Cardiorespiratory fitness in the population with different glucose metabolic statuses: low cardiorespiratory fitness increases the risk of early abnormal glucose metabolism

Rui Wang
First Hospital of Qinhuangdao
Xiaoli Liu
First Hospital of Qinhuangdao
Lanxiang Liu
First Hospital of Qinhuangdao
Xiaojiao Jia
First Hospital of Qinhuangdao
Qiang Lu (luqiang_tg@163.com)
The First Hospital of Qinhuangdao

Research article

Keywords: new-onset type 2 diabetes mellitus, pre-diabetes, Cardiorespiratory fitness, cardiopulmonary exercise testing

Posted Date: December 16th, 2020

DOI: https://doi.org/10.21203/rs.3.rs-126246/v1

Abstract

Background: Low cardiorespiratory fitness (CRF) is a risk factor for many chronic diseases. This study aims to evaluate CRF in the population with different glucose metabolism and explore its relationship with early abnormal glucose metabolism.

Method: A total of 93 participants were assigned to three groups: normal glucose tolerance (NGT); impaired glucose regulation (IGR); and newly diagnosed type 2 diabetes mellitus (T2DM) through OGTT. CPET was performed to evaluate CRF.

Results and Conclusion: The anaerobic threshold (AT), oxygen uptake (VO_2) and maximum VO_2/kg in male participants, and the AT heart rate (HR), AT systolic blood pressure (Psys) and the maximum VO_2/kg in female participants, were lower in the T2DM and IGR groups than in the NGT group. Regression analysis shows that the maximum VO_2/kg and 1-min HR recovery of female 2-h blood glucose entered into the equation, the maximum VO_2 of male participants was related to pre-diabetes and AT power was related to new-onset diabetes, the AT Psys of female participants was related to pre-diabetes and AT HR was related to new-onset diabetes. CRF was closely associated with 2-h blood glucose after glucose load and was an important risk factor for pre-diabetes and new-onset diabetes.

Introduction

According to the statistics from the International Diabetes Federation, the number of patients with diabetes in the world reached 415 million in 2015 and approximately five million people died of diabetes, while the number of Chinese adults with diabetes accounted for about 26.4% of the total number[1]. The ATP III[2] proposed that the incidence of cardiovascular events in patients with diabetes and coronary heart disease would be equal to that in non-diabetic patients with coronary heart disease within ten years. Diabetes is an important risk factor for cardiovascular disease and can increase the risk of cardiovascular disease by four to seven times.

Low cardiorespiratory fitness (CRF) is a risk factor for many chronic diseases[3]. CRF refers to the ability of the circulatory and respiratory systems to provide oxygen to the body to maintain physical activity. CRF is an objective physiological indicator of the level of physical activity and highly correlates with all-cause mortality and mortality due to cardiovascular disease. The US Aerobics Centre Longitudinal Study found that male and female CRF and all-cause mortality had a negative relationship[4]. Men with the lowest CRF levels were 3.44 times more likely to die compared with other men, and women with the lowest CRF levels were 4.64 times more likely to die compared with other women. If people with poor CRF increased their CRF to a higher level, it could significantly reduce the risk of death from cardiovascular disease. An increase by 1 MET for CRF reduced the risk of cardiovascular death by 15%[5].

Previous studies have suggested that cardiopulmonary reserve function and exercise tolerance were abnormally changed in people with impaired glucose tolerance, diabetes, and other diseases related to abnormal glucose metabolism, such as obesity and metabolic syndrome. Low CRF levels and obesity were high-risk factors for impaired fasting glucose and type 2 diabetes mellitus (T2DM)[6].

Cardiopulmonary exercise testing (CPET) is a non-invasive, quantitative, objective, continuous, and repeatable comprehensive assessment of the overall function of the human body. With CPET as the point, continuous dynamic changes in multiple system functions, such as breathing, circulation, blood, and metabolism, were integrated. Hence, the individual's cardiopulmonary function status could be comprehensively, objectively, and quantitatively evaluated, and individualised intensity exercise programmes could be developed to meet the needs of people with different health conditions. In this study, CPET was used to evaluate the CRF of the population with three different glucose metabolic statuses: NGT, impaired glucose regulation (IGR), and new-onset T2DM. Additionally, the relationship between each indicator of CRF and blood glucose, and that between low CRF and early abnormal glucose metabolism, were explored.

Materials And Methods

Study population

The 93 participants included in this study were screened for diabetes in the department of endocrinology of our hospital. Using the oral glucose tolerance test (OGTT), 30 participants were diagnosed with normal glucose tolerance (NGT), 33 with IGR, also known as pre-diabetes (including IFG and IGT), and 30 with newly diagnosed T2DM. Among the male participants, 14 had NGT, 23 had IGR, and 17 had T2DM; among the female participants, 16 had NGT, 10 had IGR, and 13 had T2DM. The age range of the male participants was 34–69 years, with an average of 51.33 ± 9.37 years. The age range of the female participants was 31–73 years, with an average of 58.10 ± 8.07 years. Given that the men and women had larger differences in the CPET data, this study analysed them separately. The exclusion criteria were as follows: patients with a previous history of diabetes, acute glucose metabolic disorder, acute infection, and liver and renal dysfunction; patients with severe mental disorder and cognitive impairment; patients with cardiovascular and cerebrovascular diseases, pulmonary disease, anaemia, abnormal thyroid function, and neurological, muscular, and joint diseases affecting the patient's exercise before CPET; and those with an inability to insist on exercise training. This study was approved by the ethics committee of the First Hospital of Qinhuangdao, and the informed consent was obtained from all participants.

