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Relationships Between Glycemic Control and Cardiovascular Fitness

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Abstract

Introduction: Diabetes is a serious health problem affecting approximately 29.1 million individuals in the United States. Another 86 million have prediabetes. The development and implementation of lifestyle modifications such as physical activity for these persons are among the most effective methods for prevention and treatment. **Objective:** The aim of this study was to examine relationships between glycemic control (HbA1c) and cardiovascular fitness (peak maximal oxygen uptake [VO₂ peak] and ventilatory threshold [VT]) in overweight/obese subjects with and without type 2 diabetes (T2DM). In addition, the influences of body mass index (BMI) and insulin sensitivity (homeostasis model assessment [HOMA %S]) on the relationship between glycemic control and cardiovascular fitness were explored. **Method:** Data were abstracted from a completed study that included 51 overweight or obese subjects with T2DM ($n = 18$), impaired glucose tolerance ($n = 8$), or normal glucose tolerance ($n = 25$). Relationships between glycemic control (HbA1c) and cardiovascular fitness (VO₂ peak and VT) were determined using correlational analysis and multiple linear regression analyses. **Results:** A statistically significant relationship was observed between HbA1c and cardiovascular fitness. However, BMI and HOMA %S did not influence the relationship between glycemic control and cardiovascular fitness. **Discussion:** HbA1c contributes to VO₂ peak and VT in obese and overweight subjects across glucose tolerance categories. Significant results were achieved despite the fact that there was a limited range of HbA1c based on the study inclusion criteria. This finding suggests that even a mild decrease in glycemic control can negatively influence cardiovascular fitness.

Keywords

glycemic control, cardiovascular fitness, diabetes, ventilatory threshold, maximal/peak oxygen consumption

Diabetes remains a serious metabolic health problem affecting approximately 29.1 million individuals in the United States alone (9.3% of the population), 8.1 million of whom remain undiagnosed (Centers for Disease Control and Prevention [CDC], 2014). Approximately 86 million individuals have prediabetes, which includes impaired fasting glucose (IFG) and impaired glucose tolerance (IGT; CDC, 2014). Over the past 32 years, the number of adults with diagnosed diabetes in the United States nearly quadrupled, from 5.5 to 21.3 million, with about 1.7 million new cases diagnosed each year. If this trend continues, as many as one of every three adults in the United States could develop diabetes by 2050. The global prevalence of type 2 diabetes mellitus (T2DM) is expected to increase from 366 million in the year 2011 to 552 million in the year 2030 (International Diabetes Federation, 2015).

Clinical trials have consistently demonstrated that people with diabetes have diminished cardiovascular fitness (maximal/peak exercise capacity, i.e., VO₂ max or peak maximal oxygen uptake [VO₂ peak]) compared to those without diabetes (Baldi, Aoina, Oxenham, Bagg, & Doughty, 2003; Brandenburg

et al., 1999; O'Connor, Kiely, O'Shea, Green, & Egaña, 2012; Regensteiner et al., 1998; Solomon et al., 2015; Vanninen, Mustonen, Vainio, Länsimies, & Uusitupa, 1992). Studies have also demonstrated that patients with diabetes reach anaerobic or ventilatory thresholds (VTs) at lower exercise intensities than those without diabetes (Bergental et al., 2013; O'Connor, Green, Kiely, O'Shea, & Egaña, 2015). This information is important as individuals with diabetes may reach peak exercise earlier than those without diabetes. The cause of this decreased

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cardiovascular fitness is not known, but chronic hyperglycemia is a possible contributor (Solomon et al., 2015). It is important to clarify the relationship between glycemic control and cardiovascular fitness because chronic elevations in glucose may alter the exercise response and affect recommendations for exercise as a treatment modality.

