Does Emotional Stress Cause Type 2 Diabetes Mellitus? A Review from the European Depression in Diabetes (EDID) Research Consortium

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- **Abstract:** According to the World Health Organization, approximately 220 million people worldwide have type 2 diabetes mellitus. Patients with type 2 diabetes not only have a chronic disease to cope with, they are also at increased risk for coronary heart disease, peripheral vascular disease, retinopathy, nephropathy, and neuropathy. The exact causes of type 2 diabetes are still not clear. Since the 17th century, it has been suggested that emotional stress plays a role in the etiology of type 2 diabetes mellitus. So far, review studies have mainly focused on depression as a risk factor for the development of type 2 diabetes mellitus. Yet, chronic emotional stress is an established risk factor for the development of depression. The present review provides an overview of mainly prospective epidemiological studies that have investigated the associations between different forms of emotional stress and the development of type 2 diabetes mellitus. Results of longitudinal studies suggest that not only depression but also general emotional stress and anxiety, sleeping problems, anger, and hostility are associated with an increased risk for the development of type 2 diabetes. Conflicting results were found regarding childhood neglect, life events, and work stress. It is important to emphasize that publication-bias may have occurred, resulting from "fishing-expeditions," where authors search their data for significant associations. Publication bias

may also be caused by the tendency of reviewers and Editors to reject manuscripts with negative results for publication. It is therefore essential that research groups, who aim to conduct a new epidemiological cohort study, prospectively describe and publish the design of their study. Future research should focus on identifying mechanisms linking different forms of stress and incident type 2 diabetes.

Introduction

Type 2 diabetes mellitus is a serious and common metabolic disorder. The World Health Organization (WHO) has estimated the number of persons with diabetes worldwide at more than 220 million (WHO, 2009). These figures are expected to rise to 366 million by 2030 (Wild et al., 2004). Besides, diabetes mellitus is associated with a two- to four-fold increased risk of coronary heart disease and also an increased risk for microvascular diseases such as retinopathy, nephropathy, and neuropathy. Patients with type 2 diabetes also have a doubled risk level for co-morbid depression compared to healthy controls, hampering the quality of life of patients (Pouwer et al., 2003; Schram et al., 2009). Moreover, a considerable number of depressed patients suffer from high levels of diabetes-specific emotional stress (Pouwer et al., 2005; Kokoszka et al., 2009). Important factors contributing to the increasing prevalence of type 2 diabetes are obesity, physical inactivity, and an increase in the number of individuals older than 65 years (Wild et al., 2004). Interestingly, stress has long been suspected as having important effects on the development of diabetes. More than 400 years ago, the famous English physician Thomas Willis (1621-1675) noted that diabetes often appeared among persons who had experienced significant life stresses, sadness, or long sorrow (Willis, 1675). One of the first systematic studies testing Willis's hypothesis was described in 1935, by the American psychiatrist Dr. W. Menninger, who postulated the existence of psychogenic diabetes and described a "diabetic personality" (Menninger, 1935). Almost thirty years later, P.F. Slawson et al. described in the *Journal of the American Medical Association* that 80% of a group of 25 adult diabetes patients gave a history of antecedent stress mainly in terms of losses, 1-48 months prior to the onset of diabetes (Slawson et al., 1963). However, this study had several important limitations, including a very small sample size, a retrospective, uncontrolled design, and a high risk of selection bias. More recently, numerous studies have been performed, elucidating the role of emotional stress as a risk factor for the development of type 2 diabetes. The majority of these studies focus on depression. However, there is growing evidence that other forms of emotional stress contribute to the development of type 2 diabetes as well.

The aim of this review is to provide an overview of studies on the relationship between different forms of emotional stress and the risk of developing type 2 diabetes mellitus, involving depression, anxiety, life events or traumata, general emotional stress, work stress, and sleeping problems. The different pathways, limitations of these findings, and implications for future research will also be discussed.

