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Correlations of high molecular weight adiponectin, tumor necrosis factor-alpha and vascular endothelial growth factors with occurrence of colonic polyps in the prediabetic population

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ABSTRACT

We aimed to explore the correlations of high molecular weight adiponectin (HMW-ADP), tumor necrosis factor-alpha (TNF-α) and vascular endothelial growth factors (VEGFs) with the occurrence of colonic polyps in the prediabetic population. Two hundred patients with prediabetes were enrolled, and their clinical data were retrospectively analyzed. They were divided into group A (75 patients with colonic polyps) and group B (125 patients without colonic polyps). Eighty patients with normal glucose tolerance in the same period were divided into group C (32 patients with normal glucose tolerance and colonic polyps) and group D (48 patients with normal glucose tolerance but no colonic polyps). The correlations of serum HMW-ADP, TNF-α and VEGF levels with plasma glucose and insulin levels were explored by Pearson's analysis. The factors influencing the occurrence of colonic polyps were determined by logistic regression analysis. Serum HMW-ADP was negatively correlated with TNF-α, VEGFs, FPG, 2hPG, FI and HOMA-IR ($r<0$, $P<0.05$), whereas serum TNF-α and VEGFs were positively correlated with FPG, 2hPG, FI and HOMA-IR ($r>0$, $P<0.05$). Age, body mass index, waist-to-hip ratio, history of smoking, history of drinking, family history of colon cancer, TNF-α and VEGF were independent risk factors [odds ratio (OR)>1, $P<0.05$], and HMW-ADP was a protective factor (OR<1, $P<0.05$). The areas under the curves of serum HMW-ADP, TNF-α, VEGFs and their combination for predicting the occurrence of colonic polyps were 0.899, 0.787, 0.908 and 0.922, respectively. The combination of HMW-ADP, TNF-α and VEGFs can effectively predict the occurrence of colonic polyps in prediabetic patients.

Keywords: prediabetes, colonic polyp, high molecular weight adiponectin, tumor necrosis factor-alpha, vascular endothelial growth factor

Abbreviations:
ADP: adiponectin
FI: fasting insulin
FPG: fasting plasma glucose
HMW-ADP: high molecular weight ADP
HOMA-IR: homeostasis model assessment-IR index
IR: insulin resistance
TNF-α: tumor necrosis factor-alpha
VEGF: vascular endothelial growth factor

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INTRODUCTION

Prediabetes is defined as the disorders of glucose metabolism, a state between diabetes mellitus and normal glucose tolerance. It is mainly manifested as impaired fasting plasma glucose (FPG) level and glucose tolerance.[1] The detection rates of colon cancer and colonic polyps in prediabetic patients aged over 40 years old in China are 4.19% and 49.50%, respectively.[2] A colonic polyp, as a precancerous lesion, is the neoplasm protruding from the mucosal surface of the colon to the intestinal cavity. It can be pathologically classified into adenoma, hyperplastic tumors and inflammatory tumors. Most colonic polyps are benign, but some of them may gradually develop into colon cancer.[3,4] Hence, it is crucial to explore easily-operated and sensitive biomarkers for the early diagnosis of prediabetes complicated with colonic polyps, identification of high-risk groups of colon cancer and prognostic evaluation.

The onset and progression of colonic polyps have been related to the imbalance of immune regulation, inflammatory response and vascular damage mediated by inflammatory factors.[5] Adiponectin (ADP) can reduce insulin resistance (IR) and regulate glucose and lipid metabolism, which is the only polypeptide hormone negatively related to inflammation and IR. High molecular weight ADP (HMW-ADP), the main active form of ADP, can simulate insulin to bind insulin receptors, thus enhancing insulin sensitivity. Besides, HMW-ADP also inhibits the activation of nuclear transcription factors by regulating the level of tumor necrosis factor-alpha (TNF-α), and alleviates inflammatory responses, thus suppressing inflammation-induced mutation of proto-oncogenes such as K-ras gene.[6] Vascular endothelial growth factors (VEGFs) are a class of potent inducing factors for vascular permeability and angiogenesis, which can significantly enhance lymphatic permeability and facilitate lymphatic hyperplasia and lymph node metastasis and infiltration in tumor cells. Besides, VEGF helps stratify colorectal polyps in different progression risk categories and effectively predicts the occurrence of polypoid adenomas.[7] Nonetheless, the expressions, roles or mechanisms of HMW-ADP and VEGFs in prediabetes complicated with colonic polyps remain elusive. In this study, therefore, the correlations of HMW-ADP, TNF-α and VEGFs with the occurrence of colonic polyps in the prediabetic population were assessed, aiming to provide valuable evidence for future prevention and treatment.

