT accumulation leads to obesity, while BAT, rich in mitochondria, enhances energy expenditure to reduce body weight and regulate metabolism [8]. Adropin promotes BAT proliferation by activating the PI3K/AKT pathway and inhibits WAT formation by downregulating the expression of transcription factors C/EBP-α, C/EBP-β, and PPAR-γ, thereby reducing obesity risk [9]. Skeletal muscle is another key tissue for Adropin-mediated energy regulation: Adropin increases the phosphorylation of protein kinase B (PKB), which upregulates the expression of glucose transporter 4 (GLUT4) on the skeletal muscle cell membrane, ultimately enhancing muscle energy metabolism and alleviating insulin resistance and obesity [10-11]. Furthermore, Adropin suppresses hepatic gluconeogenesis via downregulating the cAMP/PKA signaling pathway, inhibits protein phosphatase 2A

(PP2A), and activates the AMP-activated protein kinase (AMPK) pathway to reduce fat accumulation [12].

Our data analysis showed that Adropin was negatively correlated with TC, TG, and LDL-C, and positively correlated with HDL-C across all three BMI groups. Notably, the protective effect of Adropin against hyperlipidemia became more significant with increasing BMI, suggesting that severe Adropin deficiency in obese patients may act as an amplifier of lipid metabolic disorders [13-14]. This finding is supported by animal experiments focused on hepatic glucose and lipid metabolism: high Adropin levels reduced TG, TC, and LDL-C levels while increasing HDL-C levels in hyperlipidemic rats, a mechanism possibly linked to the AMPK pathway [15]. *In vitro* studies have demonstrated that Adropin increases AMPK phosphorylation in hepatocytes, which inhibits acetyl-CoA carboxylase activity and reduces malonyl-CoA production. This relieves the allosteric inhibition of carnitine palmitoyltransferase 1 by malonyl-CoA, thereby promoting fatty acid oxidation [16].

$25(OH)D_3$ not only regulates traditional bone metabolism and calcium-phosphorus homeostasis but also modulates insulin sensitivity, immune function, and inflammatory responses, and is associated with obesity [17].

In this study, serum $25(OH)D_3$ levels were significantly lower in the obese group, which was inversely correlated with increased homeostasis model assessment of insulin resistance (HOMA-IR) values. This suggests that $25(OH)D_3$ deficiency is associated with elevated risks of insulin resistance and obesity, consistent with a previous study showing that $25(OH)D_3$ levels are significantly reduced in hyperlipidemic patients and negatively correlated with TC, TG, LDL-C, fasting plasma glucose (FPG), fasting insulin, HOMA-IR, BMI, waist-hip ratio, and waist-height ratio, while positively correlated with HDL-C [18]. A relevant meta-analysis found that each 10 ng/mL increase in vitamin D levels was associated with an approximately 8% reduction in abdominal fat content, indicating a significant negative correlation between $25(OH)D_3$ levels and abdominal obesity risk [19]. These findings suggest that $25(OH)D_3$ inhibits preadipocyte differentiation into mature adipocytes, and its deficiency removes this inhibitory effect, promoting fat accumulation [20].

However, some studies propose an alternative perspective: $25(OH)D_3$ deficiency may not be a cause of obesity but rather a consequence. Obese patients tend to have reduced outdoor activity and sun exposure, which decreases endogenous $25(OH)D_3$ synthesis. Additionally, vitamin D supplementation did not significantly alter BMI, waist circumference, or waist-hip ratio in obese patients compared to a placebo group [21-22]. The underlying molecular mechanism may involve obesity-induced inhibition of hepatic cytochrome P450 2R1 (CYP2R1) activity, which is critical for vitamin D hydroxylation, leading to reduced $25(OH)D_3$ production [23-24].

Combining our results with previous literature, we conclude that there is an interaction between $25(OH)D_3$ and BMI. Although numerous studies have established an association between $25(OH)D_3$ deficiency and obesity, the causal relationship remains unclear, and their complex interaction complicates efforts to definitively establish causality.

