

Association of Symptoms of Type 2 Diabetic Patients With Severity of Disease, Obesity, and Blood Pressure

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OBJECTIVE— The symptoms of 430 type 2 diabetic patients were determined by a self-administered questionnaire before entry into the U.K. Prospective Diabetes Study.

RESEARCH DESIGN AND METHODS— Entry into the trial followed 2 months of dietary treatment for newly diagnosed patients with type 2 diabetes. Forty symptoms with five levels of severity were included in the questionnaire. A complaint rate was computed as the sum of symptom scores divided by the number of symptom questions answered.

RESULTS— The complaint rate was independently and positively related to BMI, fasting plasma glucose (FPG), and being a woman. Three symptoms—presence of dry mouth ($P < 0.001$), thirst ($P < 0.01$), and stomach pain ($P = 0.02$)—were related to FPG independent of sex, age, BMI, or blood pressure. Only dry mouth was related to HbA_{1c} ($P = 0.05$). Complaints of shortness of breath, swollen ankles, headaches, heartburn, sweating, wheezing, nocturia, thirst, and diarrhea increased with BMI independently of other variables. A complaint of cold extremities decreased with BMI. Heartburn, weakness of limbs, and hot flushes were positively related to blood pressure, and unsteadiness was negatively related.

CONCLUSIONS— The symptoms reported by patients with type 2 diabetes increased with FPG and markedly with BMI. The symptoms associated with obesity have been underestimated in the past.

In the treatment of diabetes, an initial aim is to reduce symptoms. Hyperglycemia is associated with the classical symptoms of thirst, polyuria, and weight loss. In addition, symptoms can arise from the frequent association of hyperglycemia with obesity or hypertension. It is therefore important to identify those symptoms associated with these three factors and to determine whether or not they are improved by therapy. We are investigating this problem in patients with type 2 diabetes, and we have used a questionnaire (C.B., A.E.F., C.J.B., J.S.Y., unpublished observations), which forms one part of the quality of life (QoL) assessment in patients in the U.K. Prospective Diabetes Study (UKPDS). The UKPDS

trial is evaluating whether improved blood glucose control will delay the complications of diabetes (2).

Symptoms that occur in diet-treated patients, and their association with hyperglycemia and other variables, provide a baseline for prospective assessment of response to therapies. The symptomatic response to therapy is important because compliance with long-term treatment is generally poor when the untreated disease is associated with few or no complaints of ill health. Compliance is even poorer if the patient feels worse when taking the treatment (3,4). If studies, such as the UKPDS, are able to demonstrate that one particular intervention is capable of reducing the inci-

dence of physical complications or mortality, a QoL assessment would permit the benefits of that intervention to be set against any physical, psychological, or economic costs.

This report considers the symptomatic well-being of patients entering the UKPDS and the extent to which these symptoms arise from the severity of their condition or to related problems, such as obesity or hypertension.

RESEARCH DESIGN AND METHODS

Patients

A total of 430 patients were studied after 2 months of dietary treatment. Their body weight, height, fasting plasma glucose (FPG), and blood pressure were measured at the same visit, and HbA_{1c} was measured 1 month later so that the degree of glycosylation would relate to the period of symptomatic assessment. Blood pressure measurement has been fully described elsewhere (5).

Choice of symptoms and questions

We selected 40 symptoms, 19 of which had previously been shown to occur in excess in treated diabetic patients, i.e., thirst, dry mouth, getting up at night to pass urine, constipation, diarrhea, unsteadiness, shortness of breath, weakness of limbs, burning or tingling or numb limbs, leg cramps, itching or discomfort when passing urine (dysuria), bad taste in the mouth, blurred vision, hot flushes, sleepiness, racing heart, and sweating more than usual (6). Six symptoms were selected as indicative of cardiovascular or respiratory problems: head pains or headaches, swollen ankles, wheezing, cold hands and feet, heart thumps or misses a beat, and painful limbs. The remaining 15 symptoms were related to the adverse consequences of drug treatment, i.e., burning mouth, blocked or runny nose, feeling sick, rash on body, itching, pain in joints of hands, shaky hands, stomach pain, heartburn, sore throat, dry cough, dry eyes, mouth ulcers, light hurting eyes, and hunger.

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Abbreviations: dBp, diastolic blood pressure; FPG, fasting plasma glucose; QoL, quality of life; sBP, systolic blood pressure; SF-36, short-form 36-item instrument; UKPDS, U.K. Prospective Diabetes Study.

