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Influence of chronic comorbidity and medication on the efficacy of treatment in patients with diabetes in general practice

Abstract

Background

Evidence on the influence of comorbidity and comedication on clinical outcomes in patients with type 2 diabetes mellitus is scarce.

Aim

To ascertain the effect of five chronic diseases (joint disorder, respiratory disease, anaemia, malignancy, depression) and three chronically used drugs (non-steroid anti-inflammatory drugs [NSAIDs], corticosteroids, antidepressants) on treatment for hypoglycaemia in patients with type 2 diabetes.

Design and setting

Retrospective cohort study in a variety of practices across Flanders, Belgium.

Method

A retrospective cohort study was conducted, based on data from Intego, a general practice-based continuous morbidity registry. Multiple logistic regression analysis was used to predict the change in glycosylated haemoglobin (HbA1c) levels related to comorbidity, comedication, and a combination of both in 3416 patients with type 2 diabetes. Adjustments were made for age, sex, and diabetes-treatment group (diet, oral antidiabetic drugs, combination treatment, insulin).

Results

Concomitant joint and respiratory disorders, as well as the chronic use of NSAIDs and corticosteroids, either separately or in combination, were significantly associated with the worsening of HbA1c levels. Anaemia, depression, malignancy, and antidepressants had no statistically significant influence on the efficacy of treatment for hypoglycaemia.

Conclusion

The presence of some comorbid diseases or drug use can impede the efficacy of treatment for type 2 diabetes. This finding supports the need to develop treatment recommendations, taking into account the presence of both chronic comorbidity and comedication. Further research must be undertaken to ascertain the effect other combinations of chronic diseases have on the efficacy of treatment of this and other diseases.

Keywords

co-medication; comorbidity; HbA1c; logistic regression; type 2 diabetes.

INTRODUCTION

Type 2 diabetes mellitus is a frequent chronic disorder.^{1,2} The recommended strategy for achieving glucose control is to establish a metabolic target and to adjust treatment to achieve this. A generally accepted target for glucose control is a glycosylated haemoglobin (HbA1c) level of <7%.³⁻⁵ However, as shown in many observational studies in primary care, only about half of those patients who have type 2 diabetes achieve this.⁶⁻⁹ There are several reasons for this quality gap.

One possible factor is the presence of non-diabetes-associated comorbidity; indeed, half of patients with chronic diseases have more than one.¹⁰ However, most actual guidelines focus on the management of single diseases¹¹ and are of limited use regarding patients with multimorbidity or limited life expectancy.¹² An optimal approach to treat combined disorders is not the same as the sum of optimal treatments for the separate disorders; this is a central thesis of complexity theory, which can offer a framework for managing the treatment of people with multimorbidity.¹³ The recent position statement of the American Diabetes Association and the European Association for the Study of Diabetes makes a first attempt to implement this approach and emphasises the need for individualised targets that take several variables, such as comorbidity, into account.¹⁴ However,

the statement remains vague and does not present any evidence relating to its principal position change. Indeed, adaption of the clinical guidelines should be based on evidence about the complex interactions in multimorbid conditions and the reciprocal influences on disease evolution and treatment effects.¹⁵

Knowledge about the influence of specific comorbidity and comedication on treatment effects is scarce.¹⁶⁻²¹ The present study seeks to contribute to the understanding of the combined effect of comorbidity and comedication on the efficacy of glucose-lowering treatment in patients with type 2 diabetes. As such, the effect that one or more of five comorbid chronic diseases (joint disorder, respiratory disease, anaemia, malignancy, depression) and three chronically used drugs (non-steroid anti-inflammatory drugs [NSAIDs], corticosteroids, antidepressants) have on the efficacy of treatment in patients with type 2 diabetes mellitus was examined.

METHOD

Design and data collection

A retrospective cohort study was performed. This compared patients who had type 2 diabetes only with:

- those who also had one or more predefined comorbid diseases;
- those who were also being treated with

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How this fits in

Most actual guidelines focus on the management of single diseases and are of limited use regarding patients with multimorbidity. Evidence supporting the update of diabetes treatment guidelines towards better application in patients with other chronic diseases or drug treatment is scarce. The results of this study show that presence of some comorbid diseases or drug use can impede the efficacy of treatment for type 2 diabetes.

one or more predefined medications; or

- those who also had one or more predefined comorbid diseases and were being treated with one or more predefined medications.

