Combined Effects of Dyslipidemia and Obesity Parameters on The Estimated Glomerular Filtration Rate in a Middle-Aged Population

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Abstract

Background

Some studies have reported that chronic kidney disease (CKD) or the estimated glomerular filtration rate (eGFR) is significantly associated with metabolic-related parameters, such as dyslipidemia and obesity. However, whether eGFR will change under the superposition of multiple specific metabolic indicators remains unclear.

Methods

Six hundred forty-six community residents aged 45–60 years without overt renal dysfunction were recruited in this cross-sectional study. eGFR was calculated by measuring serum creatinine. The visceral fat area (VFA) and subcutaneous fat area (SFA) were assessed by magnetic resonance imaging (MRI). The body mass index (BMI) and waist-hip ratio (WHR) were also evaluated. Additionally, we tested the subjects’ blood lipid levels to diagnose dyslipidemia.

Results

Compared with the subjects with neither dyslipidemia nor obesity, men with both dyslipidemia and high obesity indices, such as BMI, WHR and VFA, showed a significantly lower mean eGFR; women with dyslipidemia with high WHR, VFA or SFA also showed a significantly lower mean eGFR. With the superposition of dyslipidemia and obesity indices such as BMI and SFA, the eGFR level showed a significant decreasing trend in men; the eGFR level also showed a significant decreasing trend in women but with the superposition of dyslipidemia plus WHR or SFA. Although an independent association between metabolic variables and eGFR was not found except for BMI, some of the combined effects of each variable were related to eGFR decline. Double positivity for dyslipidemia and high obesity indices such as BMI and VFA were significant independent risk factors for eGFR reduction in men. Additionally, double positivity for dyslipidemia and high WHR were significant independent risk factors for eGFR reduction overall.

Conclusions

The combined effect of dyslipidemia and high obesity indices is significantly related to the decline in eGFR. The association is more profound in men.

Background

In the past twenty years, chronic kidney disease (CKD), a public health burden with an increasing prevalence, has received increasing attention. According to the results of a cross-sectional survey involving 47,204 subjects, the prevalence of CKD in China has reached 10.8%[1]. Additionally, increasing evidence has shown that CKD is an independent risk factor for cardiovascular disease, cognitive dysfunction, and all-cause mortality[2], which pose serious threats to the survival period and quality of
life. Therefore, the potential risk factors for CKD and identifying possible prevention strategies to curb this growing public health problem must be explored.

CKD is mainly diagnosed by a reduced estimated glomerular filtration rate (eGFR), a feasible indicator to assess renal function both in disease conditions and healthy subjects[3]. eGFR is a very sensitive clinical indicator; in subjects with an eGFR higher than 60 ml/min per 1.73 m$^2$, eGFR can also be considered a significant predictor of adverse cardiovascular events (estimated by the Framingham risk score)[4]. Additionally, a cluster of metabolic diseases correlates with the various degrees of eGFR decline. A cross-sectional study covering 33,300 Chinese adults concluded that abdominal obesity, hypertension, and dyslipidemia are independent risk factors for decreased eGFR, even for subjects with an eGFR greater than 60 ml/min per 1.73 m$^2$[5]. Another cross-sectional study recruiting 75,468 urban workers also revealed that an elevated blood pressure, fasting blood glucose, and dyslipidemia are independent risk factors for reduced eGFR, but the study did not identify a significant association between obesity and reduced eGFR[6]. A previous meta-analysis including 11 studies (N = 30,146) found that metabolic syndrome (MetS) is also an independent risk factor for decreasing eGFR. This finding shows that, under the superimposed effect of different metabolic components, renal filtration function might be also affected[7].

Therefore, because the prevalence of cardiometabolic disorders and CKD has been increasing in recent years, the potential relationship between the two must be explored. Although the increase in CKD prevalence may be due to lifestyle changes, life expectancy extension and medical technology development, considering the extensive biological effects of metabolic disorders, we should further consider and explore the impact of different metabolic factors on CKD. However, previous studies had limitations. All the studies explored the independent impact of a single metabolic parameter or overall MetS on eGFR, rather than the impact of the superposition of two specific metabolic abnormalities. Additionally, some conventional adiposity indicators are insufficient to predict the risk of adverse outcomes or reflect the wellbeing of participants. The development of anthropometrics meets the needs of clinical and epidemiological investigation and research, can accurately reflect the degree of human lipid accumulation and visceral fat content, and has its own characteristics in predicting the risk of obesity-related diseases. For example, emerging studies have recommended measuring the area of visceral or subcutaneous fat to evaluate the association between abdominal obesity and multiple adverse outcomes[8–10]. This evidence has provided more practical suggestions to prevent and manage obesity.

