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Hemodynamics and Arterial Stiffness in Response to Oral Glucose Loading in Individuals with Type II Diabetes and Controlled Hypertension

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Hemodynamics and arterial stiffness in response to oral glucose loading in individuals with type II diabetes and controlled hypertension.

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Abstract

Type 2 diabetes (T2D) is the fastest growing pandemic and is typically accompanied by various vascular complications. A central hallmark of both T2D and vascular disease is insulin resistance which causes impaired glucose transport and vasoconstriction concomitantly. Those with cardiometabolic disease display greater variation in central hemodynamics and arterial elasticity, potent predictors of cardiovascular morbidity and mortality, which may be exacerbated by concomitant hyperglycemia and hyperinsulinemia during glucose testing. Thus, elucidating central and arterial responses to glucose testing in those with T2D may identify acute vascular pathophysiologies triggered by oral glucose loading. This study compared hemodynamics and arterial stiffness to an oral glucose challenge (OGC: 50g glucose) between individuals with and without T2D. 21 healthy (48±10 yrs) and 20 participants with clinically diagnosed T2D and controlled hypertension (52±8 yrs) were tested. Hemodynamics and arterial stiffness were assessed at baseline, and 10, 20, 30, 40, 50, and 60 minutes post-OGC. Heart rate increased between 20-60 post-OGC in both groups ($p<0.05$). Central systolic blood pressure (SBP) decreased in the T2D group between 10-50 minutes post-OGC while central diastolic blood pressure (DBP) decreased in both groups from 20-60 post-OGC. Central SBP decreased in T2D between 10-50 minutes post-OGC and central DBP decreased in both groups between 20-60 minutes post-OGC. Brachial SBP decreased between 10-50 in healthy participants, whereas both groups displayed decreases in brachial DBP between 20-60 minutes post-OGC. Arterial stiffness was unaffected. An OGC alters central and peripheral blood pressure in healthy and T2D participants similarly with no changes in arterial stiffness.

Key words: OGTT, blood pressure, augmentation index, pulse wave velocity

INTRODUCTION

Type 2 diabetes (T2D) and its cardiovascular complications disease remain among the highest preventable causes of mortality globally and is characterized by insulin resistance. The reciprocal relationship between insulin resistance and endothelial dysfunction has been well-documented [1, 2] with vascular and metabolic diseases exacerbating each other. Insulin's influence on the vasculature mediates vasodilation and arterial compliance, ultimately affecting transportation of insulin and substrates to tissue for storage or metabolism [3]. Typically, insulin stimulates nitric oxide production and glucose transporter translocation, increasing vasodilation, arterial elasticity, and glucose uptake. However, insulin's vascular actions are blunted in those with insulin resistance, obesity, and hyperlipidemia [4]. In essence, poor arterial compliance is highly correlated with the presence of T2D [5]. In addition, cardiometabolic dysfunction accelerates alterations to the structure and function of the arterial tree, inducing poor arterial compliance [6] and reduced microvascular blood flow in skeletal muscle [7] and adipose tissue [8], thus exacerbating the hyperglycemia-hypertension-vascular compliance cycle. Thus, insulin resistance and endothelial dysfunction are intertwined on a cellular and molecular level, and both increase the risk of adverse cardiovascular events [9], and mortality [10]. Oral glucose testing causes both acute hyperglycemia and hyperinsulinemia, which impairs insulin-mediated endothelial nitric oxide synthase [11], potentially exacerbating risk of vascular complications.

The risk-relationship between hypertension and cardiovascular events, coronary disease, and all-cause mortality are well documented by the Framingham Heart Study [12]. Further, diastolic blood pressure (DBP) has been shown to be an independent risk factor of cardiovascular events and coronary disease [13]. Likewise, central pulse pressure is used as a predictor for cardiovascular and coronary diseases [14] and is positively associated with morbidity and mortality in T2D [15]. Furthermore, the risk of cardiovascular mortality in people with T2D, without prior cardiovascular complications, is equal to that of those with chronic cardiovascular disease without diabetes [16].

