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Impact of Long-Term Complications on Quality of Life in Patients with Type 2 Diabetes not Using Insulin

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ABSTRACT

Objectives: The complications of diabetes have the potential to greatly impact the health-related quality of life (HRQOL) of patients with type 2 diabetes. The effect of diabetic complications on HRQOL was assessed in 1233 patients with type 2 diabetes who were not using insulin.

Methods and data: Patients were aged 35 and older and had stable fasting serum glucose (FSG) after washout of antidiabetic therapy. Patients who required insulin or suffered from severe cardiovascular or hepatic disease, neuropathy, or retinopathy were excluded. Patients completed the SF-36 generic quality of life questionnaire. Demographic data, including body mass index (BMI), blood glucose hemoglobin A1c (HbA_{1c}), FSG, and the presence and severity of eight specified diabetic complications were also collected. A linear regression analysis was performed for each of the SF-36 domains and for the physical and mental health summary scales.

Results: The most prevalent diabetic complications were hypertension (46% of patients), peripheral sensory neuropathy (PSN; 12%), coronary artery disease (CAD; 8%), retinopathy (8%), and peripheral vascular disease (PVD; 7%). Most (73%) of the complications were assessed to be mild. PSN was associated with significantly lower scores (i.e., worse quality of life) in the mental health scale; CAD was associated with significant reductions of all but role-emotional and mental health scales of the SF-36; and PVD was associated with significantly lower physical and social functioning scales. Hypertension did not have an independent effect on HRQOL.

Conclusions: The presence of even mild diabetic complications has a significant impact on patients' quality of life. Early diagnosis and treatment is essential to help prevent deterioration of HRQOL in these patients.

Keywords: diabetic complications, quality of life, regression analysis, SF-36, type 2 diabetes.

Introduction

Type 2 diabetes is a considerable and evolving healthcare challenge in the Western world and in developing nations, primarily because of increased obesity, aging populations, and more sedentary lifestyles. It has been estimated that by 2010 approximately 250 million people worldwide will suffer from type 2 diabetes [1]. Complications associated with diabetes are a major cause of morbidity, mortality, and health-care costs. The cost of treating these complications in the United Kingdom in 2000 has been estimated at approximately £2 billion, or 4% of the total National Health Service budget [2]. With the estimated increase in newly diagnosed diabetes, the burden of both complications and cost will continue to be significant. Complications of diabetes can be divided into two categories: microvascular complications, which include neuropathy, retinopathy and nephropathy; and macrovascular disease, which can result in stroke, coronary artery disease (CAD), and peripheral vascular disease (PVD).

Much of the morbidity and mortality associated with Type 2 diabetes is caused by complications associated with the disease. For example, diabetic retinopathy resulting in loss of vision is the leading cause of blindness in working-aged persons in the United States [3]. Of particular concern in type 2 diabetes are the macrovascular effects that give rise to cardiac, cerebrovascular, and peripheral vascular dysfunction. The American Diabetic Association has estimated that 75% to 80% of adult diabetic patients will ultimately die as a result of macrovascular complications due to their underlying disease [4].

The diabetic complications described above not only result in physical disability and cost, but also lead to compromised health-related quality of life

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(HRQOL) [5]. The incidence (presence and number) of diabetic complications has been shown to have a significant impact on quality of life in a number of studies [6–9]. Individual studies have found that reduced quality of life is associated with diabetic neuropathy [10,11] and retinopathy [9] and with diabetic foot [12,13]. Recent findings using the SF-20 have shown that cardiovascular disease is an independently contributing factor to the reduction of quality of life in older-onset diabetes [14] and have demonstrated a link between impaired quality of life and congestive heart disease (CHD) and other macrovascular diseases [15].

The effect of glycemic control on quality of life in the short term remains controversial. Several studies found little direct relation between glycemic control and HRQOL using a number of measures [7,8,16,17], as confirmed in a small study in Pima Indians using the SF-36 [18]. Direct relationships have been found between blood glucose and quality of life in severely hyperglycemic individuals with either type 1 or type 2 diabetes [10,19].