Physical measurement and laboratory test

The height, weight, SBP, and diastolic blood pressure (DBP) were measured by trained researchers using standard technical methods. Each participant’s blood pressure was measured after sitting for 15 minutes. Only underwear was worn, and shoes were removed when measuring weight, which was accurate to 0.1 g; shoes were also removed when measuring height, and a rangefinder was used with an accuracy of 0.001 m, and body mass index (BMI = kg/m^2) was calculated. The OGTT was performed after fasting for eight hours (75 g of anhydrous glucose was taken orally under fasting, dissolved in 250–300 mL of

water, and consumed within 5–10 minutes), and venous blood was collected on an empty stomach and two hours after taking glucose, respectively. Fasting plasma glucose (FPG) and 2-h blood glucose (2-hPG) were measured.

CEPT

The exercise cardiopulmonary function tester produced by JAEGER (MasterScreen CPX JAEGER, Germany) was used with a built-in computerised synchronous treadmill exercise, and a 12-lead electrocardiogram recorder to monitor heart rate, heart rhythm, and ST-T changes. According to the maximum power estimated by the tester, the corresponding plan was selected. The indicators for gas metabolism, such as ventilation, oxygen uptake, and carbon dioxide emissions during exercise, were continuously observed while monitoring changes in heart rate and blood pressure. The maximum oxygen uptake (VO_2 max) was determined when the oxygen intake plateau appeared with an increase in the incremental exercise load. The exercise continued without increasing the oxygen intake and maintaining it for more than 30 seconds. The anaerobic threshold (AT) was determined by the V-slope method; the carbon dioxide emission curve was used to compare the inflection point of the slope of the oxygen uptake curve, which was the reference point of the position of the anaerobic threshold (AT) value. The blood pressure of participants was controlled at SBP < 150 mm Hg and DBP < 95 mm Hg before the test. The primary endpoint of exercise was that the oxygen uptake plateaued after exercise for more than six minutes and was maintained for more than 30 seconds while meeting other requirements of the test, such as the heart rate reaching 85% of the predicted maximum heart rate (220 minus age), and the respiratory exchange ratio RER > 1.1[7]. Due to physical reasons, participants with muscular and joint pain, an SBP > 220 mm Hg and a DBP > 120 mm Hg, angina symptoms, ST-segment depression or elevation, and drop in blood pressure in keeping with the positive criteria for the diagnosis of coronary heart disease and other conditions that did not meet the test requirements were excluded.

Statistical analysis

Statistical analyses were performed using SPSS 13.0 software. The measurement data were presented as ±s, and the comparison between groups was performed using analysis of variance. The SNK test was used for the comparison between groups. The count data were presented as rate, and the data comparison was conducted using the chi-square test. Pearson correlation was used for correlation analysis, and multiple linear regression (stepwise method) and logistic regression analyses were used to screen risk factors. A *P* value of less than 0.05 was considered statistically significant.

Results

Analysis results of general clinical indicators among the three groups

No significant differences in age, BMI, SBP, and DBP of male and female participants were found between the NGT, IGR, and T2DM ($P > 0.05$) groups. The male FPG level was higher in the T2DM group than in the NGT group ($P < 0.05$), but no significant difference was found between the IGR and NGT groups. The 2-h blood glucose was higher in the T2DM group than in the IGR group, and higher in the IGR group than in the NGT group. The female FPG level was higher in the T2DM group than in the NGT and IGR groups, and the 2-h blood glucose was higher in the T2DM group than in the IGR group, and higher in the IGR group than in the NGT group ($P < 0.05$), as shown in Table 1.

Comparison of CRF-related indicators among different groups

The male exercise load time, AT VO_2, maximum VO_2/kg, and oxygen uptake efficiency slope (OUES) were lower in the T2DM and IGR groups than in the NGT group, and the AT power was lower in the T2DM group than in the IGR and NGT groups ($P < 0.05$). No statistically significant differences were observed in other indicators. The female AT HR, AT systolic blood pressure (Psys), and maximum VO_2/kg were lower in the T2DM and IGR groups than in the NGT group, and the maximum heart rate (HR) and 1-min heart rate recovery (bpm) were lower in the T2DM group than in the NGT group ($P < 0.05$); no significant differences were found in other indicators, as shown in Table 1.

