

Journal of Clinical and Basic Cardiology

An Independent International Scientific Journal



Journal of Clinical and Basic Cardiology 2000; 3 (3), 173-176

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Heart-Mood-Death: The Clinical Expression of the Cholesterol-Serotonin Controversy by the Temporal Distribution of Deaths from Coronary Heart Disease and Suicide

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Cholesterol and serotonin are both involved in the pathogenesis of atherosclerosis, the underlying cause of most cases of coronary/ischaemic heart disease and of depression, a common factor in suicide. High levels are associated with heart disease and low levels with depression and suicidal behaviour. The purpose of this study was to examine the temporal distributions of deaths from coronary/ischaemic heart disease and suicide in two distinct geographic areas, Israel and Lithuania, and their relationship to environmental physical activity. Data were accumulated over three consecutive periods. A total of 18063 suicides (fatal and attempts) in Israel and 10792 suicides (fatal only) in Lithuania were analysed, as were 3179 deaths from myocardial infarction and stroke in Israel and 149294 deaths from ischaemic heart disease and stroke in Lithuania. The monthly death distribution was compared between groups and correlated with monthly parameters of solar and geomagnetic activity, space proton flux and other physical indices. Pearson correlation coefficients and their probabilities were obtained. The results showed that the monthly number of deaths from coronary/ischaemic heart disease and suicide are significantly and adversely correlated. However, despite its many common pathogenetic mechanisms with ischaemic heart disease, stroke was not related to suicide for this factor. The death distributions of ischaemic heart disease, stroke and suicide were significantly but differently related to geomagnetic activity, space proton flux, and radiowave propagation. We speculate that these findings are at least partly attributable to the role of depression-related cholesterol-serotonin interactions in the development, clinical course and prognosis of both ischaemic heart disease and suicidal behaviour. *J Clin Basic Cardiol 2000; 3: 173-6.*

Key words: ischaemic heart disease, suicide, stroke, cholesterol, serotonin

Since the experiments of Anitchskov and Chalutou in 1913 [1], researchers have recognised the dominant role of cholesterol in the pathogenesis of atherosclerosis and related diseases, including the number one killer of modern times, coronary/ischaemic heart disease. Many therapeutic strategies today focus on cholesterol lowering with diet, exercise and drugs, especially statins. These measures have led to a decrease in mortality from coronary/ischaemic heart disease in recent decades. Nevertheless, the decrease in total mortality has been much less than expected, apparently due to an accompanying increase in non-disease-related deaths. Indeed, at least one large study has shown that suicide and trauma may account for up to 70 % of all deaths. [2]

At the same time, a vast amount of new data has been accumulating in the fields of human behaviour in general, and in the neurobiochemistry of depression, aggressiveness and suicidal behaviour in particular. [3-6] The first suggestions of the importance of serotonin/5-hydroxytryptamine in human psychiatry appeared in the 1950s. [7, 8] By the 1990s, the role of serotonin in the pathogenesis of depression and suicide was confirmed, while a complicated interrelationship was noted between cholesterol and serotonin, leading many cardiologists to consider depression an important prognostic sign of major coronary events. [9] Based on these findings, our team combined these data and revealed an opposite relationship between the number and time of deaths from coronary/ischaemic heart disease and suicide and some factors of environmental physical activity. [10-13]

The aim of the present study was threefold:

1. To compare the monthly death distribution from ischaemic/coronary heart disease and suicide in two distinct geographic areas, Lithuania and Israel, in relation to the cholesterol-serotonin controversy.
2. To examine the suggestion raised by our previous observations that coronary heart disease and suicide have a strong

but negative relationship with environmental physical activity, and this affects many pathogenetic features of these two heart-mood entities:

3. To determine if the relationship of suicide to coronary/ischaemic heart disease holds true also for stroke, a disorder closely related to atherosclerosis and sharing many of the same risk factors.

Materials and methods

Four groups of suicide deaths were included, three in Israel and one in Lithuania.