Researchers have examined the relationship between glycemic control and cardiovascular fitness in several studies using various measures of glucose control (i.e., oral and intravenous tolerance, fasting glucose levels, and HbA1c) and cardiovascular fitness (i.e., VO_2 max, VO_2 peak, VT, and metabolic equivalents [METs]; Fang, Sharman, Prins, & Marwick, 2005; Regensteiner et al., 1998; Ross, Murthy, Wollak, & Jackson, 2010; Vanninen, Uusitupa, et al., 1992) and have reported inconsistent results. In one of the earliest studies to evaluate this relationship, Vanninen, Uusitupa, et al. (1992) observed no correlations between HbA1c and VT or VO_2 peak. Regensteiner et al. (1998) show that individuals with T2DM who did not have cardiovascular complications were unable to attain VO_2 max levels comparable to controls during a graded exercise test. Fang, Sharman, Prins, and Marwick (2005) examined whether HbA1c was a predictor of exercise capacity (METs) in obese adults with and without T2DM and observed that poor glycemic (HbA1c) control is correlated with diminished exercise capacity ($r = -.22, p = .009$).

The purpose of the present study was to examine the relationship between glycemic control (HbA1c) and cardiovascular fitness (VO_2 peak and VT) in overweight and obese subjects with T2DM, IGT, and normal glucose tolerance (NGT). We also examined the effect of body mass index (BMI) and insulin sensitivity (homeostasis model assessment [HOMA %S]) on the relationship between glycemic control and cardiovascular fitness. We designed this study to answer the following two research questions:

Research Question 1: What is the relationship between glycemic control (HbA1c) and cardiovascular fitness (VO_2 peak and VT levels)?

Research Question 2: How do selected personal characteristics (BMI and insulin sensitivity) influence the relationship between glycemic control and cardiovascular fitness?

Method

Design

This cross-sectional study was a secondary analysis of data collected during the screening phase of a study examining post-exercise postprandial metabolism (Quinn et al., 2006). The purpose of the original study was to investigate the effect of a single bout of aerobic exercise on postprandial metabolism and markers of oxidative stress. Postprandial markers of oxidative stress and metabolism were collected for individuals with NGT, IGT, or T2DM for 24 hr after a 30-min bout of exercise and compared to the same markers from a nonexercise day. Participants were separated into glucose tolerance categories, NGT, IGT, and T2DM. A 3-hr oral glucose tolerance

test was performed using a 75-g glucose load. The order of exercise versus nonexercise day was randomly controlled, and the days were separated by 1 month. The required number of subjects for the multiple linear regression model of VO_2 peak and VT was calculated based on the assumptions of nine predictors, with a .8 power and .05 α levels, and R^2 as .3. A total of 46 subjects were recommended for this study.

Variables examined in the present study included cardiovascular fitness (VO_2 peak, VT); cardiovascular characteristics (systolic blood pressure [SBP], diastolic blood pressure [DBP], baseline heart rate, maximal heart rate, and time on treadmill during a maximal exercise stress test); HbA1c, fasting plasma glucose, plasma insulin, and insulin sensitivity and β cell function (HOMA %S and HOMA % β); demographic characteristics (age, gender, duration of diabetes, and ethnicity); and anthropometric measurements (weight, height, and BMI).

Participants

To be eligible for this study, potential participants were required to be (a) overweight/obese (BMI 27–42 kg/m^2) with T2DM and being treated with oral diabetes medications or diet; an HbA1c, $\leq 9.0\%$; and duration of T2DM ≤ 7 years; or (b) overweight or obese without diabetes. All participants were required to be 18–55 years of age. The duration of diabetes was set to less than 7 years to limit the number and severity of complications resulting from T2DM.

Individuals in the original study were excluded if they had (a) type 1 diabetes mellitus or insulin-controlled T2DM; (b) metabolic instability over the previous 3 months (e.g., hospitalization for diabetes-related complication); (c) change in weight by 3 kg or change in diet or physical activity patterns over the previous 3 months; (d) current medications that would interfere with glucose tolerance (e.g., steroids); (e) history of significant medical illness including liver, renal, cardiovascular, or thromboembolic disease; (f) history of diabetes mellitus complications for which exercise was contraindicated; (g) history of proliferative retinopathy; (h) history of severe peripheral vascular disease and neuropathy; (i) current pregnancy; (j) physical disability that would limit their ability to walk on a treadmill; or (k) inability to comply with the study protocol.

