

Clinical features of type 2 diabetes before diagnosis and pathways to the diagnosis: a case–control study

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Aim: To identify and quantify clinical features associated with a future diagnosis of type 2 diabetes, and to record pathways to the diagnosis of diabetes. **Background:** The risk of type 2 diabetes posed by particular symptoms is largely unknown, especially in unselected populations like primary care. The current mode and setting of diagnosis in the UK are undescribed. **Methods:** This was a population-based case–control study in seven general practices in Bristol, UK. In this study, 105 cases with newly diagnosed diabetes, and 105 age- and sex-matched controls were studied. Their primary care records for two years before diagnosis were examined for symptoms previously reported to be associated with diabetes and for abnormal investigations. Differences between cases and controls were analysed by conditional logistic regression. In cases, the pathways to the diagnosis of diabetes were categorised. **Findings:** In all, 42 (40%) adults with newly diagnosed diabetes were asymptomatic at diagnosis and 84 (80%) were first detected in primary care. Five clinical features were independently associated with diabetes in multivariable analyses. Likelihood ratios for these were: thirst 36 (95% confidence interval 3.0, 440), $P = 0.005$; weight loss 5.7 (1.3, 26), $P = 0.022$; skin infections 4.6 (1.7, 12), $P = 0.002$; fasting glucose >5.6 mmol/L 38 (2.2, 640), $P = 0.012$; and random glucose >5.6 mmol/L 15 (2.5, 94), $P = 0.003$. The median time period between the onset of symptoms and diagnosis was short (8 days) in patients presenting with thirst, but much longer for those with weight loss (294 days) and skin infections (463 days). Over a quarter of patients had raised blood glucose readings, which were not followed up in the two years before diagnosis was made. **Conclusions:** Most patients with type 2 diabetes are diagnosed in primary care. Many are asymptomatic at diagnosis. Earlier diagnosis of diabetes may be possible by considering diabetes in patients with weight loss and skin infections, and ensuring that borderline abnormal tests are adequately followed up.

Key words: case–control study; diagnosis; symptoms; type 2 diabetes

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Introduction

The prevalence of type 2 diabetes has increased by 50% in 10 years (Fleming *et al.*, 2005), with diabetes

now affecting around 2.2 million people in the UK (Diabetes UK, 2006a). The true prevalence of diabetes may however be much higher, as studies have shown that around half of diabetes in the UK is undiagnosed (Thomas *et al.*, 2005; Wild *et al.*, 2005). Studies looking at diabetic retinopathy have estimated that the onset of diabetes precedes diagnosis by at least four to seven years (Harris *et al.*, 1992).

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By the time they are diagnosed with diabetes, one-third of people have already developed complications (UK Prospective Diabetes Study Group, 1990; Kohner *et al.*, 1998). It is well established that treatment of diabetes improves outcomes and prevents or delays the development of complications (UK Prospective Diabetes Study Group, 1998a; 1998b). It is therefore widely accepted that late diagnosis is a missed opportunity to prevent the development of these irreversible complications of diabetes. This supposition is supported by the evidence that those with undiagnosed diabetes have an increased risk of all-cause mortality (Wild *et al.*, 2005). Also diabetes which is detected when fasting plasma glucose is lower has fewer adverse clinical outcomes and fewer complications (Colagiuri *et al.*, 2002).

Recognising the importance of undiagnosed diabetes, Standard 2 of the UK National Service Framework for diabetes states that 'the National Health Service will develop, implement and monitor strategies to identify people who do not know they have diabetes' (Department of Health, 2001).

One possible route to the earlier diagnosis of diabetes is screening. Some primary care clinicians are enthusiastic about opportunistic or targeted screening, and a variety of risk scores have been developed to try to identify individuals at high risk of diabetes (Park *et al.*, 2002; Lindstrom and Tuomilehto, 2003), such as those with ischaemic heart disease or hypertension. However, universal screening for diabetes is not recommended at present (Wareham and Griffin, 2001). In the absence of screening, the main prospect for earlier diagnosis is prompt recognition of symptomatic diabetes. However, the risk of diabetes posed by particular symptoms is largely unknown, especially in unselected populations like primary care.