However, long-term complications, particularly microvascular disease, have been directly related to poor glycemic control [20]. Because many patients are likely to remain undiagnosed for several years before symptoms appear, many will show evidence of diabetic complications at diagnosis [21,22]. Patients with elevated blood glucose have an increased risk of numerous microvascular and macrovascular complications, all of which may negatively affect HRQOL.

The present study used baseline assessments of patients who participated in three different clinical trials, the results of which have been presented elsewhere [23–25]. In addition to standard clinical measures, the impact of long-term diabetic complications on HRQOL was assessed and is reported in this paper.

Methods

Patients

Baseline data from a total of 1233 patients from three clinical trials in type 2 diabetes were pooled. Entry criteria for these studies required that patients be over 35 years of age and receiving treatment for their diabetes in the form of dietary modifications alone or in combination with oral antidiabetic agents. One study (study A) was conducted in patients aged 65 years or older. Existing therapy was withdrawn and patients had stable fasting serum glucose (FSG) levels during a washout period prior to the baseline assessment. Severely hyperglycemic patients or those using insulin were not eligible to participate. Also excluded were patients suffering from severe neuropathy, severe CAD, and moderate or severe nephropathy. The definitions of mild, moderate, and severe diabetic complications used in all three studies are shown in Table 1. All eligible patients enrolled in these studies were included in the current analysis, provided they had completed an HRQOL questionnaire on entering the study and that sufficient demographic and clinical data were available.

The data from all three studies were pooled to give a sufficient number for statistical analysis. Interpatient variability in demographics, FSG, and hemoglobin A_{1c} (HbA_{1c}) were explicitly addressed in the analysis. In addition, "study" was retained as an explanatory factor in all regressions to correct for unobserved differences in patient populations. Patients were recruited from a total of 12 European countries.

Assessments

On entry, patients attended a clinic visit at which time data were recorded by an investigator or clinic nurse using an approved protocol and case record form. Patient demographics including age, sex, and ethnic origin were recorded. Diabetic complications were recorded as absent, mild, moderate, or severe, using the criteria shown in Table 1. Complications assessed were retinopathy, peripheral sensory neuropathy (PSN), autonomic neuropathy, diabetic foot, nephropathy, hypertension, PVD, and CAD. Both FSG and HbA_{1c} were recorded, and patients completed the SF-36 quality-of-life instrument (standard version) at the clinic visit before receiving results of any tests or investigations.

Quality-of-Life Instrument

The SF-36 is a 36-item, self-completed questionnaire with items divided into eight domains measuring physical functioning, impairment to role activities due to physical problems (role-physical), impairment to role activities due to emotional problems (role-emotional), social functioning, bodily pain, mental health, vitality, and general health perception. Another item, health transition, considers changes in health over the preceding year. Each domain is subsequently computed in terms of a score from zero (poorest well-being) to 100 (highest well-being). Summary scores on two subscales, the Physical Component score (PCS) and Mental Component score (MCS), can also be calculated [5]. The SF-36 has been validated in all the

Table 1 Classification of diabetic symptoms

Symptom	Mild	Moderate	Severe
Diabetic retinopathy	Nonproliferative: Venous dilation Microaneurysms Small hemorrhages Hard exudates	Preproliferative: Cottom-wool spots Venous abnormalities Arterial abnormalities	Proliferative: Neovascularization Fibrous tissue Hemorrhage Retinal detachment Maculopathy
PSN	Reduced vibration sensation to ankle Reduced sensation to pinprick	Absent tendon reflexes Absent sensation to pinprick	Marked sensory loss in whole leg or foot, with or without pain
Autonomic neuropathy	Loss of beat variation Sweating Facial flushing	Genitourinary problems of no other origin Postural hypotension >20 mmHg systolic BP	Cardiac arrhythmia of autonomic origin Regular urinary or fecal incontinence
Diabetic foot	Cold Reduced but palpable pulses	Medical history includes ulceration Absent pulses	Gangrenous Amputation (for nontraumatic reason)
Nephropathy			
Albuminuria	Micro, 30–300mg/day	Macro, >300mg/day	Macro, >300 mg/day
Creatinine	180–200μmol/l	Plasma 201–250 μmol/l	>250 μmol/l, nephrotoxic syndrome
Hypertension (untreated)			
Diastolic BP, supine:	85 mmHg < BP < 95 mmHg	>95 mmHg	>100 mmHg
Other:	Systolic BP < 160 mmHg	Eye fundus changes Grade III	Eye fundus changes Grade III and IV
PVD	Reduced lower limb pulses Intermittent claudication	Rest pain Absent pulses	Absent pulses Ischemia/necrosis Surgery/amputation
CAD			
Angina:	On strenuous exercise	Limits ordinary activities	Angina at rest
Previous MI:		One	More than one
NYHA heart failure:		Grade III	Grade III or IV

