Similar level of impairment in exercise performance and oxygen uptake kinetics in middle-aged men and women with type 2 diabetes

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O’Connor E, Kiely C, O’Shea D, Green S, Egaña M. Similar level of impairment in exercise performance and oxygen uptake kinetics in middle-aged men and women with type 2 diabetes. Am J Physiol Regul Integr Comp Physiol 303: R70 –R76, 2012. First published April 25, 2012; doi:10.1152/ajpregu.00012.2012.—The present study tested the hypothesis that the magnitude of the type 2 diabetes-induced impairments in peak oxygen uptake (VO2peak) and VO2 kinetics would be greater in females than males in middle-aged participants. Thirty-two individuals with type 2 diabetes (16 male, 16 female), and 32 age- and body mass index (BMI)-matched healthy individuals (16 male, 16 female) were recruited. Initially, the ventilatory threshold (VT) and peak VO2 were determined. On a separate day, subjects completed four 6-min bouts of constant-load cycling at 80% VT for the determination of VO2 kinetics using standard procedures. Cardiac output (CO) (inert gas rebreathing) was recorded at rest, 30, and 240 s during two additional bouts. Peak VO2 (ml·kg–1·min–1) was significantly reduced in men and women with type 2 diabetes compared with their respective nondiabetic counterparts (men, 27.8 ± 4.4 vs. 31.1 ± 6.2 ml·kg–1·min–1; women, 19.4 ± 4.1 vs. 21.4 ± 2.9 ml·kg–1·min–1). The time constant (τ) of phase 2 (τ2) and mean response time (s) of the VO2 response (MRT) were slowed in women with type 2 diabetes compared with healthy women (τ2, 43.3 ± 9.8 vs. 33.6 ± 10.0 s; MRT, 51.7 ± 9.4 vs. 43.5 ± 11.4 s) and in men with type 2 diabetes compared with nondiabetic men (τ2, 43.8 ± 12.0 vs. 35.3 ± 9.5 s; MRT, 57.6 ± 8.3 vs. 47.3 ± 9.3 s). The magnitude of these impairments was not different between males and females. The steady-state CO responses or the dynamic responses of CO were not affected by type 2 diabetes among men or women. The results suggest that the type 2 diabetes-induced impairments in peak VO2 and VO2 kinetics are not affected by sex in middle-aged participants.

MAXIMAL AEROBIC CAPACITY, expressed as maximum oxygen uptake (VO2peak), which is an independent risk factor for all-cause and cardiovascular disease mortality (27) has been consistently reported to be reduced in individuals with type 2 diabetes compared with nondiabetic counterparts of similar age, weight, and activity levels (8, 17, 32). Additionally, the rate of adjustment of oxygen uptake (VO2 kinetics) to steady-state exercise is slower in young and middle-aged women (8, 21, 32) and in a combined group of middle-aged men and women (4), although recent data suggests that VO2 kinetics are not impaired in older men with type 2 diabetes compared with age-matched healthy controls (42). The slowing of the VO2 kinetics response is associated with a faster onset of fatigue and lower exercise tolerance (28) and might help explain why individuals with type 2 diabetes perceive light/moderate exercise as more difficult than healthy controls (12). Ultimately this often leads to a sedentary behavior or physical inactivity, which is associated with worsening of cardiovascular outcomes and predicts mortality in people with type 2 diabetes (6, 39). The mechanisms underpinning these exercise impairments in younger and middle-aged individuals with type 2 diabetes have not been established, with some debate over whether they are due to a reduced ability to deliver O2 to (19–21) and/or reduced capacity of O2 utilization by contracting muscles (3, 15).

To our knowledge none of the previous studies explored whether the type 2 diabetes-related exercise impairments are present in younger or middle-aged men, or moreover, if these impairments are affected by sex. Preliminary observations based on a small number of subjects (n = 4 or 6 in each group) suggested that the level of impairment in exercise tolerance and peak VO2 in type 2 diabetes is larger in middle-aged women than men (34). The reason as to why middle-aged females might display a greater impairment is still unclear, and to our knowledge there is no a priori reason to support the concept that oxygen transport and utilization are affected differently by type 2 diabetes in middle-aged females and males.