Review Criteria

Articles were selected using the authors' information research databases from earlier literature searches. Additionally, MEDLINE (1966-January 2010), was searched using the following terms: risk, type 2 diabetes, depression, anxiety, stress, trauma, "life events," "work stress," and "sleeping problems." Selected papers were full text articles, reporting data from studies in human in the English language. The reference lists of identified papers were used for further leads.

The Concept of Stress

Nowadays, the term “stress” is commonly used in the psychological, biological, and medical sciences. The concept of stress has been developed in the 1930s by the endocrinologist Hans Selye, building on previous work by Cannon (fight-or-flight and conceptualization of homeostasis) and Bernard (homeostasis). Selye (1950) has defined stress as “the nonspecific response of the body to any demand,” with the body going through three universal stages of dealing with the stressor: the alarm phase (Cannon’s fight-or-flight), the resistance phase (in which resistance to the stress is built), and the exhaustion phase (when the duration of stress is sufficiently long), together encompassing the “general adaptation syndrome.” A more recent stress theory by McEwen (1998) is based on Selye’s general adaptation syndrome, but incorporates additionally the notion that the body anticipates a stress response by shifting the homeostatic set point (allostasis, or stability through change). This comes at a price though, because shifting a set point of one system (e.g., blood pressure) affects other physiological systems (e.g., kidney function), a concept which is known as allostatic load.

However, the meaning of the word “stress” has changed during the past decades. Currently, stress usually refers to the consequence of the failure of an organism- human or animal- to respond appropriately to emotional or physical threats, whether actual or imagined (Bao et al., 2008). As described above, stress symptoms commonly include a state of alarm. Signs of stress can be defined at a cognitive, emotional, physical or behavioral level. Cognitive signs are for example poor judgment, low self-esteem, poor concentration, and negative cognitions. Emotional signs include moodiness or even depression, feeling of anxiety, excessive worrying, irritability, agitation, and feeling lonely or even isolated. Physical symptoms are for example aches and pains, diarrhea or constipation, nausea, dizziness, chest pain, and rapid heartbeat. Behavioral symptoms of stress can for example include: eating too much or not enough, sleeping too much or not enough, social withdrawal, procrastination or neglect of responsibilities, increased alcohol, nicotine, or drug consumption, and nervous habits such as pacing about or nail-biting. Selye and McEwen’s exhaustion phase, during which bodily systems start to dysfunction or shut down, may also include depression, as depression is commonly regarded as a form of exhaustion, resulting from chronic emotional stress. Although the stress response of the body functions to maintain stability or allostasis, a long-term activation of the stress system can have serious, negative consequences for the body (Bao et al., 2008).

Depression, Anxiety, and the Risk of Type 2 Diabetes

Two recent meta-analyses have examined whether depression increases the risk for the onset of type 2 diabetes. Based on nine prospective epidemiological studies, Knol et al. (2006) were the first to conclude that depression increases the risk for type 2 diabetes by 37%. Two years later, Mezuk et al. (2008) were able to include a total of 13 studies that investigated depression as a risk factor for diabetes, representing 6,916 incident cases. In that meta-analytic review, the risk for incident diabetes was 60% higher in depressed participants, compared to non-depressed controls (RR 1.60, 95% CI 1.37-1.88). Engum (2007) has tested anxiety as a risk factor for the development of diabetes, using data from a large Norwegian prospective population-based study (n=37,291). Both baseline anxiety and depression were associated with an increased risk for the development of type 2 diabetes at 10 years follow-up (OR 1.5, 95% CI 1.3-1.8). Among participants with a high level of depression/anxiety at both baseline and follow-up, the risk of type 2 diabetes was even higher (OR 1.8, 95% CI 1.3-2.5). Engum found that gender was not an effect modificator of this association (Engum, 2007).

