*Occupational Medicine* 2004;**54:**250–254
DOI: 10.1093/occmed/kqh047

# Do stressful life events cause type 1 diabetes?

**Martin Cosgrove**

| | |
|---|---|
| **Background** | The link between psychological stresses and deteriorating diabetes control is well known. However, people who develop type 1 diabetes sometimes ascribe the onset of diabetes to a recent stressful event |
| **Aims** | To perform a systematic review of the literature to assess whether stressful life events can cause type 1 diabetes. |
| **Methods** | Electronic and manual literature search using appropriate key words. |
| **Results** | Older literature provides anecdotal links between stressful life events and diabetes. The difficulty in interpreting these papers is the small numbers under study and the lack of distinction between type 1 and type 2 diabetes. More recent studies, in particular from Scandinavia, demonstrate that there is no link between either the number or the severity of life events in the year up to the diagnosis and the onset of the condition. |
| **Conclusion** | Given the progress in understanding the molecular biology of diabetes, the concept that stress causes type 1 diabetes is no longer plausible. There is no evidence from large well-controlled trials that type 1 diabetes is caused by stressful life events. |
| | |
|---|---|
| **Key words** | Depression; life events; occupational; stress; type 1 diabetes. |
| **Received** | 22 April 2003 |
| **Revised** | 22 September 2003 |
| **Accepted** | 9 February 2004 |

## Introduction

Type 1 diabetes mellitus (previously juvenile onset diabetes or insulin-dependent diabetes) is generally associated with younger age at onset and lean body habitus. Patients usually present with weight loss, polyuria and polydipsia, together with a tendency towards ketoacidosis. It requires the early use of insulin to control the blood glucose in order to overcome the pancreatic β cell failure and consequent insulin deficiency [1]. Whilst in the past, type 1 diabetes was viewed as a condition occurring only in young people, it is now recognized that it can occur at any age [2,3]. Indeed, many patients who are initially thought to have type 2 diabetes (maturity onset/non-insulin dependent) but need insulin in the first year have, in fact, type 1 diabetes [1–3]. The incidence of type 1 diabetes varies with age: the peak incidence is at 12–13 years for boys and 9–12 years for girls [3]

The development of autoantibodies in early life, and the follow-up of patients with evidence of autoantibodies has shown that there is a variable, but often long interval between the development of the antibodies and the subsequent development of diabetes [4–8]. During this time, there is a progressive reduction in the level of secretion of insulin over a period of two years. Even in the cases of children who develop hyperglycaemia during an acute intercurrent illness, unless there are autoimmune markers, diabetes does not develop on follow-up [9–11].

Individuals with type 1 diabetes appear to be rendered susceptible to developing the condition by their HLA status. Ninety per cent of people with autoimmune type 1 diabetes have either HLA DR3 and/or HLA DR4 antigens compared to only 20% of the general population [12,13]. In contrast, some HLA types such as DR2 seem to have a dominantly inherited protective effect, even if present with other diabetogenic HLA types. It seems likely [14–16] that an environmental trigger, in particular with often sub-clinical enteroviral infection, will either start the autoimmune process in genetically susceptible individuals or cause pancreatic β cell cytolysis and a subsequent non-autoimmune type 1 diabetes.

Prior to the development of immunology, modern cell biology and genetics, the development of type 1 diabetes, like heart disease, cancer and stroke, was thought to be a

Cherry Hinton Medical Centre, 30 Fishers Lane, Cambridge CB1 9HR, UK.
e-mail: m.cosgrove@ntlworld.com

consequence of psychological stressors. Given that diabetes control is often linked to psychological health, this seems an intuitively plausible explanation for the development of a condition whose origins have been hard to fathom.

Whether life events or stress at work might cause or trigger the onset of diabetes is not merely an academic question for the occupational physician. For instance, if an individual is in a pension scheme which awards an injury pension. Consequently, an evidence base would be useful to confirm this type of decision.