This study found that $25(OH)D_3$ regulates blood lipids across all BMI subgroups, with a stronger protective effect observed in the obese group. Reduced $25(OH)D_3$ levels are associated with an increased risk of dyslipidemia, consistent with previous findings [25]. Chang *et al.* [26] revealed a potential mechanism: high serum $25(OH)D_3$ levels increase the AMP/ATP ratio to enhance AMPK activity, which upregulates the expression of silent information regulator 1 (SIRT1). SIRT1 inhibits fat synthesis-related genes and modulates lipid metabolism. Genetic studies suggest that vitamin D receptor (VDR) genotypes can regulate lipid metabolism-related gene expression by influencing VDR function, thereby reducing the risk of dyslipidemia [27-28]. Furthermore, $25(OH)D_3$ may indirectly affect lipid metabolism by regulating inflammatory responses, promoting calcium absorption, and modulating parathyroid hormone levels [29-30].

This study has several limitations: (1) The sample only included inpatients, and did not cover outpatients or community-dwelling individuals; (2) Confounding factors such as metabolic status, hypoglycemic medication use, and personal lifestyle habits were not fully controlled, which may have reduced the accuracy of the conclusions. The mechanisms underlying the effects of Adropin and $25(OH)D_3$ on metabolic diseases remain incompletely understood, and further animal experiments and large-scale prospective studies are needed to validate our hypotheses.

In conclusion, as BMI increases, the incidence of hyperlipidemia rises while Adropin and $25(OH)D_3$ levels decrease, indicating that both are independent protective factors against hyperlipidemia in T2DM patients. The protective effects of Adropin and $25(OH)D_3$ against dyslipidemia are enhanced in a BMI-dependent manner, which may be related to the degree of metabolic disorder in obese individuals. Therefore, the nutritional status of Adropin and $25(OH)D_3$ may have important clinical implications for obese T2DM patients, suggesting their potential for greater roles in the prevention and treatment of metabolic diseases in the future.

Conflict of Interest The authors declare no competing interest

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Submission Received: 2025-09-03 /**Revised:**2025-09-28

·论 著·

不同身体质量指数2型糖尿病患者的血脂与血清Adropin、25-羟基维生素D_3水平的研究

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摘要：目的 探讨不同身体质量指数（BMI）分层的2型糖尿病（T2DM）患者血清Adropin和25-羟基维生素D_3[25(OH)D_3]水平与血脂之间的相关性，为T2DM脂质代谢相关防治问题提供新的思路。**方法** 选取2023年5月至2024年7月在郑州市中心医院住院的T2DM患者199例作为研究对象，按照BMI分为正常组（18.5 kg/m^2≤BMI<24 kg/m^2，n=50）、超重组（24 kg/m^2≤BMI<28 kg/m^2，n=60）和肥胖组（BMI≥28 kg/m^2，n=89），收集和测量各组一般资料及空腹血糖、糖化血红蛋白、血脂四项、25(OH)D_3等实验室指标，采用ELISA法检测各组血清Adropin水平。分析各组Adropin、25(OH)D_3、血脂和其他指标的变化及相关性。**结果** 空腹血糖（FPG）、糖化血红蛋白（HbA1c）、胆固醇（TC）、三酰甘油（TG）、低密度脂蛋白胆固醇（LDL-C）、空腹胰岛素在肥胖组较正常组和超重组显著增加（P<0.05），而肥胖组的高密度脂蛋白胆固醇（HDL-C）、血清25(OH)D_3较另外两组显著下降（P<0.05）。Adropin在正常组、超重组、肥胖组中依次递减（P<0.05）。正常组合并高脂血症占比为44.00%，超重组为56.67%，肥胖组则高达69.66%，差异有统计学意义（P<0.05）。各组合并高脂血症血清Adropin和25(OH)D_3水平均显著降低。Adropin、25(OH)D_3与TC、TG、LDL-C呈负相关，与HDL-C呈正相关（P<0.05）。**结论** 在不同BMI中，血清Adropin和25(OH)D_3的降低与T2DM患者高脂血症风险增加密切相关。二者对T2DM患者的肥胖及高脂血症的预防和治疗有潜在意义。