Relationship between blood glucose and main indicators of CRF

No significant correlation was observed between male FPG and each indicator of CRF ($P > 0.05$). The 2-h blood glucose negatively correlated with incremental power, exercise load time, AT power, AT VO_2, AT HR, maximum power, maximum METS, maximum VO_2, maximum VO_2/kg, and OUES ($P < 0.05$). The female FPG negatively correlated with maximum HR and 1-min heart rate recovery. In addition, a negative correlation was observed between 2-h blood glucose and AT METS, AT VO_2/kg, AT HR, AT Psys, maximum METS, maximum VO_2/kg, maximum HR, and 1-min heart rate recovery ($P < 0.05$), as shown in Table 2.

Linear regression analysis of FPG and 2-hPG for male

Male FPG and 2-hPG were used as dependent variables, while age, BMI, incremental power, exercise load time, AT power, AT METS, AT VO_2, AT VO_2/kg, AT HR, AT Psys, maximum power, maximum METS, maximum VO_2, maximum VO_2/kg, maximum SBP, 1-min heart rate recovery, and OUES were used as independent variables. The results of the linear regression analysis showed that no indicator of FPG entered into the equation, and the AT power of 2-h blood glucose did enter into the equation, as shown in Table 3.

Linear regression analysis of FPG and 2-hPG for female

Female FPG and 2-h postprandial blood glucose were used as dependent variables, while age, BMI, AT METS, AT VO_2, AT VO_2/kg, AT HR, AT Psys, maximum METS, maximum VO_2, maximum VO_2/kg, maximum HR, maximum SBP, and 1-min heart rate recovery were used as dependent variables. The regression analysis results showed that the maximum HR of FPG entered into the equation, and the maximum VO_2/kg and the 1-min heart rate recovery of 2-h blood glucose entered into the equation, as shown in Tables 4a and 4b.

The logistic analysis of the presence or absence of pre-diabetes and new-onset diabetes in males

For the male participants, the presence or absence of pre-diabetes and new-onset diabetes was used as the dependent variable, while age, BMI, incremental power, exercise load time, AT power, AT METS, AT VO_2, AT VO_2/kg, AT HR, AT Psys, maximum power, maximum METS, maximum VO_2, maximum VO_2/kg, maximum SBP, 1-min heart rate recovery, and OUES were used as independent variables. The logistic analysis results showed that the maximum VO_2 in men was related to the presence or absence of pre-diabetes, and AT power was related to the presence or absence of new-onset diabetes, as shown in Tables 5a and 5b.

The logistic analysis of the presence or absence of pre-diabetes and new-onset diabetes in females

For the female participants, the presence or absence of pre-diabetes and new-onset diabetes was used as a dependent variable, while age, BMI, AT METS, AT VO_2, AT VO_2/kg, AT HR, AT Psys, maximum METS, maximum VO_2, maximum VO_2/kg, maximum HR, maximum SBP, and 1-min heart rate recovery were used as independent variables. The logistic analysis results showed that female AT Psys was related to the presence or absence of pre-diabetes, and AT HR was related to the presence or absence of new-onset diabetes, as shown in Tables 6a and 6b.

Discussion

As early as 20 years ago, CRF was considered to be an independent predictor of several cardiovascular diseases, diabetes, and all-cause mortality [8]. In recent years, increasing attention has focused on the relationship between CRF and glucose metabolism. Lidegaard et al.[9] discussed the roles and relationships between physical activity energy expenditure (PAEE) and CRF in abnormal glucose metabolism. The results showed that only CRF, instead of PAEE, was independently related to blood glucose levels and β-cell function, suggesting that CRF might determine the relationship between PAEE and glucose metabolism, and might be crucial for glycaemic control. The aforementioned studies pointed out that PAEE was a complex and multidimensional behaviour and thus more difficult to measure, whereas CRF was a more easily measurable variable, which partly represented past physical activity and partly individual predisposition.

Only under a certain exercise load, the body needs to mobilise the organs' potential to ensure a steady state of the internal environment. At this time, the stroke volume, ventilation (VE), VO_2, and so forth can be increased several times or dozens of times, reflecting the reserve function and working ability of the body. CRF represents the maximum capacity of the cardiopulmonary system to absorb and use oxygen during exercise. The American Heart Association recommends directly determined oxygen consumption during exercise as one of the quantitative indicators for an accurate study of motor function[10]. CPET is an assessment method that combines the measurement method for gas metabolism and exchange with the ECG exercise test. It is the currently accepted gold standard for assessing CRF, providing a very useful physiological parameter for understanding the comprehensive CRF in people with different glucose metabolic statuses under exercise load. In this study, CPET was used to evaluate CRF and related risk factors in people with different glucose metabolic statuses.

No statistically significant differences were found in age, BMI, SBP, and DBP of the male and female participants in the NGT, IGR, and newly diagnosed T2DM groups. Therefore, this study explored the relationship between blood glucose and CRF-related indicators, excluding age, weight, and blood pressure. The results showed that the maximum VO_2/kg of men and women with new-onset T2DM and pre-diabetes was lower than that in the NGT group; the OUES in men, AT HR, and AT Psys in women were also lower than those in the NGT group; the AT power of men, the maximum HR, and the 1-min heart rate recovery of women in the newly diagnosed T2DM group were lower than those in other two groups.

