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RESEARCH ARTICLE

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Serum lutein is a promising biomarker for type 2 diabetes mellitus and diabetic kidney disease in the elderly

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Abstract

Objective: To investigate the relationship between serum lutein and type 2 diabetes mellitus (T2DM) and diabetic kidney disease (DKD) in elderly individuals.

Methods: A total of 60 T2DM patients over 60 years were subgrouped into a DKD group and a non-DKD group according to their urinary microalbumin-to-creatinine ratio (UACR), while 30 age-matched non-T2DM patients were recruited in the control group. Baseline characteristics, laboratory examination results, and serum lutein levels were compared, and their correlations were analyzed. Receiver operating characteristic (ROC) curves were plotted to identify the diagnostic potential of lutein in T2DM and DKD.

Results: The lutein level in the T2DM group was significantly lower than that in the control group and was also significantly lower in the DKD group than in the non-DKD group ($p < 0.001$). Lutein levels were negatively correlated with body mass index, glycosylated hemoglobin, fasting blood glucose, triglyceride, and UACR and positively correlated with high-density lipoprotein cholesterol ($p < 0.05$). T2DM patients were divided into four groups according to the quartile of their lutein level. The proportion of T2DM and DKD gradually decreased with increasing lutein levels ($p < 0.001$). The area under the ROC curve of serum lutein in diagnosing T2DM and DKD was 0.880 and 0.779, respectively, with corresponding cut-off values of 0.433 μmol/L and 0.197 μmol/L ($p < 0.001$).

Conclusion: The serum level of lutein is negatively correlated with the incidence of T2DM and DKD in the elderly and can serve as a diagnostic marker for T2DM and DKD.

KEYWORDS
biomarker, diabetic kidney disease, lutein, type 2 diabetes mellitus

1 | INTRODUCTION

Type 2 diabetes mellitus is a chronic metabolic disease characterized by high blood glucose that causes multiorgan dysfunction and seriously endangers the health and even lives of affected people. The number of diabetes patients has been on the rise in recent years. Estimated by the International Diabetes Federation (IDF), there were up to 460 million diabetes patients throughout the world in 2020.[1] The incidence of T2DM increases with age and is much higher in people over 60 years than in adults (20.2% vs. 10.9%).[2] In addition, population aging is pronounced in China, and there were 260 million people over 60 years in the country in 2020. The number of elderly T2DM patients is increasing with the acceleration of the aging process, extension of average life, improvement of dietary and reduction of physical activities.[2] Therefore, it is of great clinical significance to pay attention to elderly T2DM patients.

Long-term chronic hyperglycemia leads to various diabetic complications. DKD is one of the most common diabetic microvascular complications, accounting for 20%–40% of complications in the Chinese population with T2DM, and has become the main cause of renal failure.[3] Compared with young adults with diabetes, elderly adults are significantly more susceptible to DKD. It has become one of the main causes of disability and death in elderly T2DM patients, posing huge societal and economic burdens. It is vital to search for biomarkers that predict T2DM and DKD early in the elderly, thus providing effective management.

Lutein is a natural oxygenated carotenoid that presents obvious antioxidation and anti-inflammatory functions.[4] It has also been accepted that T2DM and DKD are closely linked with oxidative stress and the inflammatory response.[5] The potential correlation between lutein and T2DM and DKD in the elderly, however, remains unclear.

In our study, we measured the circulating level of lutein in elderly T2DM patients, including DKD and non-DKD patients, and nondiabetic patients by triple quadrupole mass spectrometry. The correlation between lutein and the incidence of T2DM and DKD was further investigated, with the aim of highlighting the potential of lutein as an effective biomarker for the early diagnosis and treatment of T2DM and DKD in the elderly.

2 | MATERIALS AND METHODS

2.1 | Chemicals and reagents

MS-grade methanol was supplied by Thermo Fisher. Formic acid (FA) was provided by Sigma-Aldrich Co., Ltd. Lutein and acetaminophen were from Aladdin.

