

Original Article

Inverse correlation between plasma 3-chlorotyrosine and pinch strength in chronic kidney disease patients

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Background and Objectives: This cross-sectional study aimed to explore whether plasma myeloperoxidase (MPO) and its active product, 3-chlorotyrosine (3-CT), as markers of inflammation and oxidative stress, have any independent pathophysiological association with sarcopenia-related parameters in patients with chronic kidney disease (CKD). **Methods and Study Design:** A total of 292 patients, including 147 on maintenance hemodialysis (HD) and 145 non-dialyzed hospitalized patients with CKD stages 1-5, were enrolled from September 2022 to December 2023 and categorized into three groups: CKD stages 1-2, CKD stages 3-5 (non-dialysis), and CKD stage 5 (HD). Clinical data, anthropometric measurements, and body composition via bioelectrical impedance analysis were collected. Plasma MPO and 3-CT levels were measured by enzyme-linked immunosorbent assay and liquid chromatography-mass spectrometry (LC-MS), respectively. **Results:** Results showed that as kidney function declined, plasma MPO levels significantly increased across the CKD stage 1-2, stage 3-5, and HD groups [93.5 (72.3, 103.0) ng/mL, 90.8 (76.0, 106) ng/mL, and 102 (80.7, 126) ng/mL, respectively; $H = 174$, $p < 0.001$]. The prevalence of sarcopenia also increased significantly across CKD stages (17.3%, 17.1%, and 29.9%, respectively; $\chi^2 = 6.52$, $p = 0.038$). Interestingly, statistical analysis confirmed a significant inverse association between plasma 3-CT levels and pinch strength ($r = -0.148$, $p = 0.036$). However, there were no significant correlation between plasma MPO or 3-CT levels and sarcopenia. **Conclusions:** The negative association between plasma 3-CT and pinch strength suggests a link between MPO-mediated inflammation/oxidative stress and fine hand muscle dysfunction, which provides a new perspective for evaluating early, subclinical muscle dysfunction in CKD patients.

Key Words: chronic kidney disease, sarcopenia, myeloperoxidase, 3-chlorotyrosine, muscle strength

INTRODUCTION

Chronic kidney disease (CKD) is a major global public health issue that severely impacts physical and mental health.¹ The prevention and management of CKD, particularly end-stage renal disease (ESRD) and its complications in patients undergoing hemodialysis (HD), remain significant challenges in the world.² These patients often present with multiple metabolic disorders.³ Sarcopenia, a critical complication and comorbidity, is characterized by age-related progressive loss of skeletal muscle mass, accompanied by reduced muscle strength and declined physical performance.⁴ Current studies indicate that the prevalence of sarcopenia in conservatively managed CKD patients ranges from 5.9% to 9.8%.⁵ However, a meta-analysis reported the prevalence as high as 28.5% in the HD population.⁶ Importantly, sarcopenia significantly increases the risk of cardiovascular events, infection-related mortality, all-cause mortality, disability rates, and hospitalization frequency in CKD patients, especially those on HD,^{6,7} which further escalating the healthcare burden. Therefore, early screening, assessment and targeted management of sarcopenia in patients with CKD are of paramount clinical importance.

Research suggests that inflammation and oxidative

stress contribute to the development of sarcopenia in CKD patients.⁸ During muscle atrophy, markedly excessive reactive oxygen species are produced alongside impaired antioxidant capacity, resulting in heightened oxidative stress. This, in turn, induces sustained intramuscular inflammation, further perpetuating a vicious cycle that constitutes a key mechanism underlying the pathogenesis

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of sarcopenia.⁹ Myeloperoxidase (MPO), a well-recognized marker of inflammation and oxidative stress, is released from phagocytes (such as neutrophils) and subsequently catalyzes the formation of highly reactive chlorinated species, such as 3-chlorotyrosine (3-CT).^{8,10,11} These products induce oxidative damage to various biological molecules, thereby contributing to the pathogenesis and progression of CKD and its associated complications.³ However, research on plasma MPO and 3-CT associated with muscle atrophy remains limited.

In this study, a total of 292 enrolled CKD patients across stages 1–5 were included in the analysis. Given the critical role of the inflammation-oxidation axis in sarcopenia pathogenesis, we aim to explore the association between plasma MPO, 3-CT and sarcopenia as well as its core related indicators in patients with CKD, thereby providing a basis for future studies on the potential role of MPO-mediated oxidative stress in muscle function impairment and offering a novel pathophysiological perspective on muscle wasting from an inflammation-oxidation stress standpoint.

