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Abnormal Glucose Tolerance, White Blood Cell Count, and Telomere Length in Newly Diagnosed, Antidepressant-Naïve Patients with Depression

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Abstract

Chronic mood disorders have been associated with a shortened telomere, a marker of increased mortality rate and ageing, and impaired cellular immunity. However, treatment may confound these relationships. We examined the relationship of glucose tolerance, white blood cell count and telomere length to depression in newly diagnosed, antidepressant-naïve patients. Subjects with major depression (n=15), and matched healthy control subjects (n=70) underwent a two-hour oral glucose tolerance test and evaluation of blood cell count and telomere content. The depression group had significantly higher two-hour glucose concentrations and a lower lymphocyte count than control subjects (respective means [SD] for two-hour glucose were 125.0 mg/dL [67.9] vs 84.6 [25.6] (p<.001); for lymphocyte count $2.1 \times 10^9/L$ [0.6] vs. $2.5 \times 10^9/L$ [0.7] p=.028). Telomere content was significantly shortened in the depression group (87.9 [7.6]) compared to control subjects (101.0 [14.3]; p<0.01). Abnormal glucose tolerance, lymphopenia and a shortened telomere are present early in the course of depression independently of the confounding

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effect of antidepressant treatment, supporting the concept of major depression as an accelerated ageing disease.

Keywords

Major depressive disorder; Telomere; Diabetes mellitus; Immunosenescence; Lymphopenia; Glucose tolerance; Accelerated ageing; Drug-naïve

Introduction

Depression will be the second contributor to the global burden of disease by 2020, according to the World health organization (WHO). The burden of depression is due not only to psychiatric disability but also to the associated comorbidity with physical diseases. The pathophysiology underlying the comorbidity remains unclear although several mechanisms have been implicated. As an etiological explanation, the association between mood disorders, cardiovascular diseases and immune disturbances has received considerable attention (Blume et al., 2011; Brown et al., 2009; Marano et al., 2009) suggesting that both systems might contribute to the increased mortality associated with mood disorders (Lippi et al., 2009).

Diabetes mellitus has been studied as a key factor contributing to the relationship between depression and increased cardiovascular disease. Epidemiological studies show that patients with diabetes have an increased risk of developing major depression (Egede, 2005), an association first described in 1969 (Mueller et al., 1969). The prevalence of depression among patients with type 2 diabetes mellitus is twice that of the general population (Nichols and Brown, 2003), with an estimated prevalence of depression in diabetic patients of 11–15% (Anderson et al., 2001). A meta-analysis suggested that a depressed adults have a 37% increased risk of developing type 2 diabetes (Knol et al., 2006) while another study showed a 23% increased risk of developing type 2 diabetes mellitus in depressed young adults (Brown et al., 2005; Knol et al., 2007). The mechanism of the association between depression and diabetes is still unknown, although the physiological reaction to the psychological stress associated with diabetes cannot completely explain the association (Grandinetti et al., 2000). In addition, potential confounding factors that are associated with weight gain and impaired glycemic control, such as body mass index and antidepressant treatment, must be taken into account (Derijks et al., 2008).

Immune disturbances have been described in patients with depression. Both immune activation and immune suppression (Blume et al., 2011) through an impaired cellular immunity function (increased inflammatory markers, neutrophilia and lymphopenia) have been described to underlie a major depressive episode. As stated before with diabetes and depression, the mechanism of association is unknown, although lymphopenia and a reduced lymphocyte proliferative response to mitogen have been confirmed in a review in depression suggesting an immune suppression related with an increased mortality. On the same line of evidence depression is associated with decreases in the number and percentage of lymphocytes (Zorrilla et al., 2001).