Arterial stiffness, defined as thickening of the vasculature during the process of aging [17], further impairs regulation of vascular tone [18], and is exacerbated by insulin resistance, T2D, hypertension, and metabolic syndrome [19]. Increased arterial stiffness [augmentation pressure (AP), augmentation index (AIx), AIx normalized at 75 bpm (AIx@75), and pulse wave velocity (PWV)] is associated with higher risk of cardiovascular events and

all-cause mortality [20-22] while increased arterial stiffness and thickness, along with steeper slope between PWV and age are noted in patients with T2D vs age-matched healthy individuals [23].

An oral glucose tolerance test (OGTT: 75g glucose) is widely used to determine individuals' glucose metabolism and serves as a diagnostic test for T2D and pre-diabetes [24]. Previous animal studies have reported that acute hyperglycemia acts on endothelial cells, causing changes in vessel diameter and blood pressure [25-27]. Work in healthy humans illustrates central DBP (cDBP) decreases after OGC, while central SBP (cSBP), AIx, and PWV do not change [28]. However, results are not uniform, as another study showed increases in heart rate (HR) with no change in brachial SBP (bSBP) and DBP (bDBP) after OGTT [29]. In patients with T2D, there are reductions in AIx@75 with no change in cSBP and bSBP after OGTT [30], whereas Hashizume et al. [31] reported significant decreases in postprandial cSBP and bSBP with no change in bDBP. Of important note for OGTT in those with T2D is insulin's reduced ability to regulate glycemia, leading to increased circulating glucose and insulin which together act to inhibit IRS-1/PI3-k/Akt pathway that stimulates nitric oxide production [11] in favor of the MAPK/ERK pathway which stimulates endothelin-1, vasoconstriction, hyperglycemia and cell proliferation [19].

Despite the use of an oral glucose load being prolific with both its global diagnostic use, and an abundance of studies using an oral glucose load, little is known of their effects on central and peripheral hemodynamics or arterial stiffness. Therefore, the purpose of the present study was to examine central and peripheral hemodynamic responses and arterial stiffness to an oral glucose challenge among individuals with T2D and controlled hypertension vs that of healthy individuals. We hypothesized that individuals with T2D and controlled hypertension have impaired responses for on central and peripheral hemodynamics and arterial stiffness in response to an oral glucose challenge compared to individuals without T2D.

METHODS

This study was approved by the University Institutional Review Board and was carried out in accordance with the Declaration of Helsinki as revised in 2008. All participants provided written informed consent. Procedures followed were in accordance with institutional guidelines.

Participants

Participants were included in the study if they were between 18-60 years, were normal weight to obese (Body Mass Index (BMI) = 19 – 35 kg/m^2) and were weight-stable for the previous 3 months. We recruited people with a wide age and BMI range to reflect the general community. Participants were excluded if they had a BMI >35kg/m^2, or had a personal history of smoking, cardiovascular disease, stroke, myocardial infarction, uncontrolled blood pressure (seated brachial blood pressure >160/100 mmHg), peripheral arterial disease, pulmonary disease, arthritis/muscular skeletal disease, malignancy within past 5 years, or severe liver disease. Participants taking statins or anti-hypertensive medications could participate in the study and were instructed to not change their medication during the study in order to better simulate traditional oral glucose testing conditions.

After obtaining written informed consent, participants completed a medical questionnaire and had their blood pressure, height and weight evaluated to confirm eligibility. Eligible participants were placed in their respective T2D group or healthy control group. For the clinical testing visit, participants fasted for 12 hours and refrained from alcohol and exercise for 48 hrs prior. A catheter was placed in the antecubital vein of the non-dominant arm for blood draws. Baseline vascular and metabolic data were collected prior to OGC being administered.

