Effects of fitness and fatness on age-related arterial stiffening in people with type 2 diabetes

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Summary
People with type 2 diabetes (T2D) are at a greater risk of cardiovascular disease than the general population. Both non-modifiable (age) and modifiable (low aerobic fitness, high body fatness) factors are separately predictive of cardiovascular risk, although they often occur concomitantly. This study aimed to examine the (1) association between age and arterial stiffness, a subclinical marker of cardiovascular risk; and (2) effects of body fatness and aerobic fitness on age-related increases in arterial stiffness in people with T2D. Data from 64 individuals with T2D (age 59.8 ± 8.7 years, 40% female, HbA1c 8.4 ± 1.6%) were included in this cross-sectional analysis. Carotid-femoral pulse wave velocity (cfPWV) was used to quantify arterial stiffness. Aerobic fitness (relative VO2peak) was determined via indirect calorimetry during maximal exercise testing. Central body fatness was determined using waist circumference. Data were analysed using hierarchical multiple regressions. After adjustment for sex and duration of T2D, each one standard deviation (SD) increase in age (8.68 years) was associated with a 0.63 m/s increase in cfPWV (β = 0.416, p = 0.001). Following adjustment for aerobic fitness and body fatness, the standardized β was unchanged (0.417). A one SD increase in waist circumference (13.9 cm) and relative VO2peak (5.3 ml.kg⁻¹.min⁻¹) we r e a s s o c i a t e d with a similar magnitude of difference in cfPWV (0.47 m.s⁻¹ and 0.44 m.s⁻¹, respectively). Therefore, age is a significant correlate of increased arterial stiffness in T2D, with higher aerobic fitness attenuating, and higher body fatness exacerbating, this increase. Interventions aimed at improving cardiovascular outcomes in people with T2D should target both increased aerobic fitness and reduced body fatness.

KEYWORDS
age, diabetes mellitus, type 2, obesity, pulse wave velocity, VO2peak, waist circumference

What is already known about this subject?
- People with type 2 diabetes are at a greater risk of cardiovascular disease than the general population
Both non-modifiable (age) and modifiable (low aerobic fitness, high body fatness) factors are separately predictive of cardiovascular risk, although they often occur concomitantly.

Arterial stiffness is a subclinical marker of cardiovascular health and may be an important addition to inform risk beyond traditional risk factors such as blood pressure and cholesterol profile.

What does this study add?

- Age is a significant correlate of increased arterial stiffness in people with type 2 diabetes.
- Higher aerobic fitness attenuates, and higher body fatness exacerbates, this age-related increase in arterial stiffness.
- Interventions which aim to improve cardiovascular health outcomes via reductions in arterial stiffness in people with T2D should target both increased aerobic fitness and reduced body fatness.

1 | INTRODUCTION

Cardiovascular disease is the leading cause of death in people with type 2 diabetes (T2D). Arterial stiffness is a subclinical marker of cardiovascular health and may be an important indicator of cardiovascular risk beyond traditional risk factors such as blood pressure and cholesterol profile. Pulse wave velocity (PWV), which provides structural and functional information about arterial health, is the gold standard assessment of arterial stiffness, and one of the earliest clinical signs of adverse changes to the vasculature. PWV is a strong, independent predictor of mortality in people with T2D and is higher in people with T2D than in age-, sex-, and body mass index (BMI)-matched healthy controls.

Age is a significant determinant of arterial stiffness, with a 2.5-fold increase in PWV from age 20 to 91 years. Previous researchers have suggested that both aerobic fitness and body adiposity (i.e., fatness) are determinants of cardiovascular disease risk and mortality, as reduced aerobic fitness and increased body fatness are associated with higher (worse) PWV. These variables may, therefore, represent useful therapeutic targets for the prevention of age-related increases in arterial stiffness. However, as low fitness and high fatness often occur concomitantly, it is unclear whether one of these exerts a stronger influence on arterial stiffness than the other.