Data were collected between 1994 and 2008 from the Intego database, a general practice-based morbidity registration network from the Department of General Practice at the Katholieke Universiteit Leuven. In total, 90 GPs, who all use the medical software program Medidoc, collaborate in the Intego (integrated computerised network) project. These GPs work in 55 practices evenly spread across Flanders, Belgium. GPs presented themselves for inclusion in the registry; before acceptance of their data, registration performance was audited using a number of algorithms that compared their results with those of all other applicants. Only the data of the practices with an optimal registration performance were included in the database. The Intego GPs prospectively and routinely registered all new diagnoses, together with new drug prescriptions, laboratory test results, and some background information (including sex and year of birth), using keywords that are internally linked to codes.²²

Using specially-framed extraction software, new data were collected from the GPs' personal computers annually and entered into a central database. Registered data were continuously updated and historically accumulated for each patient. New diagnoses were classified according to a very detailed thesaurus, automatically linked to the second edition of the *International Classification of Primary Care* (ICPC-2) and 10th edition of the *International Classification of Diseases* (ICD-10). Drugs were classified according to the World Health Organization's Anatomical Therapeutic Chemical classification system.

To be included in this study, a patient's file had to include the diagnosis of type 2 diabetes. Patients aged <30 years at diagnosis and patients with gestational diabetes were excluded from the study.

In this study, the dependent variable was the HbA1c level. Covariables were:

- age;
- body mass index (BMI);
- socioeconomic status;
- sex; and
- treatment group (diet, oral antidiabetic drugs only, combined oral antidiabetic drugs and insulin, insulin only).

The presence versus absence of comorbidity and comedication were independent variables. Time of inclusion in the study was determined from the date of first and last contact.

Definition of comorbidity and comedication

In the context of this study, comorbidity was defined as the presence, along with type 2 diabetes, of at least one of the following five chronic medical conditions:

- joint disorders;
- respiratory disorders;
- anaemia;
- malignancies; and
- depression.

Comorbidity was restricted to these five chronic conditions because they were frequent and likely to be influential on the lives of patients with diabetes, but not a complication of diabetes. All malignancies were taken into account, except for non-melanoma skin cancer.

Comedication was defined as use of at least one of three chronic drug categories associated with the defined comorbid conditions:

- NSAIDs;
- corticosteroids; and
- antidepressants.

Diabetes-related complications such as cardiovascular and microvascular diseases were not included as comorbid conditions.

Main outcome measure

The primary outcome measure was the dichotomised change in HbA1c level from

the first to the last available level, ignoring all intermediate measures. An increase of the level at the end of the study was defined as 'worse HbA1c outcome' as the target for diabetes management is to lower HbA1c levels. This resulted in a value of 1 for the dependent variable; all other differences (improvement or stabilisation) resulted in a value of 0.

Statistical analyses

SAS (version 9.2) and R (version 2.10.0) were used to conduct stepwise logistic regression analysis. A *P*-value of <0.05 was considered statistically significant. In all analyses, male was used as the reference for sex, diet for treatment, and absent (0) for comorbidity and comedication. Age refers to the centred age of the patient. At each of the stages an interaction between age and sex, and between comorbidity/comedication and different treatment groups, was initially considered; if found to be non-significant (*P*>0.05), these were dropped from the model.

Model building

Stage 0: Treatment effect. At this stage, change in HbA1c level was modelled as a function of the treatment group, while

adjusting for potential confounders such as age and sex, together with their meaningful interactions.

Stage 1: Comorbidity effect. In this stage, the model in Stage 0 was extended with the presence or absence of each comorbid disease. The effect of each comorbidity on the change in HbA1c level was investigated and adjusted for treatment group, age, and sex; testing for the presence of an interaction between the treatment group and comorbid disorder was also undertaken. Presence of a second or third disease, additional to the first one was then investigated, adjusting for the other variables.

Stage 2: Comedication effect. Similar analyses as in Stage 1 were performed but the effect of drug treatment instead of comorbidity was examined.

Stage 3: Effect of comorbidity and comedication. In this stage, the effects of combinations of diseases and drug-treatment classes that were significant in Stages 1 and 2 were examined.

