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Combined biological tests for suicide prediction

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Abstract

Disturbances in serotonin neuroregulation and in hypothalamic-pituitary-adrenal axis activity are both likely, and possibly independent, factors in the genesis of suicidal behavior. This analysis considers whether clinically accessible measures of these two disturbances have additive value in the estimation of risk for suicide. Seventy-four inpatients with RDC major or schizoaffective depressive disorders entered a prospective follow-up study from 1978–1981, underwent a dexamethasone suppression test (DST) and had fasting serum cholesterol levels available in the medical record. As reported earlier, patients who had had an abnormal DST result were significantly more likely to commit suicide during follow-up. Serum cholesterol concentrations did not differ by DST result and low cholesterol values were associated with subsequent suicide when age and sex were included as covariates. These results indicate that, with the use of age-appropriate thresholds, serum cholesterol concentrations may be combined with DST results to provide a clinically useful estimate of suicide risk.

Keywords

Dexamethasone suppression test; cholesterol; cortisol; depressive disorder

1. Introduction

Suicide is a leading cause of death in the United States and is preceded by major depressive disorder (MDD) in the majority of cases (Barraclough et al., 1974). Accordingly, concerns over risks for suicide account for most psychiatric admissions of patients with MDD and thus the considerable expense and psychosocial disruptions that are associated with hospitalization. Such concerns are typically driven by suicidal tendencies as revealed in thoughts, plans, or behaviors but risk assessment is more complex and clinicians must weigh additional factors. These judgments have considerable importance. They underlie recommendations ranging from closer surveillance at home to involuntary psychiatric admission and they are important, as well, in determining inpatient activity levels and discharge timing. The relevant literature, though, yields little consistent evidence on which to base these estimations (Goldstein et al., 1991;Coryell and Young, in press).

Under the circumstances, a biological measure that is both clinically practical and sufficiently sensitive and specific to suicide risk would have substantial value. The failure to fully suppress plasma cortisol after a 1mg. dose of dexamethasone is one of the most widely investigated of

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potential measures. Convergent findings show hypothalamic-pituitary-adrenal (HPA) axis hyperactivity to be a risk factor for suicide in MDD (Dorovini-Zis and Zis, 1987;Nemeroff et al., 1988;Rao et al., 1989;Szigethy et al., 1994) and thus support the test's validity as a measure of suicidality. A recent meta-analysis of seven studies concluded that dexamethasone suppression test (DST) nonsuppression increases the risk for suicide by a factor of 4.6 (Mann et al – personal communication).

Total serum cholesterol concentration is another clinically accessible measure of potential value in that numerous reports have associated suicidality with low serum cholesterol levels. Some investigators sampled suicide attempters from consecutive psychiatric admissions and compared them to nonattempters (Kunugi et al., 1997;Papassotiropoulos et al., 1999;Garland et al., 2000;Guillem et al., 2002), or to well controls (Gallerani et al., 1995;Sarchiapone et al., 2000;Tripodianakis et al., 2002). Others have described samples comprised specifically of patients with MDD (Modai et al., 1994;Alvarez et al., 1999;Kim and Myint, 2004), bipolar disorder (Modai et al., 1994;Bocchetta et al., 2001), panic disorder (Modai et al., 1994;Bocchetta et al., 2001;Obrocea et al., 2002;Ozer et al., 2004), borderline personality disorder (Atmaca et al., 2003) or anorexia nervosa (Favaro et al., 2004) and these also noted significantly lower cholesterol concentrations in comparison to those of nonattempters or of controls. Thus, the relationship between serum cholesterol and suicidality does not seem to be limited to individuals with major depressive disorder. Findings that this relationship is particularly strong for violent suicide attempts (Alvarez et al., 2000;Bocchetta et al., 2001;Atmaca et al., 2003;Kim and Myint, 2004) suggest that a low plasma cholesterol concentration is a risk factor for completed suicide as well. Studies using community samples have, in fact, shown this (Lindberg et al., 1992;Zureik et al., 1996;Ellison and Morrison, 2001). One large study from Finland did not and, instead, found a significant relationship between suicide and high cholesterol concentrations (Tanskanen et al., 2000). Some have suggested that this result reflected a particularly high rate of alcohol in Finland and the tendency of excessive alcohol intake to increase both cholesterol levels and risks for suicide (Golomb et al., 2004).

Biological evidence linking cholesterol and suicidality derives from demonstrated relationships between cholesterol concentrations and serotonin measures. Serotonergic dysfunction is a well-established substrate for suicidal behavior (Mann et al., 1999;Mann et al., 2001), a relationship apparently mediated by increased aggressivity (Golomb, 1998;Oquendo et al., - In press.). Low plasma concentrations of cholesterol in turn, have been associated with low platelet 5-HT content (Delva et al., 1996), low plasma serotonin concentrations (Steegmans et al., 1996) and blunted neuroendocrine responses to MCPP (Terao et al., 1997) or fenfluramine (Muldoon et al., 1992).