This study aimed to explore the association between the combined effects of dyslipidemia and obesity on eGFR in subjects with relatively normal renal function (eGFR > 60 ml/min per 1.73 m$^2$). The distribution and accumulation of abdominal fat were expressed as the visceral fat area (VFA) and subcutaneous fat area (SFA), estimated using magnetic resonance imaging (MRI). Additionally, the body mass index (BMI) and waist-hip ratio (WHR) were evaluated. These obesity indices were investigated to determine whether they correlated with decreased eGFR independently or via the combined effects with dyslipidemia. Our findings may have a certain reference effect on specific individuals in clinical practice.
Methods

Study Participants

The data analyzed in the present study were derived from the baseline population of a community-based cohort study in Shenyang, Liaoning Province[11]. Seven hundred fifty subjects aged 40–65 years were recruited for the health examination project [Nanzhan Community Survey of Metabolic Disorders, NOVEMBER Study]. The study was approved by the Ethics Committee of the First Hospital of China Medical University. The study was performed in accordance with the principles of the Declaration of Helsinki. All the participants signed an informed consent form. Participants who met one of the following criteria were preliminarily excluded: 1) pregnant women or within the first year of the postpartum period; 2) participants with a personal history of thyroid dysfunction or currently using thyroid medications; 3) participants with a personal history of malignant tumor or other chronic wasting diseases; 4) participants without complete abdominal MRI information.

Data Collection

All the participants were required to participate in the survey after an overnight fast for at least 10 hours. Demographic information such as sex, date of birth, educational qualification, smoking and drinking status, and personal and family history of multiple diseases or medications were acquired using a standardized questionnaire. Each subject was measured for waist and hip circumference by trained nurses, and WHR was directly calculated. Weight and height were measured when the participants wore underwear without shoes. The BMI was calculated using the following formula: \( \text{BMI} = \frac{\text{weight (kg)}}{\text{height squared (m}^2)} \). Systolic blood pressure (SBP) and diastolic blood pressure (DBP) were measured twice using a mercury sphygmomanometer on the right arm after a rest period for over 30 minutes. The average of the two measurements was calculated and regarded as the final BP value.

MRI scans were obtained at the abdominal level between the L4 and L5 vertebrae in the prone position (FOV: 42 cm*42 cm; thickness: 1 cm; 6 layers; GE, USA). SFA and VFA were calculated by two technicians using SLICE-O-MATIC software (version 4.2).

Fasting venous blood was collected from each subject. The serum and plasma were stored immediately at -20°C and sent to the Endocrine Laboratory at the First Hospital of China Medical University. Additionally, each participant was asked to complete a 75-g oral glucose tolerance test, and 2-hour plasma glucose levels were also measured in the same laboratory. Serum thyroid-stimulating hormone (TSH) was detected using the Cobas 601 Analyzer (Roche Diagnostics, Basel, Switzerland). High-performance liquid chromatography (BioRad VARIANT II Hemoglobin Analyzer, California, US) was applied to detect glycosylated hemoglobin (HbA1c) in venous blood samples. Fasting and 2-hour plasma glucose, fasting serum total cholesterol (TC), low-density lipoprotein cholesterol (LDL-c), high-density lipoprotein cholesterol (HDL-c), triglycerides (TG), and serum creatinine were all measured using an autobiochemical analyzer (Mindray BS180, Shenzhen, China).
Renal filtration function was assessed by eGFR. Similar to the nationwide study conducted by Zhang et al., eGFR was calculated using the modified Modification of Diet in Renal Disease (MDRD) equation, derived from the data on patients with chronic kidney disease in China[1, 12]. The formula for calculating eGFR was as follows (Scr in mg/dL and age in years), and participants with an eGFR ≤ 60 ml/min per 1.73 m² were all excluded.

$$eGFR = 175 \times Scr^{-1.234} \times age^{-0.179} \quad [if \, female, \times 0.79]$$

**Diagnostic Criteria**

If the subjects admitted that they were taking antihypertensive drugs or the average level of SBP or DBP was higher than 140/90 mmHg, hypertension was diagnosed. According to the kit instructions, the reference interval of TSH is 0.27–4.20 mU/L. If TSH exceeds or falls below the range or if the subject admits to a personal history of thyroid disease or is currently taking thyroid medications, the subject would be diagnosed with thyroid dysfunction. Diabetes was diagnosed based on the 2018 American Diabetes Association (ADA) guidelines[13]. If the subject had self-reported diabetes or met one of the following items, diabetes was diagnosed: fasting plasma glucose ≥ 7 mmol/L; two-hour plasma glucose ≥ 11.1 mmol/L; HbA1c ≥ 6.5%.

The diagnostic criteria for dyslipidemia were extracted from the Third Report of the National Cholesterol Education Program (NCEP) Expert Panel: 1.7 mmol/L, 5.2 mmol/L, and 3.4 mmol/L were regarded as the thresholds for TG, TC and LDL-c abnormalities, respectively (described as “borderline high” in the guidelines). Additionally, 1.0 mmol/L and 1.3 mmol/L were applied as the thresholds for HDL-c abnormalities (described as a “marginal risk factor” in the guidelines) among men and women, respectively. If the subject met one of the above items or was currently taking lipid-lowering medications, dyslipidemia was determined.

