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ORIGINAL RESEARCH

The Diminished Cardiorespiratory Fitness in Cardiovascular-Kidney-Metabolic Syndrome

Yuting Liu[1], Yanting Liang[1], Huan Ma[2], Hengyuan Gao[3,4], Xinzhou Zhang[1,5]

[1]Department of Nephrology, Shenzhen People's Hospital, The Second Clinical Medical College, Jinan University, The First Affiliated Hospital, Southern University of Science and Technology, Shenzhen, Guangdong, 518020, People's Republic of China; [2]Department of Cardiology, Guangdong Cardiovascular Institute, Guangdong Provincial People's Hospital, Guangdong Academy of Medical Sciences, Southern Medical University, Guangzhou, Guangdong, 510080, People's Republic of China; [3]Department of Thyroid Surgery, the First Affiliated Hospital of Jinan University, Guangzhou, Guangdong, 510630, People's Republic of China; [4]Department of Thyroid and Breast Surgery,Shenzhen People's Hospital, The Second Clinical Medical College, Jinan University, The First Affiliated Hospital, Southern University of Science and Technology, Shenzhen, Guangdong, 518020, People's Republic of China; [5]Shenzhen Key Laboratory of Kidney Diseases, The Second Clinical Medical College, Jinan University; The First Affiliated Hospital, Southern University of Science and Technology, Shenzhen, Guangdong, 518020, People's Republic of China

Correspondence: Hengyuan Gao, Email geland136@163.com, Xinzhou Zhang, Email xinzhouzhang1946@163.com

Objective: The American Heart Association has recently emphasized the significance of the cardiovascular-kidney-metabolic (CKM) syndrome. However, the cumulative impact of these factors on cardiorespiratory fitness remains inadequately characterized. This study aimed to examine the responses observed during cardiopulmonary exercise testing (CPET) of CKM syndrome patients and explore the potential correlation between cardiorespiratory fitness and hemoglobin concentration in this cohort.

Design: Cross-sectional study.

Methods: We retrospectively collected medical data of 8206 patients who underwent CPET from 2012–2022. Among the 878 individuals enrolled, 12 were healthy controls, 809 had isolated CVD, and 57 were in CKM stage 4. After propensity score matching, 112 patients were included in the matched cohort analysis, with 56 each in the CVD and CKM groups. CPET responses were compared between the groups using propensity matched analysis. Additionally, simple mediation models were employed to investigate the potential mediating role of hemoglobin concentration in the association between CKM syndrome and peak VO_2.

Results: After propensity score-matching, CKM stage 4 was associated with diminished cardiorespiratory fitness compared to the other two groups. This included diminished exercise capacity, reflected by shorter exercise time, lower maximum workload (and its percent predicted value), and reduced peak VO2 (including its percent predicted value and peak VO2/kg). Additionally, cardiac autonomic function was impaired, as evidenced by decreased heart rate recovery (HRR) and a reduced slope of HR recovery (all $p<0.05$). Mediation model regression analysis indicated a significant and direct detrimental effect of CKM syndrome on peak VO_2 ($\beta = -228.502$; $P = 0.003$), and a significant indirect partial effect of hemoglobin concentration on the direct effect ($\beta = -335.718$; $P < 0.001$), with the percentage mediated through hemoglobin concentration of 46.9%.

Conclusion: Individuals with CKM syndrome demonstrate compromised responses to CPET manifested by diminished exercise capacity and cardiac autonomic function. While diminished peak oxygen uptake can be partly explained by hemoglobin concentration as we found, further research is necessary to understand other underlying mechanisms.

Keywords: cardiovascular-kidney-metabolic, cardiovascular disease, diabetes, chronic kidney disease, cardiorespiratory fitness, Cardiopulmonary Exercise Testing

Introduction

There is a well-established bidirectional association between the dysfunction of the heart and the kidneys, known as cardiorenal syndrome. Similarly, the concept of cardiometabolic disease has gained significant recognition in recent years. Recent studies underscore the imperative need to encompass their interplay within a broader framework termed cardiovascular-kidney-metabolic (CKM) syndrome, reflecting the clinical presentation of the pathophysiological interactions among metabolic risk factors such as obesity and diabetes, chronic kidney disease (CKD) and the cardiovascular system.[1]