Early symptoms of type 2 diabetes

Textbooks emphasise the triad of polyuria, thirst and weight loss as prominent symptoms of type 1 diabetes; however, its relevance to type 2 diabetes is less clear. Although several studies have looked at symptoms of people with type 2 diabetes (Konen *et al.*, 1996; Van der Does *et al.*, 1996; Bulpitt *et al.*, 1998; Adriaanse *et al.*, 2005; O'Connor *et al.*, 2006), few have looked at

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symptoms before diagnosis. The few who did (Singh *et al.*, 1992; Drivsholm *et al.*, 2005) used retrospective questionnaires to ask patients whether they had experienced particular symptoms, so were subject to recall bias and were unlikely to reflect what is seen in clinical practice.

Symptoms and conditions reported as occurring in diabetes include polyuria, thirst, lethargy, weight loss, visual disturbances, candidiasis, leg pains, ulcers, urinary tract infections, skin infections, dyspnoea, impotence, confusion, paraesthesia, angina, dry mouth and stroke (Konen *et al.*, 1996; Ruige *et al.*, 1997; Bulpitt *et al.*, 1998; Drivsholm *et al.*, 2005; Muller *et al.*, 2005). Many of these occur commonly in general practice and the possibility of diabetes may be overlooked.

Pathways to the diagnosis of type 2 diabetes

Type 2 diabetes can be diagnosed in a variety of settings and at any point from asymptomatic disease detected by screening, to presentation with symptoms or complications. A UK study in 1992 showed 39% of cases of diabetes presented with 'typical' symptoms (polyuria, polydipsia, weight loss or lethargy), 21% were detected by screening and 54% were diagnosed in primary care (Singh *et al.*, 1992). The current proportions of patients travelling along these different pathways are unknown.

The aims of this study were two-fold:

- 1) To examine the frequency of pre-diagnostic symptoms in people with newly diagnosed diabetes, compared to controls, so as to assess their utility in the diagnosis of diabetes in primary care.
- 2) To examine the pathways leading to the diagnosis of type 2 diabetes.

Methods

Sixteen general practices belonging to a research consortium in Bristol were invited to participate. In participating practices, computer databases were searched by practice staff using keywords to identify all patients on the practice diabetes register, diagnosed between 2001 and 2006 inclusive, and aged over 30 years. Patients treated with insulin within 30 days of diagnosis were ineligible,

to exclude those with probable type 1 diabetes. Fifteen cases per practice were randomly selected from the list of newly diagnosed patients using computer-generated random numbers. One control was matched to each case using the criteria of sex, age (to a maximum of one year) and general practice. Controls were eligible if they were alive at the time of diagnosis of their case. Cases and controls were excluded if there was no entry in the notes in the two-year period before the diagnosis of diabetes was made.

The date of diagnosis was defined as the first date at which the label diabetes was used without any expression of doubt, or the date at which diabetes treatment was commenced. The date at which tests leading to the eventual diagnosis of diabetes were first instigated was termed the investigation date. Symptoms recorded at this investigation date were defined as the presenting symptoms and were categorised into those from hyperglycaemia (polyuria, polydipsia, weight loss, lethargy, blurred vision, candidiasis and skin infections), and those from complications (chest pain, stroke, leg ulcers, parasthesia, visual loss and impotence).

Anonymised primary care records were examined for two years prior to the date of diagnosis by one author (JW). The following features were identified using a check list: polyuria, thirst, weight loss (in the absence of deliberate dieting), lethargy, blurred vision, other visual disorder, urinary tract infections, skin infections, candidiasis, other infections, foot or leg ulcers, foot or leg pain, dyspnoea, impotence, parasthesiae, confusion, angina, dry mouth and strokes or transient ischaemic attacks. Elevated blood glucose recordings or positive urinalyses occurring before the investigation date were also recorded. Each feature was timed in relation to the date of diagnosis, to give an indication of any delay in diagnosis.