METHODS

Participants

This cross-sectional study enrolled maintenance HD patients and hospitalized non-dialyzed patients with CKD stages 1–5 from the Dialysis Center of Guangzhou Red Cross Hospital between September 2022 and December 2023. The inclusion criteria were as follows: (1) Age between 18 and 80 years for both HD and CKD 1–5 patients; (2) For HD patients: a dialysis vintage of ≥ 3 months; (3) Willingness to participate and provision of signed informed consent. The exclusion criteria were: (1) Refusal to participate; (2) History of severe infection, acute cardiovascular or cerebrovascular events (e.g., stroke, acute heart failure, acute coronary syndrome), or major surgery within the preceding 3 months; (3) Diagnosis of malignant tumor; (4) Presence of neurological or psychiatric disorders; (5) Patients on peritoneal dialysis or those with a history of kidney transplantation. This study was approved by the Ethics Committee of Guangzhou Red Cross Hospital (Approval No.2023-041-01).

Grouping

The estimated glomerular filtration rate (eGFR) was calculated using the Modification of Diet in Renal Disease (MDRD) simplified formula: $\text{eGFR} [\text{mL} \cdot \text{min}^{-1} \cdot (1.73 \text{ m}^2)^{-1}] = 186 \times \text{Serum creatinine (mg/dL)}^{-1.154} \times \text{Age (years)}^{-0.203} \times (0.742 \text{ if female}) \times (1.21 \text{ if Black})$.¹² Participants were stratified into three groups based on eGFR and dialysis status: the CKD stages 1–2 group, the CKD stages 3–5 (non-dialysis) group, and the CKD stage 5 HD group. Besides, they were also divided by gender into male and female groups. Demographic and clinical characteristics were compared across the CKD stage groups, while anthropometric measurements were compared between gender groups.

Laboratory examinations

Following collection, morning peripheral venous blood samples (obtained pre-dialysis for HD patients) were centrifuged at 3000 rpm for 4 minutes at 4°C. The resulting

serum/plasma was then aliquoted and stored at -80°C. Plasma MPO levels were measured using a human MPO enzyme-linked immunosorbent assay (ELISA) kit (AE90769Hu, Shanghai Lianshuo Biotechnology Co., China). An automated biochemical analyzer (Hitachi 7600-020, Japan) was used to determine serum creatinine, prealbumin, calcium, phosphorus, and other biochemical parameters. Intact parathyroid hormone (iPTH) was measured with an electrochemiluminescence immunoassay analyzer (Roche E141, Switzerland). Plasma 3-CT levels were detected by LC-MS (HPLC1200).

Body Composition and anthropometric measurements

Body composition was assessed using a MultiScan 5000 multi-frequency bioelectrical impedance analyzer (Bodystat, UK). Measurements were performed 30 minutes before dialysis for HD patients and in the morning for non-dialyzed CKD patients. The manufacturer's instructions were followed. Specifically, patients were placed in a supine position with electrodes attached to the hand and foot on the non-fistula side (for HD patients) or the dominant side (for non-dialyzed patients). The skin at the electrode contact points was moistened with ethanol. Patients with implanted electronic devices were excluded. Resistance and reactance were recorded at a frequency of 50 kHz. Then lean body mass and phase angle were measured. Appendicular skeletal muscle mass (ASMM) and appendicular skeletal mass index (ASMI) were calculated using the following formulas: $\text{ASMM}(\text{kg}) = -3.964 + (0.227 \times \text{RI}) + (0.095 \times \text{Weight} [\text{kg}]) + (1.384 \times \text{Sex} [1 \text{ for male}; 0 \text{ for female}]) + (0.064 \times \text{X} [\Omega])$,¹³ $\text{ASMI}(\text{kg}/\text{m}^2) = \text{ASMM} / \text{Height}^2 (\text{m}^2)$. The resistance index (RI) was calculated as $(\text{Height} [\text{cm}])^2 / R$, where R is resistance (Ω) and X is reactance (Ω).