BP, blood pressure; CAD, coronary artery disease; MI, myocardial infarction; NYHA, New York Heart Association; PSN, peripheral sensory neuropathy; PVD, peripheral vascular disease.

languages used in these studies. Individual scale scores were calculated using the standard scoring from the SF-36 users' manual [5]. Scale scores were deemed to be missing if more than half the individual items were missing. If up to half the items in a scale were missing, the mean of the items present for that scale was used [5]. Aggregate component scores were only calculated if all eight component scores were available.

Statistical Methods

A general linear model was fitted using each SF-36 domain with the physical and mental health summary scales as dependent variables. The following explanatory factors were included in the model: gender, ethnic origin, and country; and presence and severity of each of the eight diabetic complications, including age, BMI, duration of diabetes, FSG and HbA_{1c}. To ensure consistency of models across the SF36 domains, all explanatory factors were retained in the model. Factors were considered to be statistically significant if the proportion of the variation (overall sum of squares) of the dependent variable that the factor explained was significantly greater than zero using an *F*-test. Type II sums of squares and significance were assessed at $p = .05$, two-sided test.

Separate analyses based on the logistic and untransformed data were performed; plots of standardized residuals against predicted values and variables such as age and BMI showed that residuals from the untransformed data were randomly distributed. The untransformed data reported here performed adequately with regard to values outside the range.

To explore the validity of pooling the studies, an analysis of variance was also performed on each of the components to compare the between-trial variability with the within-trial variability. Of the eight component scores, role-emotional ($p > .5$), body pain ($p = .429$), and vitality ($p = .146$) showed no evidence of appreciable heterogeneity. The other five scores and the two aggregate scores exhibited significant heterogeneity ($p < .001$ for all). We do not believe that this invalidates pooling the data from the three studies because the differences may be due in part to differences in age and/or sex, or other population differences. To allow for remaining unobserved variation, we included "study" as a random effect in each model.

To examine how the data compared with population norms, the mean values for each SF-36 domain from this study were compared to two reference populations: 1) the general US population aged 55–64 from the original Medical Outcome Survey (MOS) [5]; and 2) the subgroup of non-insulin dependent diabetes mellitus (NIDDM) from the MOS [5].

The software used was SAS V6.12 (The SAS Institute Inc., Cary, NC), and least square means were calculated using the generalized linear model (GLM) procedure.

Results

Patients

A total of 1233 patients were included from three studies as follows: study A (110 patients); study B (368 patients); and study C (755 patients). Patient demographics are shown in Table 2. More men than women were included in studies B and C, while more women than men were included in study A. Overall, 58% of patients were male. Almost all patients (98%) were white. The mean duration of diabetes was 70 months (SD ± 69 months), the mean FSG was 11.1 mmol/L (SD ± 3.1 mmol/L), and the mean HbA_1c_{1c} was 8.0% (SD ± 1.4%).

The most prevalent diabetic complications (Table 3) were: hypertension (46% patients), PSN (12%), CAD (8%), and PVD (7%). Other complications assessed were found in 3% or less of patients. Most of the complications were assessed to be mild (73%), and the remaining were moderate (22%) and severe (5%).

