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Relation between plasma retinol level with different types of dyslipidemia in the middle-aged and the elderly: a cross-sectional study

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ABSTRACT: Background and Aims: The plasma retinol level is used as a recommended standard to evaluate the individual's nutritional status of vitamin A. Change of blood retinol level is strongly associated with lipid metabolism disorders. Therefore, the accurate relation between plasma retinol level with different types of dyslipidemia need exploration. **Methods and Results:** A total of 538 dyslipidemia and 1116 healthy middle-aged and elderly subjects from the communities of Beijing were investigated. The Chi-square test and one-way ANOVA were used to compare the demographic characteristics. The general linear model was used to compare dietary consumption and plasma biochemical parameters. Person correlation analysis was used to explore the relationship between plasma retinol and lipids. Binary logistic regression and restricted cubic spline (RCS) were conducted to explore the association between plasma retinol and the risk of different type of dyslipidemia and the dose-response relationship. A significantly positive correlation between plasma retinol level with LDL-C and negatively correlation with HDL-C was observed. These correlations changed in patients with different types of dyslipidemia. Compared to the participates with Q_1 level of plasma retinol (<0.420μg/ml), Q_2 (0.420-0.526μg/ml), Q_3 (0.527-0.657μg/ml) and Q_4 (>0.657μg/ml) levels showed significantly increased risk of dyslipidemia and mixed dyslipidemia. And participants with Q_4 level of plasma retinol showed a sharp increased risk of hypertriglyceridemia combined with low high-density lipoprotein cholesterolemia. The RCS results indicated a non-linear (U-shaped) relation between plasma retinol and the risk of low high-density lipoprotein cholesterolemia. **Conclusion:** Elevation in plasma retinol (above 0.525 μg/ml) indicated a significantly increased risk of dyslipidemia. The recommended plasma retinol level for the middle-aged and the elderly should be different type of dyslipidemia-dependent.

Keywords: retinol; lipids; dyslipidemia; middle-aged and the elderly

1. Introduction

As an important risk factor of cardiovascular disease, dyslipidemia has become a major public health concern throughout the world. According to the latest published data, 43.3% of Chinese middle-aged and

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elderly people were dyslipidemia patients [1], highlighting that prevention and control of lipid metabolism disorder and dyslipidemia in the Chinese population is a greater medical challenge.

Vitamin A (VA) is a diet-derived fat-soluble vitamin. Recently, the role of VA in the development and regulation of lipid metabolism disorder related diseases such as obesity, insulin resistance, type 2 diabetes mellitus (T2DM), steatohepatitis, steatohepatitis, and cardiovascular disease has been extensively explored [2]. Study has found that VA could modulate the expression of a variety of genes involved in lipid metabolism [3]. Clinical dietary interventional studies also found that supplementation of VA caused significant elevation in patients' blood lipids, including TC, TG and LDL-C [4-7]. Population-based epidemiological study conducted in Chinese demonstrated that serum VA level show a significantly positive correlation with blood lipids in children and adolescents, and serum VA level was suggested a potential risk factor for dyslipidemia [8]. Furthermore, a cohort study involving 250 participants (age range 20-80 years) also observed a positive association between plasma retinol and the risk of dyslipidemia [9]. However, data from a Finnish clinical trial showed that cholesterol lowering treatment with sterol esters significantly decreased serum cholesterol level in patients with moderate hypercholesterolemia without causing significant change in serum retinol level [10]. Our previous study also found that the elderly with high plasma VA had a significantly increased risk of dyslipidemia compared with subjects with low serum retinol level [11]. However, to date, few studies have explored the relation between plasma VA level with different types of dyslipidemia (including hypercholesterolemia, hypertriglyceridemia, mixed dyslipidemia, and low high-density lipoprotein cholesterolemia) in Chinese population. Moreover, as a micronutrient, the role of VA in regulating lipids metabolism has caused researcher’s attention. Although, the WHO recommended optimal plasma retinol for health adults was greater than 0.70 μmol/L, there is still no specific plasma VA content recommendation for the elderly, especially for the elderly with different types of dyslipidemia [12]. Given that circulating VA content is closely related with lipids, the optimal plasma VA level of the elderly with abnormal lipid metabolism status might be different from the subjects with normal lipid status. We thus conducted a cross-sectional study to explore the suitable reference value for plasma retinol level in the participants with different types of dyslipidemia.

2. Materials and Methods

2.1 Study population

538 dyslipidemia and 1116 healthy participants aged 50 years and above were recruited from communities in Beijing city, China in 2019. According to the Joint Committee on the Chinese Guidelines for Lipid Management [13], different types of dyslipidemia for Chinese are defined as hypercholesterolemia (blood TC $\geq$ 6.2 mmol/L), hypertriglyceridemia (blood TG $\geq$ 2.3 mmol/L), mixed dyslipidemia (blood TC $\geq$ 6.2 mmol/L and TG $\geq$ 2.3 mmol/L) and low high-density lipoprotein cholesterolemia (blood HDL-C $\leq$ 1.0 mmol/L). Subjects currently taking VA or β-carotene supplement and lipid-lowering drugs were excluded. The study was conducted in accordance with the Declaration of Helsinki, and has been approved by the Medical Ethics Review Committee of Capital Medical University (No.2012SY23). All participants signed informed consent before the investigation and volunteered to participate in this survey.