Variables

Dependent variables. The dependent variables we used were VO_2 peak and VT.

VO_2 peak. Oxygen consumption (VO_2) reflects the volume of oxygen the body consumes and uses and can be measured during maximal and submaximal exercise testing (McArdle, Katch, & Katch, 2016). VO_2 max is measured during the latter part of a maximal exercise stress test, when oxygen consumption increases only slightly in spite of increases in exercise intensity. It represents the highest VO_2 attainable during maximal exercise and the maximal volume of oxygen the body uses during intense whole-body exercise (McArdle et al., 2016). VO_2 max is considered to be the best indicator of aerobic

Table 1. Demographic Characteristics and Body Composition by Group.

Variable	Normal Glucose Tolerance		Impaired Glucose Tolerance		Type 2 Diabetes	
	n (%)	M (SD), Range	n (%)	M (SD), Range	n (%)	M (SD), Range
Age (years)	25 (49.0)	42.8 (10.1), 23.0–55.0	8 (16.0)	46.0 (7.1), 34.0–53.0	18 (35.0)	46.9 (6.5), 34.0–55.0
Ethnicity						
African American	13 (25.0)		2 (4.0)		14 (27.0)	
Caucasian	8 (16.0)		5 (10.0)		1 (2.0)	
Hispanic	4 (8.0)		1 (2.0)		3 (6.0)	
Gender: Female	17 (33.0)		6 (12.0)		16 (31.0)	
Duration of diabetes (years)					18 (35.0)	4.1 (2.3), 0.5–7.0
Weight (kg)	25 (49.0)	95.5 (15.7), 64.1–124.2	8 (16.0)	105.6 (12.2), 92.9–130.6	18 (35.0)	100.3 (13.7), 75.6–120.2
Height (m)	25 (49.0)	1.67 (0.09), 1.4–1.8	8 (16.0)	1.73 (0.08), 1.7–1.9	18 (35.0)	1.66 (0.08), 1.5–1.8
Body mass index (kg/m ²)	25 (49.0)	34.2 (3.6), 27.7–41.2	8 (16.0)	35.4 (3.3), 30.3–40.7	18 (35.0)	36.4 (4.4), 28.1–44.1

Note. M = mean; SD = standard deviation.

capacity or cardiovascular fitness in individuals who do not have physical or psychological limitations; however, in the presence of physical or psychological limitations that prevent an individual from exercising to maximal capacity, VO_2 peak reflects the highest VO_2 that the person can attain (McArdle et al., 2016). VO_2 peak is the best indicator of near maximal cardiovascular fitness or peak exertion. Therefore, we used VO_2 peak in the present study.

VT. The VT corresponds to a disproportionate increase in V_E (minute ventilation) versus VO_2 (V_E/VO_2 ; McArdle et al., 2016) and has been validated as a key indicator of submaximal aerobic performance (Santos & Giannella-Neto, 2004). It can be represented graphically as the point of nonlinear rise in carbon dioxide production relative to O_2 consumption (Beaver, Wasserman, & Whipp, 1986). We extracted VT and VO_2 peak from the cardiopulmonary exercise test results obtained during the treadmill exercise test performed during the screening visit.

Independent variable. Our independent variable was glycemic control represented by HbA1c. We measured HbA1c with a Bayer DCA 2000 (Elkhart, IN) using the monoclonal antibody method (Nathan et al., 2008).

Covariates. Our covariates were body composition, age, gender, ethnicity, duration of diabetes, and insulin sensitivity.

