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Indoleamine 2,3-dioxygenase activation and depressive symptoms in patients with coronary artery disease

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Peak VO_2

Summary An increase in immune-stimulated synthesis of kynurenine from tryptophan by indoleamine 2,3-dioxygenase (IDO) has been observed in patients with coronary artery disease (CAD). However, neuropsychiatric correlates of IDO activation remain unexplored. We hypothesize that IDO activation, as measured by the kynurenine to tryptophan (K/T) ratio, is associated with depressive symptoms in those with CAD. This cross-sectional study recruited subjects with CAD ($n = 95$) from a cardiac rehabilitation facility. Demographic, anthropometric and cardiac data were obtained by chart review. Patients using an antidepressant were excluded. The presence of a major depressive episode or minor depression was assessed using a structured clinical interview for depression based on Diagnostic and Statistical Manual 4th edition criteria. The Center for Epidemiological Studies-Depression Scale (CES-D) was used to quantify depressive symptoms. A standardized exercise stress test was used to assess cardiopulmonary fitness as summarized using the peak volume of oxygen consumption (Peak VO_2). Kynurenine and tryptophan were assayed from fasting plasma samples to obtain the K/T ratio. Higher K/T ratios were significantly associated with higher CES-D scores ($\beta = .322$, $p = .002$) in a linear regression controlling for time since most recent acute coronary syndrome (tACS), age and sex. Twenty-four patients met criteria for depression (16 major depression; 8 minor depression). There was a trend towards higher K/T ratios in depressed vs. non-

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depressed patients (45.6 ± 20.0 μmol/mmol vs. 38.5 ± 15.7 μmol/mmol, $F = 3.778$, $p = .055$) when controlling for age, sex and tACS. Activation of IDO is associated with the severity of depressive symptoms among patients with CAD.
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1. Introduction

The prevalence of major depressive disorder (MDD) in patients with coronary artery disease (CAD) is roughly twice that of the general population (Lesperance et al., 1996; Bakish, 2001). In addition, many other CAD patients suffer from minor depression, and still others suffer from subsyndromal depressive symptoms that do not meet diagnostic criteria for depression (Hance et al., 1996). Major and minor depression have been associated with poorer quality of life (Sullivan et al., 2004) and cardiac mortality (Penninx et al., 2001), while subsyndromal depressive symptoms have been associated with poorer cardiopulmonary fitness (Lavoie et al., 2004; Swardfager et al., 2008).

Studies of patients with CAD have associated depressive symptoms with peripheral pro-inflammatory markers such as IL-6 and C-reactive protein (Su et al., 2008). Pro-inflammatory cytokines can upregulate the expression of indoleamine 2,3-dioxygenase (IDO) which catalyzes the rate-limiting step in the synthesis of kynurenine from tryptophan, increasing the plasma kynurenine to tryptophan (K/T) ratio (Schroecksnadel et al., 2006b). Elevated plasma K/T ratios have been observed in patients with CAD compared to controls (Wirleitner et al., 2003) where they have been correlated with other markers of immune activation (Wirleitner et al., 2003; Murr et al., 2007) and disease progression (Murr et al., 2007; Niinisalo et al., 2008). Thus the K/T ratio may be an important pathophysiological biomarker in those with CAD.

Previous studies have variably reported evidence of IDO activation in medically healthy depressed patients as compared to controls (Wood et al., 1978; Moller et al., 1982; Myint et al., 2007) and recently, the severity of depressive symptoms has been associated with the production of kynurenine and its metabolites in patients with major depression (Mackay et al., 2008). The possibility of a causal relationship between tryptophan catabolism and depressive symptoms was suggested by Maes et al. (2001) in a study of hepatitis C patients administered IFN-α (Bonaccorso et al., 2001; Maes et al., 2001). The resultant increase in depressive symptoms was correlated with inflammatory markers, and in susceptible patients, major depressive episodes were induced. A more recent study failed to replicate this finding, but not without presenting *post hoc* analyses implicating an imbalance of kynurenine metabolites further down the degradation pathway (Wichers et al., 2005).

The present study tests the hypothesis that IDO activation, as measured by K/T ratios, is associated with depressive symptoms in those with CAD. This study also explored relationships between the K/T ratio and cardiac factors previously associated with depressive symptoms such as obesity (McIntyre et al., 2006), poorer cardiopulmonary fitness (Lavoie et al., 2004; Swardfager et al., 2008) and specific symptoms of depression in *post hoc* analyses.

2. Method

2.1. Participants

Patients with CAD participating in a 1 year cardiac rehabilitation program involving supervised aerobic and resistance training were recruited. The Toronto Rehab Cardiac Program accepts patients recovering from ACS or cardiac procedures by physician referral. Patients were included based on histories of myocardial infarction (MI), angiographic evidence of ≥50% blockage in at least one major coronary artery, or prior revascularization such as percutaneous coronary intervention (PCI) or coronary artery bypass graft (CABG) surgery. Patients enter rehabilitation a minimum of 6—8 weeks post-CABG, 6 weeks post-MI, or 3 weeks post-PCI. Patients were excluded if they could not complete cardiopulmonary fitness testing, the Center for Epidemiological Studies-Depression (CES-D) scale or a structured clinical interview, if they were using an antidepressant, or if their medical records were otherwise incomplete. Patients were also excluded based on the presence of neurodegenerative illness, acute viral or bacterial infection, cancer, or psychiatric diagnoses other than depression. Participants provided written informed consent in accordance with local Research Ethics Boards. Consecutive patients were approached until 95 eligible patients agreed to participate (Fig. 1).

2.2. Materials

Depressive symptoms were quantified using the CES-D scale, a 20-item questionnaire scored between 0 and 60 used extensively in CAD populations (Blumenthal et al., 2003; Ried et al., 2006). Major and minor depression were diag-

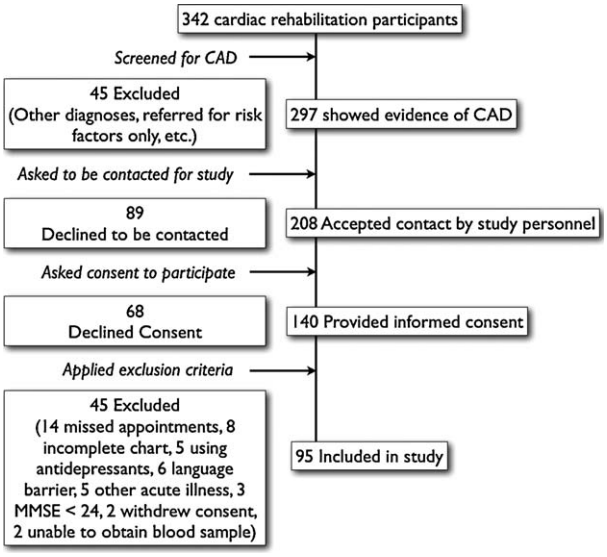

Figure 1 Flow chart of study design and recruitment details.

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