In Israel: 2359 fatal suicides recorded from 1981 to 1989 (108 consecutive months) (1595 males, 67.61 % and 764 females, 32.39 %); 2753 fatal suicides recorded from 1974 to 1992 (excluding 1989, when data were not available in Israel, for technical reasons; 216 months) (1858 males, 67.49 %, and 895 females, 32.51 %); and 15435 suicide attempts recorded from 1974 to 1992 (excluding 1989) (5438 males, 35.23 %, and 9997 females, 64.77 %). The total suicide (fatal and attempts) group in Israel (for 216 months) numbered 18063, 6159 males (34.10 %) and 11,904 females (65.90 %). (For technical reasons, the summarised deaths may be higher than the individual figures in some cases.)

In Lithuania: 10,092 fatal suicides recorded from 1990 to 1996 (84 months) (8236 males, 81.61 % and 1856 females, 18.39 %).

For comparison, data were collected on monthly hospital deaths from acute myocardial infarction (total 1892) and stroke (total 1287) at a major medical centre in Israel from 1974 to 1992 (236 months). In Lithuania, data on ischaemic/coronary heart disease (total 114,574) and stroke (total 37,720) from 1990 to 1996 (84 months) were derived from the International Disease Classification (World Health Organisation, Geneva, 1998).

To determine the relationship of these temporal distributions with environmental physical activity, physical data were collected for the same time periods from the National Geophysical Data Center, National Space Services Center, and Air Force Geophysical Laboratory, USA [14–16] and from the Izmiran Institute of the Academy of Sciences of the former USSR (for 1974–1989). [17] (For technical reasons, some of the space physical data were missing so that the number of months compared was not always equal.) Specifically, we examined solar activity, geomagnetic activity, and space proton flux > 90 MEV in addition to hours of positive and negative ionisation, sudden magnetic disturbances of the ionosphere and early morning (minimal) and noon (maximal) radiowave propagation.

Statistical analysis

Pearson correlation coefficients (r) and their probabilities (p) were calculated between monthly suicide events and deaths from coronary/ischaemic heart disease and stroke in Lithuania and Israel. Pearson correlation coefficients and their probabilities were also calculated between the monthly number of deaths from all causes under study and levels of cosmophysical parameters and compared between deaths from suicide and coronary/ischaemic heart disease/stroke. A p value of less than or equal to 0.05 was considered statistically significant; a p value of 0.06–0.1 was considered a trend. The statistical analysis was performed with the SAS software (SAS Institute, Cary, NC).

Results

Figure 1 shows the monthly distribution of attempted and fatal suicides in Israel, 1972–1992 (excluding 1989) and Lithuania, 1990–1996, and Figure 2 shows the correlation between monthly number of deaths from coronary/ischaemic heart disease and stroke and suicide in Lithuania, 1990–1996 (84-month data). Comparison of the monthly fatal suicides (n = 2359) and deaths from acute myocardial infarction (n = 1573) in Israel over 108 consecutive months (1981–1989) yielded a negative correlation (r = -0.326, p = 0.0005). Figure 3 shows the monthly correlation coefficients between number of deaths from coronary/ischaemic heart disease and suicides (fatal and non-fatal) in Israel and cosmophysical parameters (solar, ionosphere, geomagnetic field activity, space proton flux). In Lithuania, the monthly number of coronary/ischaemic heart disease-related deaths (n = 114,574) was directly correlated with the monthly solar activity indices (r = 0.24, p = 0.03); there was also a trend for a correlation with geomagnetic activity (r = 0.20, p = 0.06). By contrast, the distribution of deaths from suicide (n = 10,092) was negatively related to both monthly solar activity parameters (r = -0.60 to 0.65, p = 0.0001) and geomagnetic activity (r = -0.243 to -0.30, p = 0.003 and 0.004). Stroke-related deaths showed a significant negative relationship only with space proton flux > 90 MEV. The stroke-suicide mortality interrelationship did not achieve statistical significance (p = 0.06).

