



## Obesity and inactivity, not hyperglycemia, cause exercise intolerance in individuals with type 2 diabetes: Solving the obesity and inactivity versus hyperglycemia causality dilemma



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### ABSTRACT

Obesity, a sedentary lifestyle and type 2 diabetes are intricately linked conditions contributing to reduced exercise tolerance, significant morbidity, and premature deaths. It is unknown whether the reported exercise intolerance associated with type 2 diabetes is a direct result of the hyperglycemia, the impact of a relatively sedentary lifestyle, or increased adiposity. We hypothesize that obesity and inactivity, not hyperglycemia, cause exercise intolerance in individuals with type 2 diabetes. An analysis of the literature and results from the Goto-Kakizaki (GK) rat model of type 2 diabetes strongly support this hypothesis. GK rats were not sedentary or obese when compared with Wistar control rats and did not have exercise intolerance. Specifically, despite being hyperglycemic, GK rats demonstrated a longer treadmill run time to exhaustion ( $150.6 \pm 9.0$  vs.  $77.2 \pm 12.9$  min), further distance run ( $1506 \pm 90$  vs.  $772 \pm 129$  m), more work performed per gram muscle ( $44.0 \pm 2.8$  vs.  $21.9 \pm 3.8$  kg\*m/g) and a small increase in total vertical work performed when accounting for body mass ( $116.8 \pm 6.3$  versus  $98.9 \pm 15.2$  kg\*m). These results document preserved exercise tolerance in the non-obese, non-sedentary GK rat supporting the hypothesis that the reported exercise intolerance in models of type 2 diabetes is dependent on obesity and inactivity. Solving the obesity and inactivity versus hyperglycemia causality dilemma is important in understanding the development of type 2 diabetes and implications for future pharmacological and life style interventions.

### Background to the hypothesis

#### Exercise intolerance associated with type 2 diabetes

Type 2 diabetes has been associated with decreased exercise tolerance (for review, see Regensteiner [1]). This is an important association because exercise intolerance is a cardiovascular disease risk factor [2,3] and individuals with type 2 diabetes have an increased risk of cardiovascular disease [4,5]. Furthermore, exercise intolerance negatively impacts activities of daily living which limits performance at work, school and during recreational events. It is not clear if the exercise intolerance associated with type 2 diabetes is a direct result of the disease, the impact of a relatively sedentary lifestyle, increased adiposity [6] or a combination of these factors. This is because type 2 diabetes primarily occurs concurrently with obesity and physical inactivity [7] and can be prevented by maintaining a low body mass index and exercising regularly [7,8].

#### Tests of exercise tolerance

Most investigators have employed a maximal exercise test to examine exercise tolerance in individuals and animals with type 2 diabetes [1,9–12]. However it has recently been noted that time to exhaustion at a fixed submaximal work rate is more relevant for assessing exercise tolerance [13]. This is suggested because maximum exercise may not accurately reflect activities of daily living since the mechanism of fatigue during maximum exercise may be related to limits of cardiac output, lactate tolerance, or mental fatigue whereas exhaustion during prolonged submaximal exercise may be related to muscle soreness and substrate availability [14–20]. Importantly, exercise tolerance assessed by time to exhaustion at a fixed submaximal work rate, a more clinically relevant test, has not been documented in individuals or animals with type 2 diabetes [6]. We hypothesize that measuring time to exhaustion at a fixed submaximal work rate will help resolve the obesity and inactivity versus hyperglycemia causality dilemma.

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## An analysis of the literature

Investigators have controlled for activity and obesity when examining questions related to exercise tolerance associated with type 2 diabetes. For example, Fang and colleagues compared body mass index (BMI) and heart rate recovery (HRR, a surrogate for activity) in diabetic patients with normal and reduced exercise tolerance for age [21]. Reduced HRR is associated with poor physical fitness [22,23]. In the study by Fang and colleagues, reduced exercise capacity was associated with increasing obesity and reduced activity as noted by HRR [21].