RESULTS

Exploratory data analysis

Data from 3416 patients were analysed. There were no major differences between males and females with respect to given covariates at baseline (Table 1). On average, females were slightly older than males, and their mean HbA1c level at baseline was slightly lower. However, the percentage of patients with HbA1c >7.0 was, more or less, equal in both groups. Duration in the study ranged from 0 to 14 years, with the average being 9.9 years. Of the patients, 84% had at least one of the five comorbidities and 52% used at least one of the three medications. Two patients (one male, one female) had all five comorbidities. Most patients (80%) had joint disorders and the average BMI was 31.0. Just over half of the patients received combined treatment [oral antidiabetic drugs and insulin]; a very small proportion (3%) were treated with insulin only.

Crude data analysis

HbA1c level improved during the study period in 2046 (60%) patients. The probability of a worsening in HbA1c level, given presence compared with absence of comorbidity or comedication was higher in all cases but anaemia (Table 2). Similar observations from 2 X 2 cross-tabulation of combined comorbidity and comedication were noted.

Table 1. Mean summary statistics by sex

Variable	Female	Male	All
<i>n</i>	1643	1773	3416
Age at baseline, years (SD)	61 (13)	56 (12)	58 (13)
BMI at baseline (SD)	31.5 (11.3)	30.7 (9.8)	31.0 (11)
Duration in study, years (SD)	10 (4)	10 (4)	10 (4)
HbA1c level at baseline (SD)	7.1 (1.9)	7.2 (2.0)	7.1 (2.0)
HbA1c >7, %	38	39	38
Comorbidity, n (%)			
Respiratory	212 (13)	229 (13)	441 (13)
Anaemia	113 (7)	65 (4)	178 (5)
Depression	240 (15)	166 (9)	406 (12)
Malignancy	65 (4)	119 (7)	184 (5)
Joint disorders	1362 (83)	1365 (77)	2727 (80)
Any comorbidity	1415 (86)	1436 (81)	2851 (84)
Comedication, n (%)			
Corticosteroids	578 (35)	542 (31)	1120 (33)
Antidepressant	557 (34)	398 (22)	955 (28)
NSAID	1215 (74)	1263 (71)	2478 (73)
Any comedication	882 (54)	882 (50)	1764 (52)
Treatment, n (%)			
OAD	382 (23)	455 (26)	837 (25)
OAD and insulin	849 (52)	900 (51)	1749 (51)
Insulin	55 (3)	52 (3)	107 (3)
Diet	357 (22)	366 (21)	723 (21)

BMI = body mass index. *HbA1c* = glycosylated haemoglobin. *NSAID* = non-steroidal anti-inflammatory drug. *OAD* = oral antidiabetic drug. *SD* = standard deviation.

Table 2. Probability of increased HbA1c levels (change >0) for presence or absence of each comorbidity and comedication

Variable		Change in HbA1c, % ^a	
		≤0	>0
Respiratory disorders	Absent	60	40
	Present	56	44
Anaemia	Absent	60	40
	Present	62	38
Depression	Absent	60	40
	Present	57	43
Joints disorders	Absent	68	33
	Present	58	42
Malignancy	Absent	60	40
	Present	57	44
Corticosteroids	Absent	62	38
	Present	56	45
Antidepressants	Absent	60	40
	Present	58	44
NSAIDs	Absent	66	34
	Present	58	42
At least any of these present		60	40

^aPercentage of the subjects with better (change in HbA1c≤0) or worse (change in HbA1c>0) outcome levels at the end of the study period. Some figures total more than 100% due to rounding. HbA1c = glycosylated haemoglobin. NSAID = non-steroidal anti-inflammatory drug.