In the present study, the indicators for assessing obesity mainly included BMI, WHR, VFA and SFA. High BMI was defined as BMI ≥ 28 kg/m², regardless of sex[14]. The threshold value of WHR was 0.88 in men and 0.86 in women[15]. The optimal threshold value of VFA was set at 80 cm²[16]. Additionally, if the subject's SFA were higher than its 75th percentile, high SFA would be diagnosed[17].

**Statistical Analysis**

The above data were input into the Statistical Package for the Social Sciences version 25 (SPSS Inc., Chicago, US). All p values obtained were based on two-tailed tests, with significance levels set at 0.05. In the descriptive analysis, continuous variables were described as means and standard deviation (SD), and dichotomous variables were described as numbers and corresponding percentages. Single-sample t-test and chi-squared test were used to compare differences in continuous and dichotomous variables, respectively, between the groups with different characteristics. The Spearman correlation coefficient was applied to estimate the relationships between eGFR and variables, including age, smoking status, and
drinking status. Monovariate and multivariate linear regression were applied to analyze the effects of different variables on eGFR.

Results

Baseline Characteristics

Six hundred forty-six residents aged 45–60 years were enrolled in the final data analysis and included 319 men and 327 women. Table 1 shows the baseline characteristics overall and according to sex. Certain differences were found in the lifestyles of men and women. Among them, the proportion of smokers (78.4% vs. 4.6%; p < 0.05) and drinkers (75.2% vs. 13.5%; p < 0.05) was significantly higher in men, who had a relatively unstable dining habit (88.4% vs. 95.7%; p < 0.05) and preferred to drink tea (40.8% vs. 15.3%; p < 0.05). Additionally, the prevalence of hypertension (35.7% vs. 21.1%; p < 0.05) and dyslipidemia (63.9% vs. 45.9%; p < 0.05) were both significantly higher in men. The distribution of abdominal fat and obesity indices also showed significant differences between male and female subjects. The SFA and VFA values were lower and higher, respectively, in men (SFA: 139.87 ± 54.57 cm$^2$ vs. 189.27 ± 65.35 cm$^2$, p < 0.05; VFA: 98.16 ± 45.18 cm$^2$ vs. 67.24 ± 30.97 cm$^2$, p < 0.05). The values of BMI and WHR were both significantly higher in male subjects (BMI: 25.58 ± 3.25 kg/m$^2$ vs. 24.52 ± 3.37 kg/m$^2$, p < 0.05; WHR: 0.92 ± 0.05 vs. 0.88 ± 0.06, p < 0.05). Significant differences were found in glomerular filtration function between the groups. The mean eGFR in men was significantly lower (113.26 ± 21.17 vs. 165.30 ± 55.82; p < 0.05).
Table 1
Baseline characteristics of the participants (N = 646)

|                          | Total     | Male       | Female     |
|--------------------------|-----------|------------|------------|
| Number                   | 646       | 319        | 327        |
| Age                      | 50.22 ± 6.73 | 50.16 ± 6.83 | 50.29 ± 6.65 |
| EDU (high school or above, %) | 375 (58.0%) | 177 (55.5%)  | 198 (60.6%) |
| Smoking (N, %)           | 265 (41.0%) | 250 (78.4%)  | 15 (4.6%)   |
| Drinking (N, %)          | 284 (44.0%) | 240 (75.2%)  | 44 (13.5%)  |
| Regular diet (N, %)      | 595 (92.1%) | 282 (88.4%)  | 313 (95.7%) |
| Regular tea consumption (N, %) | 180 (27.9%) | 130 (40.8%)  | 50 (15.3%)  |
| HTN (N, %)               | 183 (28.3%) | 114 (35.7%)  | 69 (21.1%)  |
| Diabetes (N, %)          | 134 (20.7%) | 75 (23.5%)   | 59 (18.0%)  |
| Dyslipidemia (N, %)      | 354 (54.8%) | 204 (63.9%)  | 150 (45.9%) |
| Family history of hypertension (N, %) | 301 (46.6%) | 153 (48.0%)  | 148 (45.3%) |
| Family history of diabetes (N, %) | 126 (19.5%) | 67 (21.0%)   | 59 (18.0%)  |
| Family history of dyslipidemia (N, %) | 61 (9.4%)  | 30 (9.4%)    | 31 (9.5%)   |
| SFA (cm²)*               | 164.88 ± 65.10 | 139.87 ± 54.57 | 189.27 ± 65.35 |
| VFA (cm²)*               | 82.51 ± 41.60 | 98.16 ± 45.18 | 67.24 ± 30.97 |
| BMI (kg/m²)*             | 25.05 ± 3.35 | 25.58 ± 3.25 | 24.52 ± 3.37 |

Abbreviations: VFA, visceral fat area; SFA, subcutaneous fat area; BMI, body mass index; WHR, waist-hip ratio; eGFR, estimated glomerular filtration rate; EDU, educational level; HTN, hypertension

Notes: Binary variables are expressed in numbers and percentages, and continuous variables are expressed in means and standard deviations.