Similarly, Regensteiner and colleagues also controlled for BMI and physical activity as determined by self-reported activity questionnaires. In two initial studies, the investigators reported reduced maximum oxygen uptake ( $VO_2$  max) in individuals with type 2 diabetes [9,10].  $VO_2$  max is a measure of exercise capacity [24,25]. More importantly, in a later study, the investigators did not find differences in  $VO_2$  max between individuals with type 2 diabetes and control subjects when the individuals with diabetes self-reported higher levels of physical activity [11]. Taken together, the results by Regensteiner and colleagues document the importance of controlling for body weight and physical activity when assessing exercise tolerance in individuals with diabetes since the reduced exercise tolerance appears to be directly related to these initiating conditions. Specifically, when the individuals with diabetes had higher activity levels and similar BMI they did not have exercise intolerance. These results suggest that activity levels may be responsible for the differences in exercise capacity reported in the earlier studies.

In recent work by Slade and colleagues, age, BMI, and activity were matched in control subjects and individuals with type 2 diabetes. In this carefully controlled study, the investigators reported no difference in microcirculatory response following muscle contraction between control and diabetic subjects [26]. Microcirculatory response following muscle contraction is an indicator of exercise tolerance [6]. Specifically, the investigators measured blood oxygen level dependent (BOLD) changes by MRI following maximal contraction in the dorsiflexors of the leg. Following contraction, both peak and time to peak BOLD response were unchanged in individuals with diabetes, indicating normal blood flow kinetics. The kinetic response of blood flow (and by extension  $VO_2$ ) is inversely related to oxygen debt and slowing kinetics contributes to early fatigue [20,27]. Thus, when considering blood flow kinetics as a measure of exercise tolerance, the work by Slade and colleagues suggests that individuals with diabetes have normal exercise tolerance when matched for BMI and activity.

Taken together, the works of Fang and colleagues [21], Regensteiner and colleagues [9–11], and Slade and colleagues [26] support the hypothesis that when body weight and activity levels are controlled, individuals with type 2 diabetes do not have reduced exercise tolerance.

### Solving the obesity and inactivity versus hyperglycemia causality dilemma; “Which came first: the chicken or the egg?”

The critical issue of whether the exercise intolerance reported for individuals with type 2 diabetes is a direct result of the disease or the result of a sedentary lifestyle or increased adiposity can be assessed with the Goto-Kakizaki (GK) rat model of type 2 diabetes [28]. The GK model is a hyperglycemic, nonobese rat strain [28] without physical inactivity [29]. The GK rat model was developed by breeding glucose-intolerant Wistar rats [30]. The advantage of this genetic animal model is its reproducibility and healthy Wistar rats are appropriate controls because they derive from the same original strain as the GK rat. The ability to dissociate obesity, inactivity and hyperglycemia is powerful as obesity contributes to both type 2 diabetes and cardiovascular disease [31,32] and inactivity reduces endurance capacity [14,33,34].

## Statement of the hypothesis

We explored the obesity and sedentary lifestyle versus hyperglycemia causality dilemma and studied which causes exercise intolerance in a model of type 2 diabetes. Specifically, we tested the hypothesis that rats with type 2 diabetes, but without obesity or inactivity, have preserved exercise tolerance.

### Supporting data – presented as a test of the hypothesis

Non-obese and non-sedentary type 2 diabetic male Goto-Kakizaki Rats (8–10 months old) and age-matched Wistar control rats were used to evaluate the initial hypothesis. All procedures were approved by the Michigan State University Institutional Animal Care and Use Committee and complied with The American Physiological Society’s “Guiding Principles in the Care and Use of Animals”.

#### Activity levels of Wistar control and GK type 2 diabetic rats

Twelve-hour daytime and twelve-hour nighttime mean activity values, measured via radio telemetry over 8 consecutive days, are shown in Fig. 1. No difference was observed in locomotor activity between groups during the day or night cycles ( $P = 0.65$  Day;  $P = 0.38$  Night). Documentation of similar activity levels between Wistar control animals and GK rats with type 2 diabetes [29], along with the absence of obesity in the GK animals, allowed for testing the hypothesis that rats with type 2 diabetes, but without obesity or inactivity, have preserved exercise tolerance.