Height, weight (post-dialysis dry weight for HD patients), handgrip strength, and pinch strength were measured as follows. A Baseline digital handgrip dynamometer (Model 12-0091, Fabrication Enterprises Inc., USA) and a Baseline digital pinch gauge (Model 12-0081, Fabrication Enterprises Inc., USA) were used to measure grip strength and pinch strength, respectively, in the sitting position using the non-fistula/dominant hand. Pinch strength was measured by pressing the thumb and index finger together with maximal voluntary effort, with the wrist in a neutral position and the elbow flexed at 90°. Three consecutive measurements for both grip and pinch strength were recorded and the highest value was taken.¹⁴

Diagnostic criteria for sarcopenia

Sarcopenia was diagnosed according to the 2019 criteria of the Asian Working Group for Sarcopenia (AWGS): (1) Low muscle mass: $\text{ASMI} < 7.0 \text{ kg}/\text{m}^2$ for men and $< 5.7 \text{ kg}/\text{m}^2$ for women. (2) Low muscle strength: Handgrip strength $< 28 \text{ kg}$ for men and $< 18 \text{ kg}$ for women.¹⁵ Participants who met both criteria (1) and (2) were confirmed with sarcopenia.

Statistical analysis

Statistical analyses were performed using SPSS software (version 22.0). Normally distributed continuous data are presented as mean $\pm$ standard deviation (SD). Statistical differences were evaluated using two-tailed unpaired

Student's *t*-test for comparisons between two groups, or analysis of variance (ANOVA) and appropriate post hoc analyses for comparisons of more than two groups. Non-normally distributed continuous data are presented as median (25th percentile, 75th percentile) and were evaluated using the Mann-Whitney *U* test (for two groups) or the Kruskal-Wallis *H* test (for three groups). Categorical data are expressed as numbers (percentages) and were compared using the Chi-square test. Spearman's correlation analysis was employed to assess the relationships between MPO, 3-CT, and sarcopenia-related indicators. Regarding the adjustment for confounding factors, multicollinearity tests were used to evaluate the relationships between variables (no multicollinearity was found among the variables in this study, variance inflation factor <5). At the same time, covariates with a regression coefficient *p*-value <0.1 for the study outcome were included, and potential confounding factors from clinical practice and related studies were also considered. Multiple linear regression analysis and logistic regression analysis were used to identify factors associated with sarcopenia. A two-tailed *p*-value of <0.05 was considered statistically significant.

RESULTS

Baseline characteristics

Initially, 319 CKD patients who met the inclusion criteria were considered. However, 27 patients who were uncooperative during anthropometric measurements were excluded, and then the final analysis were performed among 145 non-dialyzed CKD stage 1-5 patients and 147 CKD stage 5 HD patients. Among the 292 patients above, the mean age was 67.7 ± 12.2 years. 171 (58.6%) were male,

and 69 (23.6%) were diagnosed with sarcopenia. As expected, the prevalence of sarcopenia also increased significantly with the progression of CKD stages (17.3%, 17.1%, and 29.9%, respectively; $\chi^2 = 6.52$, $p = 0.038$) (Table 1).

Description of population characteristics grouped by gender

It revealed that males had significantly higher handgrip strength ($t = 6.87$, $p < 0.001$), pinch strength ($t = 6.04$, $p < 0.001$), ASMI ($Z = -5.50$, $p < 0.001$), prevalence of sarcopenia ($\chi^2 = 19.0$, $p < 0.001$), number of patients with CKD Stage 5 HD, and lean body mass ($Z = -2.93$, $p = 0.003$) compared to females. In contrast, males had lower body mass index (BMI) ($t = -3.16$, $p = 0.020$) and younger age ($t = -4.63$, $p < 0.001$) than females. However, no significant difference was observed in the phase angle between the two groups ($p > 0.05$) (Supplementary Table 1).

Comparison of serum indicators across CKD phases

Subsequently, CKD-related serum biomarkers were detected to explore their potential associations in different stages of CKD. With the progressive decline in renal function across chronic kidney disease (CKD) stages, significant changes were observed in relevant serum biochemical indicators ($p < 0.001$). Serum creatinine ($H = 226$), a key marker of glomerular filtration function, showed a marked progressive increase, reflecting the gradual loss of renal excretory capacity for metabolic wastes. Concurrently, serum prealbumin ($H = 62.6$) and iPTH ($H = 51.4$) levels also rose steadily with CKD progression. Serum phosphorus ($H = 119$) similarly exhibited