Regular tea consumption is defined as drinking tea every day. Regular diet is defined as having at least two meals per day and having a fixed mealtime.

HTN is defined according to the current blood pressure measurement or current administration of antihypertensive medications. Dyslipidemia is defined according to the current lipid levels or current administration of lipid lowering medications. Diabetes is defined as the sum-up of self-reported diabetes and newly-diagnosed diabetes.

* indicates that the corresponding value in males are significantly different from females (p value < 0.05).
### Correlation Between The Egfr Levels And Variables

The correlation between the eGFR levels and various anthropometric and biochemical parameters according to sex is shown in Table 2. Except for dietary habits and diabetes, all the correlations were statistically significant at p < 0.001, regardless of sex. In each group with a single sex, some of the variables were also significantly correlated with eGFR. Age and VFA were both negatively correlated with eGFR in men; and age, WHR, and dyslipidemia were all significantly negatively correlated with eGFR in women.
Table 2
Spearman correlation coefficients of eGFR levels with various anthropometric and biochemical parameters

|                  | Total   |          | Male    |          | Female  |          |
|------------------|---------|----------|---------|----------|---------|----------|
|                  | r       | p-value  | r       | p-value  | r       | p-value  |
| Age              | -0.191  | < 0.001  | -0.214  | < 0.001  | -0.339  | < 0.001  |
| Smoking          | -0.518  | < 0.001  | 0.009   | 0.867    | 0.026   | 0.645    |
| Drinking         | -0.413  | < 0.001  | 0.064   | 0.258    | 0.010   | 0.863    |
| Regular diet     | 0.056   | 0.154    | -0.085  | 0.130    | -0.029  | 0.607    |
| Tea consumption  | -0.224  | < 0.001  | -0.024  | 0.667    | -0.074  | 0.184    |
| EDU              | 0.025   | 0.520    | 0.013   | 0.824    | -0.069  | 0.212    |
| BMI              | -0.175  | < 0.001  | -0.066  | 0.238    | -0.093  | 0.092    |
| WHR              | -0.275  | < 0.001  | -0.006  | 0.915    | -0.140  | 0.011    |
| VFA              | -0.326  | < 0.001  | -0.129  | 0.021    | -0.065  | 0.243    |
| SFA              | 0.250   | < 0.001  | -0.033  | 0.561    | -0.047  | 0.398    |
| HTN              | -0.222  | < 0.001  | 0.043   | 0.440    | -0.053  | 0.339    |
| Dyslipidemia     | -0.203  | < 0.001  | -0.090  | 0.107    | -0.114  | 0.039    |
| Diabetes         | 0.021   | 0.591    | 0.106   | 0.057    | 0.074   | 0.183    |

Abbreviations: EDU, educational level; VFA, visceral fat area; SFA, subcutaneous fat area; BMI, body mass index; WHR, waist-hip ratio; eGFR, estimated glomerular filtration rate; HTN, hypertension

Subgroup Comparison According to the Combination of Dyslipidemia and Obesity

Table 3 presents the mean eGFR levels of subjects with isolated dyslipidemia without obesity, isolated obesity without dyslipidemia, and subjects with or without both features. The above results were also presented according to sex. Subjects with neither high obesity indices nor dyslipidemia were set as the reference. Regarding men with either dyslipidemia or a high obesity index, the eGFR values were significantly lower in those with isolated high BMI (p = 0.009) and isolated dyslipidemia without high WHR (p = 0.046). Additionally, except for subjects with both dyslipidemia and high SFA, the eGFR levels were all significantly lower in the other three double-positive subgroups. In male subjects, the decreasing trend of eGFR reached significance with the superposition of dyslipidemia and high BMI (p = 0.002) or SFA (p = 0.045).
|                          | Male                          | Female                        |
|--------------------------|-------------------------------|-------------------------------|
| **Mean value and standard deviation (SD)** | **Mean ± SD** | **P_{t-test}** | **P_{trend}** | **Mean ± SD** | **P_{t-test}** | **P_{trend}** |
| Dyslipidemia (-) High BMI (-) | 116.984 ± 19.025 (ref.) | 0.002 | | 170.041 ± 54.388 (ref.) | 0.233 | |
| Dyslipidemia (+) High BMI (-) | 113.951 ± 23.561 | 0.118 | | 161.085 ± 63.324 | 0.119 | |
| Dyslipidemia (-) High BMI (+) | 104.211 ± 16.926 | 0.009 | | 157.313 ± 29.608 | 0.086 | |
| Dyslipidemia (+) High BMI (+) | 107.307 ± 17.176 | < 0.001 | | 161.952 ± 37.666 | 0.275 | |
| Dyslipidemia (-) High WHR (-) | 116.149 ± 22.423 (ref.) | 0.544 | | 177.356 ± 56.948 (ref.) | 0.014 | |
| Dyslipidemia (+) High WHR (-) | 110.127 ± 16.957 | 0.046 | | 169.778 ± 102.491 | 0.647 | |
| Dyslipidemia (-) High WHR (+) | 114.705 ± 17.379 | 0.474 | | 161.646 ± 47.640 | 0.002 | |
| Dyslipidemia (+) High WHR (+) | 112.566 ± 23.103 | 0.045 | | 158.242 ± 33.453 | < 0.001 | |
| Dyslipidemia (-) High VFA (-) | 116.915 ± 20.594 (ref.) | 0.058 | | 169.079 ± 55.821 (ref.) | 0.225 | |
| Dyslipidemia (+) High VFA (-) | 114.831 ± 20.972 | 0.456 | | 163.444 ± 72.288 | 0.462 | |
| Dyslipidemia (-) High VFA (+) | 113.344 ± 17.546 | 0.137 | | 167.114 ± 32.090 | 0.740 | |
| Dyslipidemia (+) High VFA (+) | 111.124 ± 22.614 | 0.002 | | 157.936 ± 31.875 | 0.009 | |
| Dyslipidemia (-) High SFA (-) | 116.025 ± 19.536 (ref.) | 0.045 | | 172.034 ± 61.533 (ref.) | 0.043 | |
| Dyslipidemia (+) High SFA (-) | 112.807 ± 21.902 | 0.052 | | 165.845 ± 71.915 | 0.419 | |
| Dyslipidemia (-) High SFA (+) | 108.791 ± 15.443 | 0.117 | | 162.337 ± 26.665 | 0.007 | |