Another possible marker of morbidity in depression that has received considerable attention in mood disorders is telomere length. Telomere length has been linked to increased senescence in patients with depressed mood (Wolkowitz et al., 2010). The telomere is a nucleoprotein complex at the end of mammalian chromosomes that maintains chromosomal integrity and consists of double-stranded 5'-TTAGGG-3' repeats. A shortened telomere has been linked to post-stroke mortality, dementia, cognitive decline (Martin-Ruiz et al., 2006),

all-cause mortality in people above age 60 (Cawthon et al., 2003), type 1 diabetes (Balasubramanyam et al., 2007), type 2 diabetes (Adaikalakoteswari et al., 2007), and cardiovascular disease (Obana et al., 2003). Patients with major depressive disorder have been found to have a shorter telomere length (Lung et al., 2007; Wolkowitz et al., 2011), a marker of increased mortality rate and ageing (Fitzpatrick et al., 2007) associated with oxidative and inflammatory stress. However, the subjects studied were not treatment-naïve, raising the question of whether this association was confounded by antidepressant treatment.

In an effort to clarify the pathophysiology of major depressive episodes, we tested the hypothesis that patients with major depression have cardiovascular and immune disturbances, and a shortened telomere. In order to avoid confounding by antidepressant medication side effects, we examined this relationship in newly diagnosed, antidepressant-naïve patients.

Materials and methods

Subjects

Patients with a major depressive disorder without psychotic features were recruited at the time of their first lifetime contact with psychiatric services for a depression. They came to clinical contact in a general academic hospital (Hospital Clinic of Barcelona). The catchment area for the hospital, Esquerra Eixample, is a relatively homogeneous middle class/upper middle class neighbourhood in the center of Barcelona. These patients were enrolled if they had never previously received antidepressant or mood-stabilizing medications. They were allowed to receive anti-anxiety medication (lorazepam) the night before blood was drawn, to a maximum of 3 mg, but not on the day of the blood sampling and oral glucose tolerance test (GTT). Healthy control subjects were recruited using advertisements. All subjects came from a larger study of diabetes in neuropsychiatric disorders (Kirkpatrick et al., 2009).

Additional inclusion and exclusion criteria for all subjects were (1) age from 18 to 64 years, (2) no history of diabetes or other serious medical or neurological condition associated with glucose intolerance or insulin resistance (eg, Cushing disease), (3) not taking a medication associated with insulin resistance (hydrochlorothiazide, furosemide, ethacrynic acid, metolazone, chlorthalidone, beta blockers, glucocorticoids, phenytoin, nicotinic acid, cyclosporine, pentamidine, or narcotics) and (4) no history of cocaine use in the previous 30 days. For control subjects, additional exclusion criteria were (1) no lifetime diagnosis of psychosis (associated with glucose intolerance; (Fernandez-Egea et al., 2009a) or major depressive disorder, 2) no current diagnosis of adjustment disorder, and (3) had not previously received psychotropic medication.

All subjects gave written informed consent for participation in the study, which was conducted with the oversight of the investigators' institutional review boards.

Assessments

All subjects were interviewed using the Spanish translation of the Structured Clinical Interview (SCID). The patients had no other history of Axis I disorder besides major depression. They were antidepressant-naïve, but no further information regarding past depressive symptoms was obtained. No subject with acute medical illness was included. For control subjects, additional exclusion criteria were (1) no lifetime diagnosis of psychosis (associated with glucose intolerance (Fernandez-Egea et al., 2009a); or major depressive disorder, 2) no current diagnosis of adjustment disorder, and (3) had not previously received psychotropic medication.

They were also administered the Dartmouth Assessment of Lifestyle Inventory (DALI), which quantifies substance abuse (Rosenberg et al., 1998), including a measure of smoking status (mean number of cigarettes per day). All subjects were given a 2-hour 75 g oral glucose tolerance test which began between 8 and 9 AM after an overnight fast. Cortisol was sampled between 8 and 9 AM prior to ingesting glucose for the GTT. Height and weight, while wearing underwear and without shoes, were recorded between the blood samplings. Body mass index (BMI) was calculated using the formula (weight [kg]/height [m]²). Further details on the GTT have been provided previously (Fernandez-Egea et al., 2009a).