The maximum VO_2 (VO_2 max) directly reflects the comprehensive ability of cardiopulmonary exercise function. In the absence of lung disease, when the haemoglobin in the blood is in the normal range, the VO_2 max mainly reflects the volume of cardiac output during exercise and is a better indicator of cardiac reserve function. The VO_2/kg is a more objective evaluation indicator after excluding the weight difference. The OUES is a dynamic oxygen uptake efficiency based on CPET and uses a logarithmic curve-fitting method to analyse the relationship between VO_2 and VE per minute during the incremental load exercise test, thus establishing a regression equation to calculate the OUES value. The OUES value is directly proportional to CRF. Twenty years earlier, studies found that women with T2DM showed decreased maximum VO_2[11]. Gürdal et al.[12] studied the exercise tolerance of patients with diabetes without coronary heart disease. They showed that the VO_2 peak and AT VO_2 of patients with diabetes were significantly lower than those of healthy adults. This might be because patients with diabetes had microangiopathy, autonomic dysfunction, energy metabolism disorders, abnormal calcium transport, and neurohumoral changes. Furthermore, these pathological changes were independent of hypertension and coronary artery disease, leading to ventricular diastolic dysfunction and impaired heart rate recovery. Moreover, the reduction in skeletal muscle content due to age in patients with diabetes and other factors jointly affected exercise tolerance[13,14].

The correlation analysis showed that female maximum HR and 1-min heart rate recovery negatively correlated with FPG, with a *P* value of about 0.03, but no significant correlation was found between the main indicators for CRF and FPG for men and women. This was consistent with the results of a previous study showing that CRF was not associated with FPG concentration in pre-diabetic men and women[15]. However, in a prospective study, CRF was associated with the progression of NGT to IFG, suggesting that CRF might play a role in the process of regulating FPG concentrations[16]. Therefore, the relationship between CRF and FPG needs to be further confirmed through large-sample studies.

The 2-hPG is closely related to multiple indicators of CRF, including the maximum VO_2/kg. Regardless of male and female FPG, no significant difference was found between the pre-diabetic and NGT groups. Furthermore, the 2-h blood glucose in the pre-diabetic group was higher than that of the normal group, suggesting that IGT in pre-diabetic populations was more significant compared with IFG, which was consistent with a foreign epidemiological survey in which

the incidence of IGT was higher than that of IFG. For the association of IGT and IFG with cardiovascular disease (CVD), as early as 20 years ago, a study on the relationship between blood glucose and CVD and the overall fatality rate by the DECODE research group showed that the simple increase in FPG caused by IFG was not an independent risk factor for CVD-related death caused by diabetes; an increase in 2-hPG caused by IGT could significantly increase the CVD-related fatality rate caused by hyperglycaemia[17]. Subsequent studies[18,19] proved that pre-diabetes diagnosed by the OGTT had a better predictive effect on adverse cardiovascular events, and IGT could increase the risk of all-cause death, coronary heart disease, and myocardial infarction. The relationship between CRF and 2-hPG level might explain why IGT instead of IFG was considered a risk factor for cardiovascular disease. It also suggested that in addition to FPG, 2-h blood glucose was also important in diabetes screening. Medical workers should promptly identify patients with pre-diabetes and new-onset diabetes through the OGTT in clinical practice.

Recent studies showed that CRF had a negative correlation with the incidence of diabetes[20]. Someya *et al.* conducted a follow-up study involving 570 male university athletes from Juntendo University in Japan for an average of 26 years (23–29 years) and found that young men with the best and moderate CRF levels had a decreased risk of developing T2DM by 74% and 60%, respectively, compared with those with worst levels[21]. Sieverdes *et al.* tracked 23,444 men aged 20–85 for 18 years and found that the prevalence of diabetes among men with low, moderate, and high CRF levels was 31.9%, 14.5%, and 6.5%, respectively. In other words, the risk of developing diabetes was reduced by 38% and 63%, respectively, for those with moderate and high CRF levels[22]. The results of two recent meta-analyses on CRF and risk of T2DM showed that improving CRF could reduce the risk of T2DM by 8%[23] and 10%[24], respectively. This study showed that the maximum VO_2/kg of men and women negatively correlated with 2-h blood glucose during the OGTT. The regression analysis showed that the maximum VO_2/kg in women was an independent risk factor for 2-h blood glucose, and the maximum VO_2 in men was an independent risk factor for the presence or absence of pre-diabetes. All these findings indicated that low CRF was closely related to elevated blood glucose and risk of diabetes.

