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Associations between trait anxiety, insulin resistance, and atherosclerosis in the elderly: A pilot cross-sectional study

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Summary
Anxiety has been shown to be associated with cardiovascular disease. Atherosclerosis is responsible for the vast majority of cardiovascular events. Recent evidence is accumulating to show that insulin resistance (IR) plays a central role in determining the clinical manifestations of established atherosclerotic lesions. The current preliminary study aimed to investigate the associations between trait anxiety, IR, and atherosclerotic progression in healthy elderly subjects with normal fasting glucose and without metabolic syndrome. Thirty-five healthy elderly subjects (19 males and 16 females, mean age 64.5±4.7 years) were enrolled in this study. Trait anxiety was measured using a questionnaire corresponding to the trait anxiety scale taken from the State and Trait Anxiety Inventory. The homeostasis model assessment (HOMA-R) and plasma leptin-to-adiponectin ratio (L/A ratio), which are convenient IR indexes calculated from fasting blood sampling, were examined. As measurements of atherosclerotic progression, we performed two ultrasound methods, namely brachial artery flow-mediated dilation (FMD), an endothelial function assessment quantitatively reflecting the endothelium-dependent vasodilation responses following hyperemia, and measurement of carotid intima-media thickness (IMT). The severity of trait anxiety was positively associated with HOMA-R and L/A ratio, and negatively associated with the percent change of brachial artery FMD (%FMD). HOMA-R and L/A ratio were positively associated with carotid IMT, and L/A ratio was negatively associated with %FMD. These data showed the associations between trait anxiety, IR indexes and endothelial dysfunction or atherosclerotic progression. This pilot study, with a

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cross-sectional design, supports the promising role of IR for clarifying the pathophysiological mechanism by which anxiety contributes to an increasing risk of atherosclerosis.

1. Introduction

Previous studies have demonstrated that trait anxiety increases the risk for morbidity and mortality of the development of cardiovascular disease (CVD) (Kawachi et al., 1994; Albert et al., 2005). Atherosclerosis is responsible for the vast majority of cardiovascular events. Trait anxiety has been reported to contribute in accelerating the evolution of atherosclerosis (Paterniti et al., 2001). Researchers have postulated that high trait anxiety tends to lead to atherosclerotic progression, resulting from physical inactivity, chronic inflammation, hypertension, cardiac autonomic abnormalities, or metabolic syndrome (Piccirillo et al., 1997; Rozanski et al., 1999; Shih et al., 2006; Engum, 2007).

In recent years, it has become clear that insulin resistance (IR), the resistance of cells to the effects of insulin to stimulate glucose uptake, plays an important role in increasing atherosclerotic risks including diabetes, hypercholesterolemia, and hypertension, and it has attracted much attention as a denominator of metabolic syndrome (Reaven, 1988; Cersosimo and DeFronzo, 2006). However, the association between trait anxiety and IR in healthy subjects with normal fasting plasma glucose (FPG) has been studied to a lesser extent.

Considering the important effects of anxiety and IR on atherosclerosis, comprehensive investigation regarding their mutual relationships is important to evaluate the pathophysiological mechanism by which trait anxiety leads to atherosclerotic progression. The current preliminary study with a small sample size aimed to investigate the associations between trait anxiety and IR or atherosclerotic progression in healthy elderly subjects with normal FPG and without metabolic syndrome. In addition, we examined the association between IR and atherosclerotic progression. Although the hyperinsulinemic euglycemic clamp (DeFronzo et al., 1979) and steady-state plasma glucose value (Shen et al., 1970) are the general standards to estimate IR, they involve complicated procedures. Thus, this study used the homeostasis model assessment (HOMA-R), which is a convenient parameter to estimate IR calculated from fasting blood insulin and glucose level (Turner et al., 1979). In addition, the plasma leptin-to-adiponectin ratio (L/A ratio), which has been proposed as a more sensitive and reliable marker of IR than HOMA-R (Diamond et al., 2004; Inoue et al., 2006), was examined in this study. As measurements of atherosclerotic progression, we underwent two ultrasound methods of brachial artery flow-mediated dilation (FMD) and carotid intima-media thickness (IMT). Endothelial dysfunction is known to appear in the initiation of early atherosclerosis (Ross, 1999). Brachial artery FMD is a non-invasive assessment method to assess endothelial function by quantitatively monitoring the vasodilation responses of vascular smooth muscle to the nitric oxide produced by endothelial cells following hyperemia (Celermajer et al., 1992). The measurement of carotid IMT using the ultrasound technique can detect morphological changes in the carotid artery, consisting of both intimal atherosclerotic processes and medial hypertrophy, without being affected by hyperemia (O'Leary et al., 1996).

This pilot study investigated a hypothesis: IR abnormalities associated with a higher trait anxiety lead to endothelial dysfunction, resulting in a clinical manifestation of established atherosclerosis.

2. Methods

2.1. Subjects

Elderly subjects in their 50s–70s were recruited from general inhabitants in Fukui prefecture, Japan, using a brochure that described the following criteria for exclusion: history of major atherosclerotic risk factors (such as hypertension, hypercholesterolemia, or diabetes mellitus), history of CVD (coronary artery disease, congestive heart failure, or hemodynamically significant valvular disease), history of neurological or psychiatric illness, chronic alcoholism, smoking, obesity with a body mass index (BMI) above 27, and continuous administration of drugs. Only postmenopausal females were included as female subjects. For the past and current psychological evaluations, the Structured Clinical Interview for DSM-IV Axis I Disorders (First et al., 1996) was used. Thirty-five subjects, consisting of 19 males aged 57–76 years (mean, 64.8 $\pm$ 5.1 years) and 16 females aged 56–74 years (64.1 $\pm$ 4.4 years), were enrolled. The study was conducted from January 2006 to February 2007, and all subjects gave written informed consent and were paid for their participation. The study protocol was approved by the Ethics Committee of the University of Fukui. All measurements, i.e., physical determinations and psychological and ultrasound measurements, were completed on the same day in this study.

2.2. Blood pressure and biochemical determinations

All subjects underwent measurement of systolic or diastolic blood pressure (BP) at the clinic three times after 10 min of rest in a supine position, and the mean of three measures of systolic or diastolic BP was used for analysis. Then, all subjects underwent venous fasting blood sampling from an antecubital vein in the right arm without having eaten breakfast. Serum lipid levels, i.e., total cholesterol (TC), high-density lipoprotein (HDL), low-density lipoprotein (LDL), and triglyceride (TG), were measured using enzymatic method. FPG was measured using a hexokinase-coupled reaction, and immunoreactive insulin (IRI) was measured using a solid-phase radioimmunoassay procedure. The IR index as assessed according to HOMA-R was