Reported associations between fitness, fatness and PWV are equivocal. Christou et al. have demonstrated strong associations between body fatness variables, but not aerobic fitness, with aortic PWV in 135 healthy men. An earlier study also reported a strong association between body fatness and PWV in 52 adults with overweight/obesity and T2D, but aerobic fitness was not measured in that study. In contrast, others have shown that aerobic fitness is inversely and moderately associated with aortic PWV in apparently healthy young people and in sedentary adults.

Although the association between age and PWV is clear in healthy adults, this has not been confirmed in people with T2D, who have a two-to-five-fold greater risk of cardiovascular disease than the general population. Understanding the associations of fitness and fatness with arterial stiffness in this population is important and may inform the development of interventions for the prevention of cardiovascular disease in this target group. In light of the contrasting evidence on the associations between age, fitness and fatness with PWV in healthy adults, and the paucity of research on these associations in people with T2D, the aims of this study were to examine the (1) association between age and PWV; and (2) effects of body fatness and aerobic fitness on age-related increases in PWV in men and women with T2D. Based on previous research, we hypothesised that there would be a positive association between age and arterial stiffness, and that higher aerobic fitness would attenuate and higher body fatness would exacerbate the age-related increase in arterial stiffness.

2 | MATERIALS AND METHODS

2.1 | Design

In this paper, we report on secondary analyses of baseline data from the ‘Exercise for Type 2 Diabetes (E4D)’ Trial (registration number ACTRN12615000475549), which was a randomized controlled trial investigating the short- and long-term efficacy, safety and feasibility of low-volume combined aerobic and resistance high-intensity interval training in people with T2D. The E4D Trial was approved by The University of Queensland Human Research Ethics Committee (ethics approval number 2015000164). Prior to enrolment, potential participants were asked to read the information sheet and had the opportunity to ask questions and have them answered, before signing an informed consent form.

2.2 | Participants

Participants were eligible for the trial if they were aged 18–80 years with a diagnosis of T2D, including a glycated haemoglobin (HbA1c) of ≥6.0%. Exclusion criteria were as per the American College of Sports
Medicine’s absolute contraindications to exercise including unstable angina, recent myocardial infarction, coronary artery disease, and uncontrolled, symptomatic heart failure. People were also ineligible if they self-reported more than 150 min of moderate physical activity or 75 min of vigorous physical activity per week.

2.3 Measures

For these analyses, we used measures of (1) arterial stiffness, (2) aerobic fitness and (3) body fatness. Individual assessments were conducted at The University of Queensland. Participants were asked to avoid strenuous exercise, caffeine, alcohol, tobacco, and maintain their normal medication regimen in the 24 h prior to testing.

2.3.1 Arterial stiffness

Assessment of arterial stiffness was completed after an overnight fast (≥12 h). Participants rested quietly, supine, in a dimly lit, temperature-controlled room (24°C) for 15 min. Measurement of arterial stiffness was completed using a Sphygmocor® XCEL (AtCor Medical Pty Ltd.). Carotid-femoral PWV (cfPWV) was used as it is the gold standard assessment of aortic arterial stiffness. For cfPWV, a cuff was placed around the mid-thigh, and a tonometer pressure sensor on the carotid artery, to simultaneously capture the pulse waveforms at femoral and carotid sites. The velocity of pulse wave from the carotid artery to the femoral artery was measured and calculated using the subtraction method, according to standardized guidelines.

2.3.2 Aerobic fitness

Participants completed a graded cardiopulmonary exercise test to determine \( \dot{V}O_2 \text{peak} \) and exercise capacity (time on test) in a temperature-controlled environment. Participants were asked to avoid food in the 2 h prior to the test and take their usual medication. For those able to walk/run, the test was completed on a treadmill. An upright or recumbent cycle ergometer test was used for those unable to use the treadmill (e.g., due to orthopaedic limitations; \( n = 9 \)). The first stage of the warm-up was completed at 4 km h\(^{-1} \) and 0% incline, or 0 W at 50–60 RPM, for 4 min. The second stage of the warm-up was completed at the same speed or revolutions per minute, but at a 4% incline or 25 W. Following the warm-up, participants exercised in continuous 1-min stages at an individualized speed and load, until voluntary exhaustion.

