

Do stressful life events cause type 1 diabetes?

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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.
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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

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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 diabetics	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	0.83 (0.49–1.42)	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
				Moved to another place	0.82 (0.57–1.18)			
				Changed jobs	0.80 (0.55–1.17)			
				Income deteriorated	0.66 (0.43–1.01)			
				Unemployed > 14 days	0.79 (0.52–1.20)			
				One or both parents seriously ill or injured	0.55 (0.30–1.00)			
				No overall figures				

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.

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