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Impaired fasting blood glucose is associated with increased endothelin-1 vasoconstrictor tone

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ABSTRACT

Aim/hypothesis: The experimental aim of this study was to determine whether ET-1-mediated vasoconstrictor tone is elevated in adult humans with impaired fasting blood glucose concentrations, independent of other cardiovascular risk factors.
Methods: Forearm blood flow (FBF: plethysmography) responses to intra-arterial infusion of selective ET_A receptor blockade (BQ-123: 100 nmol/min for 60 min) and non-selective $ET_{A/B}$ blockade (BQ-123 + BQ-788: 50 nmol/min for 60 min) were determined in 28 middle-aged, sedentary adults (17 M/11 F): 14 with normal fasting blood glucose (age: 57 ± 2 yr; 6 F/8 M; BMI: 29.2 ± 0.9 kg/m^2; glucose: 4.9 ± 0.1 mmol/L) and 14 impaired fasting blood glucose (58 ± 1 yr; 5 F/9 M; 29.6 ± 1.1 kg/m^2; 5.8 ± 0.1 mmol/L) concentrations.
Results: Selective ET_A receptor blockade elicited a significantly greater (~20%) increase in FBF in the impaired fasting glucose adults compared with the normoglycemia controls. $ET_{A/B}$ blockade resulted in a further 2-fold increase ($P < 0.05$) in FBF above that elicited by ET_A receptor antagonism in the impaired fasting glucose but not normal fasting glucose adults. There was a positive correlation between fasting blood glucose levels and the peak vascular responses to ET_A ($r = 0.44$; $P < 0.05$) and $ET_{A/B}$ ($r = 0.62$; $P < 0.05$) blockade. No other anthropometric, hemodynamic or metabolic variable was correlated with the blood flow responses to ET-1 receptor blockade.
Conclusions/interpretation: ET-1-mediated vasoconstrictor tone is elevated in adults with impaired fasting blood glucose concentrations, independent of other cardiometabolic risk factors. Enhanced ET-1 system activity may underlie endothelial vasomotor dysfunction and increased cardiovascular risk in adults with impaired fasting blood glucose concentrations.

1. Introduction

Approximately 80 million adults in the United States have impaired fasting blood glucose concentrations [1], defined as fasting plasma glucose between 5.6 and 6.9 mmol/L [2]. It has recently been reported that middle-aged adults without diabetes, but with elevated fasting plasma glucose, are at an increased risk for coronary heart disease (4). For example, Alexander et al. [3] demonstrated that adults with impaired fasting glucose are at a 50% higher risk of developing cardiovascular disease compared with adults with normal fasting glucose. The mechanisms responsible for this apparent increase in vascular risk are not fully understood. Glucose has been shown to adversely affect endothelial cell function, which may propagate the atherosclerotic process [4]. Several clinical studies have shown that impaired fasting glucose is associated with endothelial dependent vasodilator dysfunction [5,6], a central feature of atherogenesis [7].

Endothelin-1 (ET-1) is a potent vasoconstrictor peptide released by the endothelium that contributes to the regulation of vascular tone and has been implicated in the etiology of atherosclerotic vascular disease [8]. Interestingly, *in vitro*, a high glucose environment results in an elevation in endothelin-1 converting enzyme, suggesting a link between glucose and the ET-1 system [9].

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Currently, it is unknown whether ET-1 system activity is altered in adult humans with impaired fasting plasma glucose. If so, this may contribute mechanistically to impaired endothelial vasomotor function and increased cardiovascular risk in this population. Thus, the aim of this study was to determine whether ET-1-mediated vasoconstrictor tone is elevated in adult humans with impaired fasting blood glucose concentrations, independent of other cardiovascular risk factors.

2. Methods

2.1. Subjects

Twenty-eight sedentary adults participated in this study: 14 (6 F/8 M) with normal plasma glucose (<5.6 mmol/L); and 14 (5 F/9 M) with impaired fasting plasma glucose (5.6–6.9 mmol/L) concentrations. Groups were stratified according to American Diabetes Association criteria [2]. Subjects were non-smokers and free of overt cardiovascular disease. Fasting plasma lipid, lipoprotein, glucose and insulin concentrations were determined using standard techniques. HOMA-IR was calculated as previously described [10]. All women were at least 1 year postmenopausal and not taking hormone replacement therapy. Written informed consent was obtained according to the guidelines of the University of Colorado at Boulder.

2.2. Intra-arterial infusion protocol

All studies were performed between 7 AM and 10 AM after a 12-h overnight fast as previously described by our laboratory [11]. Briefly, following arterial catheterization, forearm blood flow (FBF: venous occlusion plethysmography) responses to BQ-123 (Clinalfa, AG), a selective ET_A receptor antagonist, infused for 60 min with FBF measured every 10 min. Thereafter, FBF was assessed every 10 min for an additional 60 min with the co-administration of BQ-123 and BQ-788 (Clinalfa, AG), a specific antagonist of ET_B receptors. Due to product availability, BQ-788 was infused in 7 of the 14 subjects in each group.