Accordingly, the aim of the present study was to assess whether the effect of type 2 diabetes on peak VO2 and VO2 kinetics during moderate exercise differ between middle-aged middle-aged males and females in a much larger number of participants. Based on the preliminary observations by Regensteiner et al. (34), we tested the hypothesis that the magnitude of the impairment of peak VO2 and VO2 kinetics associated with type 2 diabetes would be greater in females than males. To begin to explore the mechanistic basis of any sex-specific impairment in VO2 kinetics, the rates of adjustment of cardiac output (CO) and heart rate (HR) during exercise were also measured.

METHODS

Subjects. Sixty-four volunteers, 32 being treated for type 2 diabetes (16 males, 16 females) and 32 age- and BMI-matched healthy controls (16 males, 16 females), took part in this study (Table 1). For diabetic subjects, the time since diagnosis of diabetes was 1–11 yr (Table 1); they were treated by diet (n = 8) or oral hypoglycaemic agents (metformin monotherapy, n = 18; metformin and sulfonylurea, n = 5; sulfonylurea monotherapy, n = 1), and at the start of this study displayed no clinical evidence of ischemic heart disease (normal ECG during treadmill stress test), peripheral arterial disease (0.9 < ABI < 1.3), kidney dysfunction (consistent urinary protein < 200 mg/dl), or liver dysfunction (urinary creatinine levels < 2.2 mg/dl). Controlled hypertensives were admitted to the study but participants taking beta blockers were excluded (10). All subjects were sedentary (<1 h/wk of moderate intensity exercise per week) for the previous 6 mo, as confirmed by the use of 5-day RT3 triaxial accelerometers (Stay-Healthy, Monrovia, CA) (36), although diabetic subjects were more inactive than control subjects (Table 1). All subjects provided written consent by signing an informed consent statement, and the study protocol was approved by the local institutional review board. A physical examination, including medical history, weight, height, and blood pressure were measured, and fasting blood samples were collected. All diabetic subjects were treated with sulfonylurea monotherapy, metformin monotherapy, or metformin and sulfonylurea; none were treated with insulin monotherapy or insulin plus oral hypoglycaemic agents.

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informed consent before participation, and the study was approved by the Faculty of Health Science Research Ethics Committee and conducted in accordance with the Declaration of Helsinki (2008).

Study protocol. Each subject was tested on two occasions, separated by 72 h, and at the same time of day. Four female subjects were premenopausal (2 from each female group) and were tested during the midfollicular phase of their menstrual cycle (days 5–12). Subjects refrained from consuming caffeine and alcohol in the 24 h before testing and limited their exercise to normal activities of daily living. All exercise for the laboratory testing was performed on an electrically braked cycle ergometer (Excalibur Sport, Lode, Groningen, The Netherlands).

First, to determine ventilatory threshold (VT) and peak Vo2, subjects completed a maximum graded exercise test at 60 rpm and an initial workload of 40 W that was increased by 20 W (females) or 30 W (males) every 3 min until task failure (9). The VT was determined using the V-slope method (2, 5). Peak Vo2 was the highest 30-s mean Vo2 value recorded before the subject’s volitional termination of the test, and peak workload was the highest workload sustained for at least 1 min.

Then on a separate day, subjects performed six, 9-min bouts of cycling at 80% VT, with each bout separated by 12 min of rest. Exercise was performed initially at 10 W (“unloaded” cycling) for 3 min before completing the remaining 6 min at 80% VT. Vo2 and HR were recorded during the first four bouts, and CO was measured during the last two bouts. The resting periods applied between bouts were sufficient for HR (n = 64) and blood lactate (measured in a subgroup of n = 25) to return to baseline levels, and this is consistent with previous reports (38, 40).

Measurements. During exercise Vo2 was measured breath-by-breath (Innocor, Innovision, Odense, Denmark), CO was measured using the same system by the inert gas rebreathing technique at rest, 30 s, and 240 s (1, 14, 21), HR was recorded every 5 s (S610i, Polar Electro Oy, Finland), and stroke volume (SV = CO/HR) and arteriovenous O2 difference (a-v O2 = Vo2/CO) were estimated from these measurements. Mean arterial pressure [MAP = 0.33 systolic + 0.66 diastolic blood pressure (BP)] was measured at rest and during exercise (30 and 240 s) using manual sphygmomanometry and total peripheral resistance (TPR) was calculated (MAP/CO). Final values for all variables were averaged from responses during the final two submaximal exercise bouts.