Life Events or Traumata and the Risk of Type 2 Diabetes

In the year 2000, Mooy et al. used cross-sectional data from The Hoorn Study (n=2,262) to test whether chronic stress was associated with the prevalence of type 2 diabetes. They found that persons who had experienced significant life events during the past five years had a 1.6-fold increased risk to have type 2 diabetes compared to those who had not experienced life events. Interestingly, data from the Hoorn Study showed that life events were positively associated with the Waist-Hip-Ratio (WHR), an important risk factor for diabetes and cardiovascular disease (Mooy et al., 2000). Adjusting the association between life events and diabetes for WHR only marginally lowered the odds ratio to 1.5 (95% CI 0.9-2.4). This finding suggests that visceral adiposity does not seem to be the main link between stress and development of type 2 diabetes. Goodwin and Stein (2004) used data from the National Comorbidity Survey (n=5,877). In particular, a history of childhood neglect was associated with a higher risk of diabetes (OR 2.2, 95% CI 1.1-4.4) and this risk was higher among women (OR 4.6, 95% CI 2.3-9.3), after adjustment for age, gender, race, marital status, income, and education. A history of physical abuse or sexual abuse was not associated with diabetes (OR 0.9, 95% CI 0.5-1.5 and OR 0.9, 95% CI 0.5-1.9, respectively). It is important to emphasize that this study was limited by the retrospective design of the study. The first prospective study in this area has been described by Räikkönen et al. (2007) who used data from the Healthy Women Study (n=523) to test whether psychosocial factors predict the risk for the development of the metabolic syndrome. These researchers found that among this group of middle-aged women, baseline depressive symptoms, feeling frequently intensely angry, tensed or stressed, and very stressful life events were all associated with an increased risk to develop the metabolic syndrome during the 15-year follow-up. Finally, Kumari et al. (2004) found that men who reported to have experienced two or more life events tended to have an increased risk of diabetes (OR 1.2, 95% CI 0.9-1.7), and women (OR 1.3, 95% CI 0.8-2.1) in the Whitehall II Study, though both associations were statistically not significant.

General Emotional Stress, Anger/Hostility, and Risk of Type 2 Diabetes

Several prospective studies have tested the hypothesis that “general emotional stress” is associated with an increased risk for the development of type 2 diabetes. First, a group of Danish researchers recently reported data from a longitudinal study aiming to determine the long-term effects of general emotional stress on changes in health behavior and cardiac risk profile in men and women (Rod et al., 2009). Rod et al. analyzed data from the Copenhagen City Heart Study, involving 7,066 women and men, finding that particularly stressed men but not women were more than two times as likely to develop diabetes during follow-up (2.4; 95% CI 1.2-4.6). Interestingly, participants who had reported high levels of stress compared to those with low levels of stress were less likely to quit smoking (OR=0.6; 95% CI: 0.4-0.8), more likely to become physically inactive (1.9; 95% CI 1.4-2.6), and less likely to stop drinking during follow-up: all these factors are known to be associated with an increased risk for type 2 diabetes and could mediate the link between stress and onset of diabetes. In a Japanese community-based cohort study, the associations between perceived mental stress and the onset of diabetes were investigated (Kato et al., 2009). A total of 55,826 subjects (24,826 men and 31,000 women) aged 40-69 years were followed for 10 years. A self-administered questionnaire on medical conditions including diabetes and other lifestyle factors was completed at baseline and 5 and 10 years later. Like the Danish study, the risk of diabetes increased with an increasing stress level, especially among men. The multivariate adjusted odds ratios for high stress compared with low stress were 1.36 (95% CI 1.13-1.63) among men and 1.22 (95% CI 0.98-1.51) among women (Kato et al., 2009). Next, in another Japanese study by Toshihiro et al. (2008) among 128 male Japanese with impaired glucose metabolism, a high score on a questionnaire assessing “stress in daily life” was associated with an increased risk for the development of type 2 diabetes after a 3-year follow-up (HR 3.81, 95% CI 1.09-13.4). Golden et al. (2005) have conducted a longitudinal cohort study of 11,615 non-diabetic adults aged 48-67 years at baseline. Anger,

particularly anger temperament, appeared to be associated with onset of type 2 diabetes (HR 1.34, 95% CI 1.1-1.6), after adjustment for differences in age, ethnicity, gender, and education. Additional analyses showed that particularly a higher caloric intake and adiposity but not smoking behaviors and physical activity were potential mediators of this association. Finally, Zhang et al. (2006) analyzed data from 643 non-diabetic men with a mean age of 63 years, and found the persons who reported a high level of stress and high hostility were more likely to have higher insulin resistance levels. This result is in line with earlier studies by Surwit et al. (2002) and Raikkonen et al. (2003). In the study by Zhang et al., the association between hostility and insulin resistance was mediated by the stress hormone norepinephrine. Additionally, high level of cynicism was the crucial element of hostility that was associated with an impaired glucose metabolism (Zhang et al., 2006).