Table 1. Baseline characteristics across CKD stage

Characteristic	CKD stage 1-2 (n=75)	CKD stage 3-5 (n=70)	CKD stage 5 HD (n=147)	Statistic value	<i>p</i> value
Age (years)	66.3 ± 10.3	70.2 ± 10.7	67.1 ± 13.1	$F = 1.72$	0.181
Male, n (%)	38 (50.7)	36 (51.4)	97 (66.0)	$\chi^2 = 6.73$	0.055
Hypertension, n (%)	44 (58.7)	56 (80.0)	116 (78.9)	$\chi^2 = 8.45$	0.029
Diabetes, n (%)	19 (25.3)	58 (82.9)	97 (66.0)	$\chi^2 = 9.13$	0.014
Sarcopenia, n (%)	13 (17.3)	12 (17.1)	44 (29.9)	$\chi^2 = 6.52$	0.038

CKD, Chronic Kidney Disease; HD, Hemodialysis

Data are presented as mean $\pm$ SD for normally distributed continuous variables, median (25th and 75th percentiles) for non-normally distributed continuous variables, and n (%) for categorical variables.

$p < 0.05$ indicates statistical significance.

Table 2. Serum index comparison among CKD stage groups

Characteristic	CKD stage 1-2 (n=75)	CKD stage 3-5 (n=70)	CKD stage 5 HD (n=147)	Statistic value	<i>p</i> value
Serum creatinine (mmol/L)	83 (67.0, 106.0)	246 (176.0, 477)	900 (707.0, 1.13×10^3)	$H = 226$	<0.001
Prealbumin (mg/L)	229 (202, 266)	244 (199.0, 280.0)	301 (260, 353)	$H = 62.6$	<0.001
Serum calcium (mmol/L)	2.3 (2.2, 2.4)	2.2 (2.0, 2.3)	2.1 (1.9, 2.2)	$H = 17.6$	<0.001
Serum phosphate (mmol/L)	1.2 (1.1, 1.3)	1.3 (1.2, 1.6)	1.8 (1.5, 2.2)	$H = 112$	<0.001
iPTH (pmol/L)	3.0 (2.7, 5.6)	10.5 (6.6, 19.1)	26.4 (17.5, 45.6)	$H = 51.4$	<0.001
MPO (ng/mL)	93.5 (72.3, 103.0)	90.8 (76.0, 106)	102 (80.7, 126)	$H = 173$	<0.001
3-CT (mg/L)	1.4 (1.0, 2.1)	1.2 (0.6, 1.6)	6.4 (2.6, 10.4)	$H = 66.5$	<0.001

CKD, Chronic Kidney Disease; HD, Hemodialysis; iPTH, intact Parathyroid Hormone; MPO, Myeloperoxidase; 3-CT, 3-Chlorotyrosine.

Data are presented as mean $\pm$ SD for normally distributed continuous variables, median (25th and 75th percentiles) for non-normally distributed continuous variables, and n (%) for categorical variables.

$p < 0.05$ indicates statistical significance.

Table 3. Correlation of MPO or 3-CT with sarcopenia markers

Indicator	MPO		3-CT	
	<i>r</i>	<i>p</i> value	<i>r</i>	<i>p</i> value
Pinch strength (kg)	0.002	0.354	-0.148	0.036
Handgrip strength (kg)	-0.047	0.425	-0.091	0.200
ASMM (kg)	-0.068	0.250	-0.030	0.676
ASMI (kg/m ²)	-0.053	0.375	0.033	0.649
Phase angle (°)	-0.075	0.206	-0.023	0.744

MPO, Myeloperoxidase; 3-CT, 3-Chlorotyrosine; ASMM, Appendicular Skeletal Muscle Mass; ASMI, Appendicular Skeletal Muscle Mass Index.

Spearman's correlation analysis, *n*=292.

p < 0.05 indicates statistical significance.

Table 4. Univariate and multivariate logistic regression analyses of sarcopenia

f	Univariate		Multivariate	
	OR (95% CI)	<i>p</i> value	OR (95% CI)	<i>p</i> value
MPO (ng/mL)	1.01 (1.00, 1.02)	0.133	1.01 (1.00, 1.02)	0.153
3-CT (mg/L)	1.01 (0.97, 1.06)	0.580	1.02 (0.97, 1.08)	0.380

MPO, Myeloperoxidase; 3-CT, 3-Chlorotyrosine

The multiple linear regression model was adjusted for age, sex, Hypertension, Diabetes, BMI, prealbumin and serum creatinin.

