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Low plasma vitamin E levels in major depression: diet or disease?

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INTRODUCTION

Oxidative stress, an imbalance between levels of antioxidants and generation of pro-oxidants *in vivo*, has been suggested to be involved in the pathophysiology of major depression. Depression has been reported to be associated with enhanced activation of the immune system (Maes, 1999) and the combination of low folate and elevated homocysteine levels (Bottiglieri et al., 2000) both of which may lead to or be associated with, a state of increased oxidative stress (Floyd et al., 1999, Huang et al., 2001). The association between depression and low membrane phospholipid content of long chain ω -3 polyunsaturated fatty acids (PUFA) (Peet et al., 1998) may also be suggestive of enhanced oxidative stress as long chain ω -3 PUFA are highly oxidisable (Song et al., 2001).

Vitamin E is one of the major lipid soluble antioxidants *in vivo*, of which α -tocopherol is the dominant form (Wang & Quinn, 1999). It is a strong determinant of the susceptibility of low-density lipoprotein to oxidation (Esterbauer et al., 1991) and is one of the most important defences against membrane damage from reactive oxygen species (Wang & Quinn, 1999). Maes et al. (2000) reported that serum levels of α -tocopherol were lower in 42 patients suffering from major depression compared to healthy controls, and suggested that this might be due to decreased antioxidant defenses. In a larger study of 262 elderly subjects with depressive symptoms, plasma α -tocopherol levels were found to be lower in males, but not females, when compared to healthy controls (Tiemeier et al., 2002), although the significance of this was abolished after controlling for nutrition-related behavioural variables. Tiemeier et al. (2002) suggest that the low serum α -tocopherol levels may be due to a poor diet,

with low vitamin E intake. The present study examined dietary vitamin E intake (measured as α -tocopherol equivalents) and plasma α -tocopherol levels in a group of depressed patients from the Illawarra region of New South Wales, Australia.

METHODS

Subjects

The study was granted approval by the University of Wollongong Human Research Ethics Committee, and subjects gave written informed consent. Study subjects were recruited through local health services and the Northfields Clinic at the University of Wollongong. The major inclusion criteria were age between 18-70 years and currently satisfying the diagnostic criteria for major depression (American Psychiatric Association, 1994). Exclusion criteria were the presence of any co-existing major psychiatric disorder or serious medical disorder. Plasma vitamin E and cholesterol levels were measured in 49 subjects (29 females, 20 males), but financial limitations meant that dietary data is only available for the first 19 subjects enrolled (12 females and 7 males).

Data collection and analysis

The depression scores presented herein are those derived from administration of the Beck Depression Inventory (BDI). Other depression scores were measured, and the results of these were consistent with the BDI and are not shown. A fasted venous blood sample was taken into a tube containing EDTA to give a final concentration of 1mg/ml. Plasma was separated from erythrocytes by low speed centrifugation at 800xg, and stored at -80°C . Plasma cholesterol was determined using an enzymatic assay on a Cobas-Mira Plus automated analyser (Roche Diagnostics, Australia).

Plasma α -tocopherol was determined by reverse phase high performance liquid chromatography (HPLC) with UV detection using a modification of a method described by Kock et al., (1997). There is a strong relationship between plasma cholesterol and α -tocopherol levels (McGavin et al., 2001), thus all results presented are expressed as cholesterol standardised α -tocopherol ($\mu\text{mol } \alpha\text{-tocopherol} / \text{mmol total cholesterol}$). Dietary intake was assessed by a dietitian using a narrative diet history (Tapsell et al., 1999). Dietary histories were analysed using ESHA Food Processor (Version 8.0, ESHA Research, Oregon).

Statistical Analyses

Values for biochemical variables are given as mean \pm SEM unless otherwise stated. Statistical analyses were performed on Stata version 7 (Stata Corp. TX, USA) and SPSS version 10 (Chicago, IL). Relationships between variables were examined using Spearman's correlations and multiple regression analysis. An unpaired t-test was used to compare plasma α -tocopherol levels between the present study group and a healthy Australian population sample.