Fawcett et al (Fawcett et al., 1997) has proposed that serotonergic function and HPA-axis hyperactivity comprise independent risk factors for suicide. The former is thought to result in impulsivity and the latter in psychic pain and agitation. Insofar as both processes are independent of the other, biological measures of them should be additive in their implication of risk.

2. Methods

2.1. Subjects

An earlier report described this sample in detail (Coryell and Schlesser, 2001). Briefly, 78 individuals with Research Diagnostic Criteria (Spitzer et al., 1978) unipolar (n = 59), bipolar I (n=10), bipolar II (n = 9) or schizoaffective (n = 2) depression entered the NIMH Collaborative Depression Study (CDS) as inpatients at the Iowa site between 1978 and 1981 and, during their

hospitalization, underwent a 1 mg. DST. The DST was not included among CDS assessments but many of the subjects also participated in a concurrent study of the diagnostic correlates of dexamethasone suppression (Schlesser et al., 1980). In other cases attendings obtained the test for clinical purposes.

2.2. Procedures

All CDS participants underwent extensive baseline clinical assessments that included the schedule for affective disorders and schizophrenia (Endicott and Spitzer, 1978). The DST was typically obtained within three days of admission and post-dexamethasone cortisol samples drawn at 8 a.m., 4 p.m. and/or 11 p.m.

All subjects entered a follow-up study with direct interviews scheduled at six-month intervals for the first five years and annually thereafter.

Raters learned of completed suicides as they attempted to schedule further interviews with a given subject. In these instances, attempts were made to interview family members as to the circumstances. All identifying data for all subjects had been screened with the National Death Index at intervals so that the mortality status of subjects lost to follow-up has been ascertained. As reported previously (Coryell and Schlesser, 2001), seven (21.9%) of 32 patients with a post-dexamethasone cortisol greater than 5 μg/dl indicating nonsuppression, committed suicide in the ensuing 10 years while only one (2.2%) of the remaining 46 patients did so.

A fasting serum cholesterol determination was one of the routine admission tests obtained on the University of Iowa psychiatric units during the three years of CDS intake. A review of medical records identified values for 74 of these 78 patients.

2.3. Data analysis

Univariate comparisons of continuous variables used t-tests. Cox regression analyses were used to assess relationships between serum cholesterol concentration, DST result and the demographic variables age and sex. Survival analyses were also used to derive cumulative probabilities of suicide across groupings based on baseline cholesterol measures. All tests for significance were two-tailed with P set at 0.05.

3. Results

The eight patients who eventually committed suicide, and the remaining 66 patients, had mean (SD) fasting serum cholesterol concentrations of 185.4 (46.2) mg/dl and 213.6 (43.9) mg/dl, respectively ($t = -1.709$, $df = 72$, $P = 0.092$). Suicides and nonsuicides did not differ significantly by age. Mean (SD) values were 39.4 (16.7) and 35.4 (14.2), respectively. Cholesterol concentrations did increase significantly with age, however ($r = 0.458$, $P < 0.0001$) and, when age was entered as a covariate in a Cox regression analysis, the relationship between baseline cholesterol concentration and eventual suicide was significant (Wald $X^2 = 4.7$, $df = 1$, $P = 0.030$). Five (62.5%) of the 8 suicides and 43 (65.2%) of the nonsuicides were female. Results were little changed when sex was added as well (Wald $X^2 = 4.6$, $df = 1$, $P = 0.032$). An ROC analysis indicated that a threshold of 190 mg/dl yielded the best balance of sensitivity (0.56) and specificity (0.74).

Cholesterol concentrations did not differ by DST suppressor status; mean (SD) values were 204.1 (43.7) mg/dl and 215.2 (45.3) mg/dl for patients who were nonsuppressors and those who were suppressors, respectively. Within the latter group, the sole patient who suicided had a baseline cholesterol value of 166 while the remaining subjects had a mean (SD) value of 216.3 (45.2) (nonsignificant). Among those who had been DST nonsuppressors, the seven who

suicided had a mean (SD) baseline cholesterol concentration of 188.1 (49.1) and the remaining nonsuppressors had a mean (SD) value of 210.7 (42.2) (nonsignificant).

Previous studies of serum cholesterol levels and subsequent suicide divided cholesterol values into either three (Partonen et al., 1999) or four (Lindberg et al., 1992;Ellison and Morrison, 2001) groups. Because of the limited size of the current sample, values were ranked into three equal groups and the third with values less than or equal to 190 mg/dl were designated as high risk. Four (17.4%) of these 23 subjects and 4 (7.8%) of the remaining 52, committed suicide. A Kaplan-Meier hazard function (Fig. 1) showed that the differential risk increased progressively over the fifteen-year follow-up. The cumulative survival estimations for those with low cholesterol concentrations and for the remaining subjects were 77.3% and 81.2%, respectively.

The proportion of patients who committed suicide increased in a stepwise fashion from those who had both a normal DST result and serum cholesterol values above the bottom third to those who had an abnormal DST result and cholesterol levels in the lowest third of the distribution (Table 1).