2.2 Demographic characteristics and anthropometric measures

Participants underwent an information survey and physical examination. Information on demographic characteristics, including age, gender, education level, lifestyle factors [smoking (yes or no), alcohol drinking (yes or no) and physical activity (never, 1–3 times/week, 4–6 times/week, everyday)] and disease history [cerebrovascular accident (yes or no), chronic kidney disease (yes or no) and T2DM (yes or no)] were collected by self-administered questionnaires. All participants conducted anthropometric measures (height and weight) in community medical service center. Body mass index (BMI) was calculated as weight (kg)/height (m^2).

2.3 Dietary survey

Food Frequency Questionnaire (FFQ) was used to evaluate individual consumption of vegetable, fruit, dairy, legume, nut, red meat, light meat, fish, eggs, whole grain, cooking oil, tea drinking (yes, no) and dietary supplement (yes, no). Dietary survey documented the information, including the consumption frequencies and the amount of food consumed per day. The consumption of cooking oil was quantified based on the average by the number of family members, and monthly consumption. Completed questionnaires were randomly checked to identify and rectify data omissions and errors. Questionnaires that were inaccurately completed or contained incomplete information were excluded during data analysis.

2.4 Biochemical measurements

Fasting peripheral venous blood (5 ml) was collected from each participant in the morning, and after centrifuging at 3000 g for 15 min, the plasma was separated and stored in -80 ℃ refrigerators. Blood lipid including total cholesterol (TC), triglyceride (TG), low density lipoprotein cholesterol (LDL-C) and high density lipoprotein cholesterol (HDL-C) were measured by automatic biochemical assay. Plasma retinol was examined by high performance liquid chromatography (HPLC). To be specific, 0.2mL of serum was deproteinized with ethanol and extracted with hexane. After extraction, the extract is dried in a vacuum concentrator and dissolved in ethanol. The samples were filtered and automatically measured using the HPLC. The retinol standard was purchased from Sigma Aldrich (USA)[14]. All samples were analyzed within a single batch, and the inter-assay coefficients of variation (CV) were less than 5%. According to the recommended standard for evaluating VA nutritional status in the Chinese population, the plasma retinol concentration below 0.20 μg/mL was defined as vitamin A deficiency, and it ranged from 0.2 to 0.3μg/mL was defined as borderline vitamin A deficiency [15]. Due to the small number of the elderly people with plasma retinol concentration below 0.3 μg/mL in this study, inter-sample comparison could not be conducted. Thus, the plasma retinol concentration of the whole population was divided into 4 groups: less than 0.420 μg/ml (Q_1, n = 415), 0.420-0.526 μg/ml (Q_2, n = 415), 0.527-0.657 μg/ml (Q_3, n = 412), and above 0.657 μg/ml (Q_4, n = 412). The participants with plasma retinol concentration below 0.420 μg/mL was used for control group.

2.5 Statistical analyses

Data were statistically analyzed by SPSS 26.0 software. Graphs were drafted by the R Language 4.2.3 and Graphpad Prism 8. Quantitative variables were represented as mean ± standard deviation (SD) and

qualitative variables were expressed as *n*%. One-way ANOVA and general linear model (GLM) were used to compare the differences of demographic characters, biochemical parameters and dietary intakes between groups. χ^2 test was used to compare the categorical variables. LSD test was used for post hoc test between groups. Person correlation analysis was used to explore the relationship between plasma retinol and TC, TG, LDL-C and HDL-C. General linear model was adjusted for age, gender and BMI in comparing dietary intakes. Binary logistic regression and restricted cubic spline (RCS) were conducted to explore the association between plasma retinol and the risk of dyslipidemia and the dose-response relationship. When conducting logistic regression analysis, Model 1 was an unadjusted model. Model 2 was adjusted for age, gender, BMI, education, smoking, alcohol, tea, dietary supplement consumption, physical exercise, cerebrovascular accident (CVA), chronic kidney disease (CKD) and T2DM. Model 3 was further adjusted for vegetables, fruits, legume, cooking oil, fish, red meat, light meat, whole grain, nut, dairy and egg consumption. During RCS analysis, all confounding factors adjusted in the logistic regression models were consistently adjusted. $P < 0.05$ was considered as statistically difference.

3. Results

3.1 Demographic characteristics, and dietary intakes of participants

The demographic characteristics and dietary intake of participants were showed in **Table 1**. A total of 538 patients with dyslipidemia and 1116 healthy control individuals were enrolled in this study, including 121 patients with hypercholesterolemia, 233 patients with hypertriglyceridemia, 82 patients with mixed dyslipidemia, 66 patients with low high-density lipoprotein cholesterolemia and 36 patients with hypertriglyceridemia combined with low high-density lipoprotein cholesterolemia. There was no significant difference in age, alcohol drinking, physical exercise habit, tea and dietary supplement consumption and CVA and CKD history between groups. Differences in BMI, gender distribution, education, smoking, T2DM history, daily consumption of vegetables, whole grains, nuts and eggs were found between groups ($P < 0.05$). Patients with hypertriglyceridemia combined with low high-density lipoprotein cholesterolemia had the highest BMI as comparing with participants from other groups. Women were more likely to suffer from hypercholesterolemia and mixed dyslipidemia. And the patients with dyslipidemia were more likely to suffer from T2DM. The patients with low high-density lipoprotein cholesterolemia had the lowest daily egg and whole grains consumption. Patients with hypercholesterolemia had the lowest vegetables intake. The comparison of blood lipid levels and plasma retinol concentration of participants among groups was shown in **Table 2**. There were statistical differences in blood lipids in subjects with different types of dyslipidemia ($P < 0.05$). And patients with hypertriglyceridemia, mixed dyslipidemia, low high-density lipoprotein cholesterolemia and hypertriglyceridemia combined with low high-density lipoprotein cholesterolemia showed higher plasma retinol concentrations than the controls. Besides, hypertriglyceridemia combined with low high-density lipoprotein cholesterolemia patients had the highest retinol levels ($P < 0.05$).