MATERIALS AND METHODS

This study has been approved by the ethic committee of our hospital, and written informed consent has been obtained from all patients. A total of 200 prediabetic patients admitted to our hospital from September 2018 to March 2021 were enrolled, and their clinical data were retrospectively analyzed. Among these patients, there were 108 males and 92 females aged 39–75 years old, with an average of (53.16 ± 3.38) years old.

The inclusion criteria were as follows: 1) patients diagnosed as prediabetes according to the diagnostic criteria,[8] 2) those who had not been treated with glucocorticoids, hypoglycemic drugs, nonsteroidal anti-inflammatory analgesics or statins three months before inclusion, and 3) those whose colonoscopy confirmed no malignant tumors. The exclusion criteria included: 1) patients without acute complications of diabetes mellitus, 2) those with history of diseases in the adrenal gland, pituitary gland, hypothalamus or thyroid gland, 3) those with chronic wasting diseases or impaired vital organ function, 4) those with history of gastrointestinal surgery, 5) those compli-

cated with Crohn's disease, ulcerative colitis or other inflammatory bowel diseases, 6) those with autoimmune liver disease, chronic viral hepatitis, or drug-induced liver disease, or 7) pregnant or lactating women. The 200 patients were divided into group A (75 patients with colonic polyps) and group B (125 patients without colonic polyps).

Meanwhile, 80 patients with normal glucose tolerance values confirmed in the 75 g oral glucose tolerance test in the same period were selected. Among them, there were 44 males and 37 females aged 35–78 years old, with an average of (51.98 ± 4.75) years old. The 80 patients were divided into group C (32 patients with normal glucose tolerance and colonic polyps) and group D (48 patients with normal glucose tolerance but no colonic polyps)

After intestinal preparation, the presence of polyps was observed under an electronic colonoscope (cv-290; Olympus, Japan). The polyps were taken using biopsy forceps for pathological examination. If there were multiple polyps, the polyp with the largest diameter was used as the representative. According to the pathological results and clinical characteristics, the polyps were classified into low-risk polyps (number <3 and/or absence of high-grade dysplasia and/or tubular structure and/or diameter <1 cm) and high-risk ones (number ≥3 and/or high-grade dysplasia and/or villous structures and/or diameter ≥1 cm). According to the number, the polyps were classified into multiple polyps (number ≥3) and single ones (number ≤2).

The gender, age, body mass Index, waist-to-hip ratio, diastolic blood pressure, systolic blood pressure, history of drinking (average alcohol intake ≥25 g/d, duration ≥1 year), history of smoking (average number of cigarettes ≥1 cigarette/d, duration ≥1 year), family history of colon cancer (the number of immediate family members suffering from colon cancer ≥1) as well as number and pathological types of colonic polyps were recorded.

A total of 5 mL of fasting venous blood was collected from each subject, and centrifuged by Optima XPN ultracentrifuge (Beckman Coulter Commercial Enterprise (China) Co, Ltd) at 2500 r/min for 10 min, with a radius of 10 cm. Afterwards, the serum was stored in a –80ºC refrigerator. Then the levels of serum HMW-ADP, TNF-α and VEGFs were measured using ELISA kits (R&D Systems, USA), fasting insulin (FI) was detected by radioimmunoassay kits (Shanghai Xinyu Biotechnology Co, Ltd, China), and FPG and 2-h postprandial blood glucose (2hPG) were detected using glucose oxidase assay kits (Shanghai Enzyme Research Biotechnology Co, Ltd, China). Finally, homeostasis model assessment-IR index (HOMA-IR) was calculated based on the formula: HOMA-IR = FPG × FI/22.5.