2.2 | Subjects and study design

A total of 60 T2DM patients over 60 years admitted to the Geriatrics Department, Nanjing Drum Tower Hospital from February 2018 to October 2020 were recruited in the T2DM group. They were diagnosed based on the *Guideline for the Prevention and Treatment of Type 2 Diabetes Mellitus in China (2020 edition)*. T2DM patients were further subgrouped into the DKD group ($n = 30$, UACR ≥30 mg/g) and the non-DKD group ($n = 30$, UACR <30 mg/g) according to the UACR. During the same period, 30 age-matched non-T2DM individuals were recruited as the control group. Exclusion criteria: (1) Acute diabetic complications within three months, including lactic acidosis, hyperosmolar hyperglycemia, diabetic ketoacidosis or hypoglycemic coma; (2) Combined with severe liver damage, malignant tumors or severe immune system diseases; (3) Recent stress states, such as infection, surgery, trauma, acute cardiovascular and cerebrovascular diseases; and (4) Medication of lutein, carotenoids, vitamins and other nutritional supplements within six months.

2.3 | Anthropometric and biochemical measurements

Clinical data of all subjects, including age, sex, body weight, height, body mass index [BMI (kg/m^2) = body weight/height^2], systolic blood pressure (SBP), diastolic blood pressure (DBP) and diabetes disease course, were thoroughly recorded. Blood samples were taken from the ulnar vein in the morning after overnight fasting using an automatic biochemical analyzer to detect the following indices: hemoglobin A1c (HbA1c), fasting blood glucose (FBG), total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), triglycerides (TG), creatinine (Cr), blood urea nitrogen (BUN), uric acid (UA) and C-reactive protein (CRP). The estimated glomerular filtration rate (eGFR) was calculated using the Modification of Diet in Renal Disease (MDRD) formula. The 24-hour urine of T2DM patients was collected for measuring microalbumin and creatinine by the immunoturbidimetric method, and UACR was calculated.

2.4 | Measurement of the serum lutein level

Each 100 μl plasma sample was slowly lysed at 4°C. Then, 400 μl precooled methanol was supplied, rotated for 60 s, cultured at −80°C for 8 h, and centrifuged at 16000 *g* at 4°C for 10 min to precipitate protein. Multiple reaction monitoring (MRM) was performed to measure serum lutein levels using the SCIEX Exion LC AD system (AB SCIEX) and a QTRAP 5,500 mass spectrometer (AB SCIEX) as previously reported. Briefly, the liquid chromatography was separated by a high-performance liquid chromatography (HPLC) column (2.7 μm, 30 mm × 3.1 mm; Agilent Technologies) with the mobile phase of solvent A (0.1% FA in water) and solvent B (acetonitrile) at room temperature. A linear gradient with a flow rate of 0.3 ml/min was applied to solvent B at 10% for 0 min, 10% for 1 min, 90% for 4 min, 90% for 8 min and 10% for 9 min. The injection volume was prepared at 10 μl. Q1 and Q3 were both set at unit resolution. The drying gas temperature, flow of the drying gas, electrospray

capillary voltage and nebulizer pressure were set at 350°C, 10 L/min, 5500 V and 55 psi, respectively. Data were collected and analyzed using AB SCIEX Analyst software. Sample concentration was measured by summation of transitions, and the mean metabolite standard intensity represented the lutein level.

2.5 | Statistical analyses

Statistical analyses were performed using SPSS 22.0. Normally distributed data are expressed as the mean ± standard deviation and were compared using the independent sample *t* test between the two groups; otherwise, they are expressed as the median and interquartile and were compared using the nonparametric test. Enumeration data were compared using the chi-square test. The correlation between lutein level and other indices was assessed using the Pearson's correlation test. The diagnostic potential of lutein in T2DM and DKD was analyzed by plotting ROC curves. $p < 0.05$ was considered statistically significant.

3 | RESULTS

3.1 | MRM based lutein quantification

We quantified the level of lutein using MRM based quantification method. Product ion become a unique signature in combination with the precursor ion for MRM analysis (Figure 1A) and MRM transitions of *m/z* 104.2→74.1 and *m/z* 88.9→42.9 were established (Figure 1A). The relative peak area ratio of the lutein and internal standard acetaminophen was plotted against relative concentration (Figure 1B).