#### Test of exercise tolerance: time to exhaustion at a fixed submaximal workload

As seen in Fig. 2, when performing prolonged submaximal activity (~50–55%  $VO_2$  Max, which simulates activities of daily living) to exhaustion, GK type 2 diabetic animals ran significantly longer (Fig. 2, Panel A), significantly farther (Fig. 2, Panel B), performed more vertical work per gram muscle mass (Fig. 2, Panel C) and performed similar absolute vertical work compared to their genetic controls (Fig. 2, Panel D). Absolute vertical work (body mass  $\times$  vertical distance) and vertical work per gram of muscle mass are important to consider when assessing exercise tolerance in different sized animals [35]. These results support the hypothesis that when accounting for obesity and daily activity,

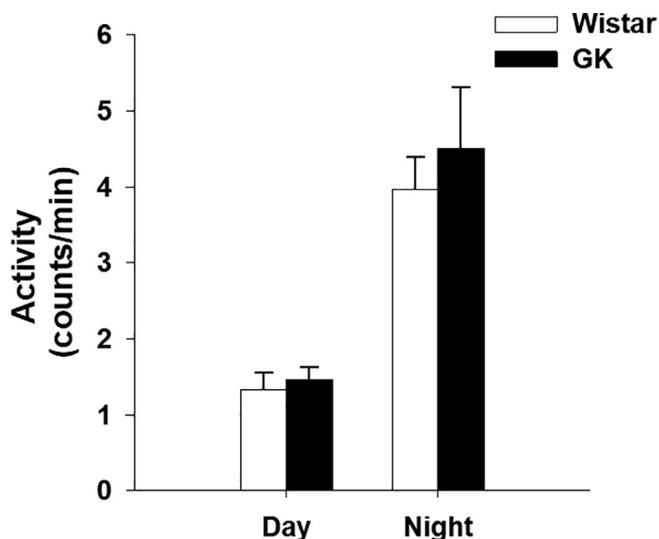
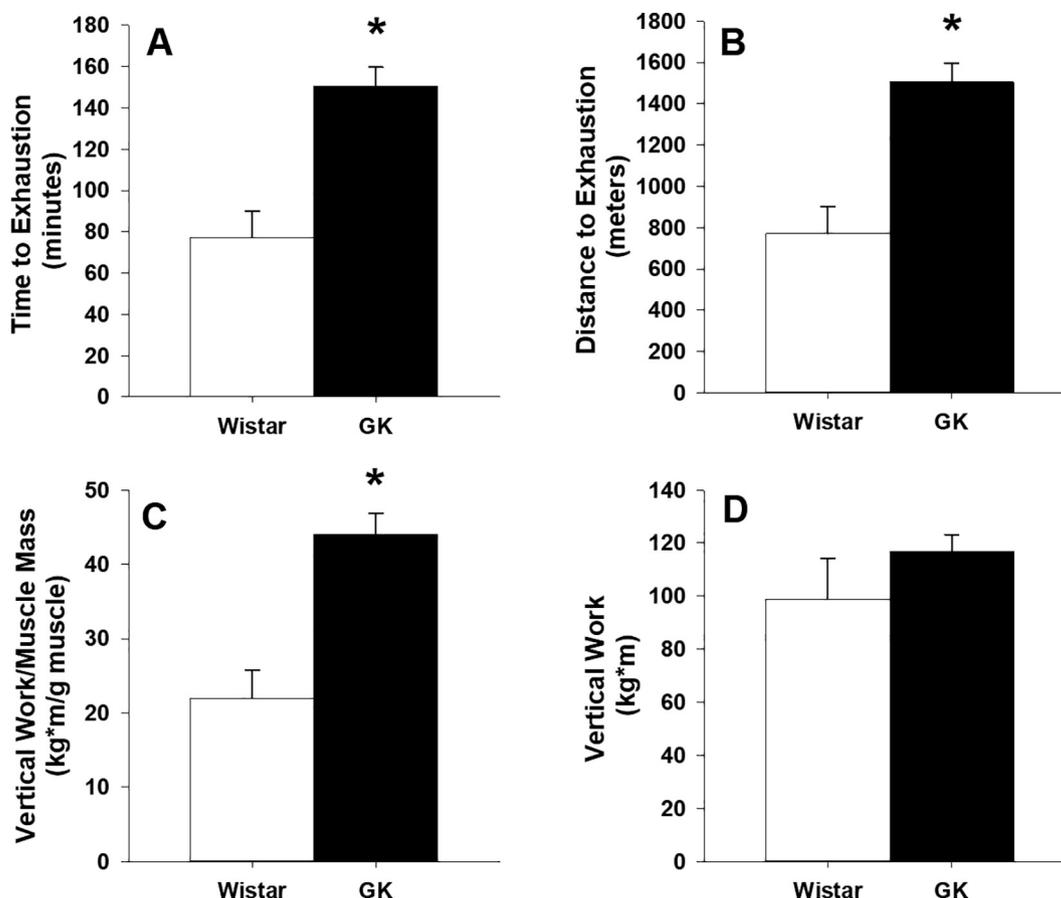