Data analysis. To determine the kinetic parameters of Vo2 at 80% VT, Vo2 responses during the first four bouts were linearly interpolated to 1-s intervals, time aligned, and averaged (21), and then finally smoothed using a 5-s moving average filter. Given that the Vo2 responses of 12 subjects revealed a small third phase, these data were fitted to either a biexponential function (equation 1) or triexponential function (equation 2) as follows:

\[
\dot{V}O_2(t) = \text{baseline } \dot{V}O_2 + A_1\left(1 - e^{-e^{(t-TD_1/\tau_1)}}\right)U_1 + A_2\left(1 - e^{-e^{(t-TD_2/\tau_2)}}\right)U_2 \quad (1)
\]

\[
\dot{V}O_2(t) = \text{baseline } \dot{V}O_2 + A_1\left(1 - e^{-e^{(t-TD_1/\tau_1)}}\right)U_1 + A_2\left(1 - e^{-e^{(t-TD_2/\tau_2)}}\right)U_2 + A_3\left(1 - e^{-e^{(t-TD_3/\tau_3)}}\right)U_3 \quad (2)
\]

Either one or the other function was selected for fitting on the basis of comparing the goodness-of-fit of these functions (26), and only parameter estimates representing the first two phases (“cardiodynamic” and “primary” phase) are presented. The presence of a third phase in 12 subjects (n = 3 per group) has minimal impact on the interpretation of our data since parameters related to the primary phase are unaffected by the presence of the third phase (41) and the outcomes of statistical analyses were unaffected by excluding these subjects. In both equations, baseline Vo2 is oxygen uptake during unloaded cycling, and A1 and A2, τ1 and τ2, and TD1 and TD2 are the amplitudes, time constants, and time delays of the first and second phases, respectively. The conditional expressions (U1 and U2) limit the fitting of a particular phase to the period at and beyond the time delay associated with that phase. Fitting the cardiodynamic phase allowed us to more accurately establish the onset of the second phase (25), although this phase cannot be always described by an exponential term (18) and so, only its amplitude and duration (TD2 − TD1) are presented (Table 2).

The Vo2 data were fitted to either function (equations 1 or 2) using a weighted least-squares nonlinear regression procedure (TableCurve 2D, Systat). Data points lying outside the 95% prediction interval during the initial fit of a model were excluded, being attributed to random events, e.g., coughing. The steady-state Vo2 response, referred to as End A, was calculated using the following formula:

\[
\text{End A} = \text{baseline } \dot{V}O_2 + A_1\left(1 - e^{-e^{(360-TD_1/\tau_1)}}\right) + A_2\left(1 - e^{-e^{(360-TD_2/\tau_2)}}\right) \quad (3)
\]

Vo2 gain was calculated as shown in equation 4:

\[
\dot{V}O_2 \text{ gain} = (\text{End A} - \text{Baseline Vo2})/\left(\text{Workload @ 80% VT} - 10W\right) \quad (4)
\]

The mean response time (MRT) represents the time to reach 63% of the overall amplitude of the response from baseline (24) and was calculated as a weighted sum of the time delay and time constant of each phase according to equation 5:

\[
\text{MRT} = A_1/(A_1 + A_2)(TD_1 + \tau_1) + A_2(A_1 + A_2)(TD_2 + \tau_2) \quad (5)
\]
HR responses from the four bouts were averaged to yield a single time-series of HR data for each subject and were then fitted using a monoexponential function (see equation 6).

\[
\text{Heart rate} = \text{baseline HR} + A[1 - e^{-(t - \text{TD})/\tau}] \quad (6)
\]

where baseline HR is the average heart rate during the 3 min cycling at 10 W, \(A\) the amplitude of the exercise response, TD the delay in rise of HR after exercise onset at 80% VT, and \(\tau\) the time constant of the response. Fitting procedures were identical to that described for oxygen uptake.

To assess the dynamic response of CO, the rate of increase of CO over the initial period compared with steady-state period of exercise was estimated as the relative or percent change in CO from baseline (%ΔCO) at 30 s compared with 240 s (%ΔCO = ΔCO30/ΔCO240 × 100). Peak oxygen pulse was calculated by dividing peak \(\dot{V}O_2\) by HR at the time peak \(\dot{V}O_2\) was achieved.

Statistical analyses. Physical characteristics and activity levels, peak physiological responses, and kinetic parameters were compared using a two-way (diabetic status vs. sex) ANOVA (PRISM, Version 5.03, GraphPad Software). Cardiovascular responses were assessed using a three-way (diabetic status vs. sex vs. time of measurement) repeated measures ANOVA (Datadesk Version 6.2.1 OS X, Data Description). Differences between groups were detected using Bonferroni’s post hoc test. Significance was set at \(P < 0.05\). All values are expressed as means ± SD.