Body composition. We used BMI as an indicator of body composition. BMI represents the body mass in relation to stature. We calculated it by dividing weight in kilograms by height in meters squared (McArdle et al., 2016). BMI ranges are typically categorized into four designations: underweight (<18.5 kg/m²), normal (18.5–24.9 kg/m²), overweight (25–29.9 kg/m²), and obese (≥ 30.0 kg/m²; CDC, 2016). The height (without shoes) was measured to the nearest whole centimeter and the weight to the nearest kilogram using a stadiometer.

Age, gender, ethnicity, and duration of diabetes. We obtained age in years, gender, ethnicity, and duration of diabetes from the screening data. The duration of diabetes was defined by the number of years from the date of T2DM diagnosis.

HOMA. We measured insulin sensitivity using HOMA (Wallace, Levy, & Matthews, 2004), a web-based computer program developed at the University of Oxford. The program uses nonlinear solutions to estimate insulin resistance and secretory characteristics. The program also accounts for variations in both hepatic and peripheral insulin resistance. The computer model can be used to determine insulin sensitivity (%S) and β -cell function (% β) from paired fasting plasma glucose and radioimmunoassay insulin, specific insulin, or C-peptide concentrations across a range of 1–2,200 pmol/L for insulin and 18–454 mg/dl for glucose.

Procedures

The University of Illinois at Chicago Office of Protection of Research Subjects granted an exemption for the further analysis of the original database. Previously identified variables (see Design section) were extracted from the existing data set.

Statistical Analysis

Statistical analyses were conducted using SPSS Version 24. Basic statistics were generated as the first step of the data analysis and included correlation analysis and comparisons of means, including frequencies and standard deviations. Relationships between glycemic control (HbA1c) and cardiovascular fitness (VO_2 peak and VT) were determined using multiple linear regression analyses. Two multiple linear regression analyses were used to determine the moderating effect of BMI, HOMA %S, gender, age, and ethnicity on the relationship between HbA1c and cardiovascular fitness for each of the dependent variables VO_2 peak and VT.

Results

Tables 1–3 present demographic, body composition, cardiovascular, and metabolic characteristics of the 51 subjects included in this study. We separated subjects into glucose tolerance categories (NGT, IGT, and T2DM). Some subjects did not complete the screening procedures, resulting in missing data

Table 2. Cardiovascular Parameters by Group.

Variable	Normal Glucose Tolerance		Impaired Glucose Tolerance		Type 2 Diabetes	
	n	M (SD), Range	n	M (SD), Range	n	M (SD), Range
Screening systolic blood pressure (mm Hg)	25	127.4 (14.3), 106.0–155.0	8	136.4 (15.6), 113.0–162.0	18	132.7 (15.2), 109.0–166.0
Screening diastolic blood pressure (mm Hg)	25	80.8 (12.7), 62.0–109.0	8	82.3 (11.3), 65.0–100.0	18	84.3 (7.7), 70.0–99.0
Heart rate baseline (bpm)	25	80.8 (10.5), 64.0–100.0	8	80.6 (11.8), 63.0–96.0	18	86.8 (9.4), 64.0–98.0
Maximal heart rate (bpm)	25	175.0 (14.9), 141.0–203.0	8	174.8 (4.3), 170.0–180.0	18	173.8 (9.0), 153.0–184.0
Time on treadmill (min)	25	8.8 (1.5), 6.4–12.0	8	8.3 (2.2), 5.0–12.0	18	7.4 (2.4), 2.4–11.5
VO ₂ peak (ml · kg ⁻¹ · min ⁻¹)	25	24.9 (5.4), 13.2–35.0 ^a	8	23.9 (7.9), 14.4–38.4	18	20.0 (6.0), 13.3–35.8 ^a
VO ₂ (L/min)	25	2.4 (0.7), 1.3–3.5	8	2.6 (0.9), 1.5–4.2	18	2.1 (0.7), 1.0–3.7
VT (ml · kg ⁻¹ · min ⁻¹)	24	17.8 (4.5), 12.2–25.9	7	18.7 (6.4), 10.9–30.1	17	15.5 (4.5), 10.2–27.6
VT (L)	24	1.7 (0.5), 1.1–3.0	7	2.0 (0.8), 1.1–3.3	17	1.5 (0.5), 0.9–3.2
VT (percentage of actual VO ₂ peak)	24	75.4 (13.5), 46.2–99.2	7	74.0 (3.5), 70.1–79.0	17	75.5 (9.8), 57.0–91.6