Analysis was performed using Stata, version 9 (StataCorp, 2005). Only variables occurring in at least 5% of the study population were examined. Differences between cases and controls were analysed using conditional logistic regression. Variables associated with diabetes in univariable stages, using a P value ≤ 0.1 , entered the multivariable analysis. A sample size calculation assumed that 20% of patients with uncomplicated diabetes would have symptoms or signs of

diabetes before diagnosis (based on a pilot study in a separate practice), and 2% in controls. For 90% power and a two-sided α of 0.05, this required 73 patients in each group. For increased generalisability, we increased the sample to accommodate all practices agreeing to participate. Ethical approval was obtained from Gloucestershire Research Ethics Committee (REC reference number 06/Q2005/58).

Results

Cases and controls

Of the 16 practices offered participation, one was unable to participate due to lack of space. Another declined as they felt that the mandate for screening was so strong that asymptomatic diagnosis following screening was the norm in their practice. Six practices did not reply. Eight responded positively, of which seven participated, five were urban and two semi-rural. The eighth replied after data collection was complete. The mean practice list size was 9900 (range 7600–13 500). The mean index of multiple deprivation score was 25 (range 8.6–49; encompassing both socioeconomic affluence and disadvantage). Total, 105 cases with newly diagnosed type 2 diabetes were studied (15 per practice). Their mean age was 63 (SD 15) years; 62 were male and 43 female.

Clinical features

Six features occurring in less than 5% of the total study population were excluded from analysis: dry mouth, cerebrovascular accident, blurred vision, impotence, ulcers and confusion. Table 1 shows the univariable analyses for the remaining 13 variables and for any recorded abnormal investigations. Pre-diagnostic features occurring both before and after tests for diabetes that were instigated are included. The timing of the features before the date of diagnosis is also shown. Five features were significantly associated with diabetes: thirst, polyuria, weight loss, skin infections and lethargy. Previous random or fasting plasma glucose ≥ 5.6 mmol/L was also significantly associated with diabetes. Of the 25 with a random glucose ≥ 5.6 mmol/L, 10 (7 cases, 3 controls) were in the range 5.6–6.9, leaving 15 (13 cases, 2 controls) with results ≥ 7.0 mmol/L.

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Table 1 Univariable analyses of symptoms and investigations occurring prior to the diagnosis of diabetes

Feature	Number (%) with this feature		Likelihood ratio (CI)	P value	Median first onset of feature prior to diagnosis in cases in days (interquartile range)
	Cases (n = 105)	Controls (n = 105)			
Symptoms					
Thirst	23 (22)	1 (0.95)	23 (12, 43)	0.002	8 (0, 17)
Polyuria	17 (16)	1 (0.95)	17 (2.5, 120)	0.006	8 (0, 97)
Weight loss	14 (13)	3 (2.9)	4.7 (2.7, 7.9)	0.015	300 (21, 470)
Skin infection*	31 (30)	13 (12)	2.4 (1.3, 4.5)	0.006	460 (290, 570)
Lethargy	28 (27)	14 (13)	2.0 (1.1, 3.6)	0.020	340 (26, 620)
Candidiasis	16 (15)	8 (7.6)	2.0 (0.87, 4.57)	0.082	230 (52, 560)
Dyspnoea	10 (9.5)	7 (6.7)	1.4 (0.55, 3.7)	0.44	340 (67, 600)
Other infection**	40 (38)	32 (31)	1.3 (0.80, 2.0)	0.22	420 (180, 690)
Parasthesia	8 (7.6)	8 (7.6)	1.0 (0.38, 2.6)	1.0	230 (66, 560)
Angina	9 (8.6)	9 (8.6)	1.0 (0.5, 1.9)	1.0	390 (130, 550)
UTI	11 (10)	13 (12)	0.85 (0.47, 1.5)	0.67	460 (300, 680)
Foot or leg pain	5 (4.8)	6 (5.7)	0.83 (0.35, 2.0)	0.74	410 (200, 530)
Visual loss	10 (9.5)	15 (14)	0.67 (0.36, 1.2)	0.23	300 (150, 470)
Investigations					
Random plasma glucose ≥ 5.6	20 (19)	5 (4.8)	4.0 (2.56, 6.24)	0.004	410 (160, 500)
Fasting plasma glucose ≥ 5.6	8 (7.6)	1 (0.95)	8.0 (4.0, 16)	0.050	420 (390, 520)
Any abnormal test***	27 (26)	6 (5.7)	4.5 (3.1, 6.5)	0.001	400 (390, 500)