Table 2 Summary of demographic and clinical characteristics for evaluable patients

Characteristic	Study A (n = 110)	Study B (n = 368)	Study C (n= 755)	All patients (n = 1233)
Gender				
Male	51	210	448	709
Female	59	158	307	524
White (% patients)	96.4	94.8	99.3	97.7
Age (years)				
Mean ± SD	75 ± 4.3	58 ± 9.0	60 ± 10.8	61 ± 10.8
Interquartile range	72–77	52–65	52–68	53–70
BMI (kg/m^2)				
Mean ± SD	26.5 ± 3.8	29.4 ± 5.1	29.0 ± 4.8	28.9 ± 4.9
Duration of diabetes (months)				
Mean ± SD	127 ± 105	72 ± 70	60 ± 57	70 ± 69
FSG (mmol/L)				
Mean ± SD	11.3 ± 3.8	11.7 ± 3.3	10.8 ± 2.7	11.1 ± 3.1
HbA_{1c} (%)				
Mean ± SD	8.0 ± 1.3	8.1 ± 1.6	7.9 ± 1.4	8.0 ± 1.4

SD, standard deviation; BMI, body mass index; FSG, fasting serum glucose.

Health-Related Quality of Life

HRQOL scores for the combined population are compared with the two reference populations in Figure 1. Patients in this survey had better physical functioning, role-physical, pain, general health, and vitality scores than patients with type 2 diabetes surveyed in the MOS during the development of the SF-36 [5]. Scores for mental health, social functioning, and role-emotional scales, however, were comparable to these reference scores (Figure 1). Although there was generally a wide variability in scores for each domain (range: 0–100 for each domain), the median score for role-physical, role-emotional, and social functioning was 100, indicating a substantial ceiling effect for these domains. The mean PCS for the pooled population was 46.6 (SD ± 9.2, range 12.1–65.3), and the mean MCS was 50.9 (SD ± 10.1, range 12.0–70.2).

Regression Analysis

The number of patients with severe complications was small (< 10) for all conditions assessed apart from hypertension. To increase numbers, patients assessed as having a severe complication were pooled with those having moderate complications for each of the eight complications assessed in Table 3. Only two patients were assessed as having moderate diabetic foot, and these patients were pooled with patients assessed as having mild diabetic foot for the same reason.

Several significant factors were identified in the regression analysis. Sex, age, BMI, and country were significant variables for most SF-36 domains. Men consistently produced higher mean scores than women. Several diabetic complications were identified as significant factors for the SF-36 domains (Table 4). These included: CAD (significant for the majority of the SF-36 domains); PVD (a significant determinant of physical and social functioning); PSN (a significant determinant of mental health and the aggregate mental component); autonomic neuropathy; and diabetic foot. In general, HRQOL scores tended to decrease, indicating poorer quality of life, in patients with more severe symptoms.

The duration of diabetes was not a significant factor in any of the SF-36 domains, nor were hypertension, retinopathy, or nephropathy. Glycemic control, as measured by either FSG or HbA_{1C}, had little apparent impact on HRQOL.

Table 3 Incidence of diabetic complications*

Study population		Study A	Study B	Study C	All patients
Complication	Severity	(n = 110)	(n = 368)	(n = 755)	(n = 1233)
Hypertension		55 (50%)	157 (43%)	356 (47%)	568 (46%)
	Mild	55	101	201	357
	Moderate	0	54	117	171
	Severe	0	2	38	40
PSN		8 (7%)	48 (13%)	92 (12%)	148 (12%)
	Mild	6	40	81	127
	Moderate	2	8	10	20
	Severe	0	0	1	1
CAD		19 (17%)	10 (3%)	66 (9%)	95 (8%)
	Mild	19	10	55	84
	Moderate	0	0	11	11
	Severe	0	0	0	0
Retinopathy		11 (10%)	37 (10%)	46 (6%)	94 (8%)
	Mild	9	28	39	76
	Moderate	2	5	5	12
	Severe	0	4	2	6
PVD		11 (10%)	35 (10%)	37 (5%)	83 (7%)
	Mild	11	23	32	66
	Moderate	0	9	2	11
	Severe	0	3	3	6
Nephropathy		3 (3%)	14 (4%)	16 (2%)	33 (3%)
	Mild	3	14	15	32
	Moderate	0	0	1	1
	Severe	0	0	0	0
Autonomic neuropathy		0 (0%)	19 (5%)	5 (1%)	24 (2%)
	Mild	0	9	4	13
	Moderate	0	9	1	10
	Severe	0	1	0	1
Diabetic foot		2 (2%)	4 (1%)	17 (2%)	23 (2%)
	Mild	2	4	15	21
	Moderate	0	0	2	2
	Severe	0	0	0	0

PSN, peripheral sensory neuropathy; CAD, coronary artery disease; PVD, peripheral vascular disease.