Abbreviations: VFA, visceral fat area; SFA, subcutaneous fat area; BMI, body mass index; WHR, waist-hip ratio; eGFR, estimated glomerular filtration rate
| Male | Female |
|------|--------|
| Dyslipidemia (+) High SFA (+) | 107.918 ± 23.915 | 154.524 ± 33.254 |
| | 0.090 | < 0.001 |

Abbreviations: VFA, visceral fat area; SFA, subcutaneous fat area; BMI, body mass index; WHR, waist-hip ratio; eGFR, estimated glomerular filtration rate

Regarding women with either dyslipidemia or a high obesity index, the levels of eGFR were significantly lower in subjects with isolated high WHR (p = 0.002) or isolated high SFA (p = 0.007). Except for BMI, the other three double-positive subgroups all showed a significantly lower eGFR in women. In female subjects, the decreasing trend of eGFR reached significance with the superposition of dyslipidemia and high WHR (p = 0.014) or SFA (p = 0.043).

Multivariate Linear Regression Analysis between eGFR and Dyslipidemia and Obesity

The abovementioned four obesity indicators (i.e., BMI, WHR, VFA, SFA) and dyslipidemia were assessed to determine whether they were independently associated with the decrease in eGFR (Table 4). According to the results of Spearman’s correlation analysis, age, sex, smoking status, drinking status, tea consumption, and hypertension were set as confounding factors in model 2. None of the confounding factors was adjusted in model 1.
### Table 4
Multivariate adjusted regression coefficients ($\beta$) of the association of eGFR with obesity indices and dyslipidemia

|                  | Total                      | Male                     | Female                    |
|------------------|----------------------------|--------------------------|----------------------------|
|                  | Model 1                    | Model 2                  | Model 1                    | Model 2                  | Model 1                    | Model 2                  |
| High BMI         | \(-14.925 \pm 5.068^*\)    | \(-6.394 \pm 4.430\)    | \(-8.553 \pm 2.814^*\)    | \(-8.192 \pm 2.861^*\)  | \(-6.038 \pm 8.967\)    | \(-4.431 \pm 9.053\)    |
| High WHR         | \(-16.674 \pm 4.228^*\)    | \(-6.168 \pm 3.778\)    | \(-0.161 \pm 2.813\)     | \(0.078 \pm 2.935\)     | \(-15.043 \pm 6.371^*\) | \(-9.258 \pm 6.599\)    |
| High VFA         | \(-23.157 \pm 3.828^*\)    | \(-3.263 \pm 3.710\)    | \(-4.171 \pm 2.453\)     | \(-4.118 \pm 2.519\)    | \(-5.944 \pm 6.914\)    | \(-1.247 \pm 7.189\)    |
| High SFA         | \(8.422 \pm 4.515\)       | \(-7.971 \pm 5.329\)    | \(-5.782 \pm 3.571\)     | \(-6.043 \pm 3.634\)    | \(-10.962 \pm 6.374\)   | \(-10.490 \pm 6.303\)   |
| Dyslipidemia     | \(-14.704 \pm 3.892^*\)   | \(-2.285 \pm 3.419\)    | \(-3.047 \pm 2.467\)     | \(-3.011 \pm 2.438\)    | \(-7.505 \pm 6.190\)    | \(0.714 \pm 6.501\)     |

**Abbreviations:** BMI, body mass index; WHR, waist hip ratio; VFA, visceral fat area; SFA, subcutaneous fat area; eGFR, estimated glomerular filtration rate

**Notes:** Model 1: crude; Model 2: adjusted for age, gender, current smoking, current drinking; tea consumption; hypertension

* indicates the regression coefficient reaches significance ($p < 0.05$).

