

**Presence of diabetes related complication at the time of NIDDM
diagnosis: an important prognostic factor**

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Running title: Risk factors of NIDDM morbidity & mortality.

Abstract

We studied the short-term natural history of patients with newly diagnosed non-insulin dependent diabetes mellitus (NIDDM), and the prognostic role of history of NIDDM related complication at the time of first NIDDM diagnosis in relation to the development of a new complication or death.

We performed a cohort study using data from the General Practice Research Database in the UK. We identified patients aged 30 to 74 years with a newly diagnosed NIDDM between 1990 and 1992 and followed them from the day of NIDDM diagnosis until June 1995. Among the 1,077 patients identified, 437 (41%) developed a NIDDM complication during the follow-up. NIDDM complications were more frequent among males and in the elderly. Sixty-seven percent of the study cohort was initially free of any complication while the remaining 360 patients presented already one or more NIDDM complication at the time of their NIDDM diagnosis. History of diabetic related complication was associated with an increased risk of developing a new NIDDM complication (RR: 1.8; 95%CI: 1.5-2.2). Mortality was also greater among patients with history of NIDDM complication (RR: 1.5; 95%CI: 1.0-2.2).

Patients with a history of any disorder related to diabetes before their clinical diagnosis of NIDDM are at increased risk of developing a NIDDM complication after the NIDDM diagnosis, as well as at increased risk of dying compared to diabetic patients with no history.

Key words: NIDDM complications, risk factors, mortality, cohort study, automated database.

Abbreviations:

BMI: Body mass index

CI: Confidence intervals

GP: General practitioner

GPRD: General Practice Research Database

IDDM: Insulin dependent diabetes mellitus

IR: Incidence rate

NIDDM: Non-insulin dependent diabetes mellitus

ONS: Office of National Statistics

RR: Relative Risk

Introduction

Non-insulin dependent diabetes mellitus (NIDDM) is a common disease that is associated with high mortality and morbidity from macrovascular and microvascular disease. It is largely the complications associated with diabetes which make it such a major public health problem. The prevalence of diagnosed diabetic patients has been estimated to be 6-7% for people aged 45-64 years, and reaching 10-12% for those aged 65 years and older^[1] with higher rates in specific ethnic groups^[2, 3].

Recently, results from the United Kingdom prospective diabetes study were published^[4, 5]. They studied newly diagnosed NIDDM patients, and found that 9 years after diagnosis, 29% of patients had a diabetes-related endpoint, and 9% died⁵. Macrovascular complications were more common than microvascular endpoints, occurring in 20% and 9% respectively.

The onset of NIDDM is usually subtle and many years may elapse before diagnosis. Harris et al.^[6] estimated a gap of 9 to 12 years between the onset of NIDDM and its clinical diagnosis. The first indication of the presence of NIDDM may actually be detected at the time of diagnosis of a NIDDM complication. In the US 15 -20% of individuals with undiagnosed NIDDM have been found to have diabetic retinopathy and 5-10% proteinuria^[1]. The UK study showed that around 50% of the newly diagnosed NIDDM patients already had indication of diabetes-related tissue damage such as retinopathy, heart disease or microalbuminuria.

Only in a few instances, epidemiological studies have separated between insulin and non-insulin dependent diabetes in relation to the prevalence of particular complications and risk factors associated with them.

We performed an observational study to assess short-term natural history of patients with newly diagnosed non-insulin dependent diabetes mellitus using the General Practice Research Database (GPRD) in the UK, and the prognostic role of history of NIDDM complication in relation with the development of a new complication.

Subjects and Methods

- *Source population*

We performed a retrospective cohort study using data from the General Practice Research Database (GPRD). This database contains computerized information entered by general practitioners in the UK^[7]. Data on about 3 million patients are systematically recorded and sent anonymously to the Office of National Statistics

(ONS). The ONS organizes this information in order to be used for research projects. The computerized information includes demographics, details of every general practitioner's consultation, notes of specialist referral and hospital admission, results of laboratory tests and a free text section. Prescriptions issued by the general practitioner are directly generated from the computer. The accuracy and validity of data has been documented in previous validation studies of the GPRD database, and reported that over 90% of all referrals are entered on the general practitioners' computers with a code that reflects the specialist's diagnosis^[8, 9, 10]. An additional requirement for participating practices is recording of the indication for all new courses of treatment. A modification of the Oxmis classification system is used by the general practitioner (GP) to register specific medical diagnoses; these codes can be directly mapped to codes from the International Classification of Diseases. A drug dictionary based on data from the Prescription Pricing Authority is used to record medicines.