Work Stress and the Risk of Type 2 Diabetes

Excessive overtime, probably due to over commitment to work has been reported to be associated with 4-fold higher risk of type 2 diabetes in Japanese men, independent of other risk factors (Kawakami et al., 1999). However, in the same study, job strain (defined as high work overload and low job control) was not significantly associated with incident diabetes (HR 1.3, 95% CI 0.5-3.6). In the Whitehall II Prospective Study (Kumari et al., 2004), an imbalance in effort-reward, suggestive of significant work stress, was associated with a higher risk to develop diabetes in men (OR 1.7, 95% CI 1.0-2.8) but not in women (0.9, 95% CI 0.4-1.9). The effort-reward imbalance questionnaire contains a number of constructs, including hostility and over commitment to work, but additional analyses showed that, in the Whitehall II study, hostility was not associated with incident diabetes (Kumari et al., 2004). In a large (n=33,336) population-based sample, tense working situation related working stress was associated with onset of diabetes after, on average, 5 years, in women (OR 3.6 95% CI 1.0-13.3) but not in men (OR 1.1, 95% CI 0.4-2.9; Norberg et al., 2006). Burn-out, resulting from chronic work stress, has also been studied as a risk factor for the development of type 2 diabetes. In a longitudinal study among 677 employed men and women (Melamed et al., 2006), a high level of baseline burn-out symptoms was associated with the development of type 2 diabetes (OR 1.8, 95% CI 1.2-2.9). Another study that was based on data from the Whitehall II Study (1991-2004) tested whether stress at work was associated with an increased risk of type 2 diabetes, in a sample of 5,895 middle aged civil servants (Heraclides et al., 2009). In that study, “psychosocial stress at work” appeared to be an independent predictor of the onset of type 2 diabetes among women, during a follow-up period of 15 years (HR 1.9, 95% CI 1.2-3.2), but not in men (HR 1.1, 95% CI 0.7-1.6). The strong association in the female group remained stable and decreased with only 20% after adjustment for life events, health behaviors, obesity, potentially confounding, and mediating factors (Heraclides et al., 2009).

Distressed Sleep and the Risk of Type 2 Diabetes

Poor sleep can be an important indicator of emotional stress. On the one hand, emotional stress can easily affect different aspects of sleep, such as initiation of sleep, sleep duration, and sleep quality. Conversely, sleeping problems may not only be a consequence of emotional stress, but are often experienced as a significant source of stress. In their recent systematic review and meta-analysis, Cappuccio et al. (2010) tested whether habitual sleep disturbances were associated with a higher incidence of type 2 diabetes. They included 10 studies, comprising a total of 107.756 male and females. Follow-up durations of the studies ranged from 4 to 32 years. It appeared that short duration of sleep (less than 5 to 6 hours per night) increased the risk for type 2 diabetes (HR 1.3, 95% CI 1.03-1.60). Difficulties in initiating sleep also increased the risk for the onset of type 2 diabetes (HR 1.6, 95% CI 1.3-2.0). Interestingly, persons with a long duration of sleep, more than 8-9 hours per night were at increased risk for incident type 2 diabetes (HR 1.5 95% CI 1.1-2.0). Difficulty in maintaining sleep was associated with an 84% higher risk to develop type 2 diabetes

(HR 1.84, 95% CI 1.4-2.4). A high body mass index (BMI) is an important potential confounder in studies that investigate sleeping problems and incidence of type 2 diabetes. Overweight is a major risk factor for type 2 diabetes that can also contribute to snoring problems and sleep apnea (and thus to sleeping problems). Therefore all 10 studies that were included in the meta-analysis of Cappuccio adjusted their analyses for BMI.