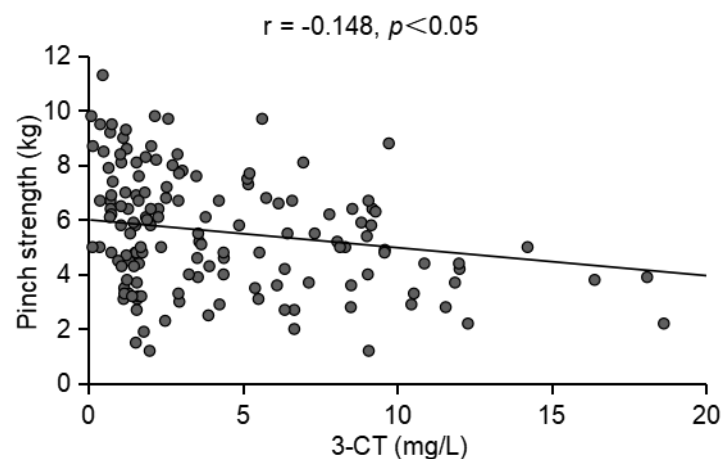
p < 0.05 indicates statistical significance.

a striking upward trend due to impaired renal excretion, while serum calcium ($H = 17.6$) showed a significant decreasing trend, which is closely associated with compromised renal activation of vitamin D and calcium-phosphorus metabolism disorders in CKD. These indicator changes collectively mirror the pathophysiological alterations accompanying renal function deterioration (Table 2).

Correlations of Plasma 3-CT and Sarcopenia among CKD Patients

Next, we aimed to investigate the changes of plasma MPO and 3-CT (a metabolite of MPO)—in the study population. Plasma MPO levels in the CKD stage 1-2, stage 3-5, and stage 5 HD groups were 93.5 (72.3, 103.0) ng/mL, 90.8 (76.0, 105.5) ng/mL, and 102 (80.7, 126) ng/mL, respectively ($H = 174$, $p < 0.001$). Plasma 3-CT levels in the CKD stage 1-2, stage 3-5, and stage 5 HD groups were 1.4 (1.0, 2.1) mg/L, 1.2 (0.6, 1.6) mg/L, and 6.4 (2.6, 10.4) mg/L, respectively ($H = 66.5$, $p < 0.001$)

(Table 2). It showed that both plasma MPO and 3-CT were significantly elevated in HD patients compared with CKD stage 1–2 and stage 3–5 non-dialyzed patients. However, spearman's correlation analysis revealed no significant correlation between plasma MPO or 3-CT levels and handgrip strength or ASMI, while a statistically significant negative correlation was shown between plasma 3-CT levels and pinch strength ($r = -0.148$, $p = 0.036$) (Table 3 and Figure 1). Logistic regression analysis showed that after adjusting for covariates with a regression coefficient $p < 0.1$ for the outcome of interest, and incorporating potential confounding factors derived from clinical practice and related studies, neither MPO(OR = 1.01; 95% CI: 1.00, 1.02) nor 3-CT(OR = 1.02; 95% CI: 0.97, 1.08) was associated with sarcopenia (Table 4). Interestingly, further multivariate linear regression analysis revealed that for each 1 mg/L increase in plasma 3-CT level, pinch strength was reduced by 0.05 kg ($\beta = -0.05$; 95% CI: -0.10, 0.00; Supplementary Table 2).

**Figure 1.** Inverse correlation between 3-CT and pinch strength. 3-CT, 3-Chlorotyrosine

DISCUSSION

In this cross-sectional study of 292 CKD patients, the sarcopenia was assessed using bioelectrical impedance analysis and dynamometry, with an overall prevalence of 23.6%. The prevalence of sarcopenia also increased significantly with the progression of CKD stages, which was consistently with previous research.¹⁶ As a recent meta-analysis shows, our study also found a high prevalence of sarcopenia (29.9%) among HD patients⁶. Interestingly, among non-dialyzed CKD stage 1-5 patients in the present study, the prevalence of sarcopenia was up to 17.2%. It was far higher than that reported in a previous cross-sectional study of 287 conservatively managed CKD patients (5.9% to 9.8%).⁵ These discrepancies may be attributed to ethnic differences among the study populations and variations in the application of sarcopenia diagnostic criteria.

Based on data from the Modification of Diet in Renal Disease study, Kopple et al. reported that men exhibited a steeper decline in BMI and arm muscle area as glomerular filtration rate (GFR) decreased.¹⁷ A separate study also corroborated an analogous gender-related discrepancy in sarcopenia.¹⁶ In line with that, we found that males had higher prevalence of sarcopenia.