Hypertension is defined according to the current blood pressure measurement or current administration of antihypertensive medications. Dyslipidemia is defined according to the current lipid levels or current administration of lipid lowering medications. High BMI was defined as BMI $\geq 28$ kg/m$^2$. High WHR was defined as WHR $\geq 0.88$ for males, and WHR $\geq 0.86$ for females. VFA $\geq 80$ cm$^2$ was defined as high, and SFA $\geq$ 75th percentile was considered high.

According to the results in model 1, high BMI, high WHR, high VFA, and dyslipidemia were all risk factors for decreased eGFR ($p < 0.05$) in the general population. Additionally, high BMI and high WHR were negatively associated with eGFR in men and women, respectively ($p < 0.05$).

However, most of the crude results in model 1 did not show significance after adjusting for multiple confounding factors. High BMI was an independent risk factor for eGFR reduction ($p < 0.05$) in men, while other obesity indicators or dyslipidemia were not independently associated with the eGFR level overall or specifically in men or women.

**Multivariate Regression Analysis between eGFR and the Combined Effects of Dyslipidemia and Obesity**

Multivariate linear regression was performed to determine the association between isolated and combined effects of obesity and dyslipidemia and eGFR (Table 5). Similarly, all the regression coefficients were adjusted for age, sex, smoking status, drinking status, tea consumption, and hypertension, and the subgroup with neither obesity nor dyslipidemia was regarded as the reference. In
the general population, none of the isolated dyslipidemia or isolated high obesity indicators showed a significant association with the variation in eGFR. However, the combined effect of dyslipidemia and high WHR is an independent risk factor for eGFR reduction (p = 0.033).
Table 5
Regression coefficients for eGFR according to combination of obesity indices and dyslipidemia

| Combination of dyslipidemia and high BMI | Total | Male | Female |
|-----------------------------------------|-------|------|--------|
| Dyslipidemia (+) High BMI (-)           | $-3.588 \pm 4.023$ | 0.373 | $-3.011 \pm 2.841$ | 0.290 | $-1.831 \pm 7.370$ | 0.804 |
| Dyslipidemia (-) High BMI (+)           | $-13.771 \pm 7.789$ | 0.078 | $-9.260 \pm 3.192$ | 0.004 | $-14.359 \pm 12.989$ | 0.271 |
| Dyslipidemia (+) High BMI (+)           | $-5.668 \pm 5.518$ | 0.305 | $-12.942 \pm 5.268$ | 0.016 | $2.355 \pm 11.821$ | 0.842 |

| Combination of dyslipidemia and high WHR | Total | Male | Female |
|-----------------------------------------|-------|------|--------|
| Dyslipidemia (+) High WHR (-)           | $-5.610 \pm 9.275$ | 0.546 | $-5.828 \pm 4.722$ | 0.221 | $-4.237 \pm 15.635$ | 0.787 |
| Dyslipidemia (-) High WHR (+)           | $-8.891 \pm 5.189$ | 0.088 | $-2.515 \pm 3.950$ | 0.526 | $-10.925 \pm 8.102$ | 0.179 |
| Dyslipidemia (+) High WHR (+)           | $-8.805 \pm 4.116$ | 0.033 | $-4.147 \pm 4.153$ | 0.319 | $-9.326 \pm 7.429$ | 0.211 |

| Combination of dyslipidemia and high VFA | Total | Male | Female |
|-----------------------------------------|-------|------|--------|
| Dyslipidemia (+) High VFA (-)           | $-1.716 \pm 5.753$ | 0.766 | $-2.623 \pm 3.954$ | 0.508 | $1.899 \pm 8.674$ | 0.827 |
| Dyslipidemia (-) High VFA (+)           | $-3.748 \pm 5.967$ | 0.530 | $-4.700 \pm 3.700$ | 0.207 | $-0.662 \pm 10.792$ | 0.951 |
| Dyslipidemia (+) High VFA (+)           | $-6.016 \pm 4.265$ | 0.159 | $-7.069 \pm 3.394$ | 0.039 | $-2.628 \pm 8.287$ | 0.751 |

| Combination of dyslipidemia and high SFA | Total | Male | Female |
|-----------------------------------------|-------|------|--------|
| Dyslipidemia (+) High SFA (-)           | $-2.685 \pm 4.296$ | 0.532 | $-3.739 \pm 2.617$ | 0.154 | $1.304 \pm 9.720$ | 0.893 |

Abbreviations: BMI, body mass index; WHR, waist hip ratio; VFA, visceral fat area; SFA, subcutaneous fat area; eGFR, estimated glomerular filtration rate

Notes: All the listed regression coefficients are adjusted for age, gender, current smoking, current drinking, tea consumption, and hypertension.