Table 1 Characteristics of participants according to different types of dyslipidemia

Variables	Control (*N* = 1116)	Dyslipidemia (*N* = 538)					*P* value
		Hypercholesterolemia (*N* = 121)	Hypertriglyceridemia (*N* = 233)	Mixed dyslipidemia (*N* = 82)	Low high-density lipoprotein Cholesterolemia (*N* = 66)	Hypertriglyceridemia Combined with Low high-density lipoprotein Cholesterolemia (*N* = 36)	
Age (years)	65.34±6.41	64.71±6.33	64.91±6.19	65.57±6.03	65.88±5.39	65.44±4.57	0.746
BMI (kg/m^2)	25.22±3.54	24.40±4.00	26.06±3.35	25.45±3.26	25.26±3.09	26.52±3.12	< 0.001
Gender, *n* (%)							< 0.001
Male	370 (33.2)	20 (16.5)	75 (32.2)	11 (13.4)	39 (59.1)	16 (44.4)	
Female	746 (66.8)	101 (83.5)	158 (67.8)	71 (86.6)	27 (40.9)	20 (55.6)	
Education, *n* (%)							0.028
Illiterate	47 (4.2)	12 (9.9)	15 (6.4)	6 (7.3)	3 (4.5)	2 (5.6)	
Primary school	172 (15.4)	11 (9.1)	43 (18.5)	16 (19.5)	10 (15.2)	5 (13.9)	
Junior high school	492 (44.1)	49 (40.5)	101 (43.3)	40 (48.8)	22 (33.3)	20 (55.6)	
High school	311 (27.9)	41 (33.9)	56 (24.0)	17 (20.7)	19 (28.8)	7 (19.4)	
Junior college and above	137 (8.3)	8 (6.7)	18 (7.7)	3 (3.6)	12 (18.2)	2 (5.6)	
Smoking, *n* (yes, %)	184 (16.5)	8 (6.7)	36 (15.5)	9 (11.0)	18 (27.3)	7 (19.4)	0.006
Drinking, *n* (yes, %)	336 (30.1)	25 (20.7)	62 (26.6)	17 (20.7)	15 (22.7)	10 (27.8)	0.111
Physical activity, *n* (%)							0.246
Never	70 (6.3)	13 (10.7)	17 (7.3)	11 (13.4)	8 (12.1)	4 (11.1)	
1-3 times/week	128 (11.5)	12 (9.9)	29 (12.4)	11 (13.4)	10 (15.2)	7 (19.4)	
4-6 times/week	124 (11.1)	13 (10.7)	27 (11.6)	10 (12.2)	10 (15.2)	5 (13.9)	
Everyday	794 (71.1)	83 (68.6)	160 (68.7)	50 (61.0)	38 (57.6)	20 (55.6)	
Tea consumption, *n* (%)	622 (55.7)	75 (62.0)	143 (61.4)	46 (56.1)	42 (63.6)	26 (72.2)	0.150
Dietary supplement, *n* (%)	255 (22.8)	27 (22.3)	56 (24.0)	14 (17.1)	8 (12.1)	10 (27.8)	0.265
CVA, *n* (%)	81 (7.3)	7 (5.8)	14 (6.0)	4 (4.9)	4 (6.1)	2 (5.6)	0.922
CKD, *n* (%)	50 (4.5)	3 (2.5)	13 (5.6)	1 (1.2)	3 (4.5)	2 (5.6)	0.554
T2DM, *n* (%)	393 (35.2)	39 (32.2)	102 (43.8)	37 (45.1)	29 (43.9)	18 (50.0)	0.020
Daily dietary intake (g/d)							
Fruits	154.97±109.32	158.97±112.86	152.53±111.32	165.11±108.87	117.05±83.87	140.38±97.71	0.339
Vegetables	309.83±133.07	271.49±133.67	287.23±131.56	288.11±135.30	321.59±129.78	304.86±122.74	0.014
Legume	30.21±27.90	32.23±29.10	31.35±27.29	28.33±24.56	22.43±16.90	23.76±14.67	0.055
Cooking Oil	30.08±20.23	28.03±15.55	29.17±16.34	30.85±18.06	31.32±14.97	28.34±13.40	0.769
Fish	19.63±16.15	20.93±21.22	19.80±18.00	18.71±16.12	19.09±14.95	18.01±10.57	0.835
Whole grain	37.24±37.23	31.21±35.72	43.84±39.49	31.84±22.26	23.81±19.46	28.37±19.87	< 0.001
Red meat	30.62±29.47	30.89±35.72	29.74±33.43	29.18±29.75	24.78±15.44	29.51±39.23	0.149
Light meat	13.83±14.60	15.85±17.81	13.03±13.28	12.54±12.02	13.66±14.15	14.78±9.68	0.366

	Nut	16.70±21.51	16.97±20.69	22.35±39.97	17.39±22.28	14.50±16.99	10.91±10.27	0.020
	Dairy	130.87±109.99	153.57±114.12	119.15±102.52	129.45±82.97	111.71±86.23	111.07±98.88	0.166
	Egg	32.75±18.54	31.79±15.96	33.20±20.23	29.01±17.86	26.03±11.10	28.27±24.41	0.013

Data was presented as mean ± standard or *n* (%). One-way ANOVA analysis was used to compare the age and BMI; R×C χ^2 test was used to compare gender, education, smoking, drinking, physical exercise between groups. General linear model (GLM) was used to compare the difference in dietary intake. Model was adjusted for age, gender and BMI. $P < 0.05$ was considered statistically significant. BMI, body mass index; CVA, cerebrovascular accident; CKD, chronic kidney disease; T2DM, Type 2 Diabetes Mellitus.