3.2 | Baseline characteristics of subjects

As shown in Table 1, there were 16 males and 14 females with a mean age of 77.27 ± 10.31 years in the control group. In addition, a total of 39 males and 21 females were recruited in the T2DM group, with a mean age of 78.85 ± 9.80 years. There was no significant difference in sex or age between the two groups (both $p > 0.05$). The variables HbA1c, FBG and TG in the T2DM group were significantly higher than those in the control group (all $p < 0.05$). In contrast, HDL-C and lutein levels in the T2DM group were significantly lower than those in the control group (all $p < 0.05$). No significant differences in BMI, SBP, DBP, TC, LDL-C, Cr, BUN, eGFR, UA or CRP were detected between the subjects in the control group and the T2DM group (all $p > 0.05$). In addition, T2DM patients were further subgrouped into a DKD group and a non-DKD group. No significant differences in age, sex, BMI, SBP, DBP, HbA1c, FBG, TC, LDL-C, HDL-C, Cr, BUN, eGFR, UA or CRP were detected between the two subgroups. A significantly longer diabetic course, higher TG, greater UACR and lower lutein level were detected in the DKD group than in the non-DKD group (all $p < 0.05$).

3.3 | The correlation between lutein level and other clinical indicators

Pearson's correlation analysis revealed that lutein levels were negatively correlated with UACR, BMI, HbA1c, FBG and TG (all $p < 0.05$, $r = 0.333$, 0.215, 0.339, 0.295 and 0.227, respectively), and positively correlated with HDL-C ($p < 0.05$, $r = 0.363$). No significant correlation was identified between lutein level and other clinical data (Table 2).

3.4 | The influence of lutein level on the incidence of T2DM and DKD in the elderly

All subjects were categorized into Q1 (0.059–0.260 μmol/L), Q2 (0.259–0.387 μmol/L), Q3 (0.387–0.697 μmol/L) and Q4 groups (0.697–4.136 μmol/L) according to the quartile of lutein level. Interestingly, the proportion of T2DM in the four groups was gradually reduced from 100.00%, 82.61% and 65.22% to 18.18%, with a significant difference ($p < 0.001$, Figure 2A). Similarly, T2DM patients were further categorized into the T1 (0.059–0.193 μmol/L), T2 (0.193–0.319 μmol/L), T3 (0.319–0.429 μmol/L) and T4 groups (0.429–1.947 μmol/L). The proportion of DKD ranked the highest in the T1 group (93.33%), followed by the T2 (46.67%), T3 (40.00%) and T4 groups (20.00%) ($p < 0.001$, Figure 2B).

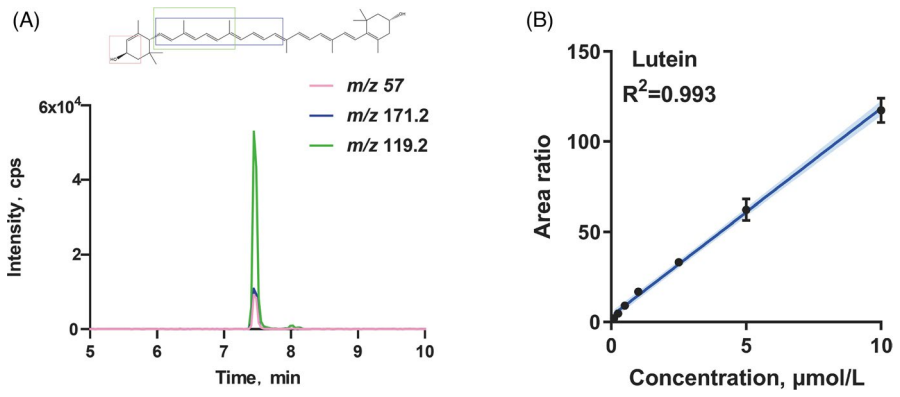

FIGURE 1 Development of MRM based target metabolite quantification method (A) and standard curve of lutein (B)

TABLE 1 Baseline characteristics of controls and T2DM patients (DKD, and non-DKD cases)