Note. Bpm = beats per minute; VO₂ = oxygen uptake; VO₂ peak = peak maximal oxygen uptake; VT = ventilatory threshold; M = mean; SD = standard deviation. ^aThe difference between mean peak maximal oxygen uptake for the normal glucose tolerance and type 2 diabetes groups was statistically significant at $\alpha < .05$ according to the Bonferroni procedure.

Table 3. Metabolic Characteristics by Group.

Variable	Normal Glucose Tolerance		Impaired Glucose Tolerance		Type 2 Diabetes	
	n	M (SD), Range	n	M (SD), Range	n	M (SD), Range
HbA1c (%)	24	5.1 (0.4), 4.3–6.0 ^a	8	5.5 (0.5), 4.9–6.2 ^a	16	7.0 (0.7), 5.7–8.7 ^a
Insulin secretion (HOMA %β)	24	154.7 (48.6), 83.7–248.1 ^b	8	161.1 (45.3), 106.9–236.3 ^c	17	109.5 (49.0), 42.7–225.5 ^{b,c}
Insulin sensitivity (HOMA %S)	24	54.9 (20.7), 27.0–95.9 ^{d,e}	8	34.9 (14.3), 23.3–61.8 ^e	17	37.0 (14.2), 16.5–71.0 ^d
Fasting glucose (mg/dl)	24	97.0 (20.8), 88.2–105.7 ^f	8	97.7 (10.1), 89.3–106.1 ^g	17	130.6 (34.6), 112.8–148.4 ^{f,g}

Note. M = mean; SD = standard deviation.

^aMean HbA1c for the normal glucose tolerance (NGT) and impaired glucose tolerance (IGT) groups differed significantly from that of the type 2 diabetes (T2DM) group at $\alpha < .01$ according to the Bonferroni procedure. ^bThe difference between mean homeostasis model assessment (HOMA) %β for the NGT and T2DM groups was statistically significant at $\alpha < .01$ according to the Bonferroni procedure. ^cThe difference between mean HOMA %β for the IGT and T2DM groups was statistically significant at $\alpha < .05$ according to the Bonferroni procedure. ^dThe difference between mean HOMA %S for the NGT and T2DM groups was statistically significant at $\alpha < .01$ according to the Bonferroni procedure. ^eThe difference between mean HOMA %S for the NGT and IGT groups was statistically significant at $\alpha < .05$ according to the Bonferroni procedure. ^fThe difference between mean fasting glucose (mg/dl) for the NGT and T2DM groups was statistically significant at $\alpha < .01$ according to the Bonferroni procedure. ^gThe difference between mean fasting glucose (mg/dl) for the IGT and T2DM groups was statistically significant at $\alpha < .05$ according to the Bonferroni procedure.

for certain variables. Of the total 51 subjects, 48 had data available for VT and HbA1c and 49 had insulin sensitivity (HOMA %S) data available.

Sample Characteristics

Demographic characteristics. The majority of subjects were middle-aged African American women ($n = 29$, 56%), 14 of whom had T2DM for a short duration (Table 1). Subjects also included Caucasian ($n = 14$, 28%) and Hispanic individuals ($n = 8$, 16%), with a disproportionate number of women ($n = 39$).