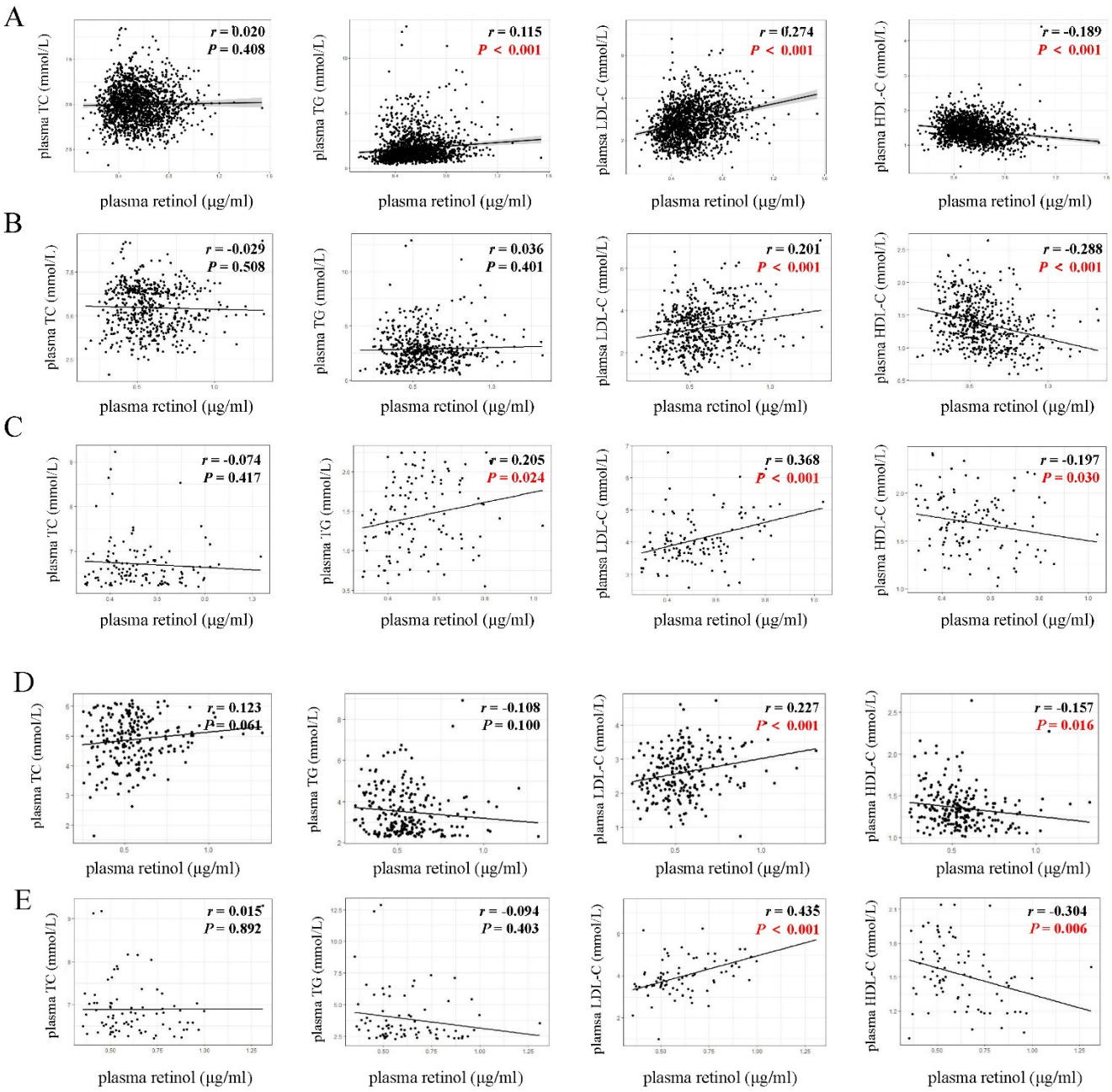
Table 2 Plasma parameters among groups

Parameters	**Control (*N* = 1116)**	**Dyslipidemia (*N* = 538)**					***P* value**
		Hypercholesterolemia (*N* = 121)	**Hypertriglyceridemia (*N* = 233)**	**Mixed dyslipidemia (*N* = 82)**	**Low high-density lipoprotein Cholesterolemia (*N* = 66)**	**Hypertriglyceridemia Combined with Low high-density lipoprotein Cholesterolemia (*N* = 36)**	
TC (mmol/L)	4.76 ± 0.76	6.70 ± 0.54 **a**	4.86 ± 0.80 **b**	6.91 ± 0.69 **abc**	3.98 ± 0.78 **abcd**	4.48 ± 0.99 **bcde**	< 0.001
TG (mmol/L)	1.28 ± 0.46	1.43 ± 0.45	3.49 ± 1.12 **ab**	4.22 ± 2.98 **abc**	1.46 ± 0.43 **cd**	4.28 ± 2.36 **abce**	< 0.001
LDL-C (mmol/L)	2.71 ± 0.70	4.10 ± 0.75 **a**	2.60 ± 0.69 **b**	3.93 ± 1.01 **abc**	2.65 ± 0.77 **bd**	2.79 ± 0.98 **bd**	< 0.001
HDL-C (mmol/L)	1.46 ± 0.28	1.69 ± 0.29 **a**	1.35 ± 0.24 **ab**	1.51 ± 0.29 **bc**	0.94 ± 0.06 **abcd**	0.85 ± 0.14 **abcd**	< 0.001
Retinol (μg/ml)	0.54 ± 0.17	0.53 ± 0.15	0.55 ± 0.17 **a**	0.62 ± 0.18 **abc**	0.63 ± 0.20 **a**	0.74 ± 0.19 **abcde**	< 0.001