关键词： 2型糖尿病；Adropin；25-羟基维生素D_3；高脂血症；身体质量指数

中图分类号： R587.2 R589.2 **文献标识码：** A **文章编号：** 1674-8182(2026)01-0057-06

Research on the correlation of serum lipid with serum Adropin and 25-hydroxylvitamin D_3 levels in patients with type 2 diabetes mellitus of different body mass indexes

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Abstract: Objective To explore the correlation of serum Adropin, 25-hydroxylvitamin D_3 [25(OH)D_3] levels with serum lipids in patients with type 2 diabetes mellitus (T2DM) stratified by different body mass indexes (BMI), and to provide new ideas for the prevention and treatment of lipid metabolism-related issues in T2DM. **Methods** A total of 199 T2DM patients hospitalized in Zhengzhou Central Hospital from May 2023 to July 2024 were selected as research subjects. They were divided into three groups according to BMI: normal weight group (18.5 kg/m^2≤BMI<24 kg/m^2, n=50), overweight group (24 kg/m^2≤BMI<28 kg/m^2, n=60), and obesity group (BMI≥28 kg/m^2, n=89). General clinical data, and laboratory indicators including fasting plasma glucose (FPG), glycated hemoglobin (HbA1c), four blood lipid indicators [total cholesterol (TC), triglycerides (TG), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C)], and 25(OH)D_3 were collected and measured. Serum Adropin levels in each group were detected by ELISA. The changes of Adropin, 25(OH)D_3, blood lipids and other indicators among groups and

DOI: 10.13429/j.cnki.cjcr.2026.01.011

基金项目： 河南省科技攻关项目（182102310089）

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出版日期： 2026-01-20

QR code for English version

their correlations were analyzed. **Results** FPG, HbA1c, TC, TG, LDL-C, and fasting insulin in the obesity group were significantly higher than those in the normal weight group and overweight group (P<0.05), while HDL-C and serum 25(OH)D_3 in the obesity group were significantly lower than those in the other two groups(P<0.05). Adropin decreased sequentially in the normal weight group, overweight group, and obesity group(P<0.05). The proportion of patients with hyperlipidemia was 44.00% in the normal weight group, 56.67% in the overweight group, and as high as 69.66% in the obesity group, with a statistically significant difference (P<0.05). In each group, T2DM patients complicated with hyperlipidemia had significantly lower serum Adropin and 25(OH)D_3 levels. The correlation of Adropin and 25(OH)D_3 with TC, TG, and LDL-C were negative, while those with HDL-C were positive(P<0.05). **Conclusion** The decrease of serum Adropin and 25(OH)D_3 is closely related to the increased risk of hyperlipidemia in T2DM patients across different BMI strata. They have potential significance for the prevention and treatment of obesity and hyperlipidemia in T2DM patients.

Keywords: Type 2 diabetes mellitus; Adropin; 25-hydroxylvitamin D_3; Hyperlipidemia; Body mass index

Fund program: Science and Technology Research Project of Henan Province(182102310089)