Oral Glucose Challenge (OGC)

An OGC (50g glucose) was given to quantify glycemic regulation and hemodynamic responses among study volunteers as previously described [8, 32]. Fasting blood samples were taken at baseline and at 10, 20, 30, 40, 50, and 60 minutes post-OGC ingestion to measure glucose responses.

Hemodynamics and Arterial Stiffness

After one hour of supine rest, central [HR, cSBP, cDBP] and peripheral [bSBP, bDBP, brachial mean arterial pressure (bMAP)] hemodynamics, and arterial stiffness [AP, AIx, AIx@75, PWV] were assessed by Mobil-O-Graph (I.E.M. Stolberg, Germany) – a brachial arterial cuff-based oscillometric device. The Mobil-O-Graph records brachial blood pressure and brachial pulse waves while central blood pressure and central pulse waveforms were calculated by ARCSolver algorithm (Austrian Institute of Technology, Vienna, Austria). The central pulse waveforms then were separated into forward and reflected pulse waves to calculate AP, AIx, and PWV. Since there is an inverse relationship between AIx and HR, the AIx then was normalized at 75 bpm by the device.

Measurements were taken in triplicate at baseline, and then once every 10 minutes post-OGC for one hour. The baseline measurements were averaged.

Blood analysis

Glycosylated hemoglobin (HbA1c) was measured at a nationally accredited pathology laboratory (Royal Hobart Hospital, Hobart, Australia). Blood glucose was measured using a YSI 2300 StatPlus (Yellow Springs Instruments, Yellow Springs, OH).

Power Calculation

A prior power calculation determined that sixteen people would be needed to detect a 30% difference in SBP between T2D and healthy control groups (power = 0.8, $\alpha = 0.05$) [33]. To account for a 10% drop-out rate, 21 individuals with T2D (13 males, 8 females) and 21 healthy individuals (13 males, 8 females) were recruited through community advertisement.

Statistical Analyses

A 2x2x7 repeated measures ANOVA was used to evaluate the effect of OGC across groups and time. All data are expressed as means ± SD. Independent samples t-tests were utilized to determine group differences for descriptive variables. Student's un-paired t-test was used to compare changes in response to OGC between groups. When data were not normally distributed Signed Rank Test was performed. For all continuous variables, a two-way repeated measures ANOVA (interactions: time: 0 – 60 min; group: T2D and healthy control) followed by a Student–Newman–Keuls post-hoc was performed. Pearson's bivariate correlation were used to evaluate relationships between variables. Significance was set at $p<0.05$. Tests were performed using SigmaStat™ statistical program (Systat Software, San Jose, CA, USA).

RESULRS

Participant Characteristics

Participant characteristics are presented in table 1. There were no significant differences for age and height between T2D and healthy control groups. However, T2D group had significant greater ($p<0.05$) weight, BMI, fasting blood glucose, and HbA_{1c} than the control group.

Central and Peripheral Hemodynamics

There were no two-way interactions on any variables (Table 2). However, HR, cSBP, cDBP, bSBP, bDBP, and bMAP were significant higher at baseline, 10, 20, 30, 40, 50, and 60 minutes post-OGC in T2D group compared to healthy control group. There were significant differences by time for HR ($F_{6,234}=24.8$, $p<0.001$), cSBP ($F_{6,234}=3.1$, $p=0.006$), cDBP ($F_{6,234}=8.2$, $p<0.001$), bSBP ($F_{6,234}=3.0$, $p=0.008$), bDBP ($F_{6,234}=8.9$, $p<0.001$), and bMAP ($F_{6,234}=8.2$, $p<0.001$) such that HR was significantly increased at 10 (only healthy control), and 20, 30, 40, 50, and 60 minutes post-OGC compared to baseline in both groups; cSBP was significant reduced at 10, 30, 40, and 50 post-OGC in T2D group and only at 60 minutes post-OGC in healthy control group compared to baseline; cDBP was significant decreased at 20, 30, 40, 50, and 60 minutes post-OGC compared to baseline in both groups; bSBP was significantly dropped at 10, 20, 40, and 50 minutes post-OGC compared to baseline in healthy control group only; bDBP was significantly lower at 20, 30, 40, 50, and 60 minutes post-OGC compared to baseline in both groups; and bMAP was significantly reduced at 10 (only T2D), 20, 30, 40, 50, and 60 minutes post-OGC compared to baseline in both groups.