Telomere DNA content (TC) was measured in blood leukocytes as previously described (Fernandez-Egea et al., 2009b). TC is directly proportional to telomere length measured by Southern blot ($r = 0.904$), can be measured with as little as 5 ng of genomic DNA, is insensitive to fragmentation of the DNA to <1 kb in length, and can be performed with DNA isolated from fresh, frozen, and paraffin-embedded tissues (Fordyce et al., 2006). Briefly, known DNA masses were UV cross-linked to a membrane, hybridized with telomere-specific oligonucleotides, end-labeled with fluorescein, and then detected with an alkaline phosphatase-conjugated anti fluorescein antibody that produces light when incubated with CDP-Star substrate. Blots were exposed to Hyper film, digitized by scanning, and the telomere hybridization signals were measured. TC for each sample is reported as a percentage of the median chemiluminescent signal from 6 replicate determinations of each patient DNA relative to the chemiluminescent signal in the same amount of a reference DNA standard (placental DNA) measured in parallel. The laboratory determining TC was blind to the subject's clinical diagnosis. Cortisol was measured using an immunoassay (ADVIA Centaur; Siemens Healthcare). The coefficient of variation was 6.5%. Glucose was measured by an Advia 2400 Analyzer (Siemens, Barcelona Spain), using glucose oxidase reagents from the same manufacturer. Intra assay reliability expressed as coefficient of variation were lower than 3.2 % for low values and lower than 2.8 % for higher values.

Statistical Analysis

The two matched groups were compared using the non-paired Student's t-test, or the χ^2 test for comparisons of proportions. Significance was defined as $p < 0.05$ for all statistical tests, and these were performed using SPSS version 17.0 for Windows.

As noted above, data came from a larger study of glucose tolerance in psychiatric disorders (Fernandez-Egea et al., 2009a). Blind to glucose tolerance, white blood cell count and telomere length, subjects with major depressive disorder and healthy controls were matched (by group means, not individual matching) on age, gender, BMI, cortisol, catchment area and smoking (number of cigarettes per day). Smoking (measured as cigarettes/day) and two hour glucose showed an abnormal distribution; however, log transformation did yield a normal distribution for the latter variable. Age and fasting glucose were analyzed with non parametric tests (Mann Whitney U test) due to non normal distribution. A t-test comparison was conducted for two hour glucose load and lymphocyte count in 15 patients with MDD and 70 controls.

Data on telomere length was available for 9 subjects with depression and 48 control subjects. These two groups were also very similar with regard to age, gender, BMI, catchment area and smoking (data not shown). Using a t-test, we compared the mean telomere length in the depression and control groups.

Results

The two groups were very similar with regard to demographic and clinical variables (see Table). The depression group had one subject of Latin American origin; the control group

had three subjects of Latin American origin, another of Indian origin and another of Asian origin; all other subjects were European Caucasians.

Mean fasting glucose concentration was similar in the depression group compared with controls (84.9 mg/dL [11.2] vs 83.4 mg/dL [6.7]; ($p=0.63$)). Cortisol values did not differ statistically between groups, with a value of 19.2 $\mu\text{g/dL}$ [8.6] for major depression group compared with 22.1 $\mu\text{g/dL}$ [6.3] for matched controls ($p=.130$). Mean two-hour glucose (2HG) concentration was significantly greater in patients with depression (125.0 mg/dL [67.9]) compared to control subjects (84.6 mg/dL [25.6]); ($p<.001$; as noted above, this analysis used log-transformed glucose values)(Figure 1). Two subjects (13%) with depression had fasting glucose values that met criteria for impaired fasting glucose ($>100\text{mg/dL}$ and $<126\text{mg/dL}$) while no control subject met the criteria ($p=.002$);(none of the subjects met fasting glucose criteria for diabetes mellitus ($\geq 126\text{mg/dL}$)). Three patients (20%) met criteria for impaired glucose tolerance ($N=2$) (a two-hour glucose concentration $>140\text{mg/dL}$ and $<200\text{mg/dL}$) or diabetes ($N=1$) (two-hour glucose concentration $\geq 200\text{ mg/dL}$) while 3 control subjects (4%) met criteria for impaired glucose tolerance ($p=.035$). Three patients had taken lorazepam the previous night; their values for glucose tolerance, telomere length, and white blood cell count did not differ statistically to those of the other patients.