This paper describes the findings of a systematic review of the medical literature up to July 2003 to establish whether there might be a link between depression, stress or life events and the onset of type 1 diabetes.

## Methods

A systematic search of the medical literature in all languages was undertaken using the Cochrane Database of Systematic Reviews, the Cochrane Database of Abstracts of Reviews of Effect, the Cochrane Central Register of Controlled Trials (1970–Jan 2003), MedLine (1966–Jan 2003), PubMed, PsychINFO (1972–Jan 2003) and HMIC (1984–Jan 2003), together with cross-referencing and a manual search in the Cambridge University Medical School library.

Terms searched for were: diabetes and depression, diabetes and depressive, diabetes and life events, diabetes and stress. Only papers which investigated the relationship between stress or life events with the onset of type 1 diabetes, insulin dependent or juvenile onset diabetes are reviewed in this paper. Papers that investigated depressive disorders in people with type 1 diabetes were excluded.

Medical reviews [17–20] were excluded from the final results but cross-referenced to ascertain whether there were other papers available in the literature.

**Table 1.** General description of studies in systematic review

| Ref. | Year | Country | No. in study with diabetes | No. of controls | Controls | Age (years) | Time before onset of DM assessed | Method | Timing |
|---|---|---|---|---|---|---|---|---|---|
| [21] | 1975 | USA | 38 | 38 | Hospital clinic population: chronically sick adolescent | 0–20 | Lifespan | Psychiatric interview | Unclear |
| [22] | 1985 | UK | 13 | 26 | Sibling, neighbour | 17–34 | 3 years | Psychological interview, LEDS score | <18 months of diagnosis |
| [23] | 1988 | UK | N/A: 6 islet cell antibody-positive relatives of 12 diabetics | 6 | Islet cell antibody-negative family members | | 5 years | Psychological interview, LEDS score | Not applicable |
| [24] | 1989 | France | 32 | 53 | 26 Hospital staff and 27 age- and sex-matched out-patients | 15–40 | 10 years and 12 months | Structured interview | <6 months after diagnosis |
| [25] | 1991 | Sweden | 338 | 528 | Community, age-, sex- and geography matched | 0–14 | 12 months | Structured questionnaire, Life Experiences Survey score | 4 weeks after diagnosis |
| [26] | 1991 | Sweden | 339 | 528 | Community, age-, sex- and geography matched | 0–14 | 12 months | Structured questionnaire, Life Experiences Survey score | 4 weeks after diagnosis |
| [27] | 1994 | Hungary | 163 | 221 | Community; patients chose two age- and sex-matched controls | 0–14 | 12 months | Structured questionnaire, modified Life Experiences Survey score | <2 weeks after diagnosis |
| [28] | 1995 | Sweden | 67 | 61 | Community, age-, sex- and geography matched | 0–14 | Lifespan and 12 months | Structured questionnaire, Life Experiences Survey score | 8 weeks after diagnosis |
| [29] | 2001 | Sweden | 349 | 979 | Community, age-, sex- and geography matched | 15–34 | 12 months | Structured questionnaire, Life Experiences Survey score | 4 weeks after diagnosis |

## Results

A total of nine papers [21–29] were found from the electronic and manual search. The summary of the nine papers can be seen in Tables 1 and 2. Five papers [21–24,27] had small numbers of diabetics and or inadequately randomized controls, two papers [25,26] had the same data and were from the same authors at the same time.