* Fungal and bacterial infections (including cellulitis, wound infections, intertrigo, tinea, boils, infected eczema, impetigo, infected ulcers, folliculitis, pustules, abscess, infected sebaceous cyst and infected insect bites).

** Any other infection treated with antibiotics (including chest infection, ear infection, eye infection, sinusitis, dental infections, tonsillitis, laryngitis and infection of unknown origin).

*** Random plasma glucose ≥ 5.6 mmol/L or fasting plasma glucose ≥ 5.6 mmol/L or urinalysis positive for glucose. Positive urinalysis occurred in less than 5% of the study population, so was not analysed independently.

Table 2 shows the results of univariable analysis of the five features that reached significance in Table 1, when only occurrences before tests for diabetes that were instigated were analysed. Table 3 shows the results of multivariable analyses of pre-diagnostic features occurring both before and after diabetes testing was instigated.

Pathways

Figure 1 summarises the pathways to the diagnosis of diabetes; 42 (40%) had symptoms related to diabetes and 42 (40%) were detected by testing asymptomatic patients. Although data were not uniformly available on the reasons diabetes testing was performed in this asymptomatic group, reasons cited in the records were as follows: screening for patients with ischaemic heart disease or hypertension ($n = 15$), family history of diabetes ($n = 2$), preoperative screening ($n = 2$), geriatric screening ($n = 1$), routine medical check ($n = 1$) and new patient check ($n = 1$).

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Discussion

Summary of main findings

Only three features were independently associated in multivariable analysis with the diagnosis of type 2 diabetes: thirst, weight loss and skin infection. Polyuria and lethargy were also associated with a future diagnosis of diabetes, but not once the other three features were included. When patients presented with polyuria or thirst, they were rapidly diagnosed, with a median interval of eight days between recording of these symptoms and the diagnosis. However, this interval was much longer for patients with weight loss, lethargy and skin infections (295, 336 and 463 days, respectively). Of all the pre-diagnostic features of diabetes, skin infections were the most common, reported by 30% of cases, with an average period of over one year between the first episode and diagnosis. When only the features occurring before testing for diabetes began were

Table 2 Univariable analysis of features occurring before tests for diabetes were instigated

Feature	Number (%) with this feature		Likelihood ratio (CI)	P value
	Cases (n = 105)	Controls (n = 105)		
Polyuria	4 (3.8)	1 (.95)	4.0 (1.5, 11)	0.22
Thirst	3 (2.9)	1 (0.95)	3.0 (0.97, 9.3)	0.31
Weight loss	9 (8.6)	3 (2.9)	3.0 (1.48, 6.10)	0.099
Skin infection	28 (27)	13 (12)	2.2 (1.5, 3.1)	0.017
Lethargy	19 (18)	14 (13)	1.4 (0.88, 2.1)	0.36

Table 3 Multivariable conditional logistic regression analysis of pre-diagnostic features of diabetes

Feature	Likelihood ratio (CI)	P value
Thirst	36 (3.0, 440)	0.005
Weight loss	5.7 (1.3, 26)	0.022
Skin infection	4.6 (1.7, 12)	0.002
Previous fasting plasma glucose ≥ 5.6 mmol/L	38 (2.2, 640)	0.012
Previous random plasma glucose ≥ 5.6 mmol/L	15 (2.5, 94)	0.003

examined, skin infections were the sole feature associated with diabetes. This suggests that the 'classical' symptoms of polyuria, thirst, weight loss and lethargy are recognised by general practitioners, and trigger the testing for diabetes.