Fig. 1. Day/night activity counts averaged over 8 consecutive days. No difference was observed in locomotor activity between GK and Wistar control rats. Values are mean  $\pm$  SE, (\* $P < 0.05$ , two-tailed  $t$ -test).



**Fig. 2.** Submaximal workload performance as determined by time to exhaustion (A), distance to exhaustion (B), vertical work performed per gram muscle mass (C), and absolute vertical work performed (D). Values represent Mean  $\pm$  SE. GK rats ran significantly longer and farther and performed more vertical work per gram muscle mass. (\*P < 0.05, two-tailed *t*-test).

exercise performance is preserved at submaximal workloads in a model of type 2 diabetes. This finding suggests that the cause of the purported exercise intolerance in individuals with type 2 diabetes is due to obesity and sedentary lifestyle that precedes the disease. This is an important consideration because clinical and observational studies document that exercise tolerance is a strong predictor of cardiovascular and overall mortality [36].

### Significance of the hypothesis

Type 2 diabetes constitutes approximately 90% of all diabetes cases and primarily occurs as a result of obesity and a sedentary lifestyle [7]. In fact, the rates of type 2 diabetes have increased markedly since 1960 in parallel with obesity [37]. As of 2015, approximately 392 million individuals currently live with type 2 diabetes compared with approximately 30 million in 1985 [38,39].

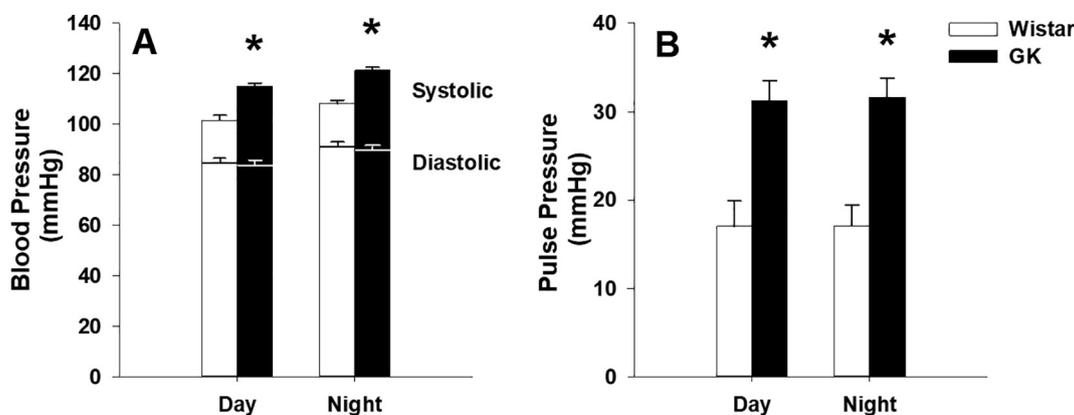
According to the national institutes of health (NIH), treatment of type 2 diabetes includes exercise and weight reduction and the onset of type 2 diabetes can be delayed or prevented with regular exercise [8,40–42]. Importantly, the benefits of exercise to treat diabetes are independent from changes in body weight [40]. However, weight loss surgery in those who are obese is also an effective measure to treat diabetes [43]. Many individuals are able to maintain normal blood sugar levels with little or no medication following surgery [44] and long-term mortality is decreased [45].

Overweight and obese individuals have lower fitness levels due, in part, to being more sedentary than the general population [46] and having excess weight [47]. Similarly, individuals with type 2 diabetes are also more likely to be overweight or obese and sedentary [47].