**Table 2.** Outcome measures of studies in systematic review comparing life events prior to diagnosis in individuals who had developed type 1 diabetes with controls

| Ref. | No. with diabetes | No. of controls | Response from diabetics (%) | Response from controls (%) | Outcome measure | Odds ratio (95% confidence interval) | Conclusions | Comments |
|---|---|---|---|---|---|---|---|---|
| [21] | 38 | 38 | Not stated | Not stated | Family losses: DM 17/34, Con 6/34; family disturbance: DM 9/34, Con 1/34; family intact: DM 12/34, Con 31/34 | | Family problems more common in diabetes | Controls were chronically sick adolescents. |
| [22] | 13 | 26 | Part of the Barts–Windsor–Middlesex Prospective Family Study | | No. of severe life events prior to onset of DM | | Higher number of life events in diabetics; higher number of severe life events in DM | Recall bias, small number |
| [23] | N/A: 6 islet cell antibody positive relatives of 12 diabetics | 6 | Nested study—part of the Barts–Windsor–Middlesex Prospective Family Study | | Development of DM in islet cell antibody-positive individuals | | Increased severe life events in 5 years prior to diagnosis | Very small numbers |
| [24] | 32 | 53 | Unclear as to how selected | Unclear as to how selected | Stressful life event in last 12 months:DM: 16/32, Con: 10/53 | | Over 10 years diabetics had fewer life events but a greater number of stressful life events in previous 12 months | Concern about controls |
| [25] | 338 | 528 | 86 | 69 | No of life events in last 12 months: DM: 628/338, Con: 981/528 | 1.19 (0.88 – 1.62) | No overall difference in life events. Subgroup analysis: increased number of life events in 5–9 year olds | |
| [26] | 339 | 528 | 86 | 67 | No of life events in last 12 months: | 1.19 (0.87–1.64) | No overall difference in life events. Subgroup analysis: increased number of life events in 5–9 year olds | |
| [27] | 163 | 221 | 80 | 79 | Stressful life events in last 12 months: DM: 366/163, Con 449/221 | 3.9 (1.14 – 13.27) | Median number of life events was the same | Not randomized controls; the selection bias of the controls is potentially very strong |
| [28] | 67 | 61 | 85 | 91 | Last 12 months: mean no. of life events: DM: 1.07 ± 1.45, Con: 1.00 ± 1.05; negative life events: DM: 0.44 ± 0.84, Con: 0.34 0.52; no. of life events in last 12 months: DM: 72/67, Con: 21/61; had a negative life event in the first 2 years of life | 1.94 | No overall difference in life events | |

**Table 2.** Continued

| Ref. | No. with diabetes | No. of controls | Response from diabetics (%) | Response from controls (%) | Outcome measure | Odds ratio (95% confidence interval) | Conclusions | Comments |
|---|---|---|---|---|---|---|---|---|
| [29] | 349 | 979 | 82 | 65 | More conflicts with partner<br>Moved to another place<br>Changed jobs<br>Income deteriorated<br>Unemployed > 14 days<br>One or both parents seriously ill or injured<br>No overall figures | 0.83 (0.49–1.42)<br>0.82 (0.57–1.18)<br>0.80 (0.55–1.17)<br>0.66 (0.43–1.01)<br>0.79 (0.52–1.20)<br>0.55 (0.30–1.00) | No overall difference in life events. Detailed assessment of individual life events shows no occupational life events associated with onset | Only large adult study undertaken; good control population; good occupational assessment |

Three papers [25,28,29] were of sufficient size and quality to provide sound data. Two of these papers [25,28] were studies of children only, while the other [29] assessed adults with type 1 diabetes.

The Swedish Childhood Diabetes Study by Hägglöf *et al.* [25] was part of a much larger study into the aetiology of type 1 diabetes involving the whole of Sweden. The number of cases invited to participate in the study was 393, representing the whole of the newly diagnosed type 1 diabetes population in the country over an 18 month period aged 0–14 years. A total of 338 accepted the invitation to join the study. The controls were matched for age and sex, and were from the same geographical location as the index cases. There were twice as many controls as there were patients with diabetes. Assessment was at 4 weeks after the diagnosis. In this study, there was a low chance of recall and selection bias and a good use of a control population. The study found that the number of life events during the year prior to the onset of diabetes in the patients with diabetes was the same as in the controls.