- *Study cohort*

Patients aged 30 to 74 years with a recorded code of non-insulin dependent diabetes made by the GP between January 1990 and December 1992, were identified through a computer search, once the practice was up-to-standard and the patient registered with the GP a minimum of one year. A patient was defined to be newly diagnosed with NIDDM when prior to the first time the code of NIDDM was recorded, there was no other code suggesting diabetes or treatment with antidiabetic drugs in the whole patient computerized medical history. The date of first time diagnosis of NIDDM was considered as the patients' start date. Persons who had a code of cancer before start date were removed from the study cohort.

All study members were followed from start date until June 1995 or until the earliest occurrence of one of the following endpoints: diagnosis of cancer, gestational, insulin dependent diabetes, drugs induced diabetes, or death.

- *Case ascertainment*

For all patients identified, through the computer search, as newly diagnosed NIDDM patients, computerized patient profiles (medical history recorded by the GP) for the follow-up period, were produced and reviewed manually. Information reviewed included demographic data and all medical information. The patient profile did not have any personal identifier. Following a systematic review of the patients profiles, first-time diagnosis of ophthalmic, neurologic, nephrologic, cerebrovascular, and cardiovascular disorders, was ascertained. Only complications recorded by the GP could be ascertained. A patient could have had more than one type of complication during follow-up period. Based on an extensive literature review, we considered a case of ophthalmic complication, when presenting with an episode of retinopathy, retinal vascular disease, cataracts, or blindness. A patient was considered a case of

neurologic complication when presenting with an episode of neuropathy, diabetic arthropathy, impotence or coma. A patient was considered a case of renal disease, when presenting with an episode of albuminuria, proteinuria, renal failure, diabetic nephropathy or metabolic disorder. A patient was considered a case of coronary heart disease complication, when presenting with an episode of angina, myocardial infarction or ischaemic heart disease. A patient was considered a case of cerebrovascular complication when developing a stroke or cerebral ischaemia. A patient with an episode of peripheral vascular disease, foot ulcers, gangrene, leg or foot amputation was considered a case of vascular complication. We identified patients with history of any of the above mentioned complications before the start date, and classified them in two groups: patients with a diabetes related complication detected before diagnosis of NIDDM, and patients whose complication was diagnosed at the same time as the NIDDM was first diagnosed. A patient could have had more than one type of complication before start date. Antidiabetic drug treatment during follow-up was recoded.

Status of hypertension, body mass index and smoking habit was assessed at the beginning of follow-up. We also assessed from the patients computerized medical record information on family history and diagnosis of hyperlipidemia, but due to underascertainment of these two factors, we did not use them in the analysis.

- *Cohort analysis*

Incidence rates of new diabetic complications were calculated. These rates were standardised for age and sex, taking the distribution of person-time in the whole NIDDM cohort as weights when calculating rates in subgroups.

We used Cox regression analysis to compute estimates of relative risk (RR) and 95% confidence intervals (CI). We analyzed the association of NIDDM history with the development of a new NIDDM complication. NIDDM history refers to history of any complication when analyzing the risk of developing any complication, and to the respective subgroup of diagnosis when analyzing specific new NIDDM complication as endpoint (e.g. when calculating the risk of an ophthalmic complication, the presence/absence of history of ophthalmic diseases were entered in the regression model). We included in the regression models the following risk factors: age grouped in four categories, sex, body mass index, hypertension, smoking habit and antidiabetic drug treatment during follow-up.

We also estimated the risk of death as a secondary endpoint.

Results

One thousand one hundred patients were found to meet the computer-based case definition of NIDDM. After review of all computerized profiles, 23 subjects were removed based on the exclusion criteria. The final study cohort included 1,077 patients with newly diagnosed NIDDM. The follow-up time ranged from 4 to 2,006 days (median=1,374 days).

Incidence and Prevalence of NIDDM complications

Distribution of history of NIDDM complications and other risk factors according to sex in the cohort of 1,077 subjects are presented in table 1. We found that 717 patients (67%) were initially free of any complication, while the remaining 360 (33%) patients already presented one or more NIDDM complication at the time of first diagnosis of NIDDM. Of these patients, 53 were diagnosed at the same time of both their NIDDM and their complication. Among the 360 patients with history of diabetes complications, 52% had cardiovascular disease, 38% had peripheral vascular disease, 14% cerebrovascular disease, 13% had an ophthalmic disorder, 3% had a neurologic related disorder and 4% a renal disease.