SPSS 23.0 software was utilized for statistical analysis. The normality was examined with the Shapiro-Wilk test. The normally distributed measurement data were expressed as ($\bar{x}$ ± s). One-way analysis of variance was carried out for the analysis of repeated data, and the least significance difference *t*-test was employed for further pairwise comparison. The correlation and influencing factors were assessed by Pearson's analysis and unconditional logistic regression analysis, respectively. Receiver operating characteristic (ROC) curves were plotted to analyze the predictive values of serum HMW-ADP, TNF-α and VEGF levels for the occurrence of colonic polyps in prediabetic patients. P<0.05 indicated that the difference was statistically significant.

RESULTS

Differences in the gender, diastolic blood pressure and systolic blood pressure among the four groups were not statistically significant (P>0.05). However, the body mass index, waist-to-hip ratio, and the number of cases with history of smoking, history of drinking and family history of colon cancer of group A were significantly higher and larger than those of group B-D (P<0.05). Group A and group C had similar numbers and pathological types of colonic polyps (Table 1).

Table 1 General data in the four groups (n, $\bar{x} \pm s$)

Group	n	Male/ female	Age (year)	Body mass index (kg/m^2)	Waist-to-hip ratio	Diastolic blood pressure (mmHg)	Systolic blood pressure (mmHg)	History of smoking	History of drinking	Family history of colon cancer	Polyp number (single/ multiple)	Polyp type (high-risk/ low-risk)
A	75	44/31	56.13±4.48[a]	24.83±1.18[a]	0.96±0.08[a]	75.63±8.65	122.53±12.32	32[a]	30[a]	13[a]	48/27	24/51
B	125	64/61	50.85±5.34	21.34±1.74	0.83±0.11	76.19±9.02	121.74±13.54	42	36	4	–	
C	32	18/15	51.39±5.28	22.98±1.28	0.86±0.09	74.86±8.85	124.85±12.88	10	9	0	18/14	10/22
D	48	26/22	52.34±4.05	22.89±1.52	0.84±0.15	74.98±9.93	122.76±13.39	14	12	1	–	
χ^2/F	–	0.211	18.899	83.007	23.932	0.832	0.754	2.961	3.849	20.698	0.570	0.006
P	–	0.976	<0.001	<0.001	<0.001	0.124	0.388	0.398	0.278	<0.001	0.450	0.939

[a]P<0.05 vs other three groups.

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The serum HMW-ADP level progressively rose in group A-D, while the levels of TNF-α and VEGF exhibited stepwise decreased in group A-D (P<0.05) (Table 2).

Table 2 Levels of serum HMW-ADP, TNF-α and VEGF ($\bar{x} \pm s$)

Group	n	HMW-ADP (μg/mL)	TNF-α (μg/L)	VEGF (μg/L)
A	75	1.32±0.28	17.86±3.38	200.39±21.57
B	125	1.67±0.25[a]	13.75±2.28[a]	157.86±22.32[a]
C	32	1.95±0.29[ab]	8.96±1.08[ab]	117.65±19.74[ab]
D	48	2.85±0.39[abc]	6.75±1.16[abc]	63.68±5.58[abc]
F		288.154	245.197	493.486
P		<0.001	<0.001	<0.001

HMW-ADP: high molecular weight adiponectin
TNF-α: tumor necrosis factor-alpha
VEGF: vascular endothelial growth factor
[a]P<0.05 vs group A, [b]P<0.05 vs group B and [c]P<0.05 vs group C.

Group A had significantly higher levels of PG, FI and HOMA-IR than those of group B-D (P<0.05) (Table 3).

Table 3 Levels of plasma glucose and insulin ($\bar{x} \pm s$)

Group	n	FPG (mmol/L)	2hPG (mmol/L)	FI (mIU/L)	HOMA-IR
A	75	6.05±0.21	10.36±1.32	14.85±3.38	3.98±1.07
B	125	5.81±0.19[a]	8.63±0.99[a]	11.06±3.49[a]	2.86±0.84[a]
C	32	4.82±0.22[a]	6.79±1.16[a]	11.35±2.98[a]	2.69±0.75[a]
D	48	4.84±0.18[a]	6.58±1.08[a]	9.25±1.75[a]	1.89±0.68[a]
F		480.278	163.98	200.854	105.98
P		<0.001	<0.001	<0.001	<0.001

2hPG: 2-h postprandial blood glucose
FI: fasting insulin
FPG: fasting plasma glucose
HOMA-IR: homeostasis model assessment-insulin resistance index
[a]P<0.05 vs group A.