Thernlund *et al.* [28] investigated 67 patients aged 0–14 years with diabetes and 61 controls matched geographically, and for age and sex. At 8 weeks after diagnosis, they assessed the psychological stresses (life events) experienced during the 12 months prior to diagnosis compared with age- and sex-matched controls. The patients with diabetes had similar scores to controls for the number of life events in the 12 months up to diagnosis. There was, however, a greater number of negative life events in the first 2 years of life in the diabetes patients.

By far the most powerful paper, and most useful to occupational physicians, was published by Littorin *et al.* [29] and studied 443 adults aged 15–34 years using 979 age- and sex-matched controls. It aimed to have a 90% power of detecting a difference of 10%. The study assessed all new cases of type 1 diabetes in Sweden during 1992 and 1993 using a postal questionnaire at 4 weeks after diagnosis. No differences were detected in the diabetics compared with controls for the number or severity of life events in the 12 months prior to the onset of the disease, apart from serious illness or hospitalization for more than a week in the preceding 12 months.

People with diabetes had experienced fewer conflicts with their parents and had broken up with friends less than the controls. Of note, a variety of work-related life events (see Table 2) were assessed which showed no differences between the controls and the people with diabetes. Littorin *et al.* [29] concluded: 'hereditary factors but not psychologically stressful life events were closely associated with the development of autoimmune type 1 diabetes'.

## Conclusion

Diabetes studies that have looked at the psychological aspects of patients with diabetes have come to varied conclusions, but more recent and larger studies have overturned the previously held belief that diabetes is caused by, or precipitated by stressful life events. When the number and severity of life events is compared with controls, there is no difference.

Whilst there is some evidence, in both the smaller and older studies as well as the larger, more randomized studies, that losses in very early childhood increase the risk of developing type 1 diabetes, there is no evidence to support the hypothesis that life events (and by inference occupational stresses) cause or precipitate diabetes. For those of us who work with a pension scheme that includes an injury pension, this means that there is no reason to award an injury pension to an employee who develops type 1 diabetes after a stressful event at work, or in a sustained occupationally stressful environment.

## References

1. Lambert P, Bingley. What is Type 1 diabetes? *Med Int* 2002;**30:**1–5.
2. Mølbak AG Christau B Marner B Borch Johnson K Nerup J. Incidence of insulin treated diabetes mellitus in age