Table 1—Clinical characteristics of diabetic patients according to sex

	Men	Women
Characteristics		
n	251	179
Age (years)	51.2 (9.46)	52.2 (9.64)
FPG (mmol/l)	8.86 (2.67)	9.72 (3.17)*
HbA _{1c} (%)	9.01 (2.14)	8.98 (2.11)
BMI (kg/m ²)	28.4 (4.63)	30.6 (7.11)†
sBP (mmHg)	130.5 (19.4)	134.5 (21.3)
dBP (mmHg)	80.3 (12.6)	80.8 (11.4)
Symptoms (% complaining of any degree of each)		
Dry mouth	63.4	69.5
Bad taste in mouth	37.8	49.7
Burning mouth	10.4	13.3
Blocked or runny nose	46.1	47.6
Sore throat	20.8	28.2
Mouth ulcers	13.7	11.0
Constipation	17.9	27.1
Diarrhea	11.9	13.9
Feeling sick	16.5	27.1
Stomach pain	15.9	28.9*
Heartburn	17.5	22.8
Hunger	72.2	76.1
Head pains or headaches	46.4	61.5*
Dry eyes	18.3	23.3
Blurred vision	48.0	51.2
Light hurting eyes	37.5	42.1
Sleepiness	61.5	72.3
Getting up at night to pass urine	70.2	79.2
Itching or discomfort when passing urine	11.3	28.3†
Sweating more than usual	27.2	46.8†
Hot flushes	14.6	47.0†
Thirst	66.8	66.1
Weakness of limbs	52.4	43.3
Tingling limbs	33.5	37.7
Burning limbs	9.3	12.7
Painful limbs	38.7	41.0
Numb limbs	25.4	24.7
Leg cramps	39.3	42.5
Swollen ankles	13.4	30.8†
Cold hands or feet	50.2	51.2
Rash on body	17.0	15.1
Itching	31.2	46.4*
Pain in joints of hands	34.3	40.2
Shaky hands	11.8	16.6
Unsteadiness	30.6	34.6
Shortness of breath	31.9	35.8
Dry cough	31.7	34.3
Wheezing	21.7	19.6
Racing heart	15.4	27.5*
Heart thumps or misses a beat	13.2	23.4*
Complaint rate	0.483	0.621*

Data are average (SD) or %. * $P < 0.01$; † $P < 0.001$.

The questionnaire was self-administered and completed just before seeing the nurse or doctor at a trial visit. A suitable

private place was used for this purpose. The subjects were asked to circle the "answer which describes whether you have

experienced the symptom in the last week and, if so, the extent to which it has bothered you." The answer options were "not at all," "a little," "moderately," "quite a bit," and "extremely." The response rate for completion of the questionnaire was 69%, and the average completion rate for an individual question was 90%.

Biochemical methods

In each clinical center, FPG was measured by a laboratory assay that was quality controlled by the UKPDS coordinating center. HbA_{1c} was measured by high-performance liquid chromatography with a Bio-Rad analyzer (Hercules, CA) at the coordinating laboratory (7).

Statistical methods

The answer options were coded 0–4. A complaint rate was computed as the sum of these scores divided by the number of symptom questions completed. The mean result for the complaint rate was 0.54, and the median result was 0.43. The distribution of this summary score was sufficiently normal to allow multiple regression analysis on age, sex, log FPG, HbA_{1c}, log BMI (log kg/m²), systolic blood pressure (sBP), and diastolic blood pressure (dBP). The presence (1) or absence (0) of each symptom was also used in a multiple logistic regression model to determine the independent effects of these variables on the complaint of a symptom.

RESULTS — Table 1 lists the clinical characteristics of the 430 patients. FPG and BMI were, on average, higher in women than in men. Both men and women with BMI values ≥ 27 kg/m² were considered overweight. The average complaint rate was higher in women. Table 1 also lists the individual symptoms as described in the questionnaire. The higher complaint rates in women were due to the excess of stomach pain, headache, dysuria, sweating, hot flushes, swollen ankles, itching, tachycardia, and palpitations (all comparisons $P < 0.01$). These symptoms include those expected to be associated with type 2 diabetes, its treatment, and cardiovascular disease.

Table 2 gives the first-order regression coefficients (b) between the complaint rate and age, sex, log FPG, HbA_{1c}, log BMI, sBP, and dBP. The complaint rate increased with the concentration of FPG and BMI. Age, HbA_{1c}, sBP, and dBP were not related to the complaint rate.

Table 2—First-order regression coefficients (b) between the complaint rate and age, sex, log FPG, HbA_{1c}, log BMI, sBP, and dBP

	Complaint rate	
	b	P
Age	-0.0023	0.342
Sex	+0.138	0.003
Log FPG	+0.193	0.014
HbA _{1c} (%)	+0.013	0.229
Log BMI	+0.257	0.037
sBP	+0.00007	0.954
sBP	+0.002	0.227

Sex is coded as 1 = men, 2 = women.