Data was presented as mean ± standard. General linear model (GLM) and LSD test were used to compare the difference in plasma parameters among groups. Model was adjusted for age, gender, BMI, education, smoking, alcohol, tea, dietary supplement consumption, physical exercise, CVA, CKD and T2DM, vegetables, fruits, legume, cooking oil, fish, red meat, light meat, whole grain, nut, dairy and egg consumption. a, compared with control groups; b, compared with hypercholesterolemia group; c, compared with hypertriglyceridemia group; d, compared with mixed dyslipidemia; e, compared with low high-density lipoprotein Cholesterolemia. TC, total cholesterol; TG, triglycerides; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; CVA, cerebrovascular accident; CKD, chronic kidney disease; T2DM, Type 2 Diabetes Mellitus.

3.2 Correlation between plasma retinol and blood lipids

The relationship between plasma retinol concentration and blood lipids (TC, TG, LDL-C, HDL-C) is shown in **Figure 1**. Plasma retinol was positively correlated with plasma TG, LDL-c and negatively correlated with plasma HDL-C in the whole population and in the control groups. In the subgroups, except for hypertriglyceridemia combined with low high-density lipoprotein cholesterolemia group, the positive relationship between plasma retinol and LDL-C still reminded ($P < 0.05$). Besides, the positive relationship between plasma retinol and TG was founded in the hypercholesterolemia and low high-density lipoprotein cholesterolemia group ($P < 0.05$). The negative relationship between plasma retinol and HDL-C was found in the all subgroups ($P < 0.05$), except in the low high-density lipoprotein cholesterolemia group and hypertriglyceridemia combined with low high-density lipoprotein cholesterolemia group. However, no linear relationship was observed between plasma retinol and TC in the whole population and in subgroups ($P > 0.05$).



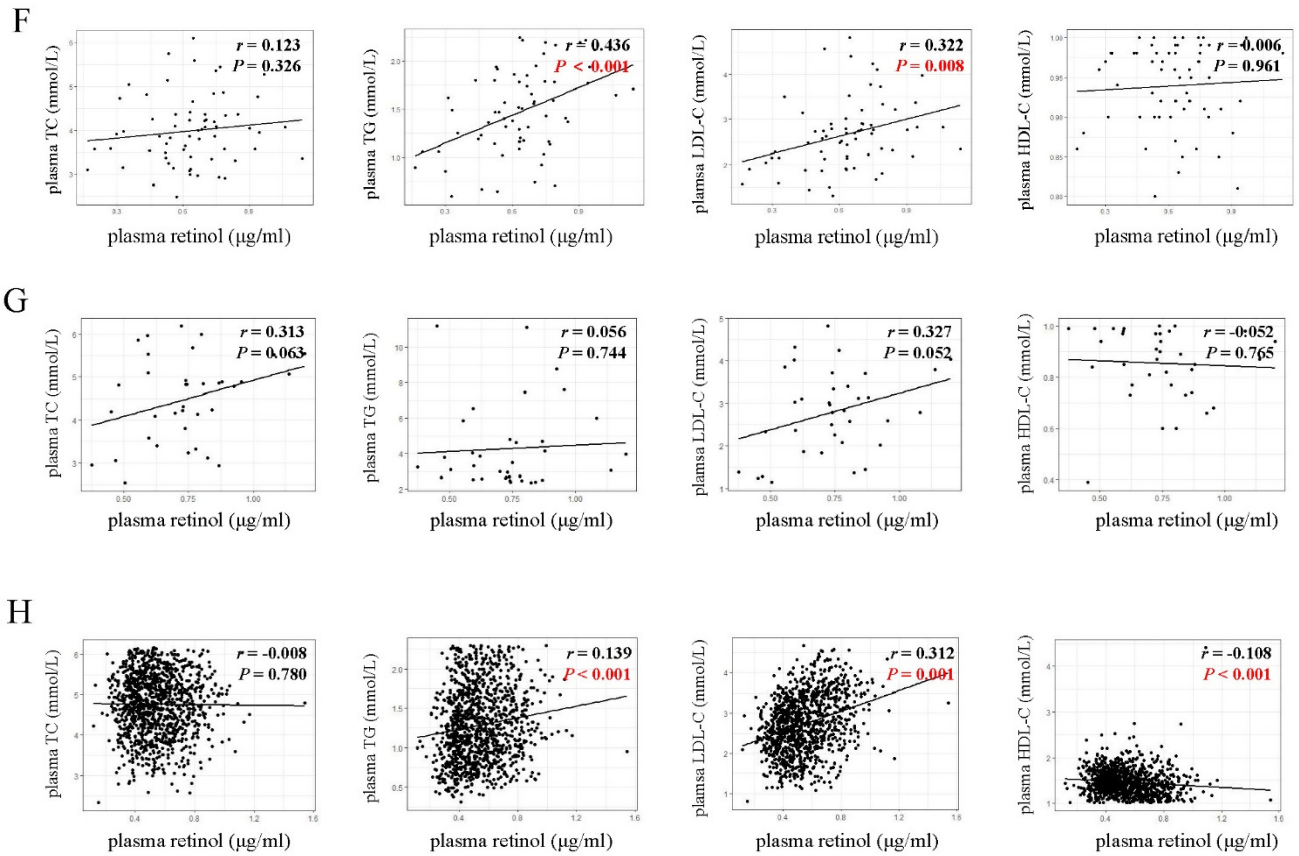


Figure 1 | Correlation between plasma retinol and lipids in the whole population(A). Correlation between plasma retinol and lipids in the the patientswith dyslipidemia(B), hypercholesterolemia(C), hypertriglyceridemia(D), mixed dyslipidemia(E), low High-Density Lipoprotein Cholesterolemia(F), hypertriglyceridemia combined with low High-Density Lipoprotein Cholesterolemia(G) and control group (H) respectively. TC, total cholesterol; TG, triglycerides; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol.