Discussion

In December 1996 *Time* magazine, quoting a study in *Neurology*, informed readers that individuals who have had one or more episodes of depression are at three times the normal risk of heart attack, similar to those with arterial hypertension or high cholesterol. [18] These data were supported by the post-infarction, late-potential study of Ladvig et al. [9], who reported that “cardiac deaths ... were significantly predicted by severe forms of post-AMI depression as revealed by univariate analysis. The evidence was stronger for predicting

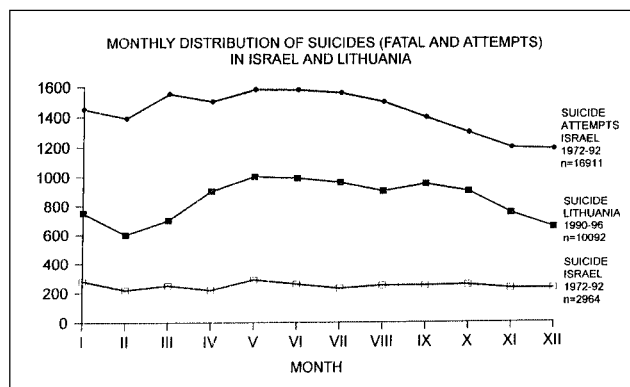


Figure 1. Distribution of monthly suicide deaths in Israel and Lithuania

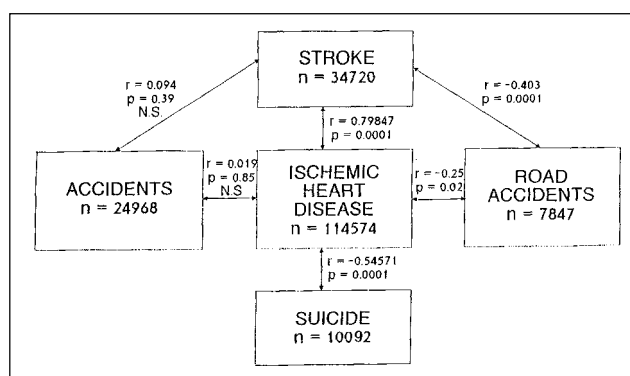


Figure 2. Pearson correlation coefficients (r) and their probabilities (p) between monthly number of deaths from IHD, stroke, suicide and accidents (Lithuania, 1990–1996, 84 months' data)

	GEOMAGN. ACTIV. K	IONIZATION HOURS (*)	SUNSPOT W	SOLAR FLUX 2800 MG/10.7 cm	IONOSPHERE MAGN. DIST. S.D	RADIOWAVE PROPAGATION FOR2 MIN. FOR2 MAX.	PROTON FLUX (>90 MEV)
1. SUICIDE /FATAL AND ATTEMPTS/ ISRAEL /n=18063/	N.S.	N.S.	N.S.	0.12 p=0.09 n=192	-0.507 p=0.0001 n=156	-0.15 p=0.05 n=156	0.425 p=0.0001 n=83
2. MYOCARDIAL INFARCTION BELINSON M.C /n=1892/	N.S.	N.S.	0.162 p=0.03 n=180	0.238 p=0.002 n=286	-0.152 p=0.019 n=286	0.320 p<0.0011 n=180	0.515 p=0.001 n=180
3. STROKE BELINSON M.C /n=1287/	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	-0.221 p=0.05 n=107

Figure 3. Correlation coefficients (r) and their probabilities (p) between number of monthly deaths from ischaemic/coronary heart disease, stroke and suicide and nine cosmophysical parameters in Israel

cardiac death (p < 0.001) than arrhythmic events (p < 0.035).” Depression is also considered a major predictor of suicide or suicide attempts by most of the studies in this field [19–21] and Fawcett and co-workers [20] have shown that suicide attempters have a predominantly low serum cholesterol level (< 160–180 mg%). Accordingly, in our previous analyses of the monthly relationship between coronary heart disease and suicide [10–13], and in the present study, we noted a highly significant and negative relationship between these two groups of deaths in both Lithuania and Israel. These observations were accompanied by findings of a very different relationship of these two groups with physical environmental activity. We attribute this difference to the role of serotonin-related mechanisms in the pathogenesis of these disorders.