Arterial Stiffness

There were no two-way interactions for any variables (Table 3). However, there were significant ($p<0.05$) differences between T2D and healthy control groups for PWV at baseline, 10, 20, 30, 40, 50, and 60 post-OGC such that the T2D group had greater PWV compared to the healthy control group. There were no changes for AP, AIx, or AIx@75.

DISCUSSION

Acute hyperglycemia caused by an oral glucose challenge, oral glucose tolerate test, or a mix-meal leads to hyperinsulinemia. Insulin is well known by its action to facilitate skeletal muscles to uptake glucose by translocating glucose transporter 4 to the cell membrane. In addition, insulin enhances the function of skeletal muscles glucose

uptake by elevating vascular perfusions that are primarily rely on nitric oxide production causing increased blood flow in skeletal muscles [3]. However, these responses are blunted in those with insulin resistance, possibly mediated by the concurrent increases in glucose and insulin which inhibits eNOS production [11]. Thus, the purpose of the present study was to compare central and peripheral hemodynamic responses and arterial stiffness to an oral glucose challenge among individuals with T2D and controlled hypertension vs healthy controls. The main finding of the present study was, a) that oral glucose challenge significantly altered HR, cSBP, cDBP, bSBP (only in T2D), bDBP, and bMAP in both T2D group and healthy control group, b) arterial stiffness was not affected by an oral glucose challenge in either the T2D or healthy control groups.

In agreement with previous studies, we observed a significant increase in HR [30] and decreases in bSBP [31] and bDBP [31, 34] within 60 minutes of oral glucose challenge in individuals with T2D or metabolic syndrome. Therefore, the responses of central and peripheral dynamics and arterial stiffness to oral glucose test, oral glucose tolerate test, or a mix-meal are not universal. In contrast to our findings, Hashizume et al. [31] stated no changes in HR after a mix-meal in individuals with T2D; while Higaki et al. [30] reported no changes in cSBP and bSBP after oral glucose tolerate test in individuals with T2D; Funada et al. [34] showed no change in bSBP after a mix-meal in individuals with metabolic syndrome. On the other hand, we did not observe any changes in arterial stiffness in individuals with T2D while Funada et al. [34] demonstrated significant reduction in AIx after a mix-meal, and Higaki et al. [30] reported significant decrease in AIx@75 after oral glucose tolerate test in individuals with T2D. However, a key difference of this study was that participants did not refrain from taking their prescribed antihypertensive medications the morning of testing.

Although we observed significant differences in participants characteristics between between healthy individuals and individuals with T2D and controlled hypertension, the responses of central and peripheral dynamics and arterial stiffness to oral glucose challenge are similar between healthy individuals and individuals with T2D and controlled hypertension. In agreement with previous studies, we observed a significant increase in HR [28-30, 36] and decreases in cSBP [30, 35, 36], cDBP [28, 35, 36], bDBP [34, 36], and bMAP [36] with no change in bSBP [29-31, 34, 35] in individuals without T2D. However, the findings were not consistent with other studies. Russell et al. [28] reported no change in cSBP after oral glucose challenge in healthy individuals while Hashizume et al. [31] and Monnard et al. [29] showed no changes in bDBP after a mix-meal and oral glucose tolerate test, respectively, in healthy individuals. On the other hand, in agreement with a previous study [28], we did not find any changes in

arterial stiffness after oral glucose challenge in healthy individuals, but this is not universal. Previous studies found significant decreases in AP [35, 36], AIx [34-36], AIx@75 [30, 36] and PWV [36] after either oral glucose tolerate test or a mix-meal in healthy individuals.