White Blood Cell (WBC) count [SD] was similar between both groups; major depression $6.4 \times 10^9/\text{L}$ [1.3] vs control group $7.1 \times 10^9/\text{L}$ [1.8] ($p=.182$). Granulocytes did not differ between both groups. Neutrophil count in major depression was $3.9 \times 10^9/\text{L}$ [0.8] and in control group $4.1 \times 10^9/\text{L}$ [1.8] ($p=.587$); Eosinophil count in major depression was $0.26 \times 10^9/\text{L}$ [0.2] and in control group $0.23 \times 10^9/\text{L}$ [0.2] ($p=.591$); Basophil count in major depression was $0.07 \times 10^9/\text{L}$ [0.01] and control group $0.02 \times 10^9/\text{L}$ [0.01] ($p=.157$). In the agranulocytes we did find differences only in the lymphocyte count. Monocyte count in major depression group was $0.38 \times 10^9/\text{L}$ [0.2] and in control group $0.41 \times 10^9/\text{L}$ [0.2] ($p=.482$).

Lymphocyte count [SD] was significantly lower in the depression group $2.1 \times 10^9/\text{L}$ [0.6] compared with control subjects $2.5 \times 10^9/\text{L}$ [0.7] ($p=.028$). (Figure 2).

Data on telomere content was available for 9 of these same subjects with depression, and for 48 control subjects. These groups were also similar with regard to age, gender, body mass index, cortisol, catchment area and smoking (data not shown). The depression disorder group had a significantly decreased mean [SD] telomere content (89.0 [7.4]) compared with control subjects (103.7 [11.3]; $p=.002$). (Figure 3)

Using a Pearson correlation analysis, 2HG, lymphocyte count and telomere length were evaluated and no significant correlation was found (data not shown)

Discussion

In this study, drug-naïve patients with depression had a higher two-hour glucose concentration than control subjects, matched for age, gender, body mass index, cortisol, catchment area and smoking.. Cortisol concentrations, a measure of stress and a risk factor for insulin resistance, were not significantly associated with two-hour glucose concentrations and did not differ significantly between groups, although there was a trend towards higher levels in controls compared with patients. Another study in first episode naïve patients showed no difference in cortisol levels between patients and controls. (Wang et al., 2012). The same article also states that more recent studies suggested that hypercortisolemia is almost exclusively a feature of very severe depressive episodes, such as are observed when depression is accompanied by psychotic symptoms.

Decreased insulin sensitivity in younger patients with major depression has previously been reported using an oral glucose tolerance test, although treatment may have confounded the results (Hung et al., 2007). Insulin resistance was also found in people with depressive symptoms in a middle-aged and elderly population (Pan et al., 2008). Insulin resistance has also been associated with moderate to severe depressive symptoms in both a follow-up survey and a cross-sectional study (Timonen et al., 2007) in which depressive symptoms were rated by self-report. One study using GTT did not find glucose intolerance in subjects with depressive symptoms. However, the fact of considering depressive symptoms and not a diagnosis of major depressive disorder, antidepressant treatment (previous and current), and a low prevalence of depressive symptoms in the study population, may have affected the results (Rhee et al., 2008).

Depressed patients also had significantly shortened telomere length and a reduced lymphocyte count, compared with matched control subjects.

Our results also extend previous findings of a shortened telomere in patients with major depressive disorder with previous antidepressant treatment (Lung et al., 2007; Simon et al., 2006; Wolkowitz et al., 2011). Pre-diabetic states such as impaired glucose tolerance have been also been associated with a shortened telomere (Adaikalakoteswari et al., 2007).