While malnutrition, inflammation, and oxidative stress are widely recognized as critical pathogenic factors, the exact underlying mechanisms driving sarcopenia in patients with chronic kidney disease (CKD) remain incompletely understood.¹⁸ Notably, these factors act synergistically to enhance muscle protein catabolism and induce a negative nitrogen balance in CKD patients, which were key pathophysiological changes contributing to sarcopenia development.¹⁹ Supporting a potential role of 3-CT as MPO-derived chlorinated product, a study conducted in HD patients and a 5/6 nephrectomized CKD mouse model demonstrated that MPO and its derived advanced oxidation protein products induce oxidative stress, thereby contributing to muscle atrophy via the CD36/NADPH oxidase pathway by inducing oxidative stress.²⁰ Furthermore, several animal studies have indicated a critical role of MPO-mediated oxidative stress in the pathology of muscle atrophy.^{21,22} Our study found that deteriorating kidney function in HD patients was associated with elevated levels of plasma MPO and 3-CT across CKD stages, accompanied by an increased prevalence of sarcopenia. Nevertheless, no direct correlation was identified between MPO or 3-CT and sarcopenia per se. This divergence may stem from the unique pathophysiology of CKD itself, which is characterized by persistent chronic inflammation,³ potentially obscuring differences between sarcopenic and non-sarcopenic groups.

Pinch and handgrip strength are direct and objective indicators of muscle strength and are closely associated with overall health status.²³ El-Katab et al. also reported a strong correlation between pinch and handgrip strength, supporting pinch strength/handgrip strength as a viable screening tool for assessing muscle strength in dialysis patients.²⁴ Interestingly, our research revealed that plasma 3-CT level had a significant negative correlation with pinch strength. Further multivariate linear regression analysis revealed that for each unit increase in 3-CT, pinch strength decreased by 0.05 kg. However, there was

no significant correlation between plasma 3-CT and sarcopenia. Several explanations may account for this discrepancy. First, small intrinsic hand muscles may be more vulnerable to MPO-mediated oxidative stress than larger forearm muscles, due to differences in metabolic rate and antioxidant capacity²⁵. Second, the AWGS cut-off values for handgrip strength and ASMI are designed to detect clinically overt sarcopenia, and may be insensitive to early or subclinical dysfunction such as that reflected by reduced pinch strength¹⁵. Additionally, a weak association with handgrip strength or ASMI, if present, might be undetectable due to limited statistical power. Collectively, these explanations reconcile the apparent paradox that 3-CT correlates with pinch strength but not with sarcopenia by AWGS criteria. Importantly, the dissociation between 3-CT and conventional sarcopenia indicators suggests that oxidative stress-related muscle impairment may vary across muscle subgroups and functional domains, rather than leading to generalized muscle loss uniformly. This observation highlights the heterogeneity of muscle dysfunction among patients with CKD.

Furthermore, this study raises the possibility that plasma 3-CT might serve as an early biomarker for pre-sarcopenia or declining fine motor function. However, cross-sectional evidence alone is insufficient for clinical use; future prospective studies are needed to establish temporal relationships, validate cut-off values, and demonstrate incremental predictive value over existing simple measures.

Here, it is the first study to investigate the association between MPO, its active metabolite 3-CT, and sarcopenia. Although we did not identify a significant correlation between plasma MPO or 3-CT and sarcopenia diagnosed by AWGS criteria, the observed negative correlation with pinch strength suggests that 3-CT is associated with impaired skeletal muscle function, particularly fine hand muscle dysfunction. This finding provides clinicians a novel perspective to evaluate muscle wasting from an inflammation-oxidation standpoint. However, as a cross-sectional study, no causal inferences can be inferred. Further large-scale prospective cohort studies and animal experiments are needed to validate these findings and elucidate the potential causal mechanisms linking MPO/3-CT to muscle dysfunction. Furthermore, this study did not collect information on patients' exercise habits (e.g., type, frequency, duration), which are known to influence muscle mass and strength. Future studies should incorporate detailed physical activity assessments to adjust for this potential confounder.

Conclusion

Although there were no significant correlation between plasma MPO or 3-CT levels and sarcopenia, MPO-derived metabolite 3-CT was significantly inversely associated with pinch strength. These findings suggest a link between MPO-mediated oxidative stress and fine hand muscle dysfunction, offering a new perspective for evaluating early, subclinical muscle dysfunction in CKD patients.

DISCLOSURE ON THE USE OF AI AND AI-ASSISTED TECHNOLOGIES

Literature search was assisted by ChatGPT (accessed August 2026). All cited references were independently verified by the authors against the primary sources.

CONFLICT OF INTEREST AND FUNDING DISCLOSURES

The authors declare no competing interests.

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