Pearson correlation analysis revealed that serum HMW-ADP was negatively related to TNF-α, VEGFs, FPG, 2hPG, FI and HOMA-IR (r<0, P<0.05), whereas serum TNF-α and VEGFs were positively related to FPG, 2hPG, FI and HOMA-IR (r>0, P<0.05) (Table 4, Fig. 1 and Fig. 2).

According to the results of the unconditional logistic regression analysis, age, body mass index, waist-to-hip ratio, history of smoking, history of drinking, family history of colon cancer, TNF-α and VEGF were all independent risk factors [odds ratio (OR) >1, P<0.05], and HMW-ADP was a protective factor (OR<1, P<0.05) for the occurrence of colonic polyps in prediabetic patients (Table 5).

Table 4 Correlation analysis results of serum HMW-ADP, TNF-α and VEGF levels with plasma glucose and insulin levels

Indicator	HMW-ADP	TNF-α	VEGF	FPG (mmol/L)	2hPG (mmol/L)	FI (mIU/L)	HOMA-IR
HMW-ADP	–	–0.613 (<0.001)	–0.587 (<0.001)	–0.398 (0.008)	–0.523 (<0.001)	–0.438 (<0.001)	–0.523 (<0.001)
TNF-α	–0.613 (<0.001)	–	0.591 (<0.001)	0.432 (0.001)	0.493 (<0.001)	0.493 (<0.001)	0.553 (<0.001)
VEGF	–0.587 (<0.001)	0.591 (<0.001)	–	0.516 (<0.001)	0.531 (<0.001)	0.502 (<0.001)	0.621 (<0.001)

2hPG: 2-h postprandial blood glucose
FI: fasting insulin
FPG: fasting plasma glucose
HMW-ADP: high molecular weight adiponectin
HOMA-IR: homeostasis model assessment-insulin resistance index
TNF-α: tumor necrosis factor-alpha
VEGF: vascular endothelial growth factor

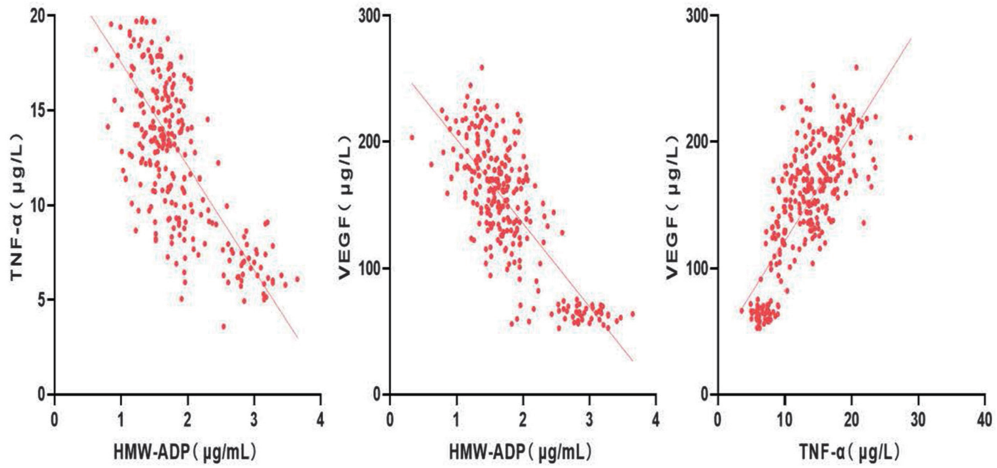

Fig. 1 Correlation analysis results among serum HMW-ADP, TNF-α and VEGF
HMW-ADP: high molecular weight adiponectin
TNF-α: tumor necrosis factor-alpha
VEGF: vascular endothelial growth factor