Previous studies have demonstrated that acute hyperglycemia significantly increases AIx in healthy individual and individuals with type 1 diabetes [37]. On the other hand, it has been showed that insulin significantly decreases AIx by using the euglycemic insulin clamp technique in healthy individuals [34-36, 38] and individuals with T2D [34, 39].

Our study was not without limitations. First, the age range in the present study was large (25-60 years old). Second, the number of women and men were not equal. Third, previous studies used oral glucose tolerate test (75g glucose) or a mix-meal while the present study used a lower dose of glucose (50g), which might affect outcomes compared to other studies. Fourth, to mimic daily life, participants with controlled hypertensions in this study continued taking anti-hypertensive medications during testing, which likely influence the variables we measured. While this is listed as a limitation, it was done by design in order to more accurately reproduce T2D diagnostic testing in the real-world setting.

In conclusion, the present study demonstrated that an oral glucose challenge alters central and peripheral hemodynamics in a similar fashion with no changes in arterial stiffness in healthy individuals and individuals with T2D and controlled hypertension.

COMPETING INTERESTS

The authors declare there are no competing interests.

AUTHOR CONTRIBUTION

Dr. Russell was responsible for the study design, obtaining human ethics approval, recruiting and testing participants, and manuscript preparation. Dr. Tai contributed to data collection and manuscript preparation. Mr. Figueroa contributed to participant recruiting and testing, and manuscript preparation.

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AVAILABILITY OF DATA AND MATERIALS

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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Table 1. Participant characteristics

	T2D (N=20)	Control (N=21)
Age (yr)	52 ± 8 (29-60)	48 ± 10 (25-60)
Sex	7 women / 13 men	8 women / 13 men
Height (m)	1.72 ± 0.07 (1.56-1.82)	1.73 ± 0.12 (1.53-1.92)
Weight (kg) *	92.6 ± 15.7 (44.0-111.2)	74.6 ± 10.5 (58.4-92.0)
Body Mass Index (kg/m^2) *	31.1 ± 4.2 (16.8-36.1)	25.0 ± 2.5 (21.1-31.8)
Fasting blood glucose (mmol/L) *	10.0 ± 3.1 (4.7-16.4)	5.3 ± 0.8 (4.3-7.2)
HbA_{1c} (%) *	7.6 ± 1.3 (5.1-10.7)	5.4 ± 0.2 (5.0-5.9)

Data are expressed as mean ± SD

*$p \leq 0.05$, different between T2D and Control

T2D, Type 2 Diabetes; HbA_{1c}, Glycosylated Hemoglobin

Table 2. Central and peripheral hemodynamics at baseline and 60 minutes post-oral glucose challenge