RESULTS

The mean age of this study sample (n=49) was 47.7 ± 11.8 (Mean \pm SD), comprised of 20 males and 29 females. Mean baseline levels for all study subjects for α -tocopherol, depression score and total cholesterol were $4.71 \pm 0.13 \mu\text{mol}/\text{mmol chol}$, 25.0 and $5.10 \pm 0.13 \text{ mmol}$ respectively. A significant inverse relationship was noted between baseline plasma α -tocopherol and depression score ($r = -0.367$, $p = 0.009$).

There was no significant difference between males and females in baseline

depression score ($M=26.4$, $F=24.1$) or α -tocopherol ($M=4.56 \pm 0.19$, $F=4.82 \pm 0.18$), and no significant association between depression score and age ($r=-0.105$, $p=0.472$). However multiple regression analysis revealed that the significance of the association between baseline α -tocopherol and depression score abolished after controlling for sex and age ($r=-0.268$, $p=0.069$). Plasma α -tocopherol levels in this depressed population were significantly lower than has been previously reported for a healthy Australian population (Ward et al., 2002), (4.71 ± 0.13 vs 5.67 ± 0.48 $\mu\text{mol}/\text{mmol}$ chol respectively, $p<0.05$).

Dietary analysis revealed that the Australian recommended daily intake (RDI) for vitamin E, namely 8mg α -tocopherol equivalents (NH&MRC, 1991), was met by 17 of the 19 subjects, with the mean (\pm SEM) intake being 25.1 ± 2.8 mg. In this subgroup, mean plasma α -tocopherol level was 4.91 ± 0.19 $\mu\text{mol}/\text{mmol}$ chol. There was no correlation between plasma α -tocopherol and dietary α -tocopherol intake in the subgroup of subjects for whom dietary data was available.

DISCUSSION

The mean plasma level of α -tocopherol in this group of depressed subjects was significantly lower than has been reported previously for a non-depressed Australian subject group (Ward et al., 2002). In agreement with Maes et al. (2000), the present study found no significant effect of gender in the relationship between plasma α -tocopherol and depression. However the significance of the association between depression score and α -tocopherol was diminished after controlling for age and sex. The Rotterdam Study, which found lower plasma α -tocopherol only in males, also found that the effect was abolished when other nutrition behaviour-related variables

were taken into account (Tiemeier et al. 2002). While the sample size in the Rotterdam study is larger than that of the present study, it also examined an elderly population (mean age = 73 y). Increasing oxidative stress with post-maturational aging is currently a widely held theory of biological aging (Schoneich, 1999), and thus the age differences between these studies may be important. Another larger scale, longitudinal study in elderly Japanese using a condensed version of the Geriatric Depression Score assessment, found no relationship between serum α -tocopherol and depression score at baseline, but found that in men only, α -tocopherol at baseline was a significant predictor of progression of depressive status at a 4 year follow-up (Shibata et al., 1999). Conversely, levels of a marker of oxidative damage to DNA were found to be positively associated to depression scores in female, but not male, Japanese workers (Irie et al., 2002). Healthy males and premenopausal females have been reported to differ in their levels of lipid oxidation markers (Ide et al., 2002), and taken together these studies suggest that it might be important to consider gender in examining the relationship between depression score and oxidative status, however in the present study no significant effect of gender was discernable.

The measurement of a single plasma antioxidant, as done in the present study, is limited in its ability to give a comprehensive indication of total oxidative stress, however as yet there is no gold standard measurement for oxidative stress. There is evidence to support the use of plasma α -tocopherol as a marker of oxidative stress, in an examination of the oxidative stress imposed by cigarette smoking plasma α -tocopherol was found to be significantly negatively correlated to plasma levels of the lipid oxidation product malondialdehyde (Liu et al., 1998), which has previously been

found to be higher in depressed patients than controls (Bilici et al., 2001). The present study is also limited by the lack of a study specific control (non-depressed) group, however we have no reason to suspect that residents of the Illawarra region, being a coastal community within 100km of Australia's largest city, differ significantly in their dietary α -tocopherol (vitamin E) intake to the average Australian intake.

The findings of the present study suggest that plasma cholesterol-adjusted α -tocopherol (vitamin E) levels are lower in depression, which is in agreement with the findings of others (Maes et al., 2000). The adequacy of α -tocopherol intake, coupled with the lack of association between plasma levels and dietary intake of α -tocopherol, suggests that lower plasma levels of α -tocopherol are less likely to be due to poor diet and may be due to some other factor associated with major depression.

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