3.3 Association of plasma retinol with the risk of different types of dyslipidemia

The relationship between plasma retinol level and the risk of dyslipidemia, hypercholesterolemia, hypertriglyceridemia, mixed dyslipidemia, low high-density lipoprotein cholesterolemia and hypertriglyceridemia combined with low high-density lipoprotein cholesterolemia is shown in **Table 3** and **Figure 2**. After adjusting for confounding factors, compared with the subjects with Q_1 level of plasma retinol, the participants with Q_2, Q_3 and Q_4 levels of plasma retinol showed increased risk of dyslipidemia (OR_{Q2vsQ1} = 1.433, P = 0.025; OR_{Q3vsQ1} = 1.985, P < 0.001; OR_{Q4vsQ1} = 1.994, P < 0.001). The trend test further demonstrated the positive relation between plasma retinol and the risk of dyslipidemia (P_{trend} < 0.001). Similarly, the positive relation between plasma retinol and the risk of mixed dyslipidemia was consistently observed (OR_{Q2vsQ1} = 3.094, P = 0.008; OR_{Q3vsQ1} = 3.314, P = 0.006; OR_{Q4vsQ1} = 5.674, P < 0.001; P_{trend} < 0.001). Compared with the participants with Q_1 level of plasma retinol, subjects with Q_3 level of plasma retinol displayed increased the risk of hypertriglyceridemia (OR_{Q3vsQ1} = 1.779, P = 0.006). When the subjects with retinol at the concentration greater than 0.658 μg/ml (Q_4), the risk of hypertriglyceridemia combined with low high-density lipoprotein cholesterolemia was significantly increased. However, the risk of low high-density lipoprotein cholesterolemia only observed in Model 1 and Model 2, after correcting for dietary factors, statistical significance disappeared.

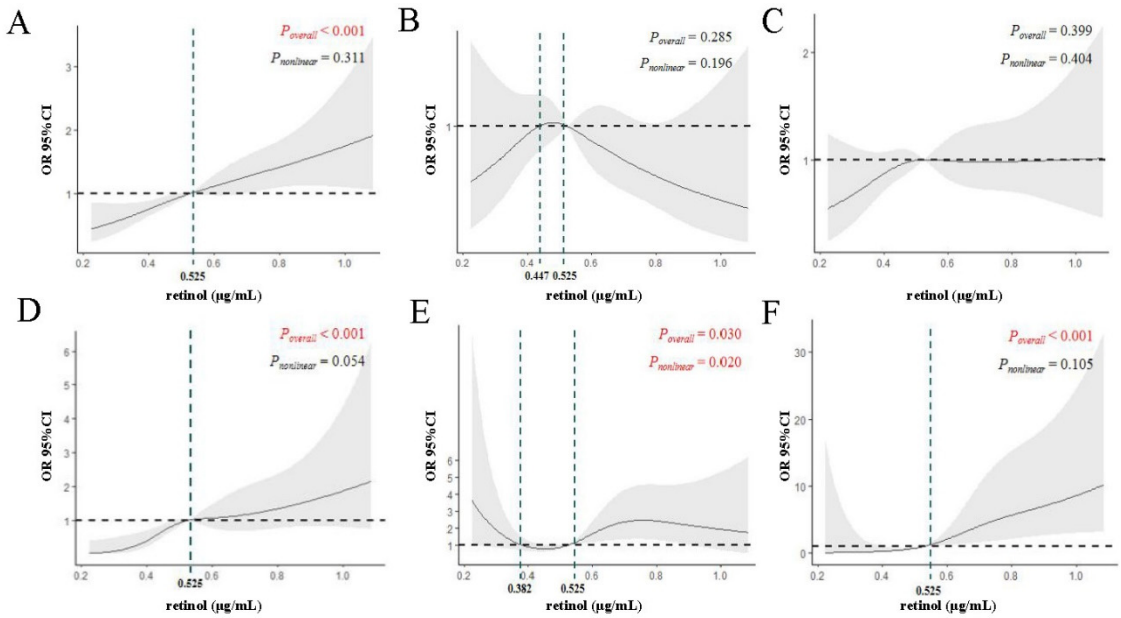


Figure 2 | RCS to explore the relationship between plasma retinol and dyslipidemia (A), hypercholesterolemia (B), hypertriglyceridemia (C), mixed dyslipidemia (D), low high-density lipoprotein cholesterolemia (E) and hypertriglyceridemia combined with low high-density lipoprotein cholesterolemia (F). Restricted Cubic Splines (RCS) plot was used to display OR and 95%CI. Model was adjusted for age, gender, BMI, education, smoking, alcohol, tea, dietary supplement consumption, physical exercise, CVA, CKD, T2DM, vegetables, fruits, legume, nut, cooking oil, fish, red meat, light meat, whole grain, dairy and egg consumption. CVA, cerebrovascular accident; CKD, chronic kidney disease; T2DM, Type 2 Diabetes Mellitus.