Among the 1,077 subjects, 437 (41%) developed a new complication related to NIDDM during an average follow-up time of three years and eight months. NIDDM complications were more frequent among males and in the elderly. Among patients with no history of NIDDM complication, 235 developed a new NIDDM complication during the follow-up period, incidence rate (IR) of 113.8 per 1,000 person-years, while among those with history, the risk of developing a new NIDDM complication was twice as greater (IR: 227.7 per 1,000 person-years), resulting in a rate ratio of 2.2 (95%CI: 1.8-2.6). The highest incidence rates of all complications were found for coronary heart disease (45.8 per 1,000 person-years) followed by vascular disease (38.5 per 1,000 person-years). In diabetic men, coronary heart disease was the new complication most frequently occurring, while among women peripheral vascular disease was the most frequent.

Risk factors for diabetic complication

Table 2 presents the risk factors associated with the development of any new NIDDM complication. Patients at increased risk were elderly, male, hypertensive and those with history of any NIDDM complication. The estimate of relative risk was not markedly different between those with previously diagnosed complication (RR: 1.7; 95%CI: 1.4-2.1) and those with a complication diagnosed at the time of the diagnosis of NIDDM (RR: 2.0; 95%CI: 1.4-3.0). Antidiabetic drug treatment during the follow-up period was associated with a protective effect on the development of a new complication.

One hundred thirteen patients developed a new ophthalmic complication (IR: 29.5 per 1,000 person-years). Retinopathy was the most frequent ophthalmic complication in all age groups as well as in males and females. Patients with history of ophthalmic disorders had a small increased risk of developing a new ophthalmic complication.

Sixty-eight patients presented a neurologic complication, more than half of them were peripheral neuropathy (62%), followed by impotence (35%). For this type of complication, age was not a predictive factor and only history of a neurologic complication was related to the development of a new neurologic complication (RR: 3.9; 95%CI: 1.2-12.8).

Nephrologic disorders was the NIDDM complication that occurred less frequently. Thirty-two patients had proteinuria, seven developed a nephropathy and four presented a metabolic disorder. Controlling for all risk factors, only history of renal disease (RR:6.3; 95% CI: 1.5-27.2) was related with the development of a new renal complication.

Among patients developing a new vascular complication, skin ulcers (28%) and venous thrombosis (21%) were at the top, followed by varicose veins (19%) and intermittent claudication (17%). Elderly patients and those with history of a vascular complication had an increased risk of developing a new vascular complication. Current smokers also presented an increased risk for a new vascular complication (RR: 2.2; 95%CI 1.5-3.3).

Coronary heart disease was the most frequent complication in our cohort of diabetic patients. The risk was five times higher among those patients with history of a coronary disease compared to those without history (RR: 5.1; 95%CI: 3.7-7.0). Other predictive factors of the development of a coronary event were, age, male gender, and no antidiabetic drug treatment (data not shown).

Cerebrovascular complication was detected in 67 patients. Along with old age, history of a cerebrovascular complication was positively associated with the development of a new complication (RR: 4.5; 95%CI: 2.4-8.6).

Mortality risk among NIDDM patients

Patients who developed a new NIDDM complication had a two fold increased risk of dying during the follow-up period compared to those with no complication (RR: 1.9; 95%CI: 1.3-2.9). Mortality rate among patients with history of a complication (40.3 per 1,000 person-years) was close to two times greater compared to diabetic patients with no history (23.2 per 1,000 person-years). In addition to history of NIDDM complication, age and smoking were the only two other risk factors associated with an increased mortality risk (table 3).

NIDDM and its complication

One third of patients newly diagnosed with NIDDM had already one or more NIDDM complication present at the time of clinical diagnosis of NIDDM. A higher proportion of patients with complication at diagnosis were found in a previous study in the UK[5,¹¹], however they performed a systematic search for complications and included a wider range of complications, biochemical and ECG abnormalities were also considered as complication. Our study only assessed complications recorded by the GP in the patient's medical history. Some minor NIDDM related complications may either not been diagnosed and/or recorded by the physician and this would have lead to an underreporting for mild complications. However a recent report on the quality of information recorded on diagnosis, hospitalization and severity of diabetes showed the high level of completeness and validity of the information recorded by the GP in this database[10].