groups over 30 years in Denmark. *Diabet Med* 1994;**11:**650–655.
3. Wareham NJ. Epidemiology of diabetes. *Med Int* 2002;**30:**11–13.
4. Ziegler AG, Hummel M, Schenker M, Bonifacio E. Autoantibody appearance and the risk for the development of childhood diabetes in offspring of parents with type 1 diabetes: the 2 year analysis of the German BABYDIAB study. *Diabetes* 1999;**48:**460–468.
5. Knip M. Vahasalo P, Karjalainen J, Louanamaa R, Akerblom HK. Natural history of preclinical IDDM in high risk siblings. Childhood Diabetes in Finland Study Group. *Diabetologia* 1994;**37:**388–393.
6. Chase HP, Garg SK, Butler-Simon N, Klingensmith G, Norris L, Ruskey CT, O'Brien D. Prediction of the course of pre-type 1 diabetes. *J Paediatr* 1991;**118:**838–841.
7. Riley W, MacLaren NK, Krischer J, *et al.* A prospective study of the development of diabetes in relatives of patients with insulin dependent diabetes. *N Engl J Med* 1990;**323:**1167–1172.
8. Vardi P, Crisa L, Jackson RA. Predictive value of intravenous glucose tolerance test insulin secretion less than or greater than the first percentile in islet cell antibody positive relatives of Type 1 (insulin dependent) diabetics patients. *Diabetologia* 1991;**34:**93–102.
9. Bhisitkal DM, Vinik AI, Morrow AL, *et al.* Prediabetic markers in children with stress hyperglycaemia. *Arch Pediatr Adolesc Med* 1996;**150:**936–941.
10. Herskowitz-Dumont R, Wolfsdorf JI, Jackson RA, Eisenbarth GS. Distinction between transient hyperglycaemia and early insulin dependent diabetes mellitus in childhood: a prospective study of incidence and prognostic factors. *J Paediatrics* 1993;**123:**347–354.
11. Shehadeh N, On A, Kessel I, *et al.* Stress hyperglycaemia and the risk for the development of type 1 diabetes. *J Paediatr Endocrinol Metab* 1997;**10:**283–286.
12. Baroni MG, Leslie D, Pozzilli P, Buzetti R. Genetics of diabetes: unravelling the complexities. In: Betteridge DJ, ed. *Diabetes, Current Perspectives*. Martin Dunitz, 2000.
13. Redondo MJ, Eisenbarth GS. Genetic control of auto-immunity in type 1 diabetes and associated disorders. *Diabetologia* 2002;**45:**605–622.
14. Lönnrot M, Korpela K, Knip M, *et al*. Enterovirus infection as a risk factor for beta cell autoimmunity in a prospectively observed birth cohort: the Finnish Diabetes Prediction and Prevention Study. *Diabetes* 2000;**49:**1314–1318.
15. Jun HS, Yoon JW. A new look at viruses in type 1 diabetes. *Diabetes Metab Res Rev* 2003;**19:**8–31.
16. Hyöty H, Taylor KW. The role of viruses in human diabetes. *Diabetologia* 2002;**45:**1353–1361.
17. Craidhead JE. Current views on the aetiology of insulin dependent diabetes mellitus. *N Engl J Med* 1978;**299:**1439–1445.
18. Surwit RS, Schneider MS, Feinglos MN. Stress and diabetes. *Diabetes Care* 1992;**15:**1413–1422.
19. Wales JK. Does psychological stress cause diabetes? *Diabet Med* 1995;**12:**109–112.
20. Talbot F, Nouwen A. A review of the relationship between depression and diabetes in adults: is there a link? *Diabetes Care* 2000;**23:**1556–1562.
21. Stein SP, Charles E. Emotional factors in juvenile diabetes mellitus; a study in the early life experiences of adolescent diabetics. *Am J Psychiatry* 1971;**28:**700–704.
22. Robinson N, Fuller JH. Role of life events and difficulties in the onset of diabetes mellitus. *J Psychosom Res* 1985;**29:**583–591.
23. Robinson N, Lloyd CE, Fuller JH, Yateman NA. Psychosocial factors and the onset of type 1 diabetes. *Diabet Med* 1988;**6:**53–58.
24. Vialettes B, Ozanon JP, Kaplansky S, Farnarier C, Suavaget E, Lassmann-Vague D. Stress antecedents and immune status in recently diagnosed type 1 (insulin dependent) diabetes mellitus. *Diabetes Metab* 1989;**15:**45–50.
25. Hägglöf N, Blom L, Dahlquist H, Lönnberg G, Sahlin B. The Swedish childhood diabetes register: indication of severe psychological stress as a risk factor for Type 1 (insulin dependent) diabetes mellitus in childhood. *Diabetologia* 1991;**34:**579–583.
26. Dahlquist G, Blom L, Lönnberg G. The Swedish Childhood Diabetes study—a multivariate analysis of risk determinants for diabetes in different groups. *Diabetologia* 1991;**34:**757–762.
27. Soletz G, Jeges S, Dahlquist G. Non-genetic risk determinants for type 1 (insulin dependent) diabetes mellitus in childhood. *Acta Paediat* 1994;**83:**730–735.
28. Thernlund G, Dahlquist G, Hanson K, *et al*. Psychological stress and the onset of IDDM in children. *Diabetes Care* 1995;**18:**1323–1329.
29. Littorin B, Sundkvist G, Nyström L, *et al*. Family characteristics and life events before the onset of autoimmune Type 1 diabetes in young adults. *Diabetes Care* 2001;**24:**1033–1037.