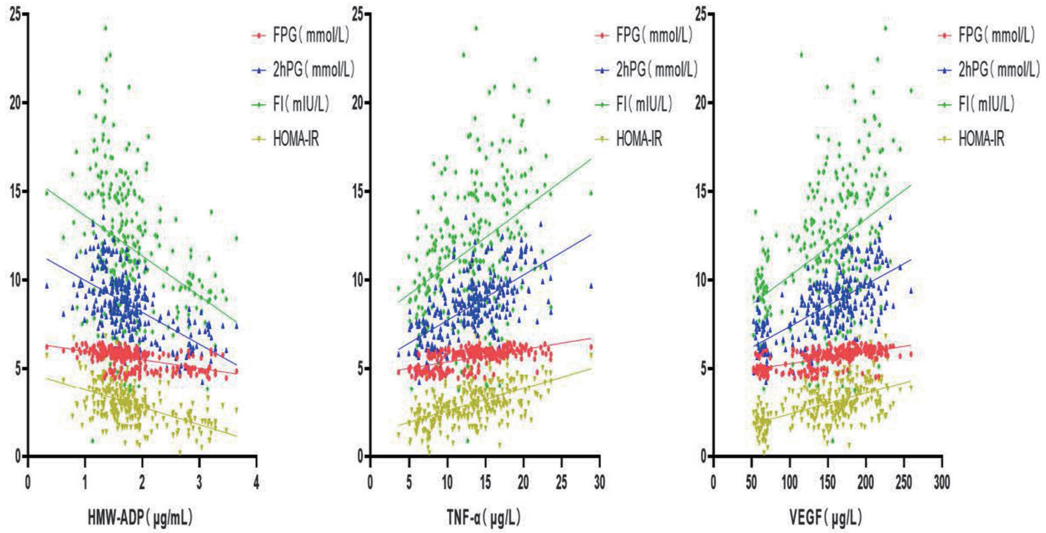

Fig. 2 Correlation analysis results of serum HMW-ADP, TNF-α and VEGF levels with plasma glucose and insulin levels

2hPG: 2-h postprandial blood glucose
FI: fasting insulin
FPG: fasting plasma glucose
HMW-ADP: high molecular weight adiponectin
HOMA-IR: homeostasis model assessment-insulin resistance index
TNF-α: tumor necrosis factor-alpha
VEGF: vascular endothelial growth factor

Table 5 Multivariate analysis results of factors affecting occurrence of colonic polyps in prediabetic patients

Indicator	Regression coefficient	Standard error	Wald χ^2	P	OR	95%CI	
						Lower limit	Upper limit
Age	0.121	0.285	13.628	0.000	3.165	1.785	4.189
Body mass index	0.862	0.452	3.634	0.045	1.889	1.564	2.672
Waist-to-hip ratio	0.352	0.136	6.162	0.006	2.369	1.325	5.750
History of smoking	0.787	0.327	5.800	0.016	2.197	1.158	4.167
History of drinking	0.065	0.012	10.264	0.000	1.546	1.168	2.465
Family history of colon cancer	1.129	0.331	11.671	0.000	3.094	1.618	5.914
HMW-ADP	–1.325	0.462	6.846	0.002	0.562	0.168	0.869
TNF-α	0.462	0.284	3.521	0.105	1.624	0.895	2.165
VEGF	0.398	0.075	4.987	0.022	1.896	1.165	3.586

CI: confidence interval
HMW-ADP: high molecular weight adiponectin
OR: odds ratio
TNF-α: tumor necrosis factor-alpha
VEGF: vascular endothelial growth factor

ROC curves displayed that the areas under the curves (AUC) of serum HMW-ADP, TNF-α, VEGFs and their combination for predicting the occurrence of colonic polyps were 0.899 (95%CI: 0.859–0.940), 0.787 (95%CI: 0.721–0.854), 0.908 (95%CI: 0.868–0.948) and 0.922 (95%CI: 0.886–0.958), respectively (Table 6, Fig. 3 and 4).

Table 6 Analysis results of values of levels of serum HMW-ADP, TNF-α and VEGFs for predicting occurrence of colonic polyps in prediabetic patients

Indicator	Cut-off value	Sensitivity	Specificity	Youden index	AUC	Standard error	P	95%CI	
								Lower limit	Upper limit
HMW-ADP	1.462	0.785	0.796	0.581	0.899	0.021	0.000	0.859	0.940
TNF-α	15.553	0.724	0.755	0.479	0.787	0.034	0.000	0.721	0.854
VEGF	172.59	0.793	0.802	0.595	0.908	0.020	0.000	0.868	0.948
Combination	–	0.911	0.805	0.716	0.922	0.018	0.000	0.886	0.958