Body composition characteristics. Body composition measurements, presented in Table 1, included screening weight, screening height, and BMI. The majority of individuals were overweight or obese by BMI status (27.1–44.1 kg/m²). Despite differences in glucose tolerance status, the entire group was fairly homogeneous with respect to BMI, with no significant

between-group differences (NGT, $M = 34.2 \pm 3.6$; IGT, $M = 35.4 \pm 3.3$; and T2DM, $M = 36.4 \pm 4.4$).

Cardiovascular characteristics. Cardiovascular variables included baseline heart rate, SBP and DBP, maximal exercise heart rate, duration of exercise, peak maximal oxygen uptake (VO₂ peak; ml · kg⁻¹ · min⁻¹), oxygen uptake (L/min), VT (ml · kg⁻¹ · min⁻¹), and VT (percentage of the actual VO₂ peak; Table 2). We observed significant inverse relationships between baseline (resting) heart rate and both VO₂ peak ($p = .003$) and VT ($p = .006$). In addition, there were significant positive relationships between time on treadmill and VO₂ peak and VT ($p < .001$, $p = .019$, respectively). There was a significant difference in VO₂ peak between subjects with NGT and T2DM ($p > .05$), with those with T2DM having a significantly lower VO₂ peak.

Metabolic characteristics. Metabolic variables included HbA1c, HOMA %β, and HOMA %S (Table 3). As expected, we observed a significantly lower HbA1c level in subjects with

Table 4. Relationships Between Glycemic Control (HbA1c) and Measures of Cardiovascular Fitness.

Variable	HbA1c					R^2
	<i>n</i>	<i>B</i>	<i>SE B</i>	β	<i>p</i>	
VO ₂ peak ^a	47	-2.78	.84	-.44	.002	.19
Ventilatory threshold ^b	44	-1.71	.69	-.34	.017	.13

Note. VO₂ peak = peak maximal oxygen uptake; SE = standard error.
^a $F(1, 46) = 10.86$. ^b $F(1, 43) = 6.20$.

NGT and IGT compared to those with T2DM ($p < .01$). HOMA %B was significantly greater in those with both NGT and IGT than in those with T2DM ($p < .01$ and $p < .05$, respectively). HOMA %S was significantly reduced in subjects with IGT and T2DM compared to those with NGT ($p < .05$ and $p < .01$, respectively). As expected, we observed significantly lower fasting glucose levels in subjects with NGT and IGT compared to those with T2DM ($p < .01$ and $p < .05$, respectively).

Relationship Between Glycemic Control (HbA1c) and Cardiovascular Fitness (VO₂ Peak and VT Levels)

The first research question aimed to determine the linear relationship between glycemic control (HbA1c) and cardiovascular fitness (VO₂ peak and VT levels). We determined these relationships using multiple regression analyses. As presented in Table 4, HbA1c explained 19% of the variance in VO₂ peak ($p = .002$) and 13% of the variance in VT ($p = .017$).

Influence of Body Composition and Insulin Sensitivity on the Relationship Between Glycemic Control and Cardiovascular Fitness

The second research question aimed to determine how selected personal characteristics (BMI and HOMA %S) influenced the relationship between glycemic control and cardiovascular fitness. We used multiple linear regression analyses to demonstrate the effects of BMI and HOMA %S on the relationship between HbA1c and the dependent variables VO₂ peak and VT. The interactions between HbA1c and BMI and HOMA %S were not significant for the variables VO₂ peak or VT. BMI and HOMA %S did not significantly change the relationships between HbA1c and VO₂ peak and VT. Age ($p = .005$) and gender ($p < .001$), however, were significant predictors of VO₂ peak (Table 5), and gender ($p = .005$) and ethnicity ($p = .001$) were significant predictors of VT (Table 6). Of the three ethnic groups represented in this study, Caucasians had the highest overall VO₂ peak levels, Hispanics had the highest VT levels, and African Americans had the lowest VO₂ peak and VT levels.

Discussion

The most important outcome from the present study, and the answer to our first research question, is that HbA1c contributed

Table 5. Multiple Linear Regression Model of VO₂ Peak.