Table 3 shows the result of a multiple regression analysis to examine whether or not the relationship between complaint rate and FPG was independent of age, sex, sBP, and BMI. The complaint rate was still related to FPG after adjustment for age and sex. Table 3 also shows the relationship between complaint rate and BMI. This relationship was weakened by adjustment of both age and sex, but an association could not be ruled out with any confidence ($P = 0.10$). Because the overall complaint rate may be associated with BMI, the individual symptoms were examined to determine their relationship to BMI and other variables.

Table 4 gives the mean FPG and HbA_{1c} values according to the extent to which symptoms bothered patients in the last week. Multiple logistic regression analysis identified three symptoms, i.e., dry mouth ($P < 0.001$), thirst ($P < 0.01$), and stomach pain ($P = 0.02$) as being positively related to FPG independent of sex, age, BMI, sBP, and dBP. The average difference in FPG between "not at all" and "quite a bit" or "extremely" was 2–3 mmol/l. Only one of these symptoms, i.e., dry mouth ($P = 0.05$) was statistically related to HbA_{1c} after adjustment.

Table 5 lists the average BMI for 10 symptoms that were related to BMI ($P < 0.01$) independently of sex, age, FPG, sBP, and dBP. BMI was higher by ~2–4 kg/m² for those responding "quite a bit or extremely" for shortness of breath, swollen ankles, headaches, heartburn, sweating, wheezing, nocturia, and thirst compared with no symptoms. Few patients complained of severe degrees of diarrhea, but those who did had a BMI 2 kg/m² greater than those without the complaint. Patients who did not complain of cold extremities were 2 kg/m² heavier than those who did.

Table 3—Results of multiple regression (b) analyses of complaint rate on log FPG and log BMI

Independent variable	Effect adjusted for	Complaint rate	
		b	P
Log FPG	—	0.193	0.014
	Sex alone	0.163	0.039
	Log BMI alone	0.188	0.018
Log BMI	Age, sex, sBP + log BMI	0.166	0.039
	—	0.257	0.037
	Age alone	0.254	0.039
	Age + sex	0.203	0.101

The association between complaint rate and log FPG was not completely removed by adjustment for age, sex, sBP, and log BMI.

Table 6 reports blood pressure results for symptoms that were positively related to sBP (heartburn and hot flushes) or dBP (weakness of limbs, heartburn, and hot flushes) independently of the other variables. The presence of a "moderate, quite a bit, or extreme" complaint was associated with a 2- to 3-mmHg higher dBP for weakness of the limbs, heartburn, and hot flushes. The presence of a complaint of unsteadiness was associated with a 3-mmHg lower sBP.

CONCLUSIONS— In newly diagnosed patients with type 2 diabetes, after 2 months of dietary treatment, the total number of symptoms was related to the concurrent FPG, even after adjustment for age, sex, sBP, and BMI. This was not true, however, for HbA_{1c}.

The FPG of those complaining "quite a bit" or "extremely" of dry mouth was

increased by 20% over those without this complaint, and the corresponding increases in FPG for thirst and stomach pain were 20 and 16%, respectively. Although stomach pain may not suggest a high blood glucose level, this association has been reported in people with diabetes (6). A preliminary analysis suggested that heartburn and a bad taste in the mouth were also associated with increasing levels of FPG (1). This was not confirmed in the present analysis in which sex, age, sBP, and BMI were controlled for.

It is interesting to note that a generic measure of health-related QoL, the short-form 36-item instrument (SF-36) (8), was related to the concentration of glycosylated hemoglobin in one study (9) but not in a second (10). In the present study, glycosylated hemoglobin was not closely related to symptoms. It has been suggested that the lack of a relationship is because patients

Table 4—FPG and HbA_{1c} (%) according to four grades of three symptoms

	Extent to which symptom bothered patient in the last week				
	Not at all	A little	Moderately	Quite a bit or extremely	
Dry mouth	n	124	139	38	65
	FPG	8.4	9.4	9.7	10.1
	HbA _{1c}	8.7	9.1	9.2	9.3
Thirst	n	127	133	48	70
	FPG	8.5	9.1	9.8	10.2
	HbA _{1c}	9.0	8.9	9.2	9.2
Stomach pain	n	293	53	15	13
	FPG	9.0	10.0	9.6	10.4
	HbA _{1c}	9.0	9.0	8.8	9.3

Data are in mmol/l (FPG) or % (HbA_{1c}). Symptoms were related to one or more of these variables independently of sex, age, BMI, and blood pressure.