Decreased lymphocyte blood count has been previously described in major depression disorder (Darko et al., 1988) implying a possible mechanism characterized by immune suppression (Zorrilla et al., 2001). Total lymphocyte count, a crude marker of immune status, has been inversely correlated with age-related frailty (Collerton et al., 2012) and subsequent mortality of elderly men (Bender et al., 1986).

All those previous findings support the concept of major depression as an accelerated ageing disease, as others have previously stated (Heuser, 2002). Decreased lymphocyte count is a marker of normal immunosenescence (Ferrando-Martinez et al., 2011), as a shortened telomere length and abnormal glycemic homeostasis (Kassi and Papavassiliou, 2008). Several authors have shown diverse abnormalities in naïve patients with a first episode of major depression; decreased adiponectin (Leo et al., 2006a), a pro inflammatory and procoagulant state (Leo et al., 2006b), decreased plasma amino acid levels (Zheng et al., 2012), and immune dysregulation (Gabbay et al., 2009) (although some patients were treatment free and not naïve). However, no study has reported in naïve patients our results, suggesting an accelerated aging state.

As other authors have described (Wolkowitz et al., 2011) as a partial explanation of the previous findings, depressed individuals may be more sensitive to the telomere-shortening effects of oxidation and inflammation due to some biochemical “co-factor” (hyperglycaemia) or due to a lack of counter-regulatory anti-oxidant and anti-inflammatory activities (immune suppression through lymphopenia). Our results suggest that those disturbances are present at the onset of the disease, allowing another causal explanation for those findings (Wolkowitz et al., 2011), that the diagnosis of major depression has several intrinsic features related with accelerated ageing.

Our study was limited by the relatively small sample sizes and a cross-sectional design. Our measure of the stress response was a single, fasting, morning cortisol sample; specific data from a twenty-four hour curve would have provided a more complete assessment. We also did not record the duration of depressive symptoms. Strengths of our study included a drug-naïve population, and a relative ethnic homogeneity of the sample. In order to evaluate the directionality of the relationship between abnormal glucose tolerance, telomere length, lymphocyte count and depression, longitudinal studies are needed.

Our results confirm that patients with major depressive disorder show subtle disturbances prior to exposure to pharmacological treatment that may contribute to their increased morbidity and mortality rate. Those disturbances behave as markers of cell ageing, which taken all together with the diagnosis of major depression, might reflect that psychiatric and physical illness represent the same pathology. Our findings are consistent with the concept of depression as a systemic disease (Wolkowitz et al., 2010)

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Figure 1.
Mean 2 hour glucose load (2HG) (mg/dL) (Error Bar: ± 2 Standard Error)

Figure 2.
Mean lymphocyte count ($10^9/L$) (Error Bar: ± 2 Standard Error)

Figure 3.
Mean telomere content (Error Bar: ± 2 Standard Error)

Table

	Depression (N=15)	Control (N=70)	
Mean Age (years)	30.7 ± 10.0	27.8± 6.8	p=.549
Gender: % Male	60.0	62.2	p=.836
% living in catchment area	80.0	68.6	p=.378
Mean BMI	23.4 ± 4.1	23.7 ± 2.9	p=.766
Mean number of cigarettes/day	9.9± 12.7	6.2 ± 8.3	p=.219
Cortisol (µg/dL)	19.2 ± 8.6	22.1± 6.3	p=.130
Mean fasting glucose (mg/dL)	84.9.4 ± 11.2	83.4 ± 6.8	p=.632
Impaired fasting glucose %	13	0	p=.002
Mean two hour glucose (mg/dL)	125.0± 67.9	84.6± 25.6	p<.001
Impaired glucose tolerance/Diabetes %	20	4	p=.035
Mean telomere content **	87.9±7.6	101.2±14.3	p=.009
Mean White Blood Cell count (10 ⁹ /L)	6.4±1.3	7.1±1.8	p=.182
Mean lymphocyte count (10 ⁹ /L)	2.1±0.6	2.5±0.7	p=.028

**

For TC (Depression N=9 and Control N=48)