### RESULTS

**Graded test.** Peak \(\dot{V}O_2\) was significantly lower in diabetic than control subjects (Table 3), but this reduction was not significantly different between males and females. Peak workload, time to failure, workload at VT, and peak oxygen pulse during the graded test were also significantly lower in both men and women with type 2 diabetes compared with their nondiabetic counterparts, but there was no sex-diabetes interaction, indicating that the magnitude of these impairments were not different between males and females.

**\(\dot{V}O_2\) and HR kinetics.** \(\dot{V}O_2\) responses during moderate exercise for representative individuals are presented in Fig. 1. Compared with control subjects, the time constant for phase 2 (\(\tau_2\)) and MRT of the \(\dot{V}O_2\) response were slowed significantly in men and women with type 2 diabetes (Table 2). The magnitude of these impairments was not different between males and females (i.e., no significant sex-diabetes interaction). HR kinetics were also significantly slowed in diabetic subjects (i.e., higher \(\tau\) values; Table 2), but the extent of slowing was similar for males and females.

**Cardiovascular responses.** Cardiovascular responses at rest and during cycling exercise are shown in Fig. 2. Individuals

### Table 3. Physiological responses to the graded test

<table>
<thead>
<tr>
<th></th>
<th>Controls</th>
<th>Type 2 diabetes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Females</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peak (\dot{V}O_2), l/min</td>
<td>1.6 ± 0.3</td>
<td>1.5 ± 0.3(\textsuperscript{ad})</td>
</tr>
<tr>
<td>Peak (\dot{V}O_2), ml·min(^{-1})·kg(^{-1})</td>
<td>21.4 ± 2.9</td>
<td>19.4 ± 4.1(\textsuperscript{ad})</td>
</tr>
<tr>
<td>Peak HR, beats/min</td>
<td>154 ± 19</td>
<td>154 ± 17</td>
</tr>
<tr>
<td>Peak RER</td>
<td>1.10 ± 0.06</td>
<td>1.13 ± 0.05(\textsuperscript{e})</td>
</tr>
<tr>
<td>Time to failure, min</td>
<td>13.1 ± 4.1</td>
<td>11.8 ± 2.7(\textsuperscript{ad})</td>
</tr>
<tr>
<td>Peak workload, W</td>
<td>115 ± 27</td>
<td>104 ± 17(\textsuperscript{e})</td>
</tr>
<tr>
<td>Workload at VT, W</td>
<td>98 ± 26</td>
<td>78 ± 14(\textsuperscript{e})</td>
</tr>
<tr>
<td>(\dot{V}O_2) at VT, ml·min(^{-1})·kg(^{-1})-1</td>
<td>15.9 ± 3.0</td>
<td>14.9 ± 3.2</td>
</tr>
<tr>
<td>Peak (\dot{V}O_2) pulse, ml·kg(^{-1})·beat(^{-1})</td>
<td>0.14 ± 0.02</td>
<td>0.13 ± 0.03(\textsuperscript{ad})</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Controls</th>
<th>Type 2 diabetes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Males</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peak (\dot{V}O_2), l/min</td>
<td>2.8 ± 0.5(\textsuperscript{e})</td>
<td>2.5 ± 0.4(\textsuperscript{ad})</td>
</tr>
<tr>
<td>Peak (\dot{V}O_2), ml·min(^{-1})·kg(^{-1})</td>
<td>31.1 ± 6.2(\textsuperscript{e})</td>
<td>27.8 ± 4.4(\textsuperscript{ad})</td>
</tr>
<tr>
<td>Peak HR, beats/min</td>
<td>161 ± 12</td>
<td>157 ± 14</td>
</tr>
<tr>
<td>Peak RER</td>
<td>1.10 ± 0.04</td>
<td>1.12 ± 0.05(\textsuperscript{e})</td>
</tr>
<tr>
<td>Time to failure, min</td>
<td>17.8 ± 3.0(\textsuperscript{e})</td>
<td>15.8 ± 2.5(\textsuperscript{ad})</td>
</tr>
<tr>
<td>Peak workload, W</td>
<td>192 ± 28(\textsuperscript{e})</td>
<td>171 ± 27(\textsuperscript{ad})</td>
</tr>
<tr>
<td>Workload at VT, W</td>
<td>160 ± 29(\textsuperscript{e})</td>
<td>132 ± 23(\textsuperscript{ad})</td>
</tr>
<tr>
<td>(\dot{V}O_2) at VT, ml·min(^{-1})·kg(^{-1})-1</td>
<td>23.3 ± 6.6(\textsuperscript{e})</td>
<td>21.3 ± 4.5(\textsuperscript{e})</td>
</tr>
<tr>
<td>Peak (\dot{V}O_2) pulse, ml·kg(^{-1})·beat(^{-1})</td>
<td>0.19 ± 0.04(\textsuperscript{e})</td>
<td>0.18 ± 0.02(\textsuperscript{ad})</td>
</tr>
</tbody>
</table>