	Control group ($n = 30$)	T2DM group ($n = 60$)	Non-DKD group ($n = 30$)	DKD group ($n = 30$)
Age (years)	77.27 ± 10.31	78.85 ± 9.80	76.70 ± 10.10	81.00 ± 9.17
Sex (male/female)	16/14	39/21	21/9	18/12
Diabetic course (years)	--	17.30 ± 9.14	13.93 ± 7.83	20.67 ± 9.23$^{\#\#}$
BMI (kg/m^2)	24.37 ± 3.86	24.98 ± 3.35	24.72 ±2.75	25.24 ± 3.66
SBP (mmHg)	137.07 ± 20.93	129.77 ± 18.94	125.73 ±18.36	133.80 ± 18.95
DBP (mmHg)	76.93 ± 12.38	71.63 ± 12.80	71.13 ± 11.92	72.13 ± 13.82
HbA1c (%)	5.48 ± 0.57	7.93 ± 1.58 ***	7.86 ± 1.72	7.99 ± 1.47
FBG (mmol//L)	4.45 ± 0.48	7.26 ± 2.40 ***	7.06 ± 1.85	7.46 ± 2.86
TC (mmol/L)	4.10 (3.42, 4.70)	3.79 (2.94, 4.45)	3.85 (2.88, 4.59)	3.63 (3.10, 4.23)
LDL-C (mmol/L)	2.08 (1.79, 2.76)	1.92 (1.39, 2.71)	2.20 ± 0.90	2.06 ± 0.88
HDL-C (mmol/L)	1.27(1.10, 1.58)	1.07 (0.91, 1.35) *	1.21 ± 0.40	1.11 ± 0.33
TG (mmol/L)	0.92 (0.71, 1.46)	1.20 (0.95, 1.78) *	1.13 (0.90, 1.46)	1.36 (1.07, 1.97) $^{\#}$
Cr (μmol/L)	66.50 (56.75, 80.25)	67.00 (56.00, 89.25)	66.50 (54.00, 83.25)	68.50 (56.75, 132.00)
BUN (mmol/L)	5.50 (4.88, 7.13)	6.40 (5.25, 8.40)	6.20 (5.13, 7.10)	6.50 (5.35, 11.55)
eGFR (ml/min/1.73m^2)	96.50 ± 21.62	92.79 ± 38.85	98.92 ± 31.26	86.65 ± 44.90
UA (mmol/L)	368.73 ± 91.86	377.35 ± 120.90	371.80 ± 131.10	382.90 ± 111.75
CRP (mg/L)	3.85 (2.75, 4.43)	3.70 (2.85, 5.35)	3.55 (3.08, 5.03)	4.10 (2.58, 5.58)
UACR (mg/g)	--	30.50 (14.80, 219.25)	14.90 (9.35, 21.15)	216.50 (48.15, 836.98) $^{\#\#\#}$
Lutein (μmol/L)	0.83 (0.49, 1.23)	0.32 (0.19, 0.43) ***	0.38 (0.29, 0.51)	0.21 (0.13, 0.37) $^{\#\#\#}$

Note: $^{*}p < 0.05$. $^{***}p < 0.001$, vs. the control group. $^{\#}p < 0.05$. $^{\#\#}p < 0.01$. $^{\#\#\#}p < 0.001$, vs. the non-DKD group.

Abbreviations: BMI, body mass index; BUN, blood urea nitrogen; Cr, creatinine; CRP, C-reactive protein; DBP, diastolic blood pressure; DKD, diabetic kidney disease; eGFR, estimating glomerular filtration rate; FBG, fasting blood glucose; HbA1c, hemoglobin A1c; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; SBP, systolic blood pressure; T2DM, type 2 diabetes mellitus; TC, total cholesterol; TG, triglycerides; UA, uric acid; UACR, urinary microalbumin-to-creatinine ratio.

3.5 | The diagnostic potential of lutein in T2DM and DKD in the elderly

We further explored the diagnostic potential of lutein in elderly T2DM and DKD patients by plotting ROC curves. The AUC of lutein in distinguishing T2DM patients from non-T2DM controls was 0.880, with a cutoff value of 0.433 μmol/L ($p < 0.001$, Figure 3A). Moreover, the AUC of lutein in diagnosing DKD was 0.779, with a cutoff value of 0.197 μmol/L ($p < 0.001$, Figure 3B). It is suggested that lutein may be a promising biomarker for diagnosing T2DM and DKD in the elderly.

4 | DISCUSSION

The present study demonstrated that serum lutein levels decreased in elderly patients with T2DM and DKD and were negatively correlated with blood glucose and UACR. In addition, low serum lutein levels predicted a high risk of T2DM and DKD in the elderly.

