Psychoneuroimmunoendocrinology Review and Commentary

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Psychoneuroimmunoendocrinology describes the interrelationship of mental, neurological, hormonal, and immunological functions, addressing the impact of cognitive images of the mind (whatever its elusive definition) on the central nervous, endocrine, and immune systems. It encompasses biofeedback and voluntary controls, impacts on physiology of thought, attitude and belief, past/present stress, placebos, social relationships, and "energy medicine." This column highlights clinical applications of cogent studies from these arenas of holistic medicine in the new millennium.

Type 1 Diabetes and Stress

Diabetes mellitus Type 1 (T1D) is an autoimmune disorder attributed to both genetic and environmental factors. This study included 107 children with diabetes (CD) and 153 nondiabetic controls of comparable age and gender distribution at the time of diagnosis. Parents of both groups completed a questionnaire on socioeconomic status and stressful life events or adverse situations at home and school. Lower social class was more prevalent among the mothers of CD (p = 0.002) versus the controls. Stressful life events, problems at home (parental abuse, parental dispute) and at school (poor performance) were more frequently observed in the CD group than in the controls (parental death: p = 0.05, job loss: p = 0.05, parental abuse: p = 0.002, quarrels between parents: p = 0.05, quarrels among siblings: p = 0.002 and poor school performance: p = 0.037). Regression analysis indicated that lower maternal social class (odds ratio [OR]: 3.86, 95% CI: 1.37-10.9), body mass index (OR: 0.87, 95%CI 0.78-0.97), increasing age (OR 1.14, 95%CI 1.02-1.27) were the factors potentially influencing the occurrence of T1D, while the 2-year period prior to diabetes occurrence emerged as the most important one (OR 2.49, 95%CI 1.14-5.42).


Comment: Children with diabetes seemed to have a history of more stressful conditions in the two years prior to diagnosis, with significantly increased frequency compared with controls. There was also a higher clustering in those of lower social class, which in itself carries more sources of stress. The authors think that pervasive stress possibly contributes to the development of type 1 diabetes in genetically susceptible individuals. Obviously, more controlled work needs to be done to confirm this relationship.

Depression and Diabetes

In 1,900 interviews (> 72% of survivors and located subjects of 3,500 household-residing adults surveyed at baseline), the 13-year cumulative risk for developing type 2 diabetes was 2.2 (5.2%) in those with major depressive disorder, but not milder depression or other forms of psychiatric disorder. This doubling of risk did not reach significance. The relationship was not weakened after all adjustments for confounders. Eaton WW et al. Depression and risk for onset of type II diabetes. A prospective population-based study. Diabetes Care 1996;19:1097.

Comment: Major depressive disorder nonsignificantly doubled the risk for onset of type 2 diabetes. Even though these statistics did not reach significance, the fact that there is a plausible mechanism which might explain this relationship makes this doubling of risk intriguing. Depression itself is a psychological stress, which evokes a greater hypothalamic-pituitary-adrenal axis response. It is known that higher levels of adrenal corticosteroids aid or abet predispositions to diabetes. And some studies have linked depression itself to higher levels of corticosteroids. Trials of relaxation-inducing techniques have the potential for improving the lot of those with unipolar depression, stress and type 2 diabetes (see below).

Diabetes and Depression

Depression is prevalent and chronic in diabetes and is associated with poor glucose regulation and poor compliance with diabetes treatment. Sixty-eight type 2 diabetic patients with poor glycemic control, 28 of whom had active major depression (DSM-III-R), completed a randomized, double-blind trial of eight weeks of treatment with nortriptyline in doses to achieve blood levels of 50-150 ng/ml. Depression improvement was gauged with the Beck Depression Inventory and glucose control was monitored with HbA1c levels. Compliance behavior was assured with medication dispensing devices and glucometers equipped...
with electronic memory. The reduction in depressive symptoms was significantly greater in depressed patients treated with nortriptyline versus those on placebo (p = 0.03). Nortriptyline was not superior to placebo in reducing HbA1c of the depressed subjects (NS) and the direct effect of nortriptyline was to worsen glycemic control, whereas depression improvement had an independent beneficial effect on HbA1c values. Major depression in diabetic patients is effectively treated with nortriptyline at the expense of a direct hyperglycemic effect. Depression improvement was reflected in better glycemic control but negated by nortriptyline’s direct effect on glycemic management, suggesting that a more ideal antidepressant agent may both restore mental health and improve medical outcome.


Comment: Nonpharmacological approaches may be more successful here (see below). It was helpful in diabetics to decrease their depression if present, but done through pharmacological means it was counterproductive. The “side” effects of drugs are a constant problem and beg for treatment with other means. Physical activity, for instance, is extremely helpful for both type 2 diabetes and for depression. The chief problem, then, is entraining motivation and willingness to participate in such a patient-dependent treatment. The quality of the physician-patient relationship deserves upregulation to provide the means by which patients will accept greater participation.

Diabetes and Depression

Of 51 patients with type 2 diabetes and major depression, for those randomly assigned in a double-blind fashion to ten weeks of individual cognitive behavioral therapy, 85% achieved remission of depression (Beck Depression Inventory ≤ 9) versus only 27% in controls receiving no specific antidepressant treatment (2p < 0.001). All participated in a diabetes education program to control for the effects of supportive attention and the possible influence of enhanced diabetes control on mood. At six-month follow-up, 70% of CBT patients versus 33% of controls achieved remission (p = 0.03). At six-month follow-up, mean HbA1c level in the CBT group was 9.5% versus 10.9% in controls (2p = 0.03).