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The state of poor CKM health significantly drives premature morbidity and mortality.[2] Multiple factors, including disturbances in cardiac and skeletal muscle function,[3–6] autonomic dysfunction,[7,8] and anaemia[9,10] contribute to the adverse prognosis of these patients. Notably, these factors often interact and exacerbate each other, leading to a cumulative impact on patient outcomes. Among these, Cardiorespiratory fitness (CRF) has emerged as an independent marker of cardiovascular well-being. Low CRF, endorsed as a clinical vital sign by the American Heart Association, is strongly linked to an elevated risk of cardiovascular disease (CVD) morbidity and mortality.[11] Besides, conditions commonly associated with CKM, such as of anemia, CKD, and diabetes, appear to have an additive detrimental effect on physical function.[12,13] Cardiopulmonary exercise testing (CPET) is a well-described technique for assessing cardiorespiratory fitness.[14,15] It provides valuable insights into the dynamics of cardiopulmonary and circulatory responses to physical stress, while also serving as a safe tool to unveil potential imbalances in parasympathetic and sympathetic activity that might remain concealed during rest.[16] However, despite its importance, comprehensive evaluations of CRF in CKM patients remain limited, highlighting a critical gap in understanding its role in this population.

Since nearly every major organ system is affected as a consequence of CKM syndrome, therefore, CPET seems to be more ideal to comprehensively evaluate the overall function of CKM patients from a functional perspective. Consequently, this study aims to evaluate the unique CPET responses of CKM syndrome patients, compare these findings with control groups, and investigate the role of hemoglobin concentration in explaining reduced cardiorespiratory fitness.

Methods

Patients and Study Design

This study was performed as a retrospective analysis in which data from CPET until maximal exhaustion were assessed in 8,206 individuals who referred for CPET between January 1, 2012 and April 26, 2022, from Guangdong Provincial People's Hospital (GDPH).

According to the *CKM Presidential Advisory* from the American Heart Association,[17] the eligibility criteria of CKM stage 0 were defined as follows: individuals attending CPET for physical examination reason, without clinical diagnosis of CVD including coronary heart disease, heart failure, stroke, atrial fibrillation, without clinical diagnosis of diabetes, hypertension, hyperlipemia and CKD, with normal BMI<23 (lower anthropometric cut points advised for Asian populations[18]). Participants eligible for CKM stage 0 were enrolled as healthy controls. The CKM stage 4 group was defined as individuals with clinical diagnosis of coronary heart disease who also had diabetes and CKD. The CVD isolated group included individuals with coronary heart disease but did not have diabetes or CKD. The exclusion criteria were 1) age <18 years; 2) with incomplete medical records and CPET data. Hemoglobin, serum creatinine, serum uric acid concentration and pulmonary function test result as well as complication, were collected from patients' medical records within a 3-month window before or after CPET. Participants provided written informed consent for anonymous clinical data using. This study was approved by the GDPH's Ethics Committee (KY2023-514) and met guidelines set by the Declaration of Helsinki.

Assessment of CPET Data

Prior to commencing the analysis, CPET data were screened for eligibility. All CPET were conducted on cycle ergometer (ERG 910 plus, SCHILLER, Switzerland) and respiratory gas exchange was analyzed using a calibrated metabolic cart (CARDIOVIT CS-200 Office ErgoSpiro, SCHILLER, Switzerland) on a breath-by-breath basis. The primary eligibility criteria encompassed the availability of exercise time, maximum workload, absolute VO_2 (l/min), absolute VCO_2 (l/min), and ventilation (VE) (l/min) throughout the entire CPET measurement. Additionally, β-blockers and calcium channel antagonists were discontinued 24 hours before testing whenever possible.

The percent predicted load was determined by calculating the actual maximum workload divided by the workload predicted based on sex and age. Peak VO_2 and peak respiratory exchange ratio (RER) were expressed as the highest 10-second averaged sample obtained during the last 20s of testing. RER was calculated as the ratio of VCO_2 to VO_2 at peak exercise. The anaerobic threshold (AT) was identified using the V-slope method, and further confirmed using other plots. Both peak VO_2 and AT VO_2 were presented in both absolute (mL/min) and relative terms (mL/kg/min). The percent predicted VO_2 was calculated as dividing

the actual VO_2 by the predicted VO_2 estimated by sex, age, and weight. The Δ oxygen consumption/Δ work rate slope (VO_2/WR) was automatically computed through the software programme, defining the ratio of the changes in VO_2 versus the changes in workload. Peak oxygen pulse (O_2 pulse), a surrogate for stroke volume, was determined by dividing peak VO_2 (mL/min) by peak heart rate (HR). The VE/VCO_2 slope was derived using linear regression, with the exclusion of the nonlinear segment of the data initiated by the onset of ventilatory compensation for metabolic acidosis.