Hypertension is defined according to the current blood pressure measurement or current administration of antihypertensive medications. Dyslipidemia is defined according to the current lipid levels or current administration of lipid lowering medications. High BMI was defined as BMI $\geq 28$ kg/m$^2$. High WHR was defined as WHR $\geq 0.88$ for males, and WHR $\geq 0.86$ for females. VFA $\geq 80$ cm$^2$ was defined as high, and SFA $\geq$ 75th percentile was considered high.


|                                | Total         | Male          | Female         |
|--------------------------------|---------------|---------------|----------------|
| Dyslipidemia (-) High SFA (+)  | -11.002 ± 5.986 | 0.067         | -10.047 ± 8.271 | 0.226          |
| Dyslipidemia (+) High SFA (+)  | -9.989 ± 5.669 | 0.079         | -10.127 ± 9.054 | 0.265          |

Abbreviations: BMI, body mass index; WHR, waist hip ratio; VFA, visceral fat area; SFA, subcutaneous fat area; eGFR, estimated glomerular filtration rate

Notes: All the listed regression coefficients are adjusted for age, gender, current smoking, current drinking, tea consumption, and hypertension.

Hypertension is defined according to the current blood pressure measurement or current administration of antihypertensive medications. Dyslipidemia is defined according to the current lipid levels or current administration of lipid lowering medications. High BMI was defined as BMI ≥ 28 kg/m². High WHR was defined as WHR ≥ 0.88 for males, and WHR ≥ 0.86 for females. VFA ≥ 80 cm² was defined as high, and SFA ≥ 75th percentile was considered high.

Compared with female subjects, male subjects showed a more profound association. High BMI was an independent risk factor for decreased eGFR in men, both isolated (p = 0.004) and combined with dyslipidemia (p = 0.016). Additionally, double positivity for dyslipidemia and high VFA was also negatively associated with the eGFR in men (p = 0.039). However, none of the regression coefficients showed significance in women.

**Discussion**

To our best knowledge, this study is the first concerning the combined effects of dyslipidemia and obesity parameters in relation to eGFR variation. Our study not only confirms some of the previous results but also supplements them. High BMI is an independent risk factor for eGFR reduction, and eGFR declines more significantly under the combined effect of high BMI and dyslipidemia, particularly in men. Regarding other obesity indicators (such as WHR, VFA, and SFA), we found no significant independent association with eGFR. However, several of the abdominal adiposity indicators can be regarded as risk factors for eGFR reduction if superimposed with dyslipidemia, overall or in men. This study provides a reference value for clinical practice. For patients with both dyslipidemia and high obesity indicators, glomerular dysfunction should be monitored for timely prevention or intervention.

Although previous studies have provided numerous conclusions regarding cardiometabolic disorders and CKD or eGFR reduction, additive interactions were not often estimated. Additionally, we could only conclude the negative impact of a fuzzy cluster of metabolic parameters on eGFR considering the definition of MetS[18], rather than obtaining the impact of a specific combination of several parameters. Previous evidence is of limited help in clinical practice. Our study provides a novel finding that, although dyslipidemia is not an independent risk factor for decreased eGFR, the eGFR of dyslipidemic men with high BMI is also significantly lower than that of double-negative men, and double positivity for dyslipidemia and high BMI is also an independent risk factor for decreased eGFR in men. Furthermore,
the double-positive group for high WHR and dyslipidemia showed a significantly lower eGFR in each sex group, and double positivity was also a significant risk factor for reduced eGFR in the general population. Additionally, the level of eGFR in the double-positive group for high VFA and dyslipidemia were significantly lower in both sexes. Double positivity for dyslipidemia and high VFA was also a significant risk factor for reduced eGFR, particularly in men.

Recently, with the continued increase in longevity and lifestyle changes in China, the prevalence of various metabolic abnormalities remains high[19–22]. The burden of CKD and end-stage renal disease (ESRD) caused by this condition is a concern. According to previous evidence, several cardiometabolic abnormalities are independent risk factors for CKD or eGFR reduction. Considering the previous evidence, a potential impact of the combined effect of dyslipidemia and various obesity phenotypes may exist. Based on most of the previous conclusions, high BMI or obesity may be an independent risk factor for decreased eGFR or CKD. For example, a recent cohort study involving 15,229 middle-aged Chinese individuals revealed that overweight/obesity (BMI ≥ 24 kg/m²) is independently associated with the risk of CKD[23]. Additionally, several studies found a negative relationship between BMI per se and eGFR values, a finding similar to the present results[24–26]. However, some scholars have different opinions. Ji et al. investigated the CKD prevalence and related risk factors in Qingdao, China. The study revealed that neither general nor central obesity shows a significant association with the risk of reduced eGFR[27]. In another Taiwanese cross-sectional study, the researchers divided 14,983 subjects into two groups—metabolically healthy and unhealthy groups. The CKD risk did not increase significantly with increasing weight in the metabolically healthy group, while the CKD risk showed an upward trend with weight in the other group. The study suggested that BMI per se is not an independent risk factor for CKD[28]. In our study, the significant association between BMI per se and eGFR confirms some of the previous evidence. Based on the previous studies, we further obtained the subjects’ WHR, VFA and SFA. The above three adiposity indicators per se did not affect eGFR. However, under the combined effect with dyslipidemia, eGFR showed significant differences and a significant decrease between different subgroups, and several of the combined effects could be considered independent risk factors for eGFR decline. The above conclusion is a supplement to the previous evidence.