Over a quarter (27 of 105) of people with newly diagnosed diabetes had abnormal tests in the two years before the diagnosis was established, but this did not lead to definitive testing. As we did not examine hospital notes from this period, the true numbers of abnormal tests may be even higher. This highlights the importance of systems for follow-up of borderline abnormalities. A random glucose ≥ 5.6 mmol/L may appear low for clinicians to consider diabetes. This figure was chosen as national and international guidelines recommend further investigations for any patient with a random glucose ≥ 5.6 (International Diabetes Federation, 2005; Diabetes UK, 2006b). In this study, the positive likelihood ratio of a borderline abnormality for diabetes was 4.5, suggesting this threshold level is appropriate.

Comparison with existing literature

This is the first study to examine the pre-diagnostic features of diabetes in unselected primary care patients. Previous studies have shown an increased prevalence of skin infections in people

with diagnosed diabetes (Muller *et al.*, 2005), but this is the first study to show the significance of skin infections before diagnosis. This study supports textbook literature, which emphasises the importance of polyuria, thirst, weight loss and lethargy in diagnosing diabetes.

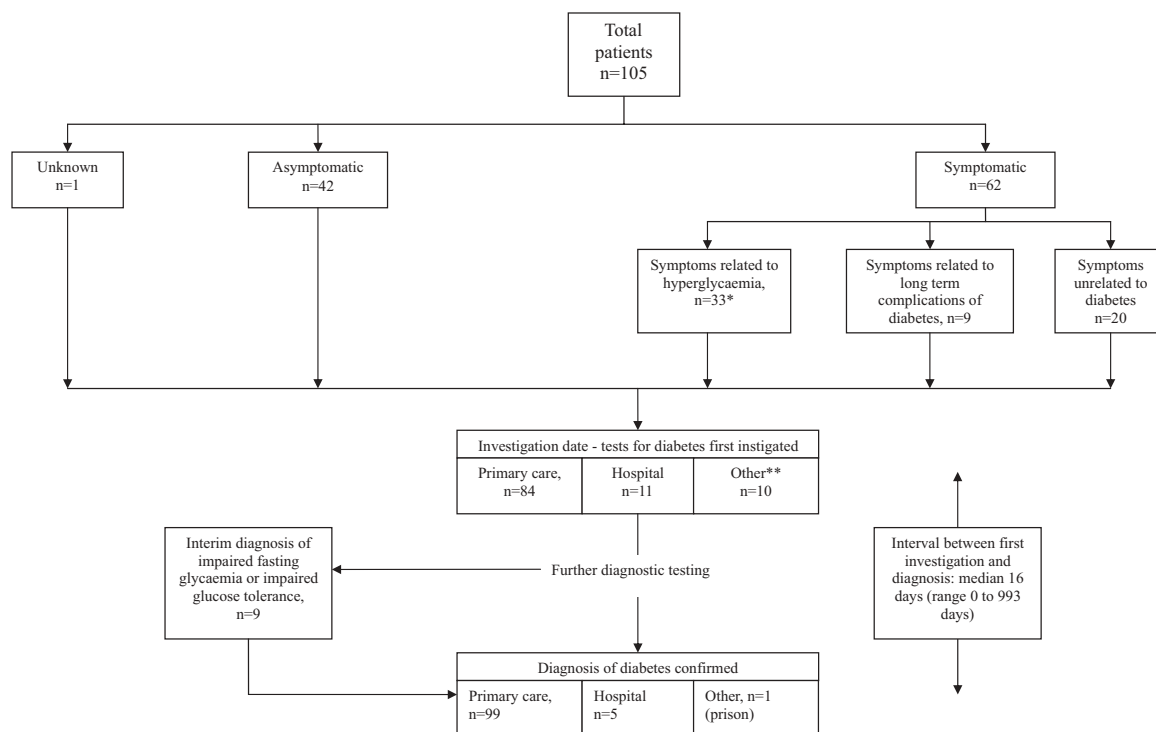
Pathways

In this small study, 80% of diabetes was first detected in primary care, and 94% of diagnoses were confirmed in primary care. This contrasts with a previous study from 1992 when only 54% of diabetes was diagnosed by general practitioners (Singh *et al.*, 1992).

Symptoms of hyperglycaemia were reported in 31% of patients, similar to a recent study of newly diagnosed patients in the US (32.3%) (O'Connor *et al.*, 2006) and to the previous UK study (39%) (Singh *et al.*, 1992).

In this study, 40% of people with diabetes were asymptomatic at diagnosis, an increase from 21% in 1992 (Singh *et al.*, 1992). Although universal screening for diabetes is not currently recommended (Wareham and Griffin, 2001), targeted screening to 'at-risk' groups has been proposed (American Diabetes Association, 2004), and this was a common mechanism in this study. Various risk scores have been developed to attempt to

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* Thirst n=16, lethargy n=14, polyuria n=10, weight loss n=7, candida n=5, skin infections n=5

**Patient self tested for diabetes n=4, pharmacy tested n=2, independent medical examination n=2, tested in prison n=1, tested at opticians n=1

Figure 1 Flow chart summarising the pathways to the diagnosis of diabetes