Values are means ± SD; \(n = 16\). Physiological responses to the graded test for men and women with and without type 2 diabetes. Significantly different from women within same diabetes status, \(\textsuperscript{P}< 0.0001\); significantly different from nondiabetic controls within the same gender: \(\textsuperscript{P}< 0.05\); \(\textsuperscript{P}< 0.01\).
with type 2 diabetes displayed significantly higher MAP ($P < 0.05$) and tended to have greater TPR values (main effect = diabetes status, $P = 0.093$) during cycling. There was a tendency for lower CO responses during exercise only among men with type 2 diabetes compared with nondiabetic men (diabetes status x sex x time interaction; $P = 0.058$); however, when the change in CO from rest to both 30 s and to 240 s was scaled to the change in power output, CO responses were almost identical (not shown) between the two groups of men, suggesting that the tendency for lower absolute values in CO among diabetic men was a consequence of lower workloads. The relative change in CO from baseline (%ΔCO, see METHODS) was not significantly affected by type 2 diabetes ($P = 0.33$). No differences were detected in estimated a-VO$_2$, SV, or HR amplitudes due to diabetic status.

**DISCUSSION**

The hypothesis that sex influences the effect of type 2 diabetes on peak VO$_2$ and exercise tolerance was based on
preliminary observations in a small sample \((n = 20)\) of subjects (34). These observations were used to suggest that the “excess limitation” in exercise capacity in women with type 2 diabetes might predispose them more to physical inactivity than their male counterparts (7, 31). The present findings, based on a much larger sample size \((n = 64)\), do not support this and demonstrate that the type 2 diabetes-induced reduction in peak \(V\dot{O}_2\) and tolerance of a maximum graded test, the speed of the dynamic response of \(V\dot{O}_2\) during moderate exercise, as well as the habitual levels of physical activity are not significantly different between males and females. Among women, analysis of the data excluding the four premenopausal subjects in the present study did not change our main findings (results not shown), indicating that our conclusions can be applied to a wider postmenopausal population.

We cannot dismiss the possibility that the different outcomes of these two studies relates to the use of different exercise modes (treadmill vs. cycling). Excess body weight, reflected in a higher body mass index, contributes to exercise intolerance in diabetic subjects and more so for weight-bearing (cycling) than nonweight-bearing (cycling) exercise (11). In the former study (34) body weight was 10% higher in diabetic subjects, raising the possibility of a greater difference in body weight in females than males and it contributing to a relatively larger reduction in exercise tolerance in females. This possibility was minimized in the present study through the use of nonweight-bearing exercise and the similar body weight and BMI between diabetic and control groups.

In addition to “peak” exercise measurements, physiological responses during submaximal exercise are also affected by type 2 diabetes (4, 8, 21, 32). The \(V\dot{O}_2\) at VT is lower in a combined group of middle-aged men and women with type 2 diabetes (34), and the dynamic response of \(V\dot{O}_2\) during low to moderate levels of submaximal exercise is slowed in young and middle-aged women (8, 21, 32) and in a combined group of middle-aged men and women with type 2 diabetes (4) but not in older men (42). The present findings of a lower ventilatory threshold (W) and slowed kinetic response of \(V\dot{O}_2\) during exercise below this threshold are consistent with these observations and extend them to show that the same impairments occur in middle-aged men. However, the extent to which these submaximal exercise responses were impaired was similar between men and women. These data reinforce the findings pertaining to peak exercise responses and further demonstrate that sex does not affect the extent to which type 2 diabetes impairs exercise responses.