Discussion

Results from this study indicate that even mild complications in patients with type 2 diabetes can have a profound effect on the patients' perceived HRQOL as measured using the well-validated and widely used SF-36 questionnaire.

The present study excluded patients with the most severe form of the disease, and consequently, the greatest number of complications. The majority of complications that occurred in the study population were assessed as being mild. Because many patients did not experience symptomatic complications, mean SF-36 scores tended to be high. Mean physical functioning, role-physical, and general health perception scores were closer to those of the US norm reference population than to scores calculated in the MOS study for patients with type 2 diabetes [5]. Scores for this patient group were also higher than those generated by Weinberger et al. [16] for a type 2 diabetes popu-

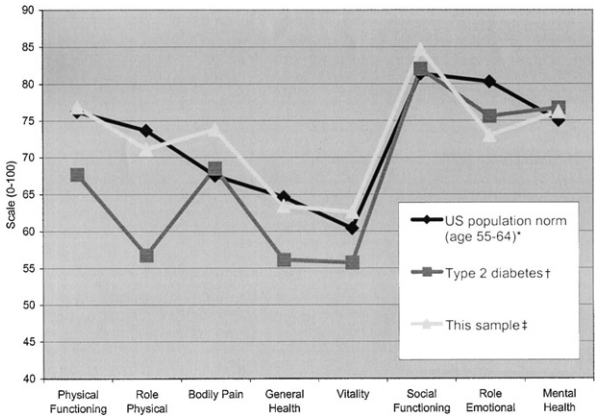

Figure 1 SF-36 scale scores: comparison with published norms.

* Norms for US general population aged 55–64, $n = 269$. See Table 10.2, Ware et al. [5]

† Norms for type 2 diabetes population (also from US), $n = 541$, See Table 10.7, Ware et al. [5]

‡ Mean age 61.0 years, $n = 1233$.

Table 4 Quantification of significant factors from the regression analysis in the eligible patient population (least squares means (95% CIs) from the full model)*