Regarding the impact of dyslipidemia on eGFR or CKD risk, the current evidence remains inconsistent. Duan et al. investigated the prevalence and associated factors of CKD and reduced eGFR in Henan Province and found that dyslipidemia is not an independent risk factor for eGFR < 60 ml/min per 1.73 m²[29]. However, two-sample Mendelian randomization studies found that reduced serum HDL-c and elevated TGs lead to significant worsening of the eGFR or CKD risk[30, 31]. A meta-analysis covering 47 trials also found that a common lipid-lowering medication, statins, significantly delays the decline of eGFR in patients with renal disease[32]. The present study also explored the potential relationship between serum lipids and eGFR from one aspect. Although some positive conclusions on the relationship between dyslipidemia and eGFR were reported, our study found no significant association between dyslipidemia per se and eGFR decline. The difference between the previous and present results may be due to sampling bias because we excluded subjects with an eGFR of less than 60 ml/min per 1.73 m² at
the beginning of the study. In the present study, only when dyslipidemia and several obesity indicators were superimposed did eGFR show a significant decrease or association with the double-positive group.

Overall, the combined effects of dyslipidemia and obesity indicators also show certain differences between different sexes. When we compare the trend of eGFR decline among subjects of different genders, there are certain differences in the results. When we conducted multivariate regression analysis in different sexes, statistical significance was only found in men. From the present results, the combined effects of dyslipidemia and obesity indicators are closely related to the eGFR reduction in men, and more restudies are warranted to confirm whether the above conclusion is valid in female subjects. Previous similar studies have also found that men who are obese or with other metabolic abnormalities may be more likely to have renal dysfunction. In a cross-sectional survey by Xiao et al., researchers found that another novel lipid accumulation index, visceral adiposity index (VAI), is more likely to be associated with CKD, especially in men[33]. Another meta-analysis suggested that compared with women, hypertensive men are generally at higher risk of CKD or ESRD. This disparity is unlikely to be explained by biological differences alone[34]. We speculate that male subjects have significantly worse lifestyles in the present study, and the prevalence of underlying diseases is also significantly higher, such as hypertension, dyslipidemia, and obesity. The above factors may be related to the significantly lower baseline eGFR in men, and the significant discrepancies in the abovementioned baseline indicators might also contribute to the sex difference of the present results.

This study has several limitations. First, this is a cross-sectional study, so the causal relationship between metabolic indicators and eGFR has not been confirmed. Second, eGFR is a variable determined by multiple factors, and its value is determined by the genetic background or environmental factors. It is somewhat one-sided to analyze the variation in eGFR only from the perspectives of dyslipidemia and obesity. Finally, the sampling scope of this study is relatively limited, only including the middle-aged urban population. Therefore, the present conclusions must be supported by more large-sample studies.

Conclusions

BMI is independently and negatively associated with a decrease in eGFR in a middle-aged Chinese population. Most importantly, the combined effects of dyslipidemia and obesity indices such as BMI and VFA are synergistically associated with the risk of eGFR reduction in men, and the combination of dyslipidemia and WHR is also associated with eGFR reduction in the general population. Accordingly, a better understanding of the combined effects of these modifiable risk factors can help promote primary prevention in susceptible subgroups.

List Of Abbreviations

eGFR, estimated glomerular filtration rate; CKD, chronic kidney disease; BMI, body mass index; WHR, waist-hip ratio; VFA, visceral fat area; SFA, subcutaneous fat area; TC, total cholesterol; LDL-c, low-density lipoprotein cholesterol; HDL-c, high-density lipoprotein cholesterol; TG, triglycerides; TSH, thyroid
stimulating hormone; HbA1c, glycosylated hemoglobin; MRI, Magnetic Resonance Imaging; MetS, metabolic syndrome; SBP, systolic blood pressure; DBP, diastolic blood pressure.

Declarations

Ethics Approval and Consent to Participate

The study was approved by the Ethics Committee of the First Hospital of China Medical University. The study was performed in accordance with the principles of the Declaration of Helsinki. All the participants signed an informed consent form.

Consent for Publication

Not applicable.

Availability of Data and Materials

The datasets used and analyzed during the current study are available from the corresponding author on reasonable request (Yaxin Lai, Email: laiyaxin811005@126.com).

Conflicts of Interests

All authors declare that there is no conflict of interest regarding the publication of this paper.

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Author Contributions

All authors contributed to the study design or concept and the analysis and interpretation of the data, and critically reviewed and edited the manuscript. All authors approved the final version and were responsible for the decision to submit the manuscript.

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