Hemodynamics

Blood pressure measurements were taken at 2-minute intervals, while a continuous 12-lead electrocardiogram and saturation monitoring (SpO_2) were recorded. HR, systolic blood pressure (SBP) and diastolic blood pressure (DBP) were analyzed both at rest and at peak exercise. The resting period were considered as the last 30s on the cycle ergometer before the start of CPET. Evaluation of hemodynamic changes during exercise testing and during the recovery period has been considered a simple and useful marker for identification of autonomic dysfunction.[19,20] These parameters are often used to assess the balance between sympathetic and parasympathetic nervous system activity, which helps in understanding autonomic function and its impairment in various clinical conditions. In this study, we defined the heart rate response during exercise to represent cardiac autonomic nervous activity, including heart rate recovery (HRR), defined as the difference between peak HR and HR one minute following test termination, the slope of HR increase (beats/s), which was defined as the ratio between change in HR from rest to peak exercise and exercise time, and the slope of HR recovery (beats/s), defined as the ratio between heart rate recovery and exercise time.

Statistical Analysis

Normality of data were verified using normal Q-Q plots and Shapiro–Wilk test. Descriptive statistics are presented as mean±standard deviations for continuous variables and as numbers and percentages for categorical variables. Data distributions were compared using the *t*-test for continuous variables and chi-square tests for categorical variables. To compare the three group, the one-way ANOVA was used, followed by the Bonferroni post hoc test.

Subsequent to the comparison of the baseline characteristics between CVD and CKM patients, rigorous adjustments for significant demographic differences between the two groups were performed via propensity score matching (PSM), The matching parameters included a caliper of 0.1 and a 1:1 matching ratio, with covariates consisting of sex and age. Further comparisons of cardiopulmonary parameters were performed in the healthy control group and the matched CVD and CKM groups.

Additionally, we conducted mediation analyses with simple mediation models, utilizing PROCESS SPSS macro version 4.1 to explore the mediation relationship within CRF, hemoglobin concentration and CKM syndrome. Specifically, we estimated the total effect of CKM on peak VO2 (c path), the effect of CKM on hemoglobin concentration (a path), the effect of hemoglobin concentration on peak VO2 while controlling for CKM (b path), and the direct effect of CKM on peak VO2 while controlling for hemoglobin concentration (c' path). The mediation effect was considered significant if the 95% confidence interval (CI) of the indirect effects did not encompass zero. The percentage mediated was calculated by dividing the indirect effect (a × b) by the total effect(c). Imbalanced baseline characteristics had been adjusted. A two-tailed value of $P < 0.05$ was considered statistically significant. All statistical analyses were performed using SPSS 27.0 (SPSS, Inc., Chicago, IL, USA).

Results

Baseline Characteristics

A total of 878 individuals were included in the final analysis (Figure 1). Baseline clinical and laboratory characteristics of the healthy controls (n=12), patients with CVD (n=809), and patients with CKM stage 4 (n=57) are listed in Table 1. In comparison to the healthy control and CVD groups, the CKD stage 4 group exhibited advanced age, elevated levels of creatinine and uric acid, and a higher prevalence of anemia, heart failure, and hypertension. After conducting propensity score matching, the matched cohort analysis included 112 patients, with 56 individuals in the CVD group and 56 in the