2型糖尿病(type 2 diabetes mellitus, T2DM)是影响人类健康的主要慢性疾病之一,其典型临床表现为持续的高血糖状态所致的多饮、多食、多尿、体质量减少,发病的核心环节在于胰岛素抵抗以及缺乏胰岛素。T2DM与身体质量指数(body mass index, BMI)的关系密切,随着BMI增大,T2DM的发病风险提高。研究发现,肥胖与T2DM的发生可能与胰岛素抵抗、免疫炎症反应、微小RNA异常表达以及脂代谢紊乱有关[1]。其原理可能是胰岛素能促进脂肪合成和储存,抑制脂肪分解,进而影响T2DM患者体内的糖脂代谢,引发脂代谢紊乱并加重稳态模型评估胰岛素抵抗指数(homeostasis model assessment of insulin resistance index, HOMA-IR)的升高 ,同时增加高脂血症的发生风险。流行病学调查发现,正常人血脂异常的发病率为20%~40%,而在T2DM患者中,血脂异常的发病率高达60%,并且BMI与血脂异常的发生呈高度相关性[2]。

Adropin蛋白是Kumar等[3]在2008年发现的一类由能量平衡基因调节的分泌性蛋白,其与肥胖、T2DM的关系密切,提示Adropin蛋白可以使胰岛素的敏感性增加,纠正脂质代谢紊乱。此外,维生素D_3也是T2DM发生的重要影响因素,25-羟基维生素D_3[25(OH)D_3]是维生素D_3在肝脏内羟化后的产物,在体内存在形式稳定,因此常被作为检测体内维生素D水平的指标。1,25-二羟维生素D_3[1,25$(OH)_2D_3$]是维生素D的活化状态,可通过与体内维生素D受体结合,在胰岛素的合成、分泌中发挥作用[4]。

本研究首次联合分析25(OH)D_3和Adropin两种指标,探讨其在BMI分层下对T2DM患者脂代谢的影响和在血脂异常背景下可能的作用,拓展T2DM脂代谢研究的视野,为T2DM脂质代谢紊乱的个体化防治提供新的思路。现报道如下。

1 对象与方法

1.1 *研究对象* 选取2023年5月至2024年7月在郑州市中心医院住院的199例T2DM患者作为研究对象。纳入标准:(1)根据WHO(1999年)的糖尿病病因学分型体系确诊为T2DM;(2)BMI≥18.5 kg/m^2;(3)年龄18~75岁。排除标准:(1)合并各种糖尿病的急性并发症,包括高血糖高渗状态、糖尿病酮症酸中毒、乳酸酸中毒及低血糖症等;(2)合并急性或慢性感染者;(3)合并自身免疫系统疾病、肝肾功能不全或恶性肿瘤者;(4)肾上腺皮质功能亢进、甲状腺功能亢进等其他内分泌系统疾病;(5)近3个月内服用过他汀类药物、激素、维生素D等可能影响血脂、25(OH)D_3水平者。将符合入组条件的患者按照国家卫生健康委员会标准进行BMI分组:正常组(18.5 kg/m^2≤BMI<24 kg/m^2)、超重组(24 kg/m^2≤BMI<28 kg/m^2)和肥胖组(BMI≥28 kg/m^2)。本研究符合《赫尔辛基宣言》要求,经郑州市中心医院医学伦理审查委员会批准(批号:ZXYY2024147),所有患者已知悉实验流程并签署知情同意书,所有数据匿名化处理。

1.2 *研究方法* 收集患者的年龄、性别、身高、体质量、血压、病程等一般资料。检测并收集患者肝肾功能、C反应蛋白等临床及实验室化验指标,采用ELISA法检测各组血清Adropin水平,采用全自动生化仪检测空腹血糖(fasting plasma glucose, FPG)、糖化血红蛋白(glycated hemoglobin, HbA1c)、血清25(OH)D_3、血脂[胆固醇(total cholesterol, TC)、三酰甘油(triglyceride, TG)、高密度脂蛋白胆固醇(high-density lipoprotein cholesterol, HDL-C)、低密度脂蛋白胆固醇(low-

density lipoprotein cholesterol, LDL-C)等指标。按照《中国血脂管理指南2023版》[2]中对高脂血症的定义分为合并高脂血症和无高脂血症,分析各组血清Adropin、25(OH)D_3与有无高脂血症和其他指标的变化及相关性。