Harris suggests that the presence of diabetic complications at the time of clinical diagnosis of NIDDM indicates that complications of NIDDM are progressing, maybe as a consequence of untreated hyperglycemia or other factors, while diabetes remains clinically undiagnosed[6]. In our study, patients with history of diabetic complications before their clinical diagnosis of NIDDM carried a two fold increased risk of developing a new complication, than patients with no history. We have no information on specific screening programs or complication detection procedures that GPs may undertake, and in reading the results of the present study one have to consider the possibility that GPs may enhance level of surveillance among patients with prior history of NIDDM related complication compared to those without history, and this fact indeed could affect the interpretation of the findings.

Age and duration of diabetes have been the most frequently mentioned risk factors in relation to development of new NIDDM complication[3,5,11]. We found the association with age, but we did not find any association between time since diagnosis and the development of the new complication. It should be noted that our average follow-up time was less than four years. Another study in elderly people showed no relationship between known diabetes duration and the incidence of either microvascular or macrovascular complication[¹²]. In accordance with previous results, we did not find significant differences in the prevalence of complications between men and women[4,5]. Also, we did not find any association with obesity, reported sometimes as a risk factor for NIDDM[¹³].

Retinopathy is the most frequent ophthalmic complication, and its development and severity is closely linked with length of time since diabetes has

been present[3,¹⁴]. Other studies with NIDDM patients estimated a crude incidence rate of retinopathy of around 15/1,000 person year [¹⁵, ¹⁶], similar to ours where 44% of patients with ophthalmic complications had retinopathy.

Of all diabetic complications, renal diseases had the smaller incidence rate in our cohort, although it has been suggested that incidence of diabetic nephropathy among NIDDM patients appears to be rising[¹⁷]. Factors related with development of a diabetic nephropathy include diabetes duration, hypertension and smoking[¹⁷, ¹⁸]. There was a six-fold increased risk of nephrologic complication among patients with some renal disorder at the time of NIDDM diagnosis. Humphrey et al.[¹⁹] reported similar findings, with a twelve-fold increase of developing renal failure among patients with proteinuria at the time of their diagnosis of NIDDM.

Diabetic patients carry an increased risk for cardiovascular disease, compared to the general population[²⁰]. In contrast to what has been suggested in the literature that heart disease affects diabetic women almost as often as diabetic men [²¹, ²²], we found a greater risk of ischaemic heart disease among men. A Swedish study showed that smoking doubled the risk of coronary heart disease in diabetic patients[²³]. We could not find this association. Of other risk factors predictive of coronary heart disease in the general population (such as smoking, blood pressure or BMI), only hypertension was an independent risk factor among NIDDM subjects in our study. Adults with diabetes are more likely than those without to have hypertension [²⁴]. Several authors have also pointed out the importance of cultural and ethnic factors in the association of diabetes and cardiovascular complications[²²,²⁵]. Information on these variables was not available in our study.

Other studies have documented an association between neuropathy and the presence of other NIDDM complications, such as retinopathy[²⁶] and peripheral vascular disease[11]. We found that patients with ophthalmic disorders had an increased risk of developing a neurologic complication (RR: 2.5; 95%CI: 1.1-5.8), as well as patients with peripheral vascular disease, who had a slightly increased risk of a new neurologic complication (RR: 1.6 ; 95%CI: 0.8-3.1).

NIDDM and Mortality

Most cohort studies of diabetes complications and mortality do not distinguish between IDDM and NIDDM. Therefore, rates from these studies tend to overestimate death rates among patients with NIDDM and may produce an invalid assessment of risk factors for mortality in NIDDM population [²⁷]. Data from the US estimated a death rate in diabetic patients around 5 per 100 person-years [27]. We found a mortality rate close to 3 per 100 person-years in our cohort.

There is conclusive evidence in the literature that the qualitative pattern of the major mortality risk factors found in the diabetic population does not differ

from the one in the general population[27,²⁸,²⁹]. However, the strength of association for some risk factors related to vascular disease appears to be greater in NIDDM[28] and some of these risk factors may act differently in diabetic subjects than in general population[³⁰]. Most deaths in persons with diabetes are due to ischaemic heart disease, which accounts for close to half of all deaths (40%)[27].

As in the general population, age should be regarded as a major determinant of mortality in NIDDM patients. Coming in a second place, hypertension and smoking have been found to be risk factors for mortality[20]. Sometimes obesity has also been identified as risk factor [30,³¹]. We found an increased risk only with age and smoking. On the other hand, we found that history of NIDDM complication before the clinical diagnosis of NIDDM was an important predictor of subsequent mortality. This could be an indicator of more advanced or severe history of diabetes disease. A recent study also reported that the presence of heart disease, cerebrovascular disease or kidney disease at the beginning of the diabetes was associated with a higher mortality [24].