2.3. Statistical analysis

Differences in subject characteristics were determined by between-group analysis of variance (ANOVA). Group differences in FBF responses to BQ-123 and BQ-123 + BQ-788 were determined by repeated-measures ANOVA. Relation between variables of interest was assessed by linear regression analysis. There were no significant main effects of gender on FBF responses to endothelin blockade or FBF × gender interactions, therefore the data were pooled and presented together. Data are expressed as means ± SEM. Statistical significance was set at $P < 0.05$.

3. Results

Subject characteristics are presented in Table 1. There were no significant differences in baseline FBF between the normal (4.4 ± 0.3 mL/100 mL of tissue/min) and impaired (4.0 ± 0.3 mL/100 mL of tissue/min) fasting blood glucose groups. FBF responses to ET-receptor blockade are shown in Fig. 1. BQ-123 elicited a significantly greater (~20%) increase in FBF in the impaired fasting glucose than normal fasting glucose groups. Moreover, the addition of BQ-788 to BQ-123 resulted in a further 2-fold increase ($P < 0.05$) in FBF in the impaired fasting glucose but not normal fasting glucose adults. In the overall study population, there was a strong and positive correlation between fasting blood glucose levels and the peak vascular responses to BQ-123 ($r = 0.44$; $P < 0.05$) and BQ-

Table 1
Selected subject characteristics.

Variable	Normal fasting glucose ($n = 14$)	Impaired fasting glucose ($n = 14$)
Age (yrs)	57 ± 2	58 ± 1
Gender, M/F	8/6	9/5
Body mass (kg)	84.9 ± 3.9	87.5 ± 3.9
Body mass index (kg/m^2)	29.1 ± 0.9	29.7 ± 1.0
Body fat (%)	36.1 ± 1.5	35.4 ± 1.6
Waist circumference (cm)	94.3 ± 3.4	99.1 ± 2.8
Systolic BP (mmHg)	124 ± 2	127 ± 3
Diastolic BP (mmHg)	79 ± 2	79 ± 2
Total cholesterol (mmol/L)	5.0 ± 0.2	5.3 ± 0.3
LDL-cholesterol (mmol/L)	3.0 ± 0.2	3.4 ± 0.2
HDL-cholesterol (mmol/L)	1.3 ± 0.1	1.2 ± 0.1
Triglycerides (mmol/L)	1.5 ± 0.2	1.5 ± 0.2
Glucose (mmol/L)	4.9 ± 0.1	5.8 ± 0.1*
Insulin (pm/L)	49.8 ± 6.6	51.0 ± 6.6
HOMA-IR	1.9 ± 0.2	2.4 ± 0.3

BP = blood pressure; HDL = high-density lipoprotein; LDL = low-density lipoprotein; HOMA-IR = homeostasis model assessment of insulin resistance; values are mean ± SEM. *$P < 0.05$ vs. normal fasting glucose.

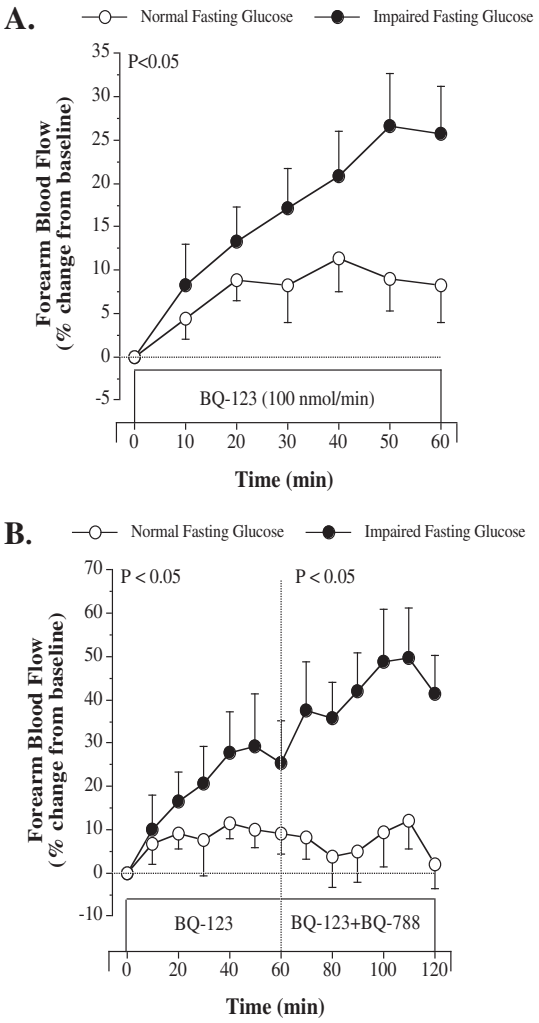

Fig. 1. Forearm blood flow responses to BQ-123 (100 nmol/min), a selective ET_A receptor antagonist (panel A) and BQ-788 (50 nmol/min), a selective ET_B receptor antagonist (panel B), in normal fasting glucose and impaired fasting glucose adults. Values are mean ± SEM. The *P* value refers to the difference in the FBF response to ET_A and $ET_{A/B}$ blockade in the normal vs. impaired fasting glucose groups.