所有研究对象由固定人员测量身高及体质量,并计算BMI。体格检查包括身高、BMI、腰臀比和血压等。采集空腹(定义为夜间禁食8~10 h)静脉血标本,在郑州市中心医院检验实验室进行血液分析,测量生化指标,如FPG、HbA1c、空腹C肽、胰岛素、肝肾功能、血清25(OH)D_3、血脂指标及HOMA-IR等。

1.3 统计学方法 所有数据的处理均由SPSS 27.0统计软件完成。服从正态分布的连续变量采用$\bar{x}\pm s$表示,不同分组间临床资料对比采用单因素方差分析,不符合正态分布的用$M(Q_1,Q_3)$表示,比较采用非参数检验;分类变量以例(%)表示,比较采用χ^2检验;Adropin、25(OH)D_3与高脂血症的关系采用logistic回归分析;Adropin、25(OH)D_3与血脂的关系采用Spearman相关性检验。P<0.05为差异有统计学意义。

2 结 果

2.1 一般资料比较 FPG、HbA1c、TC、LDL-C、TG、空腹C肽、空腹胰岛素在肥胖组较正常组和超重组显著增加(P<0.05),而肥胖组HDL-C、血清25(OH)D_3较另外两组显著下降(P<0.05)。肥胖组舒张压显著高于正常组(P<0.05),而超重组和肥胖组收缩压均显著高于正常组(P<0.05)。正常组、超重组、肥胖组Adropin依次递减,HOMA-IR依次递增(P<0.05)。见表1。

2.2 不同BMI分组与合并高脂血症的关系 正常组合并高脂血症占比为44.00%,超重组为56.67%,肥胖组则高达69.66%,三组比较差异有统计学意义(P<0.05)。见表2。

2.3 不同BMI分组合并高脂血症与血清Adropin及25(OH)D_3的关系 三组合并高脂血症者血清Adropin和25(OH)D_3水平均较无高脂血症者显著降低,差异有统计学意义(P<0.05)。见表3。

2.4 不同BMI分组中Adropin及25(OH)D_3对高脂血症影响的logistic回归分析 在不同BMI分组中将高脂血症作为因变量进行logistic回归分析,结果显示,在校正年龄、病程等混杂因素后,Adropin和25(OH)D_3降低为发生高脂血症的独立危险因素(P<0.05)。具体而言,Adropin和25(OH)D_3在正常组中每增加1单位,高脂血症发生风险分别下降18.6%和14.4%;在超重组每增加1单位,高脂血症发生风险分别下降24.6%和43.1%;在肥胖组中,每增加1单位,高脂血症发生风险分别下降57.4%和58.1%。见表4。

2.5 不同BMI分组下的Adropin、25(OH)D_3与血脂的

表1 受试者一般资料对比 ($\bar{x}\pm s$)

Tab.1 Comparison of general data of subjects ($\bar{x}\pm s$)