Pulmonary gas exchange was measured using either the Parvo (\( n = 62 \); Parvo Medics TrueOne) or Metamax (\( n = 2 \); Metamax II system, Cortex) metabolic systems. \( \dot{V}O_2 \text{peak} \) was assessed as the mean of the two highest 10-s values (where the difference in absolute \( \dot{V}O_2 \) between values was no greater than 150 ml·min\(^{-1} \)) attained during the test, and is reported relative to body weight.

2.3.3 Body fatness

A tape measure was used to assess waist circumference according to the International Society for the Advancement of Kinanthropometry Standards. Dual-energy x-ray absorptiometry (Discovery or Horizon, Hologic Inc.) was used to determine total body fat mass. To calculate BMI, bodyweight was measured using floor scales (AWB120, Avery Weigh-Tronix Bench) and height was assessed using a wall-mounted stadiometer (Seca).

2.3.4 Physical activity and energy intake

Accelerometry (Actigraph GT3X+) was used to assess physical activity levels. The Actigraph is a reliable and valid measure of physical activity in adults. Participants were asked to wear the device, on a waist belt, during waking hours, for seven consecutive days. For data to be included in analyses, participants must have had a minimum wear time of 600 min-day\(^{-1} \) on 4 days, with at least one of those a weekend day. Daily estimates of time spent in moderate to vigorous physical activity (MVPA; min-week\(^{-1} \)), and sedentary time (h-day\(^{-1} \)) were derived from the vertical axis data using ActiLife software version 6 (ActiGraph) and previously established cut-points.

Participants’ daily energy intake (kJoules) was estimated by a single investigator-administered 24 h recall, and analysed using FoodWorks (Xyris, Version 9).

2.4 Statistical analyses

Statistical analyses were conducted using SPSS version 25 for Windows (IBM). The Shapiro-Wilk test, along with visual inspection of the distribution of models’ residuals, were used to assess normality. Non-normally distributed variables (exercise capacity and energy intake) were log transformed prior to analysis. Data are presented as mean ± standard deviation for normally distributed variables, median [inter-quartile range] for non-normally distributed variables, and n (%) for categorical variables. Statistical significance was set at \( p < 0.05 \).

Pearson’s correlation coefficients were used to describe associations between baseline characteristics (age, sex, HbA\(_{1c} \), MVPA, duration of diabetes, energy intake, and anti-hypertensive use), body fatness variables, and aerobic fitness measures, with cfPWV. The strength of the correlation coefficients was interpreted as: <0.1, weak or small association; 0.1–0.5, moderate association; and >0.50, strong or large association. Sex was coded as 0, females and 1, males.

As waist circumference and relative \( \dot{V}O_2 \text{peak} \) were the indicators of fatness and fitness with the strongest correlations with cfPWV, these variables were selected for inclusion in a series of multiple regression models to investigate the associations between (a) age, (b) fatness and (c) fitness with arterial stiffness (cfPWV). Absence of collinearity between the independent variables was confirmed via inspection of the correlation coefficients (<0.7) and tolerance values (<0.1). The model for age and cfPWV was initially adjusted for sex.
TABLE 1  Participant characteristics

|                         | All (N = 64) | Range |
|-------------------------|-------------|-------|
| Demographics            |             |       |
| Female, n (%)           | 24 (40)     |       |
| Age (years)             | 59.8 ± 8.7  | 34–78 |
| Type 2 diabetes severity|             |       |
| Duration of diabetes (years) | 10.7 ± 7.9 | 0.25–31.0 |
| HbA1c (%)               | 8.4 ± 1.6   | 6.0–12.5 |
| HbA1c (mmol mol)        | 68.6 ± 17.0 | 42.0–112.0 |
| FBG (mmol L)            | 8.3 [7.1–9.8] | 4.6–16.5 |
| Lifestyle               |             |       |
| Past smoker, n (%)      | 14 (21.9)   |       |
| Energy intake (kJ day⁻¹) | 8602 [6577–9937] | 3813–20 066 |
| MVPA (min week⁻¹)       | 135 ± 108   | 6–594 |
| Sedentary time (h day⁻¹) | 10.4 ± 1.4  | 6.9–15.4 |
| Medications             |             |       |
| Oral anti-hyperglycaemic, n (%) | 54 (84.4) |       |
| Insulin, n (%)          | 15 (23.4)   |       |
| Anti-hypertensive, n (%) | 46 (71.9)   |       |
| Statin, n (%)           | 45 (70.3)   |       |