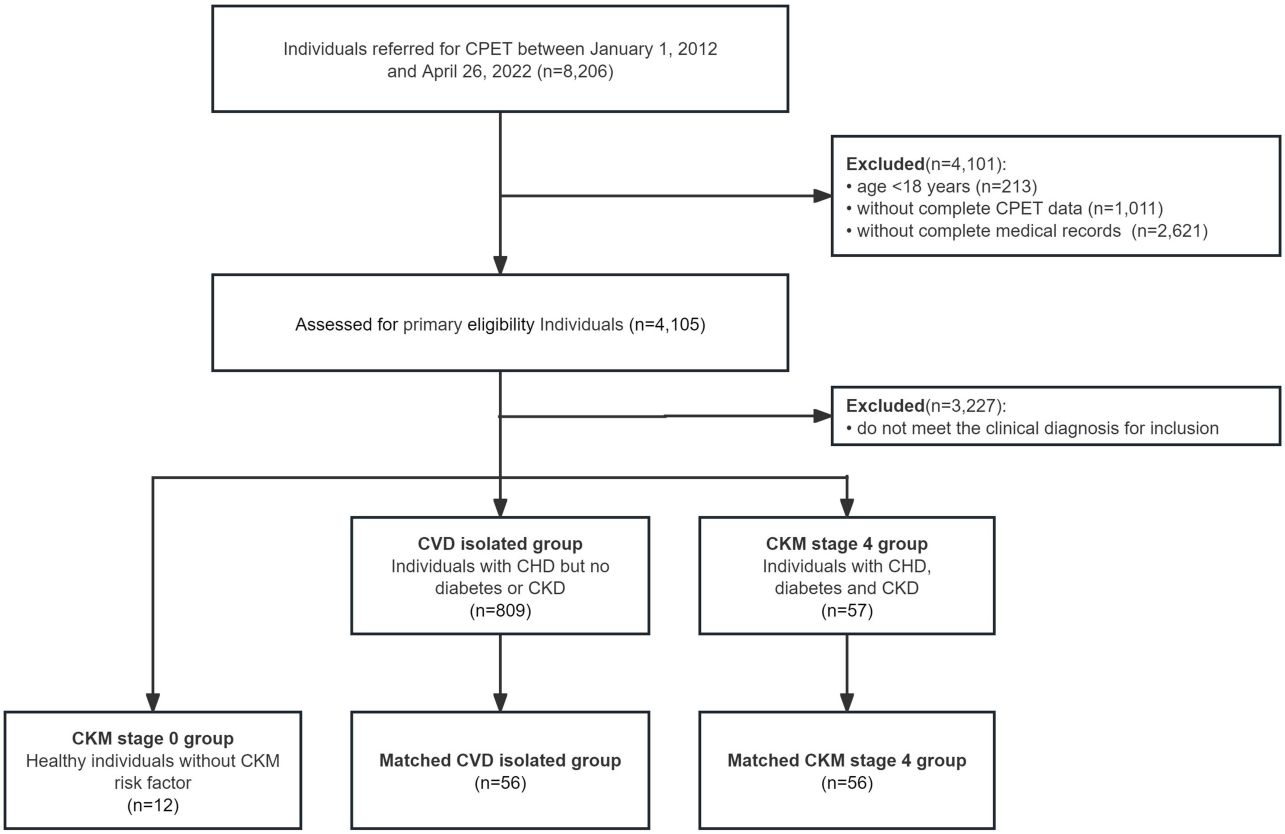

Figure 1 Flow chart of the study.
Abbreviations: CPET, Cardiopulmonary exercise testing; CVD, cardiovascular disease; CHD, coronary heart disease; CKD, chronic kidney disease; CKD, cardiovascular-kidney-metabolic.

CKM group. No significant differences were found in age, uric acid concentration, and heart failure prevalence between the CVD and CKM stage 4 groups, while creatinine, eGFR, hemoglobin, anemia and hypertension remained different.

Cardiopulmonary Exercise Testing

The results of cardiopulmonary exercise testing in the control group and matched cohorts are presented in Table 2. All groups successfully performed a high intensity cardiopulmonary exercise test to volitional exhaustion as verified by peak RER. Patients with CKM syndrome stage 4 exhibited significantly lower exercise time, max workload, percent predicted load, peak VO_2, percent predicted VO_2, peak VO_2/kg, VE/VCO_2 slope, and peak HR as well as higher rest SBP

Table 1 Patient Characteristics

	Control	Unmatched Cohort		Matched Cohort (Sex, Age)	
	n =12	CVD Isolated n =809	CKM Stage 4 n =57	CVD Isolated n =56	CKM Stage 4 n =56
Demographic					
Gender, male, n (%)	5(41.7)	626(77.4)*	47(82.5)*	52(92.9)	46(82.1)
Age (year, mean ± SD)	41.7±11.6	58.9±11.2*	67.2±10.4*#	65.7±9.8	66.9±10.2
Height (cm, mean ± SD)	164.4±8.8	165.1±7.6	166.85±7.0	166.8±5.2	166.7±7
Body mass (kg, mean ± SD)	57.2±6.9	66.5±11.6*	68.9±12.9*	68.1±10.9	68.6±12.8
BMI (kg/m^2, mean ± SD)	21.1±1.6	24.3±3.2*	24.6±3.6*	24.5±3.5	24.5±3.6

(*Continued*)

Table 1 (Continued).

