Artery Research (2014) 8, 115–118

Available online at www.sciencedirect.com

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SHORT COMMUNICATION

Endothelin-1 system activity in adults with borderline high ldl-cholesterol

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Received 12 July 2013; received in revised form 4 February 2014; accepted 24 March 2014
Available online 18 April 2014

KEYWORDS
Endothelin-1;
Vasoconstriction;
LDL-cholesterol;
Endothelium

Abstract *Background:* Modest elevations in plasma low-density lipoprotein (LDL)-cholesterol have been shown to confer a significant increase in cardiovascular risk. Endothelin (ET)-1 is a vasoconstrictor peptide with proatherogenic properties. The experimental aim of this study was to determine whether ET-1 system activity is elevated in adults with borderline high LDL-cholesterol, independent of other cardiometabolic abnormalities.
Methods: Forearm blood flow (FBF; plethysmography) responses to intra-arterial infusion of ET-1, selective ET_A receptor blockade (BQ-123), and non-selective $ET_{A/B}$ blockade (BQ-123 + BQ-788) were determined in 40 middle-aged and older adults (45–70 years): 20 with optimal/near optimal LDL-cholesterol (<3.4 mmol/L) and 20 with borderline-high LDL-cholesterol (3.4–4.1 mmol/L).
Results: Both groups demonstrated a similar, non-significant (~10%) reduction in FBF to ET-1. BQ-123 and BQ-123 + 788 elicited a modest, but significant, increase in FBF (~15–20%) in each group. However, there were no group differences in the FBF responses to either selective ET_A or non-selective $ET_{A/B}$ receptor antagonism.
Conclusion: Borderline-high LDL-C is not associated with increased ET-1 mediated vasoconstrictor tone. Disrupted ET-1 system activity may not contribute to the increased cardiovascular risk burden with borderline-high LDL-cholesterol.

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http://dx.doi.org/10.1016/j.artres.2014.03.002

Introduction

Low-density lipoprotein (LDL) cholesterol is a major atherogenic fraction of total cholesterol[1,2] and an important predictor of myocardial infarction in middle-aged adults.[3] In fact, the risk of cardiovascular disease is estimated to increase by ~30% for every 30 mg/dL rise in plasma LDL-cholesterol concentration, suggesting increased cardiovascular risk burden at levels below the clinically recognized elevated range of >130 mg/dL.[1] Indeed, the relative risk of heart disease is nearly two-fold higher in adults with borderline high LDL-cholesterol (3.4–4.1 mmol/L [130–159 mg/mL]) compared with adults with optimal/near optimal LDL-cholesterol levels (<3.4 mmol/L [130 mg/dL]).[1] Moreover, nearly 40% of the adults in the United States have LDL-cholesterol levels in the borderline high range. Thus, understanding the mechanisms involved with the increased vascular risk with borderline high LDL-cholesterol has great public health importance.

Endothelin (ET-1)-1 is a powerful vasoconstrictor peptide that in addition to contributing to the regulation of vascular tone is also involved in the development and progression of atherosclerotic vascular disease.[4,5] Indeed, enhanced ET-1 system activity elicits a proinflammatory vascular phenotype and ET-1 immunoreactivity is prominent in the walls of atherosclerotic human vessels.[6,7] Moreover, ET-1 promotes fibrous tissue formation and inhibits endothelial nitric oxide synthesis.[8,9] Increased ET-1 vasoconstrictor tone is a common characteristic of numerous cardiovascular conditions and risk factors,[10–12] including clinical hypercholesterolemia.[13] Whether this vascular impairment is already apparent in the borderline-high cholesterolemic state with its corresponding increase in vascular risk is unknown.

Accordingly, the experimental aim of this study was to determine whether ET-1 system activity is elevated in adults with borderline high LDL-cholesterol, independent of other cardiometabolic abnormalities. If so, this may contribute mechanistically to endovascular dysfunction and increased cardiovascular risk in this population.

Methods

Subjects

Forty, sedentary middle-aged adults were studied: 20 with optimal/near optimal LDL-C (<130 mg/dL) and 20 with borderline-high LDL-C (130–159 mg/dL).[14] All subjects were sedentary, non-obese, non-smokers, normotensive, non-medicated (including vitamins) and free of overt cardiovascular disease as assessed by physical examination, fasting blood chemistries and electrocardiogram and blood pressure at rest and during incremental exercise performed to volitional exhaustion. All women were at least 1 year postmenopausal and had never taken or had discontinued use of hormone replacement therapy at least 1 year before the start of the study. Written informed consent was obtained according to the guidelines of the University of Colorado at Boulder.

Intra-arterial infusion protocol

All of the studies were performed between 7 AM and 10 AM after a 12-h overnight fast in a temperature-controlled room as previously described.[15] Briefly, a 5-cm, 20-gauge catheter was inserted into the brachial artery of the nondominant arm under local anesthesia (1% lidocaine). Forearm blood flow (FBF) at rest and in response to each pharmacological agent was measured by strain-gauge venous occlusion plethysmography (D.E. Hokanson, Bellevue, Washington). To rule out the possibility of nonspecific group differences to vasoconstrictor agents, vascular responses to norepinephrine were determined. Norepinephrine was infused at a rate of 260 pmol/min for 5 min, and FBF was measured during the last 3 min. After a 20-min rest period to allow FBF to return to baseline levels, ET-1 (Clinalfa, AG) was infused at a rate of 5 pmol/min for 20 min, and FBF was measured during the last 3 min. After a 30-min rest period to allow resting FBF to return to baseline, BQ-123 (Clinalfa, AG), a selective ET_A receptor antagonist, was infused at a rate of 100 nmol/min for 60 min. FBF was measured every 10 min throughout the infusion period. After 60 min of BQ-123 infusion, FBF was measured every 10 min during the combined infusion of BQ-123 and BQ-788. BQ-788, a selective ET_B receptor antagonist, was infused at a rate 50 nmol/min for 60 min.

Statistical analysis

Differences in subject baseline characteristics and the magnitude of change in FBF to norepinephrine and ET-1 were determined by between-groups analysis of variance (ANOVA). Group differences in FBF responses to BQ-123 and BQ-123+BQ-788 were determined by repeated-measures ANOVA. There were no significant gender interactions, therefore the data were pooled and presented together. Data expressed as means ±SEM. Statistical significance was set at $P < 0.05$.

Results

Selected subject characteristics are presented in Table 1. By design, total cholesterol and LDL-C levels were the only variables significantly different ($p < 0.05$) between the groups. The vasoconstrictor response to norepinephrine was not significantly different between the groups optimal/near optimal (from 4.0 ± 0.3 to 3.0 ± 0.3 mL/100 mL tissue/min) and borderline high (from 4.1 ± 0.3 to 3.0 ± 0.2 mL/100 mL tissue/min) LDL-C groups. Resting FBF was reduced by ~10% in response to ET-1 in both the optimal/near optimal (from 4.0 ± 0.2 to 3.6 ± 0.2 mL/100 mL tissue/min) and borderline high (from 3.9 ± 0.2 to 3.6 ± 0.3 mL/100 mL tissue/min) LDL-C groups (Fig. 1). In response to BQ-123, there was a significant increase in FBF (~15%) from baseline in both groups. The addition of BQ-788 did not significantly alter FBF in either group (Fig. 1). Importantly, there were no group differences in FBF responses to either BQ-123 ($P = 0.77$) or BQ-123 + BQ-788 ($P = 0.51$).

Discussion

The ET-1 system not only plays a central role in the regulation of vascular tone, but is also involved in the etiology