Note: Data are presented as mean ± standard deviation for normally distributed variables, median [interquartile range] for non-normally distributed variables, and n (%) for categorical variables. Range is presented as minimum, maximum. Abbreviations: FBG, fasting blood glucose; HbA1c, glycated haemoglobin; MVPA, moderate to vigorous physical activity, assessed by accelerometry.

and duration of diabetes, before examining the changes in the standardized regression coefficients resulting from introduction of both waist circumference and relative VO₂peak. The models for waist circumference and cfPWV, and for relative VO₂peak and cfPWV, were adjusted for age, sex, and duration of diabetes, before adjustment for the fitness and fatness variables respectively. The covariates were selected on the basis of the correlation coefficients in this study (Table S1) and on previously reported associations. Estimates of cfPWV in 10-year age categories were derived from the regression models to illustrate the joint associations between waist circumference and relative VO₂peak with cfPWV.

3 | RESULTS

Data from 64 individuals with T2D (mean age 59.8 ± 8.7 years, 40% female, HbA1c 8.4 ± 1.6%, duration of T2D 10.7 ± 7.9 years) were included in the analyses. There were no missing data on any variable. Summaries of participant characteristics and outcome variables are presented in Tables 1 and 2, respectively. Based on published reference values, compared with a population of the same age with no cardiovascular risk factors, our sample had elevated cfPWV (9.2 m s⁻¹ vs. 8.3 m s⁻¹). The mean waist circumference of our sample (109 cm) was above the upper threshold for cardiovascular disease risk (i.e., greater than 102 and 88 cm for males and females, respectively). Our sample also had lower than average relative VO₂peak (24.4 ml kg⁻¹ min⁻¹; 25th percentile for age and sex on average [range 5th to 95th percentile]).

Pearson’s correlations between arterial stiffness, demographics, T2D severity, lifestyle, medications, body fatness, and aerobic fitness variables are summarized in Table S1. Scatterplots with regression equations are shown in Figure 1A-C. Age (r = 0.467, p ≤ 0.001), duration of diabetes (r = 0.245, p ≤ 0.05) and waist circumference (r = 0.304, p ≤ 0.05) were positively and moderately associated with cfPWV. Relative VO₂peak (r = −0.281, p ≤ 0.05) was negatively and moderately associated with cfPWV.

3.1 | Arterial stiffness and age

The results of the hierarchical multiple regression analyses to investigate associations between age, body fatness, and aerobic fitness with cfPWV are shown in Table 3. After adjustment for sex and duration of diabetes, the standardized beta for the relationship between age and cfPWV was 0.416. This indicates that each one standard deviation increase in age (8.68 years) was associated with a 0.63 m s⁻¹ increase in cfPWV. Following adjustment for both aerobic fitness and body fatness, the standardized beta was largely unchanged (0.417).

3.2 | Arterial stiffness and waist circumference

The regression models for the relationship between waist circumference and cfPWV show that, after adjustment for age, sex, and
duration of diabetes, the standardized beta for waist circumference was 0.315 (Table 3). This indicates that each one standard deviation increase in waist circumference (13.9 cm) was associated with a 0.47 m·s⁻¹ increase in cPWV. When relative VO₂Peak was added to the model, this estimate was attenuated to 0.35 m·s⁻¹.
3.3 Arterial stiffness and relative VO$_{2\text{Peak}}$

In the regression models for the relationship between relative VO$_{2\text{Peak}}$ and cfPWV, after adjustment for age, sex and duration of diabetes, the standardized beta for relative VO$_{2\text{Peak}}$ was $-0.296$ (Table 3). This indicates that for each one standard deviation increase in relative VO$_{2\text{Peak}}$ (5.3 ml·kg$^{-1}$·min$^{-1}$), there was a 0.44 m·s$^{-1}$ decrease in cfPWV. When waist circumference was added to the model, this estimate was attenuated to 0.22 m·s$^{-1}$.