In the late 1980s, a series of publications appeared in the neuropsychiatric literature [22, 23] and also in JAMA [24, 25] on the results of depression therapy with transcranial magnetic stimulation, and changes in melatonin, a derivative of serotonin, with changes in the magnetic field. [26, 27] All showed some sort of antagonistic effect of lipids, including cholesterol and serotonin-related metabolic and behavioural phenomena. This was followed by studies of the relationship between levels of cholesterol-serotonin and their derivatives melatonin and 5-hydroxyindoleacetic acid (5-HIAA) with signs of aggressiveness, depression, and self-destructive behaviour in humans, using high-low fat diets, and in monkeys, using measurements of 5-HIAA in the CSF and the brain cortex. [28, 29] Depression was found to be related to a low level of serotonin and melatonin and an increase in the number of serotonin receptors in human blood platelets and in brain cortex. Furthermore, in a study in our center [30], our team demonstrated that the level of prolactin, a close associate of serotonin, rises on days of high levels of geomagnetic activity, when a trend to a decrease occurs in both suicide (attempts and deaths) and severity of migraine, a neurovascular phenomenon also related to serotonin activity. [27, 31] These findings were supported by our 1995 study [10] indicating a negative relationship between monthly suicide number and the geomagnetic activity index (K) over a 107-month period. [10, 12] Recently, The Scandinavian and The West of Scotland Statin Studies [32–34] have pointed to the important role of cholesterol-lowering drugs (statins) in preventing heart disease. These findings were accompanied by evidence that some of these drugs, and low-fat diets, decrease the serotonin level in the central nervous system while increasing aggressive behaviour and depressive and suicidal episodes [4, 6] leading to little change in overall mortality. [21] The differences found among the different types of statins were attributed to the differing ability of these agents to cross the blood-brain barrier and thereby to affect the level and neurobiologic function of serotonin. [35, 36] Finally, it has been demonstrated under experimental conditions that the serotonin-related endothelial-derived relaxing factor (EDRF) is seriously damaged by atherosclerotic plaques, which in turn inhibit the normal vascular response to vasospasm [37] and may predispose affected individuals to plaque rupture, the principal underlying mechanism of coronary thrombosis and myocardial infarction, and a great proportion of sudden cardiac deaths.

The latter study may also explain our surprising finding that the number of deaths from stroke, which is very closely related pathogenetically and statistically with coronary heart disease, was not significantly associated temporally with suicide, also a strongly and adversely correlated entity with coronary heart disease. This may be due to the great proportion of stroke deaths that occur late after the acute event and/or differences in some stroke and coronary heart disease risk factors, (such as the presence of atrial fibrillation or high alcohol consumption. [38, 39] Indeed, one of our earlier studies indicated that atrial fibrillation, but not heart attacks, is adversely correlated with the daily geomagnetic activity level [40], as is the ratio of deaths from coronary heart disease and stroke. [13] We accepted that 85 % of all strokes in developed countries are ischaemic, ie, involve the transport of thrombi by the bloodstream from the enlarged left atrium to the brain, especially in the presence of atrial fibrillation or in patients after myocardial infarction.

In 1997 additional evidence was published showing the close levels between mood and vascular pathology. Everson et al. [41], in the conclusion of their four-year observation of the progression of carotid artery atherosclerosis, noted that: "Hopelessness is an independent predictor of cardiovascular

disease and mortality in both American and Finnish populations." The temporal distribution of the prevalence of the subsequent cardiovascular or behavioural events can be influenced by environmental physical factors.

Conclusions

1. The monthly number of deaths from coronary/ischaemic heart disease is significantly and negatively correlated to the monthly number of deaths from suicide.
2. Despite their many common pathogenetic mechanisms and similar temporal distribution of deaths, coronary/ischaemic heart disease and stroke do not show a similar temporal relationship with deaths from suicide.
3. The monthly number of deaths from coronary/ischaemic heart disease, stroke and suicide are significantly related, though in opposite directions, to some environmental physical activity parameters.
4. Depression-related mechanisms involving the serotonin-cholesterol interaction are presumed to play a role in the development, clinical course and prognosis of both ischaemic heart disease and suicidal behaviour, with involvement of changing levels of environmental physical activity.

Acknowledgement

We are grateful for the editorial and secretarial help of Mrs. Gloria Ginzach and Mrs. Melanie Kawe.

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