Lutein is an oxygen-containing carotenoid that is extensively distributed in deeply colored vegetables, fruits and eggs. The human body cannot synthesize lutein, which is absorbed completely through food intake and exogenous supplementation. Lutein mainly accumulates in the macular area of the retina, which filters blue light and protects the retina. It is conventionally believed to be a favorable component to prevent age-related macular degeneration, cataracts, retinal ischemia, retinitis pigmentosa and diabetic retinopathy.[6] A growing number of studies have revealed the strong antioxidation and anti-inflammatory properties of lutein. Epidemiologic evidence has supported the biologic functions of lutein in protecting the cardiovascular system, improving cognitive function, preventing carcinogenesis, enhancing immunity and inhibiting aging.[7]

Multiple studies have shown that serum lutein levels are negatively correlated with T2DM and relevant indices. A population-based cross-sectional study identified a significant correlation between low lutein levels and high HbA1c levels, although the authors did not report a correlation between serum carotenoids and diabetes.[8] Another cross-sectional study involving 1597 Australian adults indicated that serum lutein levels were inversely correlated with T2DM, and FBG, fasting insulin and two-hour post-load plasma glucose levels decreased with increasing quintiles of lutein levels.[9] A recent meta-analysis demonstrated that high dietary intake and circulating levels of lutein are correlated with a low risk of T2DM.[10] In a streptozotocin-induced rat model of T2DM, eight weeks of lutein treatment significantly decreased FBG and increased glucose tolerance and antioxidant enzyme activities in the serum, heart and

kidneys.[11] Therefore, lutein is believed to be an antioxidant with the potential to decrease blood glucose. In the present research, we consistently found that serum lutein was negatively correlated with HbA1c and FBG, and the proportion of T2DM in the elderly decreased with increases in the level of lutein. However, a prospective case–control study showed no prospective correlation between baseline plasma lutein level and the risk of T2DM in middle-aged and elderly women within 10 years.[12] The causal relationship between lutein level and the incidence of T2DM still requires further exploration.

TABLE 2 The correlation between lutein level and other clinical indicators

	Lutein	
	***r* Value**	***p* Value**
Age (years)	−0.222	0.836
Sex (male/female)	−0.178	0.173
BMI (kg/m^2)	−0.215	0.042
SBP (mmHg)	0.136	0.200
DBP (mmHg)	0.144	0.177
HbA1C (%)	−0.339	0.001
FBG (mmol//L)	−0.295	0.005
TC (mmol/L)	0.117	0.270
LDL-C (mmol/L)	0.099	0.353
HDL-C (mmol/L)	0.363	0.000
TG (mmol/L)	−0.227	0.032
Cr (μmol/L)	−0.159	0.135
BUN (mmol/L)	−0.157	0.139
eGFR (ml/min/1.73m^2)	0.056	0.599
UA (mmol/L)	−0.091	0.396
CRP (mg/L)	−0.173	0.103
UACR (mg/g)	−0.333	0.009

Abbreviations: BMI, body mass index; BUN, blood urea nitrogen; Cr, creatinine; CRP, C-reactive protein; DBP, diastolic blood pressure; eGFR, estimating glomerular filtration rate; FBG, fasting blood glucose; HbA1c, hemoglobin A1c; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; SBP, systolic blood pressure; TC, total cholesterol; TG, triglycerides; UA, uric acid; UACR, urinary microalbumin-to-creatinine ratio.

The development and progression of T2DM and its complications are closely linked with oxidative stress and the inflammatory response. Hyperglycemia not only produces reactive oxygen species (ROS) but also impairs antioxidant capacity by damaging enzymes and antioxidants, leading to oxidative damage and chronic inflammation and resulting in a variety of complications.[13] Lutein is able to alleviate microvascular complications in T2DM patients through antioxidation and anti-inflammatory mechanisms as well as the regulation of relevant genes and signaling pathways.[14] In recent years, the beneficial effect of lutein on the development of diabetic retinopathy has been demonstrated. Multiple population studies have confirmed the low lutein level in the plasma and retina of patients with diabetic retinopathy.[15] Consistently, its protective effects on diabetic retinopathy by alleviating oxidative stress and inflammation as well as promoting neuroprotection, have been validated in animal studies.[16] In addition, a variety of carotenoids, such as astaxanthin,[17] lycopene[18] and zeaxanthin,[19] are capable of protecting against DKD by reducing oxidative stress and inflammation. However, to our knowledge, there is no research on the role of lutein in the occurrence and development of DKD. Our work demonstrated that lutein levels were inversely correlated with UACR in T2DM patients. The incidence of DKD showed a decreasing trend with increasing levels of lutein. We, therefore, suggested that lutein may be a promising biomarker for predicting DKD in the elderly, and its exact mechanism requires in-depth explorations in future.