The multivariable regression equations were used to derive estimates of cfPWV in 10-year age groups for different values of waist circumference and relative VO$_{2\text{Peak}}$ (see Figure 2A,B, respectively). Estimates of cfPWV for different combinations of waist circumference and relative VO$_{2\text{Peak}}$ are shown in Figure 2C.

4 DISCUSSION

The first aim of this study was to examine the association between age and arterial stiffness (cfPWV) in men and women with T2D. Our findings indicate that age is a significant determinant of increased arterial stiffness in this study sample, irrespective of sex and duration of diabetes. As hypothesised, higher aerobic fitness attenuated, and higher body fatness exacerbated, the age-related increase in arterial stiffness. The effects of aerobic fitness and body fatness were similar in magnitude, although in opposite directions, providing early indications that both are important determinants of age-related arterial stiffening in people with T2D.

To our knowledge, this is the first study to investigate the individual and combined effects of aerobic fitness and body fatness...
on arterial stiffness in people with T2D. Other researchers have reported positive associations between fatness\textsuperscript{13,14} and inverse associations between fitness\textsuperscript{15,16} with arterial stiffness in various populations, including healthy men, adults with overweight and obesity, healthy young people and sedentary adults. However, most of these studies estimated aerobic fitness using submaximal exercise tests\textsuperscript{15,16}; our findings confirm these associations using a gold standard, objective measure of aerobic fitness. A previous study of people

**FIGURE 2** Estimates of carotid-femoral pulse wave velocity by (A) age and waist circumference, (B) age and relative VO$_2$Peak and (C) waist circumference and relative VO$_2$Peak (for mean age of sample of 59.8 years). All estimates are adjusted for sex and duration of diabetes.
with metabolic syndrome examined the relationship between aerobic fitness and arterial stiffness but did not account for body fatness.11

Our findings show that, while age is the strongest determinant of arterial stiffness, both body fatness and aerobic fitness moderate the relationship between age and arterial stiffness, with effects in opposite directions. By carefully assessing the separate relationships between body fatness and aerobic fitness, we show that a 13.9 cm increase in waist circumference and a 5.3 ml·kg⁻¹·min⁻¹ increase in relative VO₂peak are associated with about the same magnitude of difference in arterial stiffness (0.47 and −0.44 m·s⁻¹, respectively). In joint analyses, these effects are modified: higher fitness attenuates the positive association between waist circumference and arterial stiffness, and vice versa.

The mechanisms underlying the association between aerobic fitness and arterial stiffness are not fully understood, although it has been suggested that high aerobic exercise, resulting from high levels of aerobic exercise, prevents unhealthy arterial remodelling and dysfunction. That is, physical exercise from an early age decreases calcium deposits in aortic the wall,30 which reduces arterial stiffness. High aerobic fitness is also associated with improved metabolic risk factors for T2D, including glucose metabolism and inflammation31; the presence of these risk factors has been implicated in the pathogenesis of increased arterial stiffness.32,33