项目	正常组(n=50)	超重组(n=60)	肥胖组(n=89)	F/H值	P值
病程(年)	6.10±2.34	6.87±3.34	5.81±2.71	2.540	0.081
年龄(岁)	52.92±11.18	53.62±9.60	51.28±12.42	0.834	0.436
收缩压(mmHg)	127.58±13.00	133.93±13.79[b]	135.38±16.38[b]	4.605	0.011
舒张压(mmHg)	77.94±7.30	79.60±6.34	82.64±14.47[b]	3.282	0.040
FPG(mmol/L)	6.33±1.66	6.86±1.24	7.57±2.27[bc]	7.484	0.001
HbA1c(%)	7.38±1.51	7.89±1.65	8.70±2.24[bc]	8.320	<0.001
TC(mmol/L)	4.17±1.12	4.39±1.23	4.72±1.56[bc]	3.075	0.048
TG(mmol/L)[a]	1.19(0.87,1.66)	1.44(1.05,2.02)	1.85(1.30,2.87)[bc]	26.184	<0.001
HDL-C(mmol/L)	1.20±0.38	1.10±0.46	0.74±0.35[bc]	27.359	<0.001
LDL-C(mmol/L)	2.15±0.96	2.29±0.85	2.70±0.96[bc]	6.687	0.002
血肌酐(μmol/L)	61.69±17.65	69.09±15.44	67.00±21.31	2.228	0.111
空腹胰岛素(μIU/mL)	5.42±2.93	7.93±5.43	10.65±8.82[bc]	9.807	<0.001
空腹C肽(ng/mL)[a]	1.74(1.17,2.45)	2.12(1.41,2.69)	2.56(1.20,3.42)[bc]	7.531	0.023
25(OH)D_3(ng/mL)	22.20±8.06	20.64±8.06	14.50±5.41[bc]	24.282	<0.001
Adropin(ng/mL)	21.76±9.93	17.19±7.69[b]	14.38±7.71[bc]	12.599	<0.001
HOMA-IR[a]	1.40(0.81,2.04)	1.83(1.32,3.47)[b]	2.62(1.42,4.74)[bc]	27.927	<0.001

注:[a]为数据以$M(Q_1,Q_3)$表示;与正常组比较,[b]P<0.05;与超重组比较,[c]P<0.05。

相关性　在不同BMI分组中，Adropin、25(OH)D_3与TC、TG、LDL-C均呈显著负相关，与HDL-C呈显著正相关(P<0.05)。见表5。

表2　不同BMI分组与合并高脂血症的关系　[例(%)]

Tab.2　Relationship between different BMI groups and hyperlipidemia　[case(%)]

组别	例数	无高脂血症	合并高脂血症	χ^2值	P值
正常组	50	28(56.00)	22(44.00)		
超重组	60	26(43.33)	34(56.67)	8.982	0.011
肥胖组	89	27(30.34)	62(69.66)		

表3　不同BMI分组合并高脂血症与血清Adropin及25(OH)D_3的关系　(ng/mL)

Tab.3　Relationship of hyperlipidemia with Adropin and 25(OH)D_3 in different BMI groups　(ng/mL)

组别		无高脂血症	合并高脂血症	t值	P值
正常组	25(OH)D_3	27.07±6.27	16.01±5.39	6.580	<0.001
	Adropin	27.54±7.75	14.40±7.19	6.144	<0.001
超重组	25(OH)D_3	26.86±7.29	15.89±4.69	7.075	<0.001
	Adropin	23.49±6.16	12.38±4.69	7.938	<0.001
肥胖组	25(OH)D_3	19.38±4.18	11.49±3.56	9.504	<0.001
	Adropin	21.91±5.35	9.73±4.64	11.340	<0.001

表4　不同BMI分组高脂血症与Adropin及25(OH)D_3的二元logistic回归

Tab.4　Binary logistic regression of hyperlipidemia with Adropin and 25(OH)D_3 in different BMI groups

变量	组别	β	SE	Wald	OR值	95%CI	P值
25(OH)D_3	正常组	−0.265	0.106	6.305	0.856	0.657~0.989	0.012
	超重组	−0.517	0.234	4.951	0.569	0.328~0.971	0.026
	肥胖组	−0.894	0.363	6.079	0.419	0.215~0.695	0.014
Adropin	正常组	−0.187	0.076	5.997	0.814	0.614~0.956	0.014
	超重组	−0.285	0.119	5.783	0.754	0.511~0.968	0.016
	肥胖组	−0.745	0.236	9.937	0.426	0.228~0.798	0.001

注：因变量为高脂血症；校正协变量为年龄、病程、血压、HOMA-IR。

表5　不同BMI分组下的Adropin、25(OH)D_3与血脂的相关性

Tab.5　Correlation of Adropin and 25(OH)D_3 with blood lipids in different BMI groups