provide an evidence base for targeted screening (Park *et al.*, 2002; Lindstrom and Tuomilehto, 2003). None of these evidence-based approaches were being systematically used in the practices studied. Further research into the value of screening, and dissemination of the current evidence to primary care clinicians could help to rationalise screening programmes.

Strengths and limitations of this study

This study was relatively small, and only from one area, yet it produced highly significant results in the analyses. In this study, we chose to look at symptoms that had been reported previously with diabetes. With this approach, we would miss previously unreported features; however, the alternative – of coding all clinical features in cases

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and controls – would have had an unacceptably high risk of identifying false-positive associations. One potential weakness of this study is that the results are dependent on the quality of record keeping. Doctors may ask patients in whom diabetes is suspected specifically about the commonly known symptoms of diabetes (and presumably record them), whereas controls may be less likely to be asked specifically about these symptoms. The opposite – of more recording of symptoms when no diagnosis is apparent – is also possible but less likely. This is a potential problem with all retrospective studies, yet in this study the data were recorded before the outcome of interest was known reducing the potential for reporting bias. The matched design also helps compensate for any variations in testing and recording between different practices. Another

possible source of bias that cannot be excluded is verification bias; that is, that those with symptoms known to be associated with diabetes are more likely to receive a diagnosis of diabetes. Selection bias is also a possibility as not all practices, which were approached, agreed to participate. However, the advantage of the study design is that by using data from primary care records, results are likely to reflect the symptoms that are reported in clinical practice. This research provides a useful direction for future research, such as a larger retrospective or a prospective study to validate and expand on these findings.

Implications for clinical practice

Primary care clinicians have a central role in the diagnosis of diabetes, with 80% of diabetes being first detected in primary care. This study suggests potential improvements for the early detection of diabetes. Clinicians should be alert to the possibility of diabetes in patients with any skin infection, lethargy or weight loss, especially given that testing for diabetes is quick, cheap and non-invasive. Furthermore, patients with borderline abnormalities in glucose testing or urinalysis need systematic follow-up – which not all are currently receiving.

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