Obesity and sedentary lifestyle are intricately linked conditions responsible for at least 300,000 premature deaths and significant morbidity [46]. The results from this study and an analysis of the literature suggest that obesity and sedentary lifestyle, but not hyperglycemia, lead to exercise intolerance.

The mechanisms mediating the preserved exercise tolerance in GK rats are unknown but likely reflect increased substrate availability. In support of this concept, fasting glucose, as expected, was higher in GK rats compared with Wistar control non-diabetic rats ( $242 \pm 7$  versus  $154 \pm 59$  mg/dL,  $P < 0.05$ ), perhaps providing enhanced glucose availability to working muscles. In work by Coggan and colleagues, endurance capacity of healthy individuals, as measured by time to exhaustion at a fixed submaximal work rate, was increased by more than 20% following carbohydrate ingestion after 2 h of exercise. The authors concluded that increased plasma glucose availability delayed fatigue by increasing carbohydrate oxidation [15]. Further, it has been shown that glucose oxidation during exercise is elevated in individuals with diabetes [48]. Accordingly, elevated plasma glucose in GK rats may have enhanced endurance capacity at submaximal workloads by providing greater substrate availability.

Although hyperglycemia may have preserved exercise tolerance in the diabetic GK rats, it was also directly associated with increased cardiovascular disease (CVD) risk factors. Specifically, high fidelity recordings of intravascular arterial blood pressure obtained 20 s every minute via radio telemetry during eight consecutive days documented significant CVD risks in GK rats. GK rats had daily systolic hypertension without a difference in diastolic blood pressure (Fig. 3, Panel A). Since systolic blood pressure was markedly elevated in GK rats and diastolic blood pressure was not different between GK and their genetic controls,



**Fig. 3.** Day/night systolic and diastolic arterial pressure (A) and pulse pressure (B) averaged over 8 consecutive days. GK systolic pressure and pulse pressure were significantly higher than Wistar controls during both day and night while no difference was seen in diastolic pressure. Values are mean  $\pm$  SE, (\* $P < 0.05$ , two-tailed  $t$ -test).

pulse pressure (systolic minus diastolic arterial pressure) was also elevated in GK rats (Fig. 3, Panel B). This is an important finding since systolic hypertension and elevated pulse pressure are powerful cardiovascular risk factors [49–51]. Specifically, increased pulse pressure is consistent with CVD [49–51] and significant vascular dysfunction. Importantly, vascular dysfunction is consistently reported in individuals and animals with type 2 diabetes [52–54] and has been reported to be a result of hyperglycemia-induced oxidative stress [55].

Recent work supports the concept that hyperglycemia independently contributes to CVD risk factors [56–58]. Specifically, individuals with impaired glucose tolerance have a two-fold increased risk of macrovascular disease [59,60]. Furthermore, hyperglycemia and CVD are tightly related such that there is an 18% greater risk for CVD per 1% increase in glycosylated hemoglobin [5] for individuals with either type 1 or 2 diabetes. The relationship between hyperglycemia and CVD is also supported by results obtained in individuals with pre-diabetes. Individuals with pre-diabetes do not exhibit elevated fasting blood glucose but following an oral glucose load, glucose levels remain elevated longer than healthy controls. These individuals have a 58% increase in CVD risk factors [61]. Thus, even when frank diabetes is not present, CVD risk factors remain evident due to episodes of elevated glucose. Furthermore, intensive treatment of hyperglycemia in individuals with type 2 diabetes has been shown to significantly reduce CVD risk factors, demonstrating that controlling glycemia alone can reduce risk [62]. Thus, hyperglycemia, independent of obesity and sedentary lifestyle promotes cardiovascular disease.

In conclusion, the hypothesis that the reported exercise intolerance associated with type 2 diabetes is a result of obesity and sedentary lifestyle is supported by an analysis of the literature and the non-obese, non-sedentary GK rat model of type 2 diabetes. Specifically, the GK rat model of type 2 diabetes had preserved exercise tolerance when performing at a fixed submaximal work rate. Concomitantly, GK rats showed increased cardiovascular disease risk factors. Importantly, the use of the GK animal allows for the study of the type 2 diabetes hyperglycemic state without the confounding influence of obesity and inactivity.

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#### Conflict of interest statement

No conflicts of interest, financial or otherwise, are declared by the

author(s).

#### Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.mehy.2019.01.013>.

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