AUC: area under the curve
CI: confidence interval
HMW-ADP: high molecular weight adiponectin
TNF-α: tumor necrosis factor-alpha
VEGF: vascular endothelial growth factor

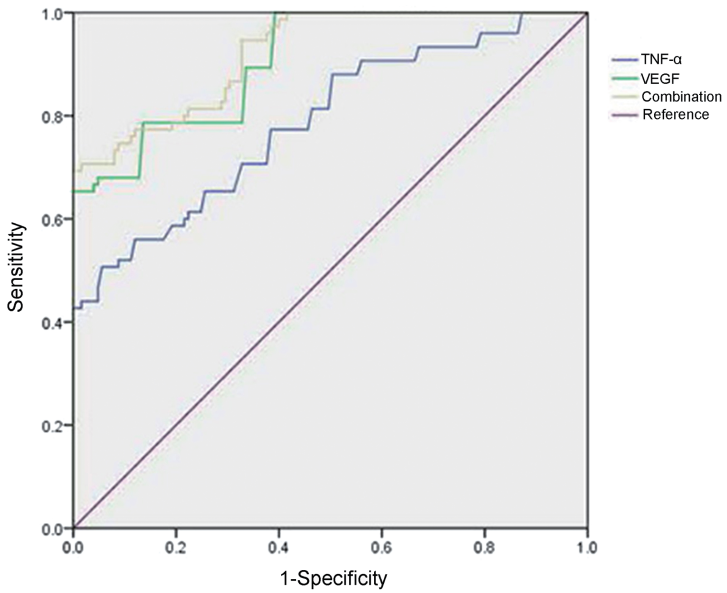

Fig. 3 ROC curves of serum TNF-α and VEGF levels and their combination for predicting occurrence of colonic polyps in prediabetic patients
ROC: receiver operating characteristic
TNF-α: tumor necrosis factor-alpha
VEGF: vascular endothelial growth factor

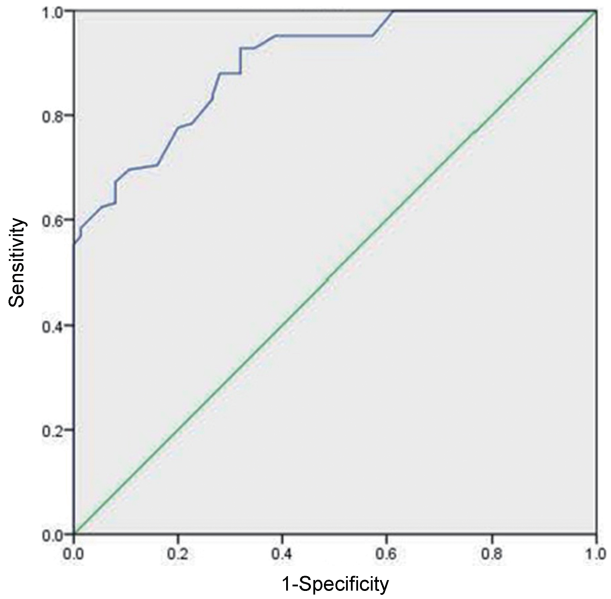

Fig. 4 ROC curve of serum HMW-ADP level for predicting occurrence of colonic polyps in prediabetic mellitus

HMW-ADP: high molecular weight adiponectin
ROC: receiver operating characteristic

DISCUSSION

At present, it is widely-accepted that colonic polyps can be induced by factors such as inflammatory bowel disease, hyperinsulinemia/IR and bad living habits.[9,10] Soltani et al found that the plasma glucose level had a close correlation with the occurrence of colonic polyps, as an independent risk factor for multiple polyps.[11] Deng et al reported that 52.99% (248/468) of prediabetic patients suffered from colonic polyps.[2] Likewise, 75 of the 200 prediabetic patients (37.50%) in this study were complicated with colonic polyps. Hence, it is necessary to further assess the molecular mechanism and serum markers of prediabetes complicated with colonic polyps for the early screening and identification of high-risk groups.