There are several mechanisms by which high body fatness potentially exerts a detrimental effect on arterial stiffness. Excess adipose tissue, leading to adipose tissue dysfunction and insulin resistance,34 can result in the activation of the renin-angiotensin system,35 low-level chronic inflammation,36 and systemic oxidative stress.37 This lipotoxic state reduces nitric oxide bioavailability and increases vascular tone, which results in arterial stiffening.38 This state may be amplified in T2D.39 Another mechanism may be the elevated circulating levels of leptin that are seen in both obesity and increased arterial stiffness40: leptin exerts a receptor-mediated influence on vascular tone, stimulates vascular smooth muscle proliferation and migration, and induces oxidative stress in endothelial cells.41 Leptin also increases sympathetic nervous system activation which elevates blood pressure, resulting in increased distension pressure and matrix synthesis, ultimately causing increases in vascular thickness and arterial stiffness.42 Another link between arterial stiffness, body fatness and T2D is osteocalcin. Osteocalcin is a bone-derived hormone that modulates glucose metabolism and fat distribution,43 with low circulating levels implicated in obesity44 and associated adverse metabolic outcomes such as T2D.45 Animal studies have shown that undercarboxylated osteocalcin (ucOC) stimulates the phosphoinositide 3-kinase/protein kinase B (PI3K/Akt) signalling pathway to upregulate nitric oxide in vascular cells, protecting endothelial function and preventing atherogenesis46; consequently, low serum ucOC is also associated with high arterial stiffness.47 We did not measure bio-markers which may have elucidated the mechanisms underlying these relationships, and future research could address this.

Given our findings, lifestyle interventions (e.g., regular exercise and dietary changes) that increase aerobic fitness and reduce body fatness are required to reduce arterial stiffness and consequently improve cardiovascular health outcomes in people with T2D. While any modality of regular aerobic exercise should be encouraged, some modalities such as high-intensity interval training may be particularly beneficial for improvements in aerobic fitness in people with lifestyle-induced cardiometabolic disease.38 Where changes in body fatness are the target, current guidelines promote high volumes of aerobic exercise for weight loss and weight loss maintenance (300–420 min·week⁻¹ of at least moderate intensity).49 Of note, a reduction in central adiposity may be achieved with a lower volume of aerobic exercise (100–150 min·week⁻¹ of at least moderate intensity).49 and in the absence of clinically meaningful weight loss.50 Moreover, given the combination of diet and exercise has a greater impact on body composition than exercise alone,51 inclusion of a parallel diet intervention is also recommended to elicit reductions in body fatness. As clinically meaningful increases in aerobic fitness are likely to occur more quickly than reductions in body fatness, increasing fitness may represent a more useful early therapeutic focus for reducing arterial stiffness in people with T2D before reductions in fatness can be achieved. Specifically, in the present study, we show a 5.3 ml·kg⁻¹·min⁻¹ increase in relative VO₂peak is required to reduce cfPWV. This is likely to be achieved in a shorter period than the 13.1 cm reduction in waist circumference that is required to achieve the same reduction cfPWV. Notably, a recent meta-analysis by Liu et al.52 demonstrated an increase in relative VO₂peak of 4.8 ml·kg⁻¹·min⁻¹, but a reduction in waist circumference of only 2.2 cm, following up to 16 weeks of exercise training in people with T2D.

Limitations of the current study are worth noting. As the cross-sectional nature of this study restricts the ability to determine causation, future studies should prospectively evaluate the association between aerobic fitness, body fatness and arterial stiffness in people with T2D. Another limitation is the relatively small sample size. While the study indicates an influence of fitness and fatness on age-related arterial stiffness in people with T2D, the results should be interpreted with caution until they can be replicated in a larger sample. Finally, although the measurement of waist circumference in clinical settings is feasible and provides meaningful risk prediction beyond traditional body composition markers (e.g., BMI), it relies on the accurate application of methods and does not differentiate between subcutaneous adipose tissue and visceral adipose tissue.53

5 CONCLUSION

Our results provide preliminary evidence that age is a significant correlate of increased arterial stiffness in people with T2D, with higher aerobic fitness attenuating, and higher body fatness exacerbating, this increase. The moderating effects were similar in magnitude, although in opposite directions, indicating that both are important for reducing arterial stiffness in people with T2D. Therefore, interventions which aim to improve cardiovascular health outcomes via reductions in arterial stiffness in people with T2D should target both increased aerobic fitness and reduced body fatness. Larger studies are needed to confirm these findings.
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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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Additional supporting information may be found in the online version of the article at the publisher’s website.

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