变量	组别	TC		TG		HDL-C		LDL-C	
		r值	P值	r值	P值	r值	P值	r值	P值
25(OH)D_3	正常组	−0.369	0.007	−0.368	0.008	0.585	<0.001	−0.615	<0.001
	超重组	−0.621	<0.001	−0.416	0.003	0.356	0.007	−0.627	<0.001
	肥胖组	−0.377	<0.001	−0.311	0.003	0.654	<0.001	−0.350	0.001
Adropin	正常组	−0.461	0.002	−0.404	0.003	0.426	0.002	−0.498	<0.001
	超重组	−0.482	<0.001	−0.531	<0.001	0.462	<0.001	−0.448	<0.001
	肥胖组	−0.403	<0.001	−0.325	0.002	0.640	<0.001	−0.368	<0.001

3　讨　论

近年研究发现Adropin及25(OH)D_3对糖脂代谢有影响，为T2DM患者的肥胖及高脂血症的预防和治疗提供了新的思路和靶点。本研究采用横断面研究设计，探讨不同BMI的T2DM患者的血清Adropin和25(OH)D_3水平与血脂之间的相关性。

Adropin是近年来发现的一种能量调节蛋白，可以参与糖代谢、脂肪代谢等多种生理过程，与肥胖、糖尿病、心血管等疾病的关系密切[5]。

本研究中随着BMI的升高，血清Adropin阶梯式下降，提示低Adropin水平可能与代谢紊乱相关，这一结果与动物实验中Adropin改善代谢的结论相对应[6]。此外，研究发现肥胖人群中Adropin水平显著降低，本研究的结果与其一致[7]。Adropin可能通过多种方式调节代谢。脂肪组织中最常见的是白色脂肪和棕色脂肪，白色脂肪过度积累会导致肥胖，而棕色脂肪富含线粒体，可增加能量消耗起到减轻体质量和调节代谢的作用[8]。Adropin可通过激活PI3K/蛋白激酶B(protein kinase B，PKB)通路来促进棕色脂肪的增殖，并下调转录因子C/EBP-α、C/EBP-β和PPAR-γ的表达来抑制白色脂肪生成，进而降低肥胖的发生风险[9]。骨骼肌是Adropin调节能量代谢的重要组织，Adropin可通过提高PKB的磷酸化，从而增加骨骼肌细胞膜表面的葡萄糖转运蛋白4(glucose transporter 4，GLUT4)的数量，最终提高肌肉组织的能量代谢，达到减轻胰岛素抵抗和肥胖的作用[10-11]。此外，Adropin还可通过下调cAMP/PKA信号通路抑制肝脏糖异生、抑制蛋白磷酸酶2A(protein phosphatase 2，PP2A)，激活AMP依赖的蛋白激酶(AMP-activated

protein kinase, AMPK)通路减少脂肪堆积等[12]。

本研究数据分析发现，3组中Adropin均与TC、TG、LDL-C呈负相关，与HDL-C呈正相关，随着BMI的增加，Adropin对减少高脂血症发生风险的作用更显著，提示肥胖患者Adropin的严重缺乏可能成为脂代谢紊乱的放大器[13-14]。这一发现也在肝脏的糖脂代谢层面获得动物实验支持，高水平Adropin可以降低高脂血症大鼠体内的TG、TC和LDL-C，并增加HDL-C，推测其可能与AMPK通路相关[15]。体外实验中发现，Adropin可以增加肝细胞的AMPK磷酸化，进而抑制乙酰辅酶A羧化酶的活性，并减少丙二酰辅酶A的生成，从而解除丙二酰辅酶A对肉碱脂酰转移酶1的变构抑制作用，进而促进脂肪酸氧化[16]。