Comment: In a second study by the author above, a combination of cognitive behavioral therapy + diabetes education was an effective, nonpharmacological treatment for major depression in type 2 diabetic patients, and for improved glycemic control as well. Although the authors did not conclude what mechanism is involved, it is logical to think that the CBT and resolution of the depression would downregulate the activity of the hypothalamic-pituitary-adrenal axis, improving steroid levels and reducing adverse effects on blood sugar regulation. Relaxation training and behavioral therapy have potential benefits in a panoply of disease entities.

Diabetes and Meditation

Psychological distress is linked to impaired glycemic control among diabetics. In 11 adult type 2 diabetics, participation in the Mindfulness Based Stress Reduction program with diet and exercise regimen held constant, resulting in HbA1c reduction at one month by 0.48% (p = 0.03); mean BP fell 6 mm Hg (p = 0.009), body weight remained unchanged, and Symptom Checklist 90-Revised (for measures of anxiety, depression, somatization, and general psychological distress) scores improved.


Comment: This is a small pilot study, leading us to think that relaxation procedures may be helpful for type 2 diabetics. Blood pressure fell significantly, as we might expect. A very high percentage of patients learn the meditative techniques easily. And the marvel of this therapy is that it is free of untoward side effects. Meditation must be used cautiously in bipolar depression and those with border-line or paranoid personality disorders. Otherwise, there are few if any contraindications.

Diabetes and Qi Gong

In 26 randomly selected type 2 diabetics, HbA1c levels fell from 8.13 to 7.33% in those randomized to undergo two hours of qi gong group sessions once weekly for four months versus 8.29 to 8.17 in controls on routine antidepressant treatment (2p < 0.01). Controls then underwent the same training and HbA1c fell to 7.23% (p < 0.005).


Comment: Qi gong is not listed as an agent approved for use in diabetes. Neither is laughter (see below). Qi gong has been increasingly studied within the envelope of exercise studies and stress management studies, among others. Students and practitioners of qi gong are found to have greater equanimity about life events and survive life’s stresses with less discomfort.

Blood Sugar and Laughter

In 19 diabetic patients (mean age 63, mean body mass index 23.5, mean HbA1c 7.2, not on insulin), the mean blood sugar two hours after a 500 kcal meal rose 6.8 mmol/l (121 mg/dl) above fasting levels in those who had attended a 40-minute dry lecture versus a rise of 4.3 mmol/l (77 mg/dl) in those who attended a comedy show during which their laughter level was 4–5/5 (2p < 0.005). In 5 healthy nondiabetics (age 53.6, BMI 24.3, HbA1c 4.87%), the increases in blood sugar were 2.0 and 1.2 mmol/l (not significant).


Comment: Laughter significantly ameliorated the two hour postprandial blood sugar rise after a 500 kcal meal compared with those attending a dry lecture. Laughter is, at my last glance, not on the list of agents from which one can choose to regulate untoward blood sugars. Perhaps if we coached our diabetic patients to lighten up, notice opportunities to laugh at themselves and humorous situations, they might reduce their HbA1c and reduce their intake of antidiabetic agents, including drugs.
Metabolic Syndrome and Psychosocial Stress

The metabolic syndrome is a cluster of related metabolic and cardiovascular derangements including visceral obesity, insulin resistance, blood and tissue dyslipidemia, and high blood pressure, often associated with neuroendocrine and immunological dysregulations. The etiology of this syndrome is clinically highly relevant because it predisposes to life-threatening complications, such as diabetes mellitus, kidney failure, cardiovascular disease, and certain cancers. Contributing factors include a sedentary lifestyle combined with increased dietary fat intake and psychosocial stress. From an anthropological viewpoint, however, metabolic syndrome can be considered as a maladaptive consequence of an initially successful adaptation to high environmental demands. As opposed to prehistoric times—when environmental demands were usually energy-costly (e.g., fight/flight/hunt) and nutritional resources often inadequate—energy-utilizing actions no longer provide an optimal solution to deal with present-day societal demands.


Comment: This analysis reflects the interactions between psychosocial stress and nutrition and how these affect emotional and metabolic components of the metabolic syndrome. An understanding of these interactions is helpful to arrive at effective treatment and prevention of the metabolic syndrome. For instance, metabolic syndrome has been linked to obesity, in turn linked to sedentary lifestyle. As with both MS and diabetes, increased activity is a paramount line item in treatment. Understanding the family and societal motivations toward sedentary lifestyle becomes an important part of both prevention and treatment. Motivating patients to become more active can require a host of elements in the physician plan, including supplying of information, offering and suggesting choices for activities, starting with easy steps, providing feedback (e.g., pedometers), finding a group activity, utilizing imagery, speaking with challenging language, leading by example, becoming the exercise group organizer, providing for rewards with achievement, and telling stories of success. This is much harder than writing a prescription.

Psychoneuroimmunoendocrinology

Robert Anderson is a family physician who has authored several major books: Stress Power!, Wellness Medicine, Clinician’s Guide to Holistic Medicine, and The Scientific Basis for Holistic Medicine. Anderson founded the American Board of Integrative Holistic Medicine, is a past president of the American Holistic Medical Association, past assistant clinical professor of family medicine at the University of Washington, and present adjunct instructor in the Art of Primary Care at Bastyr University.

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