Complication	Severity	Physical functioning	Role physical	Bodily pain	General health	Aggregate physical component	Vitality	Social functioning	Role emotional	Mental health	Aggregate mental component
Hypertension	None	60.67 (49.94,71.40)	56.01 (35.30,76.72)	70.87 (57.09, 84.66)	52.44 (41.52,63.36)	40.66 (35.53,45.79)	61.32 (49.65,72.98)	86.22 (75.54,96.90)	73.25 (52.85,93.65)	80.60 (70.45,90.76)	54.47 (48.54,60.40)
	Mild	58.73 (47.93,69.53)	53.49 (32.62,74.37)	71.32 (57.47,85.16)	51.89 (40.93,62.86)	40.12 (34.96,45.29)	60.96 (49.25,72.67)	87.71 (76.98,98.43)	74.07 (53.50,94.64)	79.92 (69.72,90.12)	54.82 (48.86,60.79)
	Moderate/ severe	58.19 (47.28,69.10)	58.74 (37.65,79.82)	70.36 (56.39,84.33)	52.57 (41.45,63.69)	40.13 (34.91,45.34)	60.21 (48.35,72.08)	86.63 (75.79,97.47)	77.38 (56.71,98.04)	82.63 (72.30,92.95)	55.69 (49.66,61.71)
PSN	None	63.37 (52.06,74.68)	54.04 (32.11,75.98)	72.41 (57.96,86.86)	53.75 (42.16,65.35)	40.39 (34.97,45.81)	63.62 (51.26,75.98)	88.76 (77.53,99.98)	79.95 (57.98,100)	85.49* (74.73,96.25)	56.74* (50.49,63.00)
	Mild	61.15 (50.20,72.10)	52.60 (31.40,73.80)	66.72 (52.62,80.82)	52.42 (41.22,63.62)	40.05 (34.81,45.29)	58.81 (46.87,70.74)	86.12 (75.18,97.06)	71.21 (50.37,92.06)	79.21* (68.81,89.61)	53.96* (47.91,60.01)
	Moderate	53.07 (40.29,65.85)	61.60 (36.92,86.27)	73.43 (57.11,89.75)	50.73 (38.02,63.43)	40.47 (34.49,46.45)	60.06 (46.37,73.76)	85.68 (73.08,98.27)	73.93 (49.71,98.15)	78.45* (66.54,90.37)	54.27* (47.37,61.18)
CAD	None	69.90† (59.82,79.99)	73.19† (53.83,92.56)	77.66† (64.84,90.49)	58.89† (48.84,68.94)	45.47† (40.81,50.13)	67.80* (57.04,78.57)	90.81* (80.86,100)	77.25 (58.49,96.01)	82.06 (72.69,91.44)	56.16 (50.78,61.55)
	Mild	61.67† (50.83,72.51)	58.92† (38.04,79.80)	73.40† (59.52,87.28)	53.45† (42.63,64.26)	42.22† (37.20,47.23)	60.11* (48.50,71.72)	84.41* (73.66,95.17)	68.16 (47.89,88.42)	80.30 (70.17,90.42)	54.16 (48.37,59.95)
	Moderate	46.02† (31.16,60.87)	36.12† (6.64,65.61)	61.49† (41.95,81.03)	44.57† (28.63,60.50)	33.22† (25.41,41.04)	54.58* (37.85,71.30)	85.33* (70.24,100)	79.29 (48.58,100)	80.79 (66.23,95.34)	54.65 (45.63,63.68)
Retinopathy	None	60.70 (50.30,71.10)	60.21 (40.10,80.31)	71.12 (57.82,84.43)	53.93 43.30,64.56)	41.25 (36.25,46.25)	60.88 (49.57,72.19)	88.32 (78.00,98.64)	79.36 (59.57,99.14)	80.80 (70.94,90.66)	54.94 (49.16,60.71)
	Mild	61.31 (50.14,72.47)	56.34 (34.81,77.86)	73.27 (59.00,87.54)	51.74 (40.47,63.01)	40.70 (35.35,46.05)	61.30 (49.22,73.38)	87.03 (75.99,98.07)	75.22 (53.94,96.50)	79.99 (69.47,90.51)	55.06 (48.88,61.23)
	Moderate/ severe	55.59 (42.23,68.94)	51.69 (25.78,77.60)	68.16 (50.66,85.66)	51.23 (37.68,64.79)	38.96 (32.72,45.19)	60.31 (45.73,74.88)	85.20 (71.66,98.74)	70.12 (44.80,95.44)	82.36 (69.68,95.05)	54.98 (47.78,62.19)
PVD	None	66.53† (56.08,76.98)	55.90 (35.67,76.13)	71.53 (58.11,84.94)	53.15 (42.64,63.66)	42.36 (37.40,47.31)	60.85 (49.67,72.04)	90.81* (80.38,100)	73.16 (53.24,93.08)	79.55 (69.80,89.30)	53.57 (47.85,59.29)
	Mild	60.84† (50.12,71.55)	56.51 (35.82,77.19)	68.57 (54.83,82.31)	47.95 (37.22,58.68)	40.74 (35.71,45.78)	57.86 (46.37,69.36)	83.07* (72.41,93.73)	71.65 (51.30,92.00)	75.58 (65.57,85.58)	51.87 (46.06,57.69)
	Moderate/ severe	50.23† (36.17,64.29)	55.83 (28.30,83.36)	72.46 (54.30,90.62)	55.80 (40.58,71.01)	37.81 (30.80,44.82)	63.78 (47.86,79.69)	86.67* (72.66,100)	79.88 (52.90,100)	88.02 (74.17,100)	59.54 (51.44,67.63)
Nephropathy	None	58.42 (47.91,68.92)	55.01 (34.71,75.32)	67.12 (53.72,80.53)	53.32 (42.61,64.02)	39.98 (34.94,45.02)	58.48 (47.09,69.86)	84.83 (74.42,95.23)	73.18 (53.24,93.13)	78.91 (68.99,88.83)	53.86 (48.04,59.67)
	Mild	59.98 (47.95,72.00)	57.14 (33.96,80.33)	74.58 (59.01,90.15)	51.29 (39.12,63.45)	40.62 (34.94,46.31)	63.18 (50.12,76.25)	88.87 (76.83,100)	76.61 (53.81,99.41)	83.19 (71.82,94.56)	56.13 (49.56,62.70)
Autonomic neuropathy	None	53.90 (44.50,63.30)	47.97 (30.01,65.94)	65.90 (53.87,77.93)	47.28 (37.78,56.77)	38.29 (33.75,42.83)	57.42 (47.27,67.56)	78.88* (69.62,88.15)	67.03 (49.22,84.84)	73.28* (64.44,82.12)	52.22 (46.98,57.46)
	Mild	58.75 (43.81,73.69)	64.34 (34.38,94.29)	80.30 (60.44,100)	61.77 (46.19,77.34)	44.59 (37.45,51.74)	57.94 (41.65,74.23)	86.67* (70.81,100)	78.99 (50.60,100)	75.85* (61.68,90.03)	52.12 (43.87,60.37)
	Moderate	64.94 (48.68,81.20)	55.93 (24.43,87.43)	66.36 (45.82,86.89)	47.86 (31.41,64.30)	38.02 (30.48,45.57)	67.14 (49.33,84.94)	95.00* (79.21,100)	78.67 (47.69,100)	94.02* (78.52,100)	60.64 (51.93,69.35)