The dynamic or “kinetic” response of \(V\dot{O}_2\) during submaximal exercise is potentially an important determinant of muscle fatigue and exercise tolerance (13). Factors that contribute to \(O_2\) supply might influence this dynamic response, including CO and blood flow to contracting muscles. The kinetic response of CO during submaximal cycling as well as peak cycling exercise appears to be normal in adult women with
uncomplicated type 2 diabetes (21, 33), and absolute levels of CO during steady-state cycling are also normal in a combined group of men and women with type 2 diabetes (3). This was also the case in the present study with similar absolute levels and rates of adjustment of CO during moderate exercise between subjects with and without type 2 diabetes (Fig. 2). Although in the present study CO responses (l/min) at 30 and 240 s tended to be lower in males with type 2 diabetes compared with healthy males (Fig. 2), this was as a result of diabetic males cycling at a significantly lower workloads, as when the changes in CO were scaled to changes in workload, CO responses among the two groups of men were almost identical.

In contrast, the dynamic response of vascular conductance in the contracting calf muscle is slowed in females with type 2 diabetes (23), and steady-state measurements of leg blood flow during cycling (16, 20) are reduced in male and females with type 2 diabetes. These data raise the possibility that the slowed dynamic response of VO₂ and the poorer exercise tolerance in men and women with type 2 diabetes is due to a slower, and perhaps smaller, adjustment in vasodilation and muscle blood flow, although this should be tempered by the present findings of normal adjustments in TPR and, presumably, vascular resistance in the contracting muscles. In addition, the abnormal VO₂ kinetic responses in type 2 diabetes during submaximal exercise can also be influenced by the ability of active muscles to utilize oxygen given the observations of a lower mitochondrial content (35) and abnormal mitochondrial function (15, 30, 35) in muscles of diabetics compared with healthy controls.

The present findings are limited to middle-aged participants, where the majority of women were postmenopausal. However, we cannot exclude the possibility that sex may affect the type 2 diabetes-induced reductions in exercise tolerance in younger participants. It is well established that estrogen confers a beneficial effect on the endothelium-dependent vascular function in healthy nondiabetic premenopausal females compared with males and postmenopausal females, referred to as the “female advantage” (29, 37). However, these greater levels of endothelium-dependent vasodilation observed in nondiabetic premenopausal females compared with males are tempered by the presence of type 2 diabetes, so that the endothelium-dependent vasodilation function is similar between premenopausal females and age-matched males with type 2 diabetes (37). This would suggest that type 2 diabetes impairs the vasodilatory function and possibly oxygen delivery and exercise tolerance in premenopausal women to a larger extent than in age-matched men or postmenopausal women. Further research is needed to elucidate this. The men in the present study were numerically older than women. This, however, impacts minimally on the interpretation of our data given that when the four premenopausal women were excluded from the female groups (two from each group) the mean ages of all groups were identical and the statistical outcomes were unaffected.

**Perspectives and Significance**

Exercise intolerance and impaired exercise VO₂ responses are consistent features of type 2 diabetes. Individuals with type 2 diabetes, who were younger (mean age = 42 yr) than those studied in the present study, also perceive light to moderate exercise as more difficult than healthy controls (12), and this might contribute to their relatively lower levels of physical activity (32) and increased risk of cardiovascular outcomes and all-cause mortality in later life (6, 39). The present study shows that middle-aged males and females with type 2 diabetes exhibit a similar degree of exercise intolerance and impairment in exercise VO₂ response, and that they were also more inactive than the healthy controls, despite the fact that individuals with type 2 diabetes and control groups were sedentary. Although the perception of effort during exercise has not been studied in middle-aged individuals with type 2 diabetes, the present findings suggest that the association between exercise intolerance, VO₂ responses, increased perception of effort, and reduced physical activity is a feature of diabetes in younger and middle-aged individuals. Further research is required to establish the causal link between these exercise variables. In addition, given that exercise training can normalize the exercise VO₂ responses in type 2 diabetes (8, 22), further research is also required to establish the extent to which impairments in exercise VO₂ contribute to exercise intolerance, heightened perception of effort, and increased levels of physical inactivity in this disease.

**GRANTS**

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**DISCLOSURES**

No conflicts of interest, financial or otherwise, are declared by the author(s).

**AUTHOR CONTRIBUTIONS**


**REFERENCES**

SIX-SPECIFIC EFFECTS ON $\dot{V}O_2$ KINETICS IN TYPE 2 DIABETES