25(OH)D_3不仅参与传统意义上的骨质代谢和钙磷代谢的调节，还涉及胰岛素敏感性、免疫功能及炎症反应的调控，并与肥胖相关[17]。

本研究结果发现，肥胖组的血清25(OH)D_3的水平显著下降，这与HOMA-IR的升高相反，提示25(OH)D_3的缺乏与胰岛素抵抗及肥胖的发病风险相关。本研究的结果与另一项研究结论类似：高脂血症患者中25(OH)D_3水平明显降低，且与TC、TG、LDL-C、FPG、空腹胰岛素、HOMA-IR、BMI、腰臀比、腰高比呈负相关，与HDL-C呈正相关[18]。此外，相关Meta分析发现，维生素D每升高10 ng/mL，腹部脂肪含量可降低约8%，25(OH)D_3水平与腹部肥胖风险存在显著的负相关[19]。结合以上结果发现，25(OH)D_3可抑制前脂肪细胞分化为成熟脂肪细胞，而25(OH)D_3缺乏会解除这种抑制作用，促进脂肪堆积[20]。

然而，也有部分研究提出不同的观点，认为25(OH)D_3缺乏可能并非肥胖的原因，更可能是肥胖的结果：肥胖患者户外活动减少导致日照时间不足会降低体内25(OH)D_3的合成，且补充维生素D组的肥胖患者的BMI、腰围、腰臀比等较安慰剂组相比无明显变化[21-22]。这种观点的分子机制可能是：肥胖状态会抑制线粒体细胞色素P450 2R1(CYP2R1)的活性，在肝脏中CYP2R1主要参与维生素D羟化，其活性降低导致25(OH)D_3降低[23-24]。

结合本研究及既往文献，可以认为25(OH)D_3与BMI存在交互作用。尽管目前许多研究已经揭示了25(OH)D_3缺乏与肥胖之间的关联，但仍无法说明其因果关系，这种复杂的相互作用使明确因果关系的研究变得更具挑战性。

本研究发现不同BMI分层中，25(OH)D_3均对血脂有调节作用，且在肥胖组呈现更强的保护效应。25(OH)D_3水平降低与血脂异常风险增加有关，这与既往的研究结果相似[25]。Chang[26]的研究揭示了这种现象可能的原因：高水平的血清25(OH)D_3可升高单磷酸腺苷/三磷酸腺苷(AMP/ATP)的比值来增强AMPK活性，进而增强沉默调节蛋白1(silence information regulator 1, SIRT1)的表达。而SIRT1可以抑制脂肪合成相关基因，调节脂质代谢。基因层面上的研究提示维生素D受体基因型可通过影响维生素D受体的功能，调控脂代谢相关基因表达，降低血脂异常的发病风险[27-28]。此外，25(OH)D_3可能通过调节机体炎症反应、促进钙吸收和调节甲状旁腺激素水平等方式间接影响脂代谢[29-30]。

本研究存在以下局限性：(1)样本仅纳入住院患者，未覆盖门诊或社区人群；(2)由于患者的代谢水平、降糖药物的影响以及个人生活习惯等混杂因素未能完全控制，仍可能导致结论的准确性下降。目前关于Adropin及25(OH)D_3对代谢性疾病的影响机制尚不完全明确，要证实上述推测还需要开展动物实验及大样本前瞻性研究。

综上所述，随着BMI的增加，Adropin与25(OH)D_3水平下降时高脂血症的发生率反而上升，说明二者是T2DM患者高脂血症的独立保护因素，Adropin与25(OH)D_3对血脂异常的保护效应呈现BMI依赖性增强，这可能与肥胖状态下机体的代谢紊乱程度有关。因此，针对肥胖的T2DM患者，Adropin和25(OH)D_3的营养状态可能具有重要的临床意义。以上表明，二者未来有望在预防和治疗代谢性疾病方面发挥更大的潜力。

利益冲突 本文所有作者均声明不存在利益冲突

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收稿日期:2025-09-03 **修回日期**:2025-09-28 **编辑**:许煜晗