Variable	<i>B</i>	<i>SE B</i>	<i>t</i>	<i>p</i>	95% CI
Age	-0.223	0.075	2.617	.013	[-3.75, -0.070]
Gender	-7.223	1.414	-5.108	.000	[-10.086, -4.361]
Ethnicity					
African American	-3.151	1.652	-1.098	.064	[-6.495, 0.192]
Caucasian	-1.095	1.874	-0.584	.563	[-4.889, 2.699]
HbA1c (%)	-8.641	7.154	-1.208	.235	[-23.124, 5.842]
HOMA %S	-0.159	0.185	-0.860	.395	[-0.534, 0.216]
BMI	-1.635	1.095	-1.494	.144	[-3.852, 0.581]
HbA1c · BMI	0.186	0.182	1.023	.313	[-0.182, 0.555]
HbA1c · HOMA %S	0.025	0.033	0.754	.455	[-0.042, 0.093]

Note. $n = 48$. $F(9, 38) = 9.337$, $p < .001$. BMI = body mass index; HbA1c = measure of glycemic control; HOMA %S = homeostasis model assessment, insulin sensitivity; VO₂ peak = peak maximal oxygen uptake; SE = standard error; CI = confidence interval.

Table 6. Multiple Linear Regression Model of Ventilatory Threshold.

Variable	<i>B</i>	<i>SE B</i>	<i>t</i>	<i>p</i>	95% CI
Age	-0.018	0.076	-0.243	.810	[-0.172, 0.135]
Gender	-3.964	1.338	-2.962	.005	[-6.681, -1.248]
Ethnicity					
African American	-5.968	1.556	-3.835	.001	[-9.126, -2.809]
Caucasian	-1.532	1.753	-0.874	.388	[-5.092, 2.027]
HbA1c (%)	-6.983	6.660	-1.048	.302	[-20.503, 6.538]
HOMA %S	-1.08	0.173	-0.624	.537	[-0.459, 0.243]
BMI	-1.139	1.022	-1.115	.272	[-3.213, 0.935]
HbA1c · BMI	0.163	0.170	0.960	.344	[-0.182, 0.508]
HbA1c · HOMA %S	0.017	0.031	0.544	.590	[-0.407, 0.081]

Note. $n = 48$. $F(9, 38) = 4.904$, $p < .001$. BMI = body mass index; HbA1c = measure of glycemic control; HOMA %S = homeostasis model assessment, insulin sensitivity; VO₂ peak = peak maximal oxygen uptake; SE = standard error; CI = confidence interval.

to VO₂ peak and VT in obese and overweight subjects across glucose tolerance categories. The magnitudes of the effects of HbA1c on VO₂ peak and VT were small, however, possibly because the HbA1c required for study inclusion was $\leq 9.0\%$.

The sample comprised 51 participants, mostly overweight or obese, middle-aged, African American women, whom we grouped into glucose tolerance classifications (NGT, IGT, and T2DM) based on oral glucose tolerance testing. Despite differences in glucose tolerance status, the group was fairly homogeneous with respect to BMI. Only 9.0% ($n = 6$) had BMI values less than 30 kg/m², and 13.7% ($n = 8$) had values greater than 40 kg/m².

There was a wide range of VO₂ peak among the study subjects; however, the mean VO₂ peak was in the lower physical fitness range based on gender and age (McArdle et al., 2016). The VO₂ peak of the T2DM group was significantly lower than that of the NGT group; a finding that previous researchers had

also noted (Regensteiner et al., 1998). Solomon et al. (2015) demonstrated similar findings in subjects with varying degrees of glucose tolerance, observing lower VO_2 max and a shorter walking time in patients with T2DM compared to controls. Regensteiner et al. (1998) observed a significantly lower VO_2 at submaximal workloads in patients with T2DM compared to controls. Impaired oxygen delivery and a reduction in cardiac output most likely contribute to decreased maximal exercise performance in persons with T2DM (Regensteiner et al., 1998). Likewise, abnormal oxygen uptake during submaximal exercise most likely contributes to limitations in exercise intensity and endurance in these subjects.