The increase in heart rate during exercise and heart rate recovery (HRR) after exercise are considered to be the results of the interaction between the sympathetic and parasympathetic nervous systems. HRR in one minute after peak exercise refers to the decrease in heart rate in one minute after the end of the exercise, and the difference between the maximum exercise heart rate and the heart rate in the subsequent minute is an indicator of the excitability of the parasympathetic nerve in the body. Abnormal HRR is the result of the inhibitory effect on the re-excitability of parasympathetic nerves, which reflects the cardiac autonomic neuropathy. Currently, HRR is used for the prognostic evaluation of diseases, such as coronary heart disease, congestive heart failure, pulmonary hypertension, and chronic obstructive pulmonary disease. Röhling et al.[25] pointed out that important CRF-related parameters correlated with cardiac autonomic nerve function in patients with recently diagnosed type 1 or type 2 diabetes. Previous studies demonstrated that the relationship between slow HRR and risk of diabetes was not consistent. In 2017, a systematic review or meta-analysis[26] showed that the reduction in HRR showed a dose-dependent relationship with the increased risk of diabetes. The measurement of HRR should be recommended as part of the routine clinical risk assessment of diabetes. In this meta-analysis, a total of 9113 participants were involved in four cohort studies, with an average follow-up period of 8.1 years. The results showed that the slowest HRR was associated with a higher risk of diabetes (OR 1.66, 95% CI 1.16–2.38): HRR decreased by ten beats per minute, and OR for diabetes was 1.29 (95% CI 1.13–1.48). The overall study used 1-min HRR as an exposed linear dose-response relationship. In this study, the 1-min HRR of female participants in the T2DM group was lower than that of the normal group. The 1-min HRR was related to FPG and OGTT 2-h blood glucose. The multiple linear regression analysis showed that the 1-min HRR was an independent risk factor for 2-h blood glucose during the OGTT in the female population, suggesting that the 1-min HRR was related to elevated blood glucose.

Researchers explored the mechanisms by which CRF reduced the incidence and risk of death of patients with diabetes from different aspects. Wientzek et al. collected fasting blood and CRF of 100 participants before and after four months, investigated their physical activities, and analysed their FPG levels and metabolites. The results showed a positive correlation between CRF and protective factors for T2DM[27]. Tanisawa et al. conducted a study at the gene level and found that CRF was related to the glycosylated haemoglobin (HbA1c) level, and this correlation was independent of the genetic risk of diabetes derived from 11 single-nucleotide polypeptide sites[28].

Conclusion

This study showed that patients with pre-diabetes and new-onset type 2 diabetes decreased CRF. Furthermore, CRF was closely related to 2-h blood glucose during the OGTT after glucose load and was an important risk factor for pre-diabetes and new-onset diabetes. Therefore, the test and analysis of exercise CRF in people with different glucose metabolic statuses can non-invasively detect impaired cardiopulmonary function early and guide individuals to exercise rationally, thus reducing the occurrence and development of diabetes and cardiovascular and cerebrovascular complications.

Declarations

Ethical approval and consent to participate

This study was approved by the ethics committee of the First Hospital of Qinhuangdao, and the informed consent was obtained from all participants.

Consent for publication

All authors final approval of the version to be published.

Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship and/or publication of this article.

Funding

Qinhuangdao science and technology research and development plan project: 201805A122

Author contributions

RW designed the study, carried out subject recruitment and final approval of the manuscript. QL assisted recruitment, collected the data and wrote the manuscript. LXL and XLL assisted in study design, data interpretation and manuscript revision. XXJ analysed the data and assisted recruitment. All authors read and approved the final manuscript.

Acknowledgements

None.

Availability of data and material

All data generated or analysed during this study are included in this published article.