continued

Table 4 Continued

Complication	Severity	Physical functioning	Role physical	Bodily pain	General health	Aggregate physical component	Vitality	Social functioning	Role emotional	Mental health	Aggregate mental component
Diabetic foot	None	57.44 (47.22,67.67)	59.57 (39.83,79.30)	66.88 (53.65,80.11)	50.73 (40.33,61.13)	39.71 (34.79,44.62)	57.47 (46.38,68.56)	82.76* (72.50,93.02)	71.69 (52.28,91.09)	78.53 (68.87,88.19)	53.04 (47.37,58.71)
	All severities	60.95 (48.34,73.56)	52.59 (28.18,77.00)	74.82 (58.75,90.89)	53.87 (40.92,66.83)	40.90 (34.89,46.91)	64.19 (50.52,77.86)	90.95* (78.51,100)	78.11 (54.13,100)	83.57 (71.61,95.53)	56.95 (50.01,63.89)
Study		$P < .05$									
Country					$P < .05$		$P < .05$	$P < .05$		$P < .05$	$P < .05$
Gender		$P < .05$	$P < .05$	$P < .05$	$P < .05$	$P < .05$	$P < .05$	$P < .05$		$P < .05$	
Race				$P < .05$	$P < .05$						
Age		$P < .05$	$P < .05$			$P < .05$	$P < .05$			$P < .05$	$P < .05$
BMI		$P < .05$	$P < .05$	$P < .05$	$P < .05$	$P < .05$	$P < .05$	$P < .05$	$P < .05$		
Duration of diabetes											
Fasting blood glucose level											
HbA_{1c} (%)											

($p < .05$, *F*-test): The following explanatory factors were included in the model: gender, ethnic origin, country, presence and severity of each of the eight diabetic complications, age, body mass index, duration of diabetes, FSG and HbA_{1c}. Factors were considered to be statistically significant if the proportion of the variation (overall sum of squares) of the dependent variable that the factor explained was significantly greater than zero using an *F*-test.

* Statistically significant difference

BMI, body mass index; CAD, coronary artery disease; PSN, peripheral sensory neuropathy; PVD, peripheral vascular disease.

lation, although the latter were older than our population and had a longer mean duration of diabetes (10.3 vs. 5.7 years), suggesting a higher rate of diabetic complications.

The regression analysis of a number of potential contributing factors on HRQOL was studied. Age and sex were consistently associated with HRQOL. Lower HRQOL scores were associated with lower age, whereas consistently higher scores were reported by men. Duration of diabetes had no apparent impact on HRQOL, while FSG and HbA_{1c} were the only significant covariates in isolated domains. In the vitality domain, for example, average scores decreased with elevated blood glucose levels, although the converse was observed for HbA_{1c}. Results from the United Kingdom Prospective Diabetes Study (UKPDS) indicate that the HRQOL of patients with type 2 diabetes is not affected by intensive interventions aimed at improving blood glucose control. However, patients who had hypoglycemic events during the study had more mood disturbance and tension and reduced work satisfaction [26].