Our second research question addressed the influence of the personal characteristics of BMI and insulin sensitivity on the relationship between glycemic control and cardiovascular fitness. Using multiple linear regression, we found that neither BMI nor HOMA %S influenced the relationship between glycemic control and cardiovascular fitness.

Implications

Exercise is a recommended treatment modality for overweight and obese individuals with and without T2DM. Research demonstrates, however, that cardiovascular fitness may decrease as glycemic control worsens. A thorough understanding of the relationship between glycemic control and cardiovascular fitness is important for improving clinicians' ability to make appropriate treatment recommendations and exercise prescriptions in overweight and obese adults across the spectrum of glucose tolerance. In the present study, this relationship is most apparent in the magnitude of the difference in the VO_2 peak ($\text{ml} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$) between patients with T2DM compared to subjects with NGT and IGT. These findings demonstrate a relationship between HbA1c and cardiovascular fitness, which is consistent with findings from several other studies that have used different measurements of glucose dynamics (Fang et al., 2005; Regensteiner et al., 1998; Solomon et al., 2015; Vanninen, Uusitupa, et al., 1992). The most important implication of the present analysis is that improvements in glycemic control may contribute to improved cardiovascular fitness and possibly exercise endurance. The identification of more specific changes in glycemic control and the effects on cardiovascular fitness will allow for further refinement of interventions to prevent the development the complications that result from diabetes.

Limitations

Sample size and homogeneity of the subjects decreased the power and likelihood of detecting differences in the outcomes in the present study. As a result, our ability to generalize these findings to overweight and obese subjects with T2DM is limited, which indicates the need for additional studies with similar hypotheses. Also, this study was a secondary data analysis, and a limitation of any secondary data analysis is missing data. In particular, the group of subjects with IGT was small. This

group was not included in the initial enrollment criteria and emerged as a metabolic category during screening as a result of baseline laboratory measurements. To make statistical comparisons between subjects based on glucose tolerance status more widely generalizable, more subjects should be included in each group. Therefore, we recommend a larger sample size for future research.

Conclusions

Our findings in the present study demonstrated that glycemic control, as measured by HbA1c, contributed to cardiovascular fitness in obese and overweight subjects. The relationship observed was weak, however, as the range of the HbA1c in this study was limited based on the inclusion criteria. In spite of the fact that subjects in this small study had relatively well-controlled glycemia, we still observed significant relationships between HbA1c and VO_2 peak and VT. Neither insulin sensitivity nor BMI significantly affected these relationships.

These findings support the hypothesis that cardiovascular fitness is, in part, determined by glycemic control and that the ability of individuals to achieve cardiovascular fitness may decrease as glycemic control worsens. Based on these outcomes, it is possible that even mildly elevated HbA1c levels may contribute to decreased cardiovascular fitness. Additional studies with similar hypotheses and a larger sample size are needed to confirm this hypothesis.

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Author Contributions

Elizabeth W. Moxley contributed to conception, design, acquisition, analysis, and interpretation; drafted the manuscript; critically revised the manuscript; gave final approval; and agrees to be accountable for all aspects of work ensuring integrity and accuracy. Donald Smith contributed to acquisition and interpretation; gave final approval; and agrees to be accountable for all aspects of work ensuring integrity and accuracy. Laretta Quinn contributed to conception, design, acquisition, analysis, and interpretation; drafted the manuscript; critically revised the manuscript; gave final approval; and agrees to be accountable for all aspects of work ensuring integrity and accuracy. Chang Park contributed to analysis and interpretation; critically revised the manuscript; gave final approval; and agrees to be accountable for all aspects of work ensuring integrity and accuracy.

Declaration of Conflicting Interests

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