References

1. NCD Risk Factor Collaboration (NCD-RisC). Worldwide Trends in Diabetes Since 1980: A Pooled Analysis of 751 Population-Based Studies With 4.4 Million Participants. *Lancet* 2016; 387:1513-1530.
2. Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection,Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) finalreport. *Circulatio.* 2002; 106:3143-3421.
3. Holtermann A, Marott JL, Gyntelberg F, et al. Self-reported cardiorespiratory fitness: prediction and classification of risk ofcardiovascular disease mortality and longevity–a prospectiveinvestigationin the CopenhagenCityHeart Study. *J Am Heart Assoc* 2015; 4:e001495.
4. Blair SN, Kohl HW 3rd, Paffenbarger RS Jr, et al. Physical fitness and all-cause mortality. Aprospective study of healthy men and women. *JAMA* 1989; 262: 2395-2401.
5. Blair SN, Kohl HW 3rd, Barlow CE, Paffenbarger RS Jr, Gibbons LW, Macera CA. Changes in physical fitness and all-cause mortality. Aprospective study of healthy and unhealthy men. *JAMA* 1995; 273: 1093-1098.
6. Lee DC, Sui X, Church TS, et al. Associations of cardiorespiratory fitness and obesity with risks of impaired fasting glucose and type 2 diabetes in men. *Diabetes Care* 2009; 32:257-262.
7. Myers J, Coke L, Fletcher GF, et al. Clinician's guide to cardiopulmonary exercise testing in adults: a scientific statement from the American Heart Association. *Circulation* 2010; 122:191-225.
8. Wei M, Gibbons LW, Mitchell TL, et al. Theassosiation between cardiorespiratory fitness and impaired fasting glucose and type 2 Diabetes Mellitus in men. *Ann Intern Me.* 1999;130:89-96.
9. Lidegaard LP, Hansen AL, Johansen NB, et al. Physical activity energy expenditure vs cardiorespiratory fitness level in impaired glucose metabolism. *Diabetologia* 2015; 58:2709-17.
10. Fleg JL, Piña IL, Balady GJ, et al. Assessment of functionalcapacityin clinical and research applications: an advisory from the Committee on Exereise Rehabilitation and Prevention Council on Clinical Cardiology, American Heart Association. *Circulation* 2000; 102:1591-1597.
11. Regensteiner JG, Bauer TA, Reusch JE, et al. Abnormal oxygen uptake kinetic responses in women with type II diabetes mellitus. *J Appl Physiol (1985)* 1998; 85:310-7.
12. Gürdal A, Kasikcioglu E, Yakal S, et al. Impact of diabetes and diastolic dysfunction on exercise capacity in normotensive patients without coronary artery disease. *Diab Vasc Dis Res* 2015; 12:181 188.
13. Leenders M, Verdijk LB, van der Hoeven L, et al. Patients with type 2 diabetes show a greater decline in muscle mass, muscle strength, and functional capacity with aging. *J Am Med Dir Assoc* 2013; 14: 585 592.
14. Carnethon MR, Jacobs DR Jr, Sidney S, et al; CARDIA study. Influence of autonomic nervous system dysfunction on the development of type 2 diabetes: the CARDIA study. *Diabetes Care* 2003; 26 :3035 3041.
15. Gatterer H, Ulmer H, Dzien A, et al. High cardiorespiratory fitness is more beneficial in pre-diabetic men than women. *Clinics* 2011; 66:747–751.
16. Wei M, Gibbons LW, Mitchell TL, et al. The association between cardiorespiratory fitness and impaired fasting glucose and type 2 diabetes mellitus in men. *Ann Intern Med* 1999; 130:89-96.
17. Glucose tolerance and mortality: comparison of WHO and American Diabetes Association diagnostic criteria. The DECODE study group. European Diabetes Epidemiology Group. Diabetes Epidemiology: Collaborative analysis Of Diagnostic criteria in Europe. *Lancet* 1999; 354:617-21.
18. Qing Q, Dekker JM, de Vegt F, et al. Two prospective studies found that elevated 2-hr glucose predicted male mortality independent of fasting glucose and HbAlc. *J Clin Epidemiol* 2004; 57:590-596
19. Barr EL, Zimmet PZ, Welborn TA, et al. Risk of Cardiovascular and all-cause mortality in individuals with diabetes mellitus impaired fasting glucose and impaired glucose tolerance: the australian diabetes, obesity, and lifestyle study(AusDiab). *Circulation* 2007; 116:151-157.
20. Juraschek SP, Blaha MJ, Blumenthal RS, et al. Cardiorespiratory Fitness and Incident Diabetes: The FIT (Henry Ford Exercise Testing) Project. *Diabetes Care* 2015; 38:1075-81.
21. Someya Y, Kawai S, Kohmura Y, et al. Cardiorespiratory fitness and the incidence of type 2diabetes: a cohort study of Japanese male athletes. *BMC Public Health* 2014; 14: 493.

22. Sieverdes JC, Sui X, Lee DC, et al. Physical activity, cardiorespiratory fitness and the incidence of type 2 diabetes in a prospective study of men. *Br J Sports Med.* 2010; 44(4): 238-244.
23. Tarp J, Støle AP, Blond K, et al. Cardiorespiratory fitness, muscular strength and risk of type 2 diabetes: a systematic review and meta-analysis. *Diabetologia* 2019; 62:1129-1142.
24. Qiu S, Cai X, Yang B, et al. Association between cardiorespiratory fitness and risk of type 2 diabetes: a meta-analysis. *Obesity (Silver Spring)* 2019; 27:315-324.
25. Röhling M, Strom A, Bönhof GJ, et al. Cardiorespiratory Fitness and Cardiac Autonomic Function in Diabetes. *Curr Diab Rep* 2017; 17:125.
26. Qiu SH, Xue C, Sun ZL, Steinacker JM, Zügel M, Schumann U. Attenuated heart rate recovery predicts risk of incident diabetes: insights from a meta-analysis. *Diabet Med* 2017; 34:1676-1683.
27. Wientzek A, Floegel A, Knüppel S, et al. Serum metabolites related to cardiorespiratory fitness,physical activity energy expenditure, sedentary time and vigorous activity. *Int J Sport Nutr ExercMetab* 2014; 24: 215-226.
28. Tanisawa K, Ito T, Sun X, et al. High cardiorespiratory fitness can reduce glycated hemoglobinlevels regardless of polygenic risk for Type 2 diabetes mellitus in nondiabetic Japanese men. *Physiol Genomics* 2014; 46: 497-504.