As the most vital bioactive form of ADP, HMW-ADP can regulate immunity, inflammatory responses, metabolism and insulin effect. Horakova et al found that the total adiponectin level in serum had a negative correlation with metabolic risk factors, so the former effectively predicted the occurrence of impaired glucose regulation and type 2 diabetes mellitus.[12] Besides, Yanai et al reported that ADP-knockout mice had lower phosphorylation levels of insulin-stimulated insulin receptor substrate-1 (IRS-1), IRS-2 and Akt in the liver than those of wild-type mice, and the liver insulin signal in ADP-knockout mice was obviously damaged, thus inducing IR.[13] Moreover, Polito et al reported that the low level of HMW-ADP was caused by IR, because insulin inhibited the expression of ADP that can activate the insulin signaling pathway.[14] Nevertheless, the association between HMW-ADP and prediabetes complicated with colonic polyps remains elusive. The results of this study showed that the serum HMW-ADP level in group A was lower than those of group B-D. In addition, the HMW-ADP level was correlated with the levels of plasma glucose and insulin, and HMW-ADP was a protective factor for colonic polyps in prediabetic patients.

The results may be attributed to the following reasons. First, the trimers and monomers

of HMW-ADP can bind G protein-coupled receptors on the liver cell membrane or skeletal muscle to modulate glucose metabolism. Meanwhile, HMW-ADP stimulates skeletal muscle cells to absorb glucose, alleviates the insulin sensitivity and enhances the inhibition of insulin on gluconeogenesis. However, the increase of glucose may augment the sensitivity to oxidative stress by reducing antioxidants through the enzymatic conversion of glucose to sorbitol, excessively producing peroxides in mitochondria, and decreasing glutathione and nicotinamide adenine dinucleotide phosphate. In addition, IR and IR-triggered hyperinsulinemia can induce the growth of colon cells, resulting in canceration.[15] Second, HMW-ADP elevates the expression of stromal cell-derived factor-1 (SDF-1) via the NF-κB/AP-1, ERK/p38 mitogen-activated protein kinase (MAPK) and β1 integrin signaling pathways, and the high expression of SDF-1 is a risk factor for the poor prognosis of patients with colon cancer.

The immunoregulatory imbalance and inflammatory responses mediated by inflammatory cytokines are associated with the onset and progression of intestinal polyps.[16] The abnormally activated intestinal T cells can induce the release of various pro-inflammatory cytokines, such as IL-6 and TNF-α, by monocytes and macrophages, and then inflammatory cells invade the intestinal mucosa and destroy intestinal homeostasis. Wu et al reported that the up-regulation of TNF-α may participate in the malignant process of polyps, as an independent risk factor for the occurrence of high-risk adenomas.[17] VEGFs can induce the mitosis, migration and proliferation of endothelial cells, enhance microvascular permeability and elevate the expression of extracellular matrix degrading enzyme, thus contributing to angiogenesis.[18] Mehrabani et al reported that VEGFs contributed to lymphangiogenesis, lymph node metastasis and lymphatic hyperplasia around tumors via the PI3K and MAPK signaling pathways.[19] In this study, the levels of TNF-α and VEGF displayed stepwise decreases in group A-D, which were positively related to the levels of FPG, 2hPG, FI and HOMA-IR. In addition, the levels of TNF-α and VEGF were risk factors for the occurrence of prediabetic colonic polyps. Moreover, we also found that the serum HMW-ADP level was negatively correlated with TNF-α and VEGF levels, suggesting that HMW-ADP protected cells and reduced inflammatory responses and severity of cell injury by effectively suppressing the formation and release of TNF-α and VEGF. Furthermore, AUC of the combination of the three indicators in the prediction of prediabetic colonic polyps was 0.922. Therefore, it is necessary to closely monitor the changes of serum HMW-ADP, TNF-α and VEGF levels in prediabetic patients to prevent colonic polyps and colon cancer.

In conclusion, prediabetic patients complicated with colonic polyps has low expression of serum HMW-ADP and high expressions of TNF-α and VEGF, which are closely associated with the levels of plasma glucose and insulin. In addition, the combination of HMW-ADP, TNF-α and VEGFs can effectively predict the occurrence of colonic polyps in prediabetic patients. Regardless, this study is limited. The relationship between these three indicators and colorectal cancer was not further analyzed. Hence, it is necessary to prolong the follow-up time to clarify the roles of HMW-ADP, TNF-α and VEGFs in the onset and progression of colorectal cancer.

AUTHOR CONTRIBUTION

HZ and LZ contributed equally to this study.

DISCLOSURE STATEMENT

All authors declare that they have no conflicts of interest.

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