Table 5—BMI for 10 symptoms

	Extent to which symptom bothered patient in the last week			
	Not at all	A little	Moderately	Quite a bit or extremely
Head pains or headache	28.4 (177)	29.9 (123)	30.6 (36)	30.8 (39)
Shortness of breath	28.5 (250)	31.2 (90)	30.5 (17)	31.6 (14)
Swollen ankles	28.4 (298)	33.8 (51)	32.3 (11)	32.1 (15)
Heartburn	28.9 (297)	31.5 (58)	28.5 (8)	32.6 (6)
Sweating more than usual	28.8 (239)	30.1 (73)	30.0 (20)	31.5 (39)
Wheezing	29.0 (291)	30.6 (54)	32.5 (8)	32.6 (9)
Getting up at night to pass urine	28.3 (102)	29.8 (146)	29.1 (72)	30.4 (63)
Diarrhea	29.1 (321)	31.3 (37)	28.6 (2)	32.0 (6)
Thirst	28.2 (128)	29.1 (128)	31.1 (47)	30.8 (68)
Cold hands or feet	30.5 (185)	28.4 (107)	26.9 (31)	28.4 (50)

Data are in kg/m² (n). Symptoms were related to BMI independently of sex, age, FPG, and blood pressure.

with type 2 diabetes have significant comorbidity and complications that mask the relationship, that regimens used to improve glycemic control lower QoL, and that the generic SF-36 is less sensitive to the effects of poor control than a type 2 diabetes-specific instrument would be (10). However, our symptomatic enquiry was confined to the last week before assessment, and HbA_{1c} relates to the last 2 months. The fact that only current symptoms tend to be reported may explain the relative lack of association. Repeated symptomatic assessments may be required to investigate the relationship between symptoms and HbA_{1c}, and the relationships between blood glucose and changes in symptoms will be investigated in the longitudinal study of these patients. In the present cross-sectional analysis, only 3 of a possible 19 symptoms were related to blood glucose. However, it must be remembered that patients may have improved their dietary regimen, reducing possible associations. Also, patients entering a clinical trial may be expected to be relatively fit compared with all patients with type 2 diabetes, and this may obscure relationships with, say, blood glucose and age.

The association between obesity and symptoms has not been previously studied in diabetic patients. More complaints of shortness of breath, wheezing, swollen ankles, heartburn, and sweating in obese patients are easy to understand. Similarly, fewer complaints of cold hands and feet were expected. Less easy to understand are the complaints of headaches, nocturia, diarrhea, and thirst, especially because those symptoms were related to BMI independently of FPG and blood pressure. It appears

that the symptoms associated with obesity have been underestimated in the past.

In treated hypertensive patients, morning headache, weakness of limbs, and nocturia are associated with higher levels of blood pressure (11). In the present diabetic population, blood pressures were much lower, and these relationships were not observed. In fact, unsteadiness tended to be associated with lower levels of blood pressure. A similar association with heartburn remains unexplained, as does the positive relationship between hot flushes and blood pressure.

Table 6—sBP and dBP for four symptoms

	Extent to which symptom bothered patient in the last week		
	Not at all	A little	Moderately, quite a bit, or extremely
Weakness of limbs			
sBP	131.7	133.7	130.8
dBP	78.7	83.6	80.2
n	194	116	61
Unsteadiness			
sBP	133.1	129.9	130.3
dBP	81.0	78.4	80.4
n	252	88	33
Heartburn			
sBP	131.1	138.1	130.3
dBP	79.7	84.1	82.5
n	298	58	17
Hot flushes			
sBP	130.8	136.0	137.2
dBP	79.7	82.6	82.9
n	266	54	50

Blood pressure data are in mmHg. Symptoms were related to either sBP or dBP independently of sex, age, FPG and BMI. The "moderately," "quite a bit," and "extremely" groups are combined to provide sufficient numbers.

In the UKPDS, the consequences of symptomatic changes are being evaluated by an assessment of other areas of QoL. These include psychological well-being (anxiety, depression, vigor, fatigue, confusion, and hostility), subjective cognitive changes, satisfaction at work, and performance of work and usual activities (1). A preliminary analysis revealed increasing FPG concentrations at higher anxiety and fatigue levels (1).

The QoL of diabetic patients is being investigated in other studies, although the tendency is to report summary scores without an assessment of the underlying symptoms. Using the Medical Outcomes Study 20-question short form, diabetic patients have worse scores for physical and role functioning than both the general population and hypertensive patients (12). The same was true for health perceptions but not for mental health, which was similar in all three groups (12). The latter study, and other methods of assessing QoL in diabetic patients (13), did not concentrate on symptomatic well-being to the extent of the questionnaire used in the present study; however, Testa and Simonson (14) used 75 side effect and symptom questions but suggested that the treated hypertensive patients had more problems than the diabetic patients. The evaluation of symptoms and other aspects of QoL in the UKPDS is expected to add to the benefit-risk evalua-

tions required for the evaluation of improved glucose control.

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