The results of RCS curve also showed a positive correlation of plasma retinol with the risk of dyslipidemia and mixed hyperlipidemia. We found an inverted U-shaped relationship between plasma retinol level and the risk of hypercholesterolemia and an U-shaped relationship between plasma retinol levels and the risk of low high-density lipoprotein cholesterolemia in middle-aged and elderly people. The subjects with plasma retinol below 0.525 μg/ml showed a decreased risk of dyslipidemia. And the subjects with plasma retinol ranged from 0.447 to 0.525 μg/ml may increase the risk of hypercholesterolemia. When the concentration of plasma retinol was over 0.525 μg/ml, the risk of mixed dyslipidemia and the risk of hypertriglyceridemia combined with low high-density lipoprotein cholesterolemia increased dramatically. The risk of low high-density lipoprotein cholesterolemia increasing dramatically in the subjects with plasma retinol concentration below 0.382 μg/ml. Additionally, RCS curve also showed that subjects with plasma retinol concentration above 0.525 μg/ml increased the risk of low high-density lipoprotein cholesterolemia.

4. Discussion

The present study explored the relation between plasma retinol with different types of dyslipidemia in the middle-aged and the elderly. Differences in BMI, gender, education, smoking and T2DM history, daily intake of vegetables, whole grains, nut, and eggs was found between dyslipidemia patients and the controls. A large cross-sectional survey found that the age-standardized prevalence of dyslipidemia was 36.2% in males and 33.4% in females [16], with a higher prevalence in males than in females, and similar results have been found in other studies [17]. Inconsistently, in the present study we found that the prevalence of dyslipidemia was higher

in women than in men. The possible reason for this is that the participants in this study were older than 50 years of age, which is older compared to previous studies. Women in the transition period of menopause are prone to have various lipid metabolism disorders due to the changes in hormone levels [18]. Studies have shown that patients with dyslipidemia frequently have clinical manifestations of diabetes or pre-diabetes [19], which is consistent with the results of this study.

In this study, plasma retinol level was found to be positively correlated with plasma TG and LDL-C levels, but negatively correlated with HDL-C level. Previously, it has been reported that circulating VA level was positively correlated with blood TC and LDL-C [20]. Involvement of vitamin A in lipid metabolism has been reported by previous study, demonstrating that interaction of VA with its receptor could promote hepatic fatty acid degradation and the synthesis of large amounts of TG-rich VLDL particles, which leading to increased hepatic TG production, resulting in the elevation of plasma TG [21-22]. However, the correlation between plasma retinol and TC was not found in the whole population and in patients with any type of dyslipidemia in the present study. Considering the opposite correlation of VA with plasma LDL-C and HDL-C, we therefore speculated the non-significant correlation of VA with blood TC might be the net effect of VA with LDL-C and HDL-C. Consistent with the results in the whole population, an opposite correlation of plasma LDL-C and HDL-C with retinol was observed in the patients with dyslipidemia, but the correlation of plasma retinol with TG disappeared. In the subgroup analyses, significantly positive correlation of plasma retinol with LDL-C and negative correlation with HDL-C were detected in patients with hypercholesterolemia, hypertriglyceridemia, and mixed dyslipidemia, but the correlation between plasma retinol level and HDL-C was not observed in patients with low high-density lipoprotein cholesterolemia. The differences between studies may be attributed to the limited sample size or the disruption of individual retinol metabolic homeostasis caused by abnormal lipid metabolism.

As a fat soluble vitamin, retinol is packaged in nascent chylomicron and mostly transported to the liver, from which it is later secreted as nascent very low-density lipoprotein (VLDL) [23]. Nascent VLDL is hydrolyzed by lipoprotein lipase to IDL and further metabolized to LDL [24]. In the circulation, retinoids are also present in LDL and HDL formed from VLDL [25]. Recent study has shown that plasma retinol level is associated with apolipoproteins A1 (ApoA1) and B (ApoB), which are major components of HDL and LDL [26]. Apolipoprotein D (ApoD) is predominantly found in HDL, and small amounts were detected in LDL and VLDL [27]. As a component of lipocalin proteins (a plasma retinol-binding protein), ApoD is also strongly associated with plasma retinol level. Therefore, the close relation between retinol and apolipoproteins might further explain the significant correlation of blood retinol with LDL-C and HDL-C levels. Abnormal lipid metabolism status was commonly accompanied with alternations in the storage and metabolism of retinol, which might result in the change of retinol in blood [9]. Besides, dietary retinol intake-dependent alteration of hepatic storage and plasma concentration of retinol has been observed in experimental animals [28]. In the human body, 80% of retinol is stored in the form of retinyl esters in hepatic stellate cells [29], and changes in lipoprotein levels under different dyslipidemia status might induce the alterations in hepatic retinol

mobilization. We therefore speculated that disturbance of retinol homeostasis-mediated by abnormal lipids metabolism contributes to the different associating profile of circulating retinol with lipids in the patients with different type of dyslipidemia.