Moreover, our results also revealed a positive correlation between serum lutein and HDL-C in T2DM patients, which was consistent with previous findings.[20] Lutein in the circulation system is mainly transported by HDL-C, and high circulating HDL-C levels contribute to the absorption and biologic functions of lutein.[4] It has been reported that the level of serum lutein is negatively associated with inflammatory markers, such as leukocyte count and CRP.[21] Our data showed a negative correlation between serum lutein level and CRP, although no significant difference was yielded, which may be attributed to the generally low CRP levels in subjects and the small sample size.

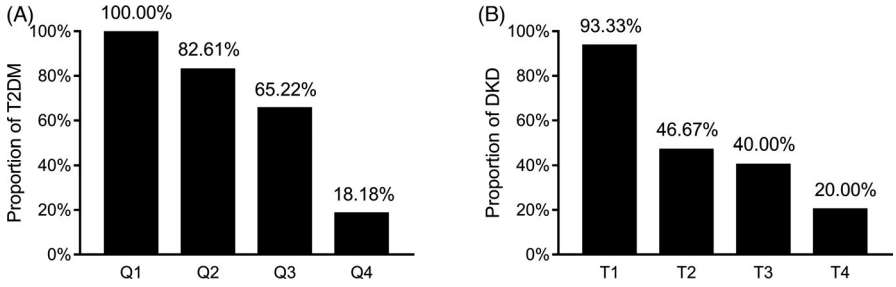

FIGURE 2 Influence of lutein level on the incidence of T2DM and DKD in the elderly. (A) All subjects were categorized into Q1 (0.059–0.260 μmol/L), Q2 (0.259–0.387 μmol/L), Q3 (0.387–0.697 μmol/L) and Q4 group (0.697–4.136 μmol/L) according to the quartile of the lutein level. The proportion of T2DM in the Q1, Q2, Q3 and Q4 groups. (B) T2DM patients were further categorized into T1 (0.059–0.193 μmol/L), T2 (0.193–0.319 μmol/L), T3 (0.319–0.429 μmol/L) and T4 groups (0.429–1.947 μmol/L) according to the quartile of the lutein level. The proportion of DKD in the T1, T2, T3 and T4 groups

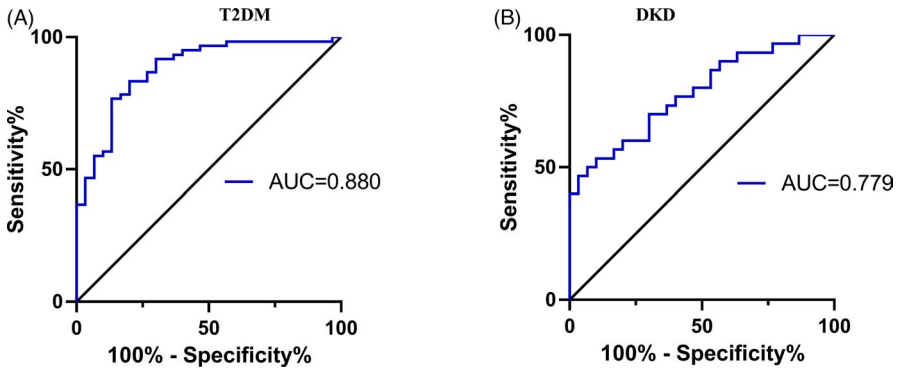

FIGURE 3 Diagnostic potential of lutein in T2DM and DKD in the elderly. The diagnostic potential of lutein in T2DM (A) and DKD (B) in the elderly by plotting the ROC curves

Serum lutein level is affected by dietary intake. We did not record the dietary situation of the recruited subjects, and as a result, we were unable to analyze whether the change in lutein levels was caused by individualized dietary intake or disease conditions. In addition, follow-up data were lacking, and the causal relationship between the change in lutein level and the incidence of T2DM and DKD was unclear. Large-scale prospective studies in multicenter institutions are needed to validate our findings.

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CONFLICT OF INTEREST

The authors declare that there are no conflicts of interest.

AUTHOR CONTRIBUTIONS

Fenghui Pan and Man Li contributed to the design of the study; Wenxia Cui and Lei Gao performed the experiments; Xiaoting Shi and Haiyan Yang contributed to the data collection and statistical analysis; Fenghui Pan wrote the manuscript and Yun Hu participated in the critical revision of the manuscript.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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