	Control	Unmatched Cohort		Matched Cohort (Sex, Age)	
	n =12	CVD Isolated n =809	CKM Stage 4 n =57	CVD Isolated n =56	CKM Stage 4 n =56
Comorbidities and laboratory measures					
Creatinine (μmol/l, mean ± SD)	66.7±16.7	79.0±15.5	204.3±203.3*#	82.7±15.6	204.8±205.1#
eGFR (mL/kg/1.73 m^3, mean ± SD)	107.0±25.5	87.6±14.3*	40.6±16.0*#	82.2±13.6	40.8±16.1#
Uric acid (μmol/l, mean ± SD)	329.3±105.2	401.2±104.1	440.5±133.4*#	416.4±91	441.6±134.5
Hemoglobin (g/dl, mean ± SD)	137.7±12.9	139.8±16.1	126.3±21.6*	142.5±13.4	126.1±21.8#
Anemia (<12 g/dl), n (%)	0	65(8.0)	18(31.6)#	2(3.6)	18(32.1)#
HF, n (%)	0	11(1.4)	5(8.8)#	1(1.8)	5(8.9)
Stroke, n (%)	0	23(2.8)	4(7.0)	2(3.6)	4(7.1)
AF, n (%)	0	36(4.4)	3(5.3)	4(7.1)	3(5.4)
Hypertension, n (%)	0	342(42.3)	43(75.4)#	28(50.0)	42(75.0)#
Dyslipidemia, n (%)	0	131(16.2)	9(15.8)	5(8.9)	8(14.3)
Over weight, n(%)	0	534(66.0)	37(64.9)	44(78.6)	36(64.3)
Depression, n (%)	1(8.3)	20(2.5)	0	3(5.4)	0
Anxiety, n (%)	1(8.3)	39(4.8)	2(3.5)	4(7.1)	2(3.6)
Abnormal static pulmonary function, n (%)	2(25)	179(34.6)	15(41.7)	20(35.7)	15(26.8)

Table 2 Physiological Measures During the Cardiopulmonary Exercise Testing of Healthy Controls, CVD and CKM Patients

	Control	Matched Cohort (Sex, Age)		P for CVD vs con	P for con vs CKM	P for CVD vs CKM
	n =12	CVD Isolated n =56	CKM Stage 4 n =56			
CPET parameters						
Exercise time(s)	480.3±85.1	433.7±125.0	372.3±103.5	0.586	**0.009**	**0.014**
Max workload(Watt)	123.2±38.2	98.0±38.3	74.9±30.0	0.074	**<0.001**	**0.002**
Percent predicted load (%)	97.4±26.7	81.8±29.4	60.3±18.4	0.574	**0.007**	**<0.001**
Peak RER	1.2±0.1	1.2±0.1	1.2±0.1	0.954	0.429	1
AT VO_2 (mL/min)	989.7±215.4	886.4±267.3	810.5±206.5	0.905	0.224	0.643
AT VO_2 (mL/kg/min)	21.3±13.0	19.2±19.6	14.2±11.1	1	0.774	0.605
Peak VO_2(mL/min)	1486.9±391.4	1289.8±404.1	1008.3±343.2	0.307	**<0.001**	**<0.001**
Percent predicted VO_2 (%)	78.8±14.1	72.9±21.0	59.7±29.7	1	**0.01**	**0.002**
Peak VO_2/kg (mL/kg/min)	25.8±5.9	19.2±5.9	14.8±4.6	**<0.001**	**<0.001**	**<0.001**
VO_2/WR(mL/min/watt)	9.6±1.3	9.6±1.9	9.3±5.2	1	1	1
O_2 pulse (mL/beat)	9.5±1.7	10.4±3.1	8.4±2.3	0.798	0.690	**<0.001**
VE/VCO_2 slope	26.8±5.1	31±7.3	33.9±6.7	0.224	**0.009**	0.128
Hemodynamics parameters						
Rest HR (bpm)	76.8±8.9	75.6±15.0	78.9±13.4	1	1	0.620
Peak HR (bpm)	156.6±22.3	125.8±21.8	117.8±22.3	**<0.001**	**<0.001**	0.182
Rest SBP (mm Hg)	115.7±16.7	133.1±21.0	135.5±23.8	0.07	**0.033**	1
Peak SBP (mm Hg)	155.4±18.1	179.3±30.4	171.3±32.9	0.078	0.423	0.609
Rest DBP (mm Hg)	72.0±9.8	77.7±12.9	75.5±11.5	0.527	1	1
Peak DBP (mm Hg)	75.1±8.2	88.7±14.6	80.5±16.7	**0.033**	0.937	**0.028**

Notes: Values present as means±sd. *P* values calculated by Bonferroni post hoc test. *P* value marked in bold indicates statistically significant.