In summary, patients with a history of any disorder related to diabetes before their diagnosis of NIDDM are at about twice the risk of developing a NIDDM complication compared to diabetic patients without such history. They have also a fifty percent greater risk of dying.

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Table 1: Distribution of main characteristics among the cohort of NIDDM patients according to sex^a

	<u>Total</u> 1077	<u>Men</u> 627	<u>Women</u> 450
Age at NIDDM diagnosis			
30-49 years	172 (16.0)	112 (17.9)	60 (13.3)
50-59 years	294 (27.3)	179 (28.5)	115 (25.6)
60-69 years	393 (36.5)	215 (34.3)	178 (39.6)
70-74 years	218 (20.2)	121 (19.3)	97 (21.6)
History of NIDDM complication			
No	717 (66.6)	418 (66.7)	299 (66.4)
Yes	360 (33.4)	209 (33.3)	151 (33.6)
Smoking status^b			
Non-smoker	644 (59.8)	355 (56.6)	289 (64.2)
Smoker	219 (20.3)	143 (22.8)	76 (16.9)
Ex-smoker	132 (12.3)	85 (13.6)	47 (10.4)
Body Mass Index^b			
Low (<22)	47 (4.4)	20 (3.2)	27 (6.0)
Medium-low (22-24.9)	133 (12.3)	72 (11.5)	61 (13.6)
Medium-high (25-27.9)	218 (20.2)	156 (24.9)	62 (13.8)
High (≥28)	533 (49.5)	294 (46.9)	239 (53.1)
Hypertension	371 (34.4)	183 (29.2)	188 (41.8)
Antidiabetic drug treatment	650 (60.4)	362 (57.7)	288 (64.0)
New NIDDM complication during follow-up	437 (40.6)	271 (43.2)	166 (36.9)
Deaths during follow-up	118 (10.9)	79 (12.6)	39 (8.7)

^a Number in parentheses are percentages

^b Percentages may not sum to 100% due to missing values.

Table 2: Relative risk of developing a new NIDDM complication associated with history of NIDDM complication and other risk factors.

	Relative Risk ^a (95% CI)	
History of NIDDM complication		
No	1	
Yes	1.8	(1.5 - 2.2)
Age at NIDDM diagnosis		
30-49 years	1	
50-59 years	1.3	(0.9 - 1.8)
60-69 years	1.7	(1.2 - 2.5)
70-74 years	1.9	(1.3 - 2.8)
Sex		
Males	1	
Females	0.8	(0.7 - 1.0)
Hypertension		
No	1	
Yes	1.3	(1.1 - 1.6)
Smoking status		
Never smoker	1	
Smoker	1.1	(0.9 - 1.4)
Ex-smoker	1.1	(0.8 - 1.5)
Body mass index		
Low / medium (<25)	1	
Medium-high (25-27.9)	1.1	(0.8 - 1.5)
High (≥28)	0.9	(0.7 - 1.2)
Antidiabetic drug treatment		
No	1	
Yes	0.7	(0.6 - 0.9)

^a Estimates are adjusted for history of any NIDDM complication, age, sex, hypertension, smoking, body mass index and antidiabetic drug treatment, using Cox regression.

Table 3: Relative risk of dying associated with history of NIDDM complication and other risk factors.

	Relative Risk ^a (95% CI)	
History of NIDDM complication		
No	1	
Yes	1.5	(1.0 - 2.2)
Age at NIDDM diagnosis		
30-49 years	1	
50-59 years	2.0	(0.8 - 4.6)
60-69 years	3.0	(1.3 - 6.8)
70-74 years	4.6	(2.0 - 10.8)
Sex		
Males	1	
Females	0.7	(0.5 - 1.1)
Hypertension		
No	1	
Yes	1.1	(0.7 - 1.6)
Smoking status		
Never smoker	1	
Smoker	2.6	(1.6 - 4.1)
Ex-smoker	1.5	(0.8 - 2.7)
Body mass index		
Low / medium (<25)	1	
Medium-high (25-27.9)	1.2	(0.7 - 2.2)
High (≥28)	0.7	(0.4 - 1.2)
Antidiabetic drug treatment		
No	1	
Yes	1.2	(0.8 - 1.7)

^a Estimates are adjusted for history of NIDDM complication, age, sex, hypertension, smoking, body mass index and antidiabetic drug treatment, using Cox regression.

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