Tables

TABLE 1 Comparison of general data and CPET-related indicators among groups

	Males					Females		
Variables	NGT	IGT	T2DM	F/X^2	*P*	NGT	IGT	T2DM
n	14	23	17	–	–	16	10	13
Age	48.14±8.70	52.70±9.40	52.12±9.79	1.118	0.335	57.88±7.75	57.6±5.74	58.77±10.27#
BMI	26.83±2.20	27.44±4.55	26.86±4.01	0.153	0.890	24.01±2.67	25.00±2.93#	24.78±2.80
SBP	127.79±18.30	127.74±11.72	131.00±16.10	0.271	0.764	120.50±13.98	125.90±24.15	125.93±19.78
DBP	87.29±14.01	81.39±12.04	87.35±11.92	1.478	0.238	77.00±12.97	79.50±11.66	74.92±14.69
FPG	5.15±0.42	5.53±0.76	5.88±0.74#	3.184	0.047	4.85±0.45	5.29±0.58	6.20±1.54#&
2-hour blood glucose	6.28±0.83	9.17±1.15#	13.22±2.48#&	21.258	0.000	6.39±1.05	9.68±0.75#	13.76±3.89#&
Incremental power (W)	23.21±3.17	22.61±3.33	20.88±4.04	1.925	0.158	15.31±1.25	15.00±2. 36	14.23±1.88
Exercise load time (min)	7.78±1.25	7.00±0.70#	7.04±0.98#	3.323	0.044	7.74±2.17	7.23±1.62	6.81±1.31
Anaerobic threshold power (W)	132.14±23.78	118.43±15.33	102.35±26.31#&	7.463	0.001	82.94±20.32	79.30±17.78	73.85±16.04
Anaerobic threshold METS	5.86±1.55	5.10±0.79	5.02±1.11	2.638	0.081	4.91±0.83	4.45±0.85	4.38±0.97
Anaerobic threshold VO_2 (ml/min)	1600.36±310.06	1408.26±213.38#	1316.29±231.71#	5.222	0.009	1090.40±176.25	1063.00±269.75	995.54±230.69
Anaerobic threshold VO_2/kg (ml/min/kg)	19.89±5.86	17.87±2.74	17.46±3.99	1.494	0.234	17.16±2.88	15.57±2.97	15.35±3.42
Anaerobic threshold HR (bpm)	134.36±15.23	126.65±16.14	121.06±12.75#	3.056	0.056	138.88±12.96	127.8±10.12#	121.69±17.78#
Anaerobic threshold O_2/HR (ml/beat)	12.01±2.39	11.26±2.02	10.87±1.59	1.284	0.286	8.55±1.33	8.13±1.48	7.71±2.07
Anaerobic threshold Psys (mmHg)	168.64±17.85	161.96±17.59	161.59±15.74	0.833	0.441	170.40±14.59	161.69±19.78#	145.19±16.66#
Anaerobic threshold Pdia (mmHg)	94.79±15.14	88.09±9.44	86.35±8.51	2.521	0.090	89.40±7.01	80.50±11.70	80.00±9.41
Maximum power (W)	170.71±33.53	152.96±22.82	141.59±32.99#	3.884	0.028	104.60±23.07	101.56±25.64	92.38±19.57
Maximum METS	7.52±1.69	6.55±0.80	6.65±1.40	2.783	0.071	6.02±0.82	5.86±0.90	5.53±0.88
VO_2 (ml/min)	2056.93±332.73	1810.87±226.97#	1756.53±346.86#	4.423	0.017	1441.50±216.88	1312.69±314.57	1262.00±246.92
VO_2 /kg (ml/min /kg)	28.33±5.95	22.97±2.79#	21.29±4.95#	3.222	0.041	25.12±2.85	19.55±3.18#	18.37±3.10#
HR (bpm)	153.93±15.44	143.35±17.76	141.29±16.24	2.507	0.092	152.00±12.40	145.00±6.48	137.62±14.86#
O_2/HR (ml /beat)	13.41±2.17	12.84±2.47	12.48±2.19	0.638	0.533	9.95±1.42	9.15±1.41	8.68±2.22
Maximum Psys (mmHg)	191.21±28.59	187.61±20.21	187.00±16.57	0.168	0.846	192.20±29.94	177.77±23.74	165.06±26.47#
Maximum Pdia (mmHg)	94.57±10.00	90.35±10.22	87.82±10.12	1.720	0.189	90.00±7.57	81.81±12.46	81.23±9.48
VE/VO_2	35.49±5.97	35.67±4.85	35.21±4.97	0.040	0.961	31.81±3.36	34.67±4.76	33.76±4.29
VE/VCO2slope	28.37±3.15	29.75±4.02	28.70±2.47	0.859	0.429	27.56±3.40	30.24±3.65	29.97±3.63
OUES (L/min)	1926.00±288.55	1640.90±316.17#	1541.22±265.28#	6.996	0.002	1369.66±232.63	1280.83±356.26	1187.59±247.67

1-minute heart rate recovery (bpm)	136.57±14.75	126.96±15.55	125.94±15.08	2.287	0.112	135.81±14.34	130.60±9.01	122.46±11.86#

Notes: Comparison between the same gender groups: #, compared with the normal group, p <0.05; &, compared with the pre-diabetes group, p <0.05.