Potential Pathways That Link Stress with Incident Diabetes

Emotional stress can increase the risk for the development of type 2 diabetes through different pathways. The first pathway is via behavioral mechanisms. Emotional stress was found to be associated with unhealthy lifestyle behaviors, i.e., inadequate eating behaviors in terms of quality and quantity of food, low exercise levels, smoking and alcohol abuse (Bonnet et al., 2005; Rod et al., 2009). All these factors are well-known risk factors for the development of type 2 diabetes. The second pathway is via physiological mechanisms. Chronic stress reactions and depression are often characterized by long term activation of the hypothalamic-pituitary-adrenal axis and the sympathetic nervous system which were found to be associated with the development of abdominal obesity, and this may explain why depression or chronic stress increases the risk of diabetes (Björntorp, 2001; Vogelzangs et al., 2008).

Chronic stress can also initiate changes in immune system activity. There is experimental and clinical evidence that a rise in the concentration of pro-inflammatory cytokines and glucocorticoids, particularly cortisol, in response to chronic stress and often in depression, both contribute to the behavioral changes associated with depression (Leonard and Myint, 2009). In addition, activation of the immune system can provoke neuroendocrine and neurotransmitter changes that are similar to those provoked by physical or psychological stressors (Anisman, 2009). Sleep disturbance and depression were also associated to hypercytokinemia and activated innate immunity (Pickup, 2004). Interestingly, Pickup (2004) also described convincing evidence that an ongoing cytokine-induced acute-phase response is closely involved in the pathogenesis of type 2 diabetes. Thus, inflammatory processes may be a common antecedent of stress vulnerability, depression, and type 2 diabetes, which can develop in parallel or in succession. Although the above-mentioned potential pathways give a slight indication of what is happening, we still know very little about the mechanisms by which different forms of emotional stress increase the risk of diabetes incidence and progression. It is important for future research to explore these and other potential pathways in detail.

Conclusion

In general, the research findings described in this review support the notion that different forms of emotional stress are associated with an increased risk for the development of type 2 diabetes, particularly depression, general emotional stress, anxiety, anger/hostility, and sleeping problems. Conflicting results were found regarding childhood neglect/abuse, life events, and work stress. In several papers, childhood traumata and life events have been linked with higher odds of type 2 diabetes, but these studies were all limited by a cross-sectional design. Moreover, results from longitudinal studies in that area had conflicting results. A longitudinal study based on data from the Healthy Women Study showed that persons who had experienced life events were at increased risk for the metabolic syndrome, including impaired fasting glucose (Räikkönen et al., 2007), while another longitudinal study (Kumari et al. ,2004) found no significant association between life events and incident diabetes.

An important limitation of the present study is that it is common practice among researchers to use datasets of longitudinal epidemiological studies for explorative analyses, so-called “fishing expeditions,” where the results determine which paper will be written. As a result, negative outcomes (such as stress is not associated with incident diabetes) are often not submitted for publication, and are perhaps more often rejected for publication. In order to avoid publication bias, randomized

controlled trials now have to be registered prospectively in a clinical trial registry. For epidemiological cohort studies, such a registry is still not available, and as a result we may thus expect that positive findings are over-present in the scientific literature.

Clinical Implications and Directions for Future Research

At this moment the clinical implications of the present review are limited. More rigorous research is needed. In order to test whether stress is indeed causally associated with incident depression, a large randomized controlled trial is needed, testing whether adequate stress-reduction, probably over a long period, is associated with a reduction in the incidence rate of type 2 diabetes. Such a trial could also explore the potential psychophysiological and behavioral mechanisms that can link stress with the development of type 2 diabetes. These mechanisms should of course also be studied in well designed cohort studies.

(More information on the European Depression in Diabetes (EDID) Research Consortium is at www.edid-research.eu.)

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