Abbreviation: CVD, cardiovascular disease; CKM, cardiovascular-kidney-metabolic syndrome; CPET, Cardiopulmonary Exercise Testing; RER, respiratory exchange ratio; AT, anaerobic threshold; HR, heart rate; SBP, systolic blood pressure; DBP, diastolic blood pressure.

compared to the control group. When comparing patients with CKM to those with CVD, we observed similar trends in exercise time, max workload, percent predicted load, peak VO_2, percent predicted VO_2, and peak VO_2/kg. It is notable that there was a graded decline in peak VO_2/kg across the study groups. Additionally, O_2 pulse was significantly lower, and peak DBP was higher in the CKM group compared to the CVD group. There was a nonsignificant trend toward lower AT VO_2 in CVD and CKM compared with the controls. No statistically significant differences were observed between the groups in terms of RER, VO_2/WR, rest HR, peak SBP, and rest DBP.

Figure 2 illustrates that patients with CKM exhibited significantly compromised overall cardiac autonomic nervous activity compared to those with CVD and the control group. Specifically, CKM patients displayed a notably lower HRR when compared to the other two groups (8.6±6.4 vs 15.0±9.6 vs 23.7±6.1; p=0.015, p<0.001, respectively). Additionally, the slope of HR increase in the CKM group was significantly lower than that in the control group (0.107±0.047 vs 0.167 ±0.034, p<0.001). Furthermore, the slope of HR recovery also demonstrated a significant reduction in the CKM group in comparison to the other two groups (0.074±0.052 vs 0.114±0.063 vs 0.156±0.043; p=0.033, p=0.007, respectively).

The Relationship Within CRF, Hemoglobin Concentration and CKM Syndrome

Figure 3 depicts the mediation models employed to assess whether hemoglobin concentration plays a mediating role in the adverse impact of CKM syndrome on cardiorespiratory fitness. Notably, regression a (β= −16.381[−23.537,-9.224]; P < 0.001) indicated that CKM syndrome leads to diminished hemoglobin concentration, and b (β =6.545[2.802, 10.289]; P =0.008) establishes a statistically significant direct relationship between higher hemoglobin concentration and enhanced peakVO_2. Additionally, a direct effect (β = −228.502[−377.424, −79.579]; P = 0.003) was observed for the adverse outcome of CKM syndrome on peakVO2. Our mediational hypothesis received validation, as the confidence intervals did not include zero (β = −335.718[−478.635, −192.801]; P < 0.001), and the percentage mediated through hemoglobin concentration was 46.9%. The results remained consistent after adjusting for imbalanced baseline characteristics between the two groups (Figure S1). Therefore, hemoglobin concentration has a partial mediation effect on the relationship between CKM syndrome and cardiorespiratory fitness.