TABLE 2 Correlation between blood glucose and main indicators of cardiopulmonary function

	Males				Females			
	FPG		2-h blood glucose		FPG		2-h blood glucose	
Variables	r	p	r	p	r	p	r	p
Incremental power (W)	-0.081	0.562	-0.312	0.021	-0.056	0.736	-0.243	0.136
Exercise load time (min)	-0.117	0.398	-0.308	0.024	-0.276	0.088	-0.201	0.221
Anaerobic threshold power (W)	-0.216	0.117	-0.585	0.000	-0.156	0.344	-0.288	0.075
Anaerobic threshold METS	-0.176	0.203	-0.268	0.050	-0.179	0.275	-0.380	0.017
Anaerobic threshold VO_2 (ml/min)	-0.249	0.069	-0.398	0.003	-0.049	0.769	-0.221	0.176
Anaerobic threshold VO_2/kg (ml/min/kg)	-0.164	0.240	-0.237	0.088	-0.177	0.282	-0.383	0.016
Anaerobic threshold HR (bpm)	-0.233	0.090	-0.292	0.032	-0.288	0.076	-0.417	0.008
Anaerobic threshold Psys (mmHg)	-0.256	0.062	-0.135	0.330	0.221	0.176	0.348	0.030
Anaerobic threshold Pdia (mmHg)	-0.115	0.409	-0.228	0.097	-0.025	0.878	-0.039	0.813
Maximum power (W)	-0.123	0.375	-0.453	0.001	-0.172	0.294	-0.277	0.087
Maximum METS	-0.174	0.209	-0.296	0.030	-0.263	0.105	-0.417	0.008
VO_2 (ml/min)	-0.233	0.091	-0.402	0.003	-0.074	0.653	-0.185	0.259
VO_2 /kg (ml/min/kg)	-0.171	0.217	-0.292	0.032	-0.260	0.110	-0.422	0.007
HR (bpm)	-0.209	0.129	-0.227	0.099	-0.348	0.030	-0.413	0.009
Maximum Psys (mmHg)	-0.142	0.306	-0.064	0.645	0.163	0.321	0.213	0.192
Maximum Pdia (mmHg)	-0.127	0.361	-0.191	0.166	-0.005	0.976	0.026	0.873
VE /VCO_2slope	0.186	0.178	0.044	0.750	0.270	0.096	0.258	0.112
OUES (/min)	-0.216	0.117	-0.454	0.001	-0.127	0.440	-0.165	0.314
1-minute heart rate recovery (bpm)	-0.249	0.070	-0.213	0.122	-0.334	0.037	-0.407	0.010

TABLE 3 Linear regression analysis of 2-hour postprandial blood glucose in men

Variables	B	Std.Error	Beta	t	p	95% *CI*
Constant	18.838	1.720	–	10.952	0.000	15.385~22.291
Anaerobic threshold power	-0.079	0.014	-0.607	-5.458	0.000	-0.108~-0.050

In theequation, R Square = 0.369, F = 29.793, and p = 0.000.

TABLE 4a Linear regression analysis of female FPG

Variables	B	Std.Error	Beta	t	p	95% *CI*
Constant	9.649	1.881	–	5.130	0.000	5.837~13.460
Maximum HR	-0.029	0.013	-0.348	-2.261	0.030	-0.055~-0.003

In theequation, R Square = 0.121, F = 5.113, p = 0.030

TABLE 4b Linear regression analysis of 2-hour postprandial blood glucose in women

Variables	B	Std.Error	Beta	t	p	95% *CI*
Constant	30.141	5.950	–	5.065	0.000	18.073~42.209
MaximumVO_2/kg	-0.426	0.196	-0.328	-2.179	0.036	-0.823~-0.029
1-minute heart rate recovery	-0.090	0.44	-0.306	-2.036	0.049	-0.181~0.000

In theequation, R Square = 0.263, F = 6.422, p = 0.004

TABLE 5a Logistic analysis of the presence or absence of pre-diabetes in men

Variables	B	S.E	Wald	p	EXP(B)	95% *CI*forEXP(B)
MaximumVO_2	-0.003	0.002	5.094	0.024	0.997	0.997~1.000
Constant	7.209	3.007	5.747	0.017	1351.848	–

TABLE 5b Logistic analysis of the presence or absence ofnew-onset diabetes in men

Variables	B	S.E	Wald	p	EXP(B)	95% *CI*forEXP(B)
Anaerobic threshold power	-0.053	0.021	6.683	0.010	0.948	0.911~0.987
Constant	6.348	2.465	6.633	0.010	571.410	—

TABLE 6a Logistic analysis of the presence or absence of pre-diabetes in women

Variables	B	S.E	Wald	p	EXP(B)	95% *CI*forEXP(B)
Anaerobic thresholdpsys	0.120	0.051	5.497	0.019	1.127	1.020~1.245
Constant	-19.395	8.170	5.636	0.018	0.000	–

TABLE 6b Logistic analysis of the presence or absence of new-onset diabetes in women

Variables	B	S.E	Wald	p	EXP(B)	95% *CI*forEXP(B)
Anaerobic thresholdHR	-0.102	0.042	6.084	0.014	0.903	0.832~0.979
Constant	13.193	5.456	5.484	0.016	536862.1	–