		Baseline	10	20	30	40	50	60
HR (bpm)	T2D (N=20)	66 ± 8	65 ± 7	69 ± 9†‡	70 ± 8†‡	71 ± 8†‡‖	70 ± 9†‡	70 ± 8†‡
	Control (N=21)	56 ± 10*	58 ± 10*†	59 ± 11*†	60 ± 10*†	61 ± 10*†‡‖	61 ± 10*†‡	62 ± 9*†‡‖
cSBP (mmHg)	T2D (N=20)	127 ± 12	121 ± 9†	123 ± 9	122 ± 10†	120 ± 11†‖	122 ± 10†	123 ± 10
	Control (N=21)	111 ± 12*	112 ± 12*	109 ± 12*‡	110 ± 13*	109 ± 13*	109 ± 13*	108 ± 12*†‡
cDBP (mmHg)	T2D (N=20)	87 ± 10	85 ± 8	83 ± 7†	83 ± 7†‡	80 ± 11†‡	82 ± 8†	83 ± 9†
	Control (N=21)	78 ± 8*	77 ± 9*	75 ± 9*†‡	75 ± 9*†‡	75 ± 9†‡	73 ± 10*†‡¶	75 ± 9*†η
bSBP (mmHg)	T2D (N=20)	135 ± 13	130 ± 11†	131 ± 9†	131 ± 12	130 ± 12†	129 ± 13†	131 ± 12
	Control (N=21)	120 ± 12*	120 ± 12*	118 ± 12*	119 ± 13*	118 ± 13*	118 ± 12*	118 ± 13*
bDBP (mmHg)	T2D (N=20)	86 ± 10	84 ± 8	82 ± 7†	82 ± 7†‡	81 ± 9†‡	82 ± 8†‡	82 ± 9†
	Control (N=21)	77 ± 8*	76 ± 9*	74 ± 9*†‡	74 ± 9*†‡	74 ± 9*†	72 ± 10*†‡‖¶#	74 ± 9*†η
bMAP (mmHg)	T2D (N=20)	109 ± 11	105 ± 8†	105 ± 7†	104 ± 8†	103 ± 9†	103 ± 9†	104 ± 10†
	Control (N=21)	97 ± 9*	96 ± 10*	94 ± 10*†‡	94 ± 9*†‡	94 ± 10*†	93 ± 10*†‡#	94 ± 10*†‡η

Data are expressed as mean ± SD

*p<0.05 different from T2D, †p<0.05 different from baseline, ‡p<0.05 different from 10, ‖p<0.05 different from 20, ¶p<0.05 different from 30, #p<0.05 different from 40, ηp<0.05 different from 50

bDBP, brachial diastolic blood pressure; bSBP, brachial systolic blood pressure; cDBP, central diastolic blood pressure; cSBP, central systolic blood pressure; HR, heart rate

Table 3. Arterial stiffness at baseline and 60 minutes post-oral glucose challenge

		Baseline	10	20	30	40	50	60
AP (mmHg)	T2D (N=20)	10.8 ± 6.7	10.2 ± 7.3	11.4 ± 8.0	11.1 ± 8.7	10.5 ± 7.4	9.6 ± 8.8	11.0 ± 7.4
	Control (N=21)	10.4 ± 3.5	10.6 ± 4.5	9.9 ± 5.4	10.3 ± 6.1	9.4 ± 4.9	10.7 ± 7.1	9.0 ± 6.3
AIx (%)	T2D (N=20)	26.1 ± 14.0	26.2 ± 14.1	26.1 ± 12.0	25.6 ± 16.7	25.4 ± 13.6	22.6 ± 17.0	25.8 ± 15.5
	Control (N=21)	31.0 ± 10.2	31.4 ± 14.6	28.8 ± 16.6	28.1 ± 15.1	27.8 ± 15.7	28.3 ± 17.0	24.8 ± 16.0
AIx@75 (%)	T2D (N=20)	21.3 ± 12.5	20.4 ± 13.8	22.9 ± 11.0	23.3 ± 15.5	22.2 ± 12.7	19.5 ± 15.9	23.3 ± 14.4
	Control (N=21)	20.3 ± 10.4	21.8 ± 14.6	20.3 ± 15.2	19.7 ± 13.5	20.4 ± 13.1	20.5 ± 16.2	17.8 ± 14.9
PWV (m/s)	T2D (N=20)	7.8 ± 0.9	7.7 ± 0.9	7.7 ± 0.9	7.7 ± 0.9	7.7 ± 0.9	7.7 ± 1.0	7.8 ± 0.9
	Control (N=21)	6.8 ± 1.0*	6.8 ± 1.1*	6.8 ± 1.0*	6.8 ± 1.0*	6.8 ± 1.0*	6.8 ± 1.1*	6.8 ± 1.0*

Data are expressed as mean ± SD

*$p<0.05$ different from T2D

AP, augmentation pressure; AIx, Augmentation Index; AIx@75, Augmentation Index Normalized at 75 Beats Per Minute; PWV, Pulse Wave Velocity