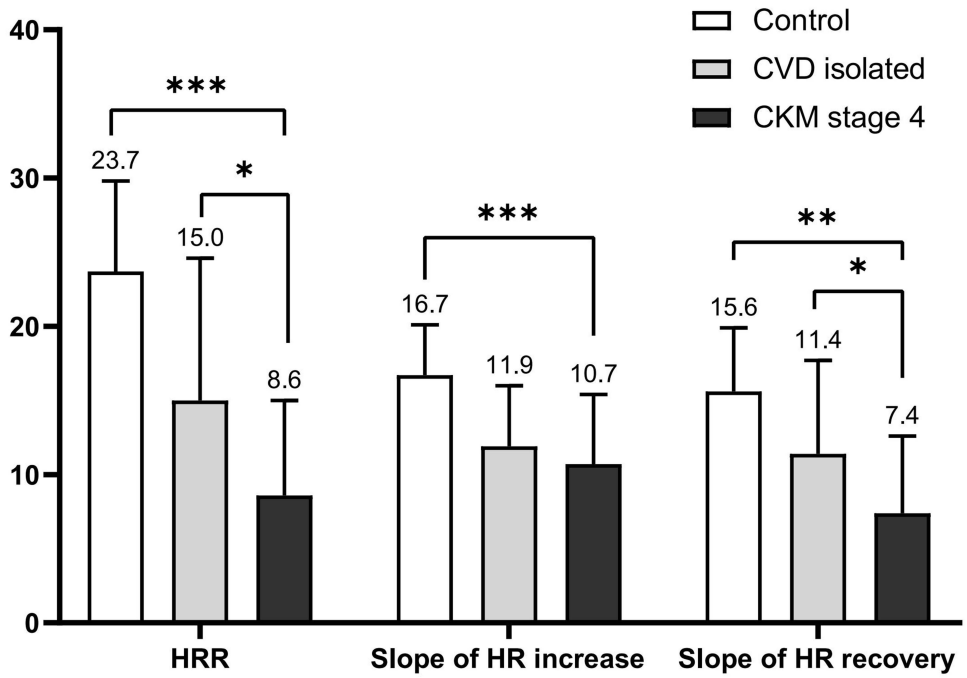

Figure 2 Cardiac autonomic nervous activity parameters of healthy controls (n=12), CVD isolated (n=56) and CKM patients (n=56). It shows the mean value of HRR, the slope of HR increase (presented in hundredfold sizes) and the slope of HR recovery (presented in hundredfold sizes), respectively.
Note: *P* values calculated by Bonferroni post hoc test; *: p<0.05; **: p<0.01; ***: p<0.001.
Abbreviations: CVD, cardiovascular disease; CKM, cardiovascular-kidney-metabolic syndrome; HRR, heart rate recovery; HR, heart rate.

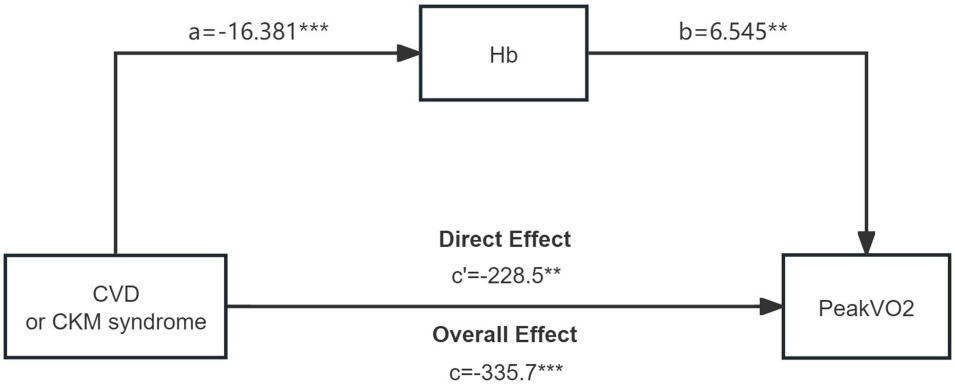

Figure 3 A mediation model of the association between CKM syndrome and cardiorespiratory fitness through hemoglobin concentration. Path coefficients are shown. It shows hemoglobin concentration as mediator of the effect of CKM syndrome on peakVO_2.
Note: ** $p<0.01$; *** $p<0.001$.
Abbreviations: Hb, hemoglobin concentration; CVD, cardiovascular disease; CKM, cardiovascular-kidney-metabolic syndrome.

Discussion

The main finding of our analysis was that cardiopulmonary function in CKM stage 4 patients exhibited impairments when compared to healthy controls in CKM stage 0. Furthermore, these impairments were still pronounced when compared to CVD isolated patients, and part of this effect was mediated by hemoglobin changes. Additionally, we observed impaired autonomic nervous responses to peak exercise in CKM patients.

In our study, we observed compromised exercise responses in patients with CKM syndrome stage 4, encompassing two key aspects. The first pertains to reduced exercise capacity, which is evidenced by diminished exercise duration, maximal workload, peak VO_2, and O_2 pulse. Previous studies have suggested that coronary heart disease, CKD and diabetes in isolation can independently lead to a reduction in exercise capacity.[21–23] Our present study goes a step further, revealing that the confluence of cardiovascular, kidney, and metabolic diseases can exacerbate this phenomenon. This exacerbation is particularly notable in peak oxygen uptake, suggesting the presence of intricate and potential interactions among metabolic risk factors, CKD, and the cardiovascular system, all of which have a profound impact on overall health status.

The underlying mechanisms behind reduced exercise capacity in individuals with CKM remain unclear. Similar to previous studies demonstrating an association between anaemia and impaired subjective physical function,[12,24] our research also identifies hemoglobin concentration as a partial explanation for the decline in peak VO_2 in CKM syndrome. Both metabolic diseases and CKD can be secondary to anemia,[10,25] leading to a reduced oxygen-carrying capacity. Although anemia is a well-described risk factor for diminished physical capacity, many studies have primarily focused on severe levels of anemia. Our findings reveal that lower hemoglobin levels, even before the onset of anemia, are associated with decreased exercise capacity. These results underscore the importance of monitoring hemoglobin levels in these patients early in clinical practice.