Inclusion of complications as factors affecting HRQOL demonstrated that HRQOL impairment was most prevalent among patients with these diabetic complications. That many patients have complications at the time of diagnosis, some of which cannot be treated, suggests that significant, potentially irreversible impairment of HRQOL may already have occurred in a number of patients at the time of presentation. In the present population, CAD was the factor most frequently associated with a significant reduction in HRQOL, affecting the physical domains in particular. With early intervention, however, many diabetic complications can be prevented. Research has shown that treatment of the risk factors associated with macrovascular disease is effective in type 2 diabetes and that the occurrence of CAD can be reduced if patients are diagnosed before complications develop [27,28]. Furthermore, significant associations with specific domains of the SF-36 reflected the facets of patients' lifestyle affected by other diabetic complications. For example, Table 4 shows a significant association between PVD and the physical functioning domain.

Hypertension was not a significant factor in any of the SF-36 domains, a not altogether surprising finding since hypertension is asymptomatic in the majority of patients. Treatment of hypertension is nonetheless very important in this patient group. Results from the recent UKPDS study have shown that intensive treatment of hypertension in type 2

diabetes decreases the risk of macrovascular and microvascular complications [29] without affecting HRQOL [26]. Similarly, there was no association between mild retinopathy and HRQOL, although it is expected that severe disease would impact on HRQOL. Impaired visual acuity in patients with type 2 diabetes has been associated with reduced HRQOL as measured by the SF-20 [15].

The findings relating HRQOL to blood glucose were ambiguous, as would be expected in a population with a mean FSG of 11.1 mmol/l [7,8,16,17]. The impact of blood glucose on HRQOL appears to be due to its important role in the development of diabetic complications. Drug effects were not evaluated in this study, because none of the patients was receiving drug therapy at the time of assessment and all had completed a drug therapy washout period of at least three weeks prior to the baseline assessment.

This study used the SF-36 to assess HRQOL. The advantages of this instrument are that it is short and easily completed by the patient, is comprehensive, and is supported by a wealth of reference data, allowing for comparison between the study population and reference populations. One disadvantage of using a generic instrument such as the SF-36 in a specific disease or condition is its potential lack of sensitivity. Small changes in HRQOL may be more easily detected using a disease-specific instrument such as the diabetes care profile. That we were able to demonstrate differences in quality of life in this study using the SF-36, a potentially insensitive instrument, suggests that the impact of these complications on quality of life is substantial.

Even though this sample of more than 1200 patients was large, some complications occurred only in a small number of patients, and hence, results for patients with nephropathy, autonomic neuropathy, and diabetic foot should be interpreted with caution. Research into more severely disabled patients would be needed to clarify the impact of these complications on HRQOL.

A limitation of this study was the need to pool three separate patient populations to generate a sufficiently large number for analysis. Heterogeneity between studies was detected, and was retained as a random effect in the models to allow for unobserved variation between populations. However, the differences observed between the studies casts some doubt on the general applicability of the final results.

It is interesting to note that CAD was the most frequent complication significantly associated with various SF-36 domains, which indicates that this complication has a profound effect on quality of life. Concomitant hypertension and dyslipidemia may contribute to this macrovascular complication in diabetic patients [27], along with hyperinsulinemia [28]. Thus, while the principal aim of long-term treatment is to improve glycemic control, alleviation of these cardiovascular risk factors is also of importance, both clinically and in terms of improving patients' quality of life.

Conclusion

This study has shown that diabetic complications, particularly CAD, have a profound effect on the HRQOL of patients with type 2 diabetes. Even the presence of mild diabetic complications has a significant impact on HRQOL, while biochemical markers of the disease did not appear to directly affect HRQOL. To improve HRQOL in patients with type 2 diabetes, early diagnosis of the disease and aggressive management of risk factors are necessary to prevent or delay the development of diabetic complications and the ensuing deterioration of HRQOL.

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