4. Discussion

With control for age and sex, lower baseline serum cholesterol concentrations were clearly associated with eventual suicide in this group of inpatients with MDD. DST results were also predictive of eventual suicide yet bore little relationship to cholesterol concentrations. These findings are consistent with the hypothesis that HPA-axis hyperactivity and serotonergic deficits, here implied by low serum cholesterol levels, comprise orthogonal risk factors for suicide.

The clinical application of these two determinations presupposes appropriate thresholds to separate test results indicative of high risk from those that imply lower risk. A threshold of 5μg/dl for cortisol levels drawn at 0800 or 1400 following dexamethasone at 2300 is the most widely used to designate individuals as having HPA-axis hyperactivity but this was derived as being optimal for the separation of melancholia and nonmelancholic conditions rather than the prediction of eventual suicide. A different threshold appears to offer a better separation of psychotic and nonpsychotic MDD (Schatzberg et al., 1983) and the same may be true for the identification of eventually suicidal MDD patients. This possibility has not been explored. Unfortunately, our working data set lists each individual’s suppressor status but not their post-dexamethasone cortisol values.

Likewise, the four studies that have described associations between baseline cholesterol and subsequent suicide assigned subjects to three or four groups on the basis of these concentrations and found that the risk for suicide fell progressively across groups from low to high concentrations (Lindberg et al., 1992;Neaton et al., 1992;Zureik et al., 1996;Ellison and Morrison, 2001). Though none of these studies conducted ROC analyses to identify optimal thresholds, the step-wise increase in risk across groups of three and four suggest that a clear breakpoint may not have emerged.

As did Lindberg et al (Lindberg et al., 1992), we found that the relationship between serum cholesterol concentration and subsequent suicide was significant only with control for age. This renders more problematic the use of cholesterol concentrations as a clinical tool for estimating suicide risk in that thresholds appropriate for specific age cohorts will apparently be necessary. Because low cholesterol levels have been associated with suicide in large community-based studies, normal distributions from the ambient population may supply provisional thresholds.

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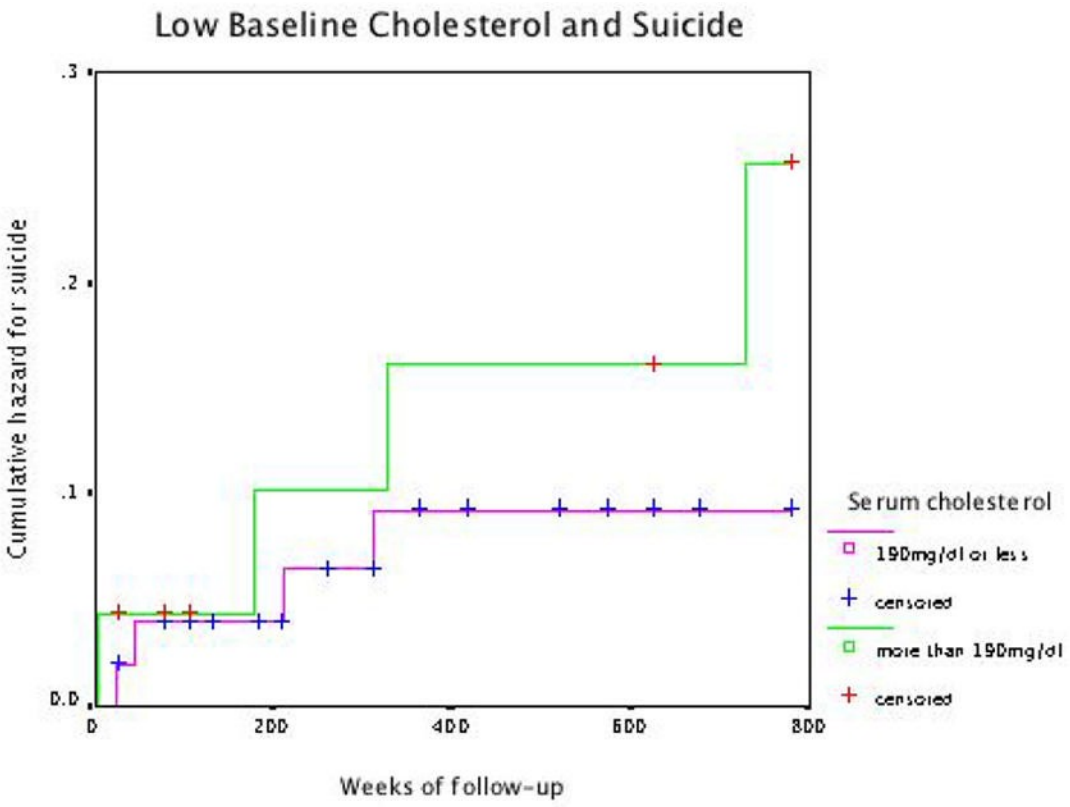

Figure 1.
Low Baseline Cholesterol and Sucide

Table 1

Risk Indicators and Suicide

plasma cholesterol ≤190 mg/dl	DST nonsuppression	n	# (%) suicide	Survival analysis: cumulative probability, %
no	no	30	0	0
yes	no	13	1 (7.7%)	10.0
no	yes	21	4 (19.0)	20.9
yes	yes	10	3 (30.0)	40.9