In addition to oxygen-carrying capacity, optimal oxygen delivery and utilization during exercise involve a complex interplay of various physiological functions, including pulmonary ventilation, gas exchange, cardiac output, and peripheral skeletal muscle oxygen extraction. Our result found that the O_2 pulse of CKM patients was further impaired than isolated CVD populations. According to the Fick's law, the O_2 pulse represented the product of stroke volume (representing cardiac output) and arteriovenous oxygen content difference (CaO2-CvO2, representing skeletal muscle oxygen utilization). CKM syndrome appears to lead to impairment in both aspects. Patients with diabetes showed nearly a 20% lower end-diastolic volume at rest and during exercise, thereby limiting stroke volume in accordance with the Frank-Starling mechanism.[26] Also, mitochondrial dysfunction is commonly observed in patients with moderate CKD and metabolic disease,[27,28] which could lead to compromised peripheral oxygen utilization. The intricate metabolic interplay among mitochondrial dysfunction, inflammation, and oxidative stress may collectively contribute to poor physical performance. Additionally, cardiomyopathy and vasculopathy associated with metabolic and uremic disease could also exacerbate cardiac dysfunction, contributing to the reduced exercise capacity observed in CKM syndrome.[29,30] Pulmonary hypertension secondary to left ventricular dysfunction

and vascular endothelial dysfunction, as well as obstructive or restrictive pulmonary dysfunction due to mild fluid retention, may further complicate oxygen delivery and utilization.[31] Further mechanistic research is needed to better understand the underlying pathophysiology of reduced physical fitness in patients with CKM, particularly through integrated physiological approaches and consideration of these additional pathways.

According to our findings, another notable compromised aspect of CKM syndrome's exercise response is its impact on cardiac autonomic function, as evidenced by its effect on heart rate regulation and recovery. The heart rate response to dynamic exercise typically follows a well-defined pattern primarily under autonomic nervous system control.[32] At the onset of exercise, there is a rapid increase in heart rate, primarily mediated by vagal inhibition. As exercise continues, sympathetic activity gradually increases, resulting in a progressive acceleration of heart rate. Following exercise, a reduced heart rate response occurs, driven by a combination of vagal reactivation and diminished sympathetic stimulation, with the latter playing a more prominent role in the delayed deceleration of heart rate. Prior research has demonstrated that autonomic dysfunction is common in individuals with CKD or metabolic disorders, and it is closely linked to the onset, progression, and prognosis of various diseases.[33–35] Our results indicated that the coexistence of metabolic diseases and CKD presented an addictive effect on autonomic nervous dysfunction in CVD patients. While diminished exercise capacity and compromised cardiac autonomic function are well-established as negative prognostic indicators in the general population, further exploration is needed to determine their specific prognostic implications in the CKM population.

Limitation

Several limitations of the study should be noted. Firstly, the retrospective design and stringent inclusion/exclusion criteria led to a small number of healthy subjects, which introduced potential biases, such as baseline imbalances (eg, a higher proportion of women in the control group) and incomplete or inconsistent data collection. While key demographic characteristics were carefully matched where possible, these limitations should be considered when interpreting the results. Secondly, we did not employ a predefined threshold for autonomic disorders based on heart rate recovery (HRR), as is common in other studies. This was due to the substantial variability in HRR threshold values in the existing literature. Instead, we opted to compare absolute HRR values, which offer a more comprehensive dataset. Thirdly, we lacked detailed information on medications beyond β-blockers and calcium channel antagonists, which could have influenced CPET outcomes, particularly regarding autonomic function and exercise capacity. Moreover, the study occurred over the time span of 10 years during which time, there have been significant changes in guideline directed medical therapy (SGLT2 inhibitors, ARNI) uptake that might confound the results. Lastly, it is important to acknowledge that this investigation focused on individuals with both coronary heart disease and comorbid diabetes mellitus and chronic kidney disease, representing stage 4 of CKM syndrome. Consequently, generalizability to other kinds of CKM syndrome populations or clinical settings requires further research.

Conclusions

In conclusion, the study has demonstrated that cardiopulmonary function and the autonomic nervous response to peak exercise are impaired in patients with stage 4 CKM syndrome. This dysfunction is further linked to hemoglobin concentration, suggesting a potential mediating factor. These findings underscore the need for further research to explore the mechanisms by which hemoglobin concentration affects cardiopulmonary fitness in CKM syndrome, as well as to identify targeted interventions that could improve patient outcomes.

Data Sharing Statement

The data underlying this article will be shared on reasonable request to the corresponding author.

Ethics Approval and Consent to Participate

Participants provided written informed consent for anonymous clinical data using. This study was approved by the GDPH's Ethics Committee (KY2023-514) and met guidelines set by the Declaration of Helsinki.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors report no conflicts of interest in this work.

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