Given the fact that under normal physiological conditions, plasma retinol level was precisely maintained within a narrow range, the WHO currently recommends the use of plasma retinol level to evaluate VA nutritional status in healthy individuals [12]. However, abnormal lipid metabolism can disrupt the homeostatic balance of VA. According to the Joint Committee on the Chinese Guidelines for Lipid Management, dyslipidemia is classified based on the following thresholds: plasma TC ≥ 6.2 mmol/L, plasma TG ≥ 2.3 mmol/L, and plasma HDL-C < 1.0 mmol/L [13]. The inconsistent risk profiles for patients with different types of dyslipidemia might be caused by the interaction between plasma retinol and lipoproteins. Plasma retinol shows no correlation with TC, while its association with TG varies in different groups. The results from logistic regression and RCS further revealed that plasma retinol level was not linked to the risk of hypercholesterolemia or hypertriglyceridemia. Notably, patients with hypertriglyceridemia combined with low high-density lipoprotein cholesterolemia had the highest plasma retinol level among all subgroups. These data demonstrated that elevated plasma retinol level significantly related with increased risk of hypertriglyceridemia combined with low high-density lipoprotein cholesterolemia, suggests that the combined effects of blood TG and HDL-c on plasma retinol level. In subgroup analyses, circulating retinol level was found to have a significant negative correlation with HDL-C. This relation was not observed in the patients with low high-density lipoprotein cholesterolemia. RCS analyses indicated that both low and high plasma retinol levels correlated with increased risk for low high-density lipoprotein cholesterolemia, indicating a non-linear relation between plasma retinol with the risk of low high-density lipoprotein cholesterolemia. Considering the significantly positive correlation between blood LDL-c and retinol, as well as the impact of HDL-c/LDL-c ratio on the risk of dysilipidemia [30], we speculated that the disturbance of HDL-c/LDL-c ratio in response to different VA nutritional status might contribute to the risk of low high-density lipoprotein cholesterolemia in the middle aged and the elderly.

As a carrier of VA, retinol-binding protein 4 (RBP4) is produced by the liver and adipose tissue and transports retinol through the circulation to peripheral tissues [31]. Positive correlation between plasma RBP4 and retinol level has been reported by previous study [32]. Additionally, plasma RBP4 concentration was also found positively associating with plasma total VLDL and LDL particles, but negatively correlated with larger HDL particles [33]. Moreover, studies also reported an association between elevated circulating RBP4 level and hypertriglyceridemia and hypercholesterolemia [34], but this relationship was not observed in patients with low high-density lipoprotein cholesterolemia [35]. These results suggested that changes in plasma RBP4 in patients with different types of dyslipidemia may also contribute to the differences in plasma retinol. Increase in circulating RBP4 level could accelerate the mobilization of hepatic retinol to circulation, resulting in elevation of plasma retinol. We therefore speculated that the increase of plasma retinol level in patients with dyslipidemia might due to the increase of circulating RBP4 level accompanied by abnormal lipid metabolism.

Studies have found that individuals with dyslipidemia commonly have higher blood retinol concentration [9,36]. Long-term high-dose VA therapy has been shown to cause elevated plasma retinol , TG and TC, but decreased HDL-C levels [37-38]. These findings further demonstrated a bidirectional regulating relation between retinol and lipid metabolisms.

Totally, our data suggested that elevated plasma retinol level correlated with the risk of dyslipidemia and the association might be dyslipidemia type-dependent. Therefore, individual's lipid metabolic status and pathophysiological level should be took into consideration during the setting individual's VA intake standards and recommending appropriate plasma VA level. In view of the important role of VA in the regulation of lipid metabolism in the body [39], it is necessary to carry out studies on exploring the hepatic VA reserves in individuals with different types of dyslipidemia.

Our findings suggested that plasma retinol was positively associated with the risk of mixed dyslipidemia and hypertriglyceridemia combined with low high-density lipoprotein cholesterolemia in the middle aged and the elderly, while plasma retinol showed a U-shaped relationship with the risk of low high-density lipoprotein cholesterolemia. However, no correlation was found between plasma retinol and the risk of developing hypercholesterolemia and hypertriglyceridemia in the elderly, which may be related to the weak correlation of plasma retinol with TC and TG. In our study, the risk of dyslipidemia, mixed dyslipidemia and hypertriglyceridemia combined with low high-density lipoprotein cholesterolemia were increased in the subjects with plasma retinol level greater than 0.525μg/ml. And the risk of low high-density lipoprotein cholesterolemia in the elderly is significantly increased when the plasma retinol level is below 0.382 μg/ml or above 0.525 μg/ml. These results further hint that the evaluation of VA nutritional status should base on individual's lipids metabolism status. Abnormal lipid metabolism *in vivo* might alter the homeostatic balance of VA metabolism, therefore weakening the reference value of plasma retinol level in evaluating individual's vitamin A nutritional status, especially for individuals with different types of dyslipidemia.

There are some limitations of this study. Firstly, the hepatic VA reserve and plasma RBP4 level were not measured in the present study, thus our data could not reveal the underlying mechanisms of plasma retinol level with the risk of different types of dyslipidemia. Secondly, the cross-sectional study was conducted in Chinese elderly, therefore, caution should be exercised in extrapolating our findings to other populations, and prospective cohort studies are needed for causality determination. Although these limitations, the strength of our study is the exploration of plasma retinol level with different types of dyslipidemia. Our data might provide scientific reference for formulating dietary reference intake standard of VA for the elderly, especially the elderly with different types of dyslipidemia.

5. Conclusion

In summary, plasma retinol is positively correlated with TG and LDL-C, and negatively correlated with HDL-C in the elderly population. Elevated plasma retinol may be a potential parameter for the diagnosis of mixed hyperlipidemia, low high-density lipoprotein cholesterolemia and hypertriglyceridemia combined with low high-density lipoprotein cholesterolemia in the middle-aged and the elderly. The relationship between

plasma retinol level and low high-density-lipoprotein cholesterolemia was U-shaped. These results will provide a certain basis for accurate evaluation of the nutritional status of vitamin A in the elderly, especially the elderly with different types of dyslipidemia.

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