Multivariate analysis

In each stage of model building, age and sex were covariates of interest; as such,

Table 3. Effect of treatment on HbA1c evolution in relation to presence of chronic comorbidity and medication, obtained using multiple logistic regression analysis. Results are adjusted for age and sex

	Diet only, OR (95% CI)	Oral drugs, OR (95% CI)	Combination, OR (95% CI)	Insulin only, OR (95% CI)
No comorbidity, no medication	1.00	1.39 (1.16 to 1.66)	1.36 (1.07 to 1.74)	0.96 (0.67 to 1.37)
Comorbidity				
Joint disorders	1.04 (0.71 to 1.53)	1.57 (1.00 to 2.47)	1.32 (0.73 to 2.36)	2.51 (1.05 to 6.02)
Respiratory disorders	0.81 (0.51 to 1.27)	1.55 (0.92 to 2.62)	2.00 (0.97 to 4.11)	3.06 (1.05 to 8.91)
Respiratory + joint disorders		1.34 (1.11 to 1.69)		
Medication				
Corticosteroids	1.31 (1.13 to 1.52)	1.39 (1.16 to 1.66)	1.35 (1.06 to 1.72)	0.97 (0.68 to 1.38)
NSAID	1.34 (1.14 to 1.58)	1.36 (1.13 to 1.62)	1.34 (1.05 to 1.70)	0.97 (0.68 to 1.39)
Corticosteroids + NSAID	1.41 (1.21 to 1.64)	1.38 (1.16 to 1.65)	1.36 (1.07 to 1.73)	0.99 (0.69 to 1.41)
Comorbidity + medication				
Respiratory + joint disorders + NSAID	0.95 (0.57 to 1.57)	1.53 (0.85 to 2.75)	1.55 (0.69 to 3.50)	4.32 (1.23 to 15.13)

BMI did not significantly add to the modelling. Reference group for all OR: patients with no medication, no comorbidity, diet only. No interaction between treatment effect and treatment group. All results given in bold are statistically significant. BMI = body mass index. NSAID = non-steroidal anti-inflammatory drug. OR = odds ratio.

they were kept in all subsequent models, even if they were not always found to be significant.

Stage 0: Treatment effect

The odds of increased HbA1c levels at study end (worse outcome) were around 40% higher for patients on oral antidiabetic drugs or a combination of oral antidiabetic drugs and insulin than for patients treating their diabetes with diet alone (Table 3).

Stage 1: Comorbidity effect

A significant increase in HbA1c level was associated with the presence of joint disorders in the groups of patients treated with oral antidiabetic drugs (odds ratio [OR] 1.57) and insulin only (OR 2.51) while, in patients treated with insulin only, respiratory disorders were found to have a significant effect (OR 3.06) (Table 3). Effects of anaemia, depression, and malignancy on treatment efficacy were not found to be significant.

When investigating the effect of an additional comorbidity, only the effect of both respiratory and joint disorders was found to be significant (OR 1.34). There was no interaction with treatment group.

Stage 2: Comedication effect

The effect of corticosteroids and NSAIDs on outcome was significant, separately as well as in combination (Table 3). No significant interaction between treatment group and comedication was noted: corticosteroids/oral antidiabetic drugs (*P*-value 0.12); corticosteroids/oral antidiabetic drugs and insulin (*P*-value 0.27); corticosteroids/insulin (*P*-value 0.99); NSAIDs/oral antidiabetic drugs (*P*-value 0.96);

NSAIDs/oral antidiabetic drugs and insulin (*P*-value 0.86); and NSAID/insulin (*P*-value 0.52). There was a 30–40% higher chance that the HbA1c levels were increased at the end of the study period if comedication was present.

Stage 3: comorbidity and comedication effect

The odds of elevated HbA1c levels at the end of the study for patients with joint and respiratory disorders, who were taking NSAIDs and insulin, were four times that of patients treating their diabetes with diet only, who did not belong to this class of comorbidity and comedication. Other combinations were not significant.

DISCUSSION

Summary

In this study, the coexistence of joint and respiratory disorders, with or without the

prescription of corticosteroids, NSAIDs, or both, was associated with poorer glucose control compared to no comorbidity. This is meaningful in relation to joint problems because these reduce physical activity that is considered a cornerstone of optimal diabetes control.^{1,23} Additionally, joint problems tend to be unstable over time, resulting in irregular increases and decreases of the type and dosage of drugs taken, which make stable glycaemia control more difficult to achieve.

Of interest is the large proportion (>80%) of patients who had joint disorders. These findings are in line with those of other recent studies about the association between diabetes and various musculoskeletal manifestations.²⁴ In addition, the findings that respiratory disorders are associated with poor glycaemic control are in agreement with several findings in literature.²⁵⁻²⁷ There was no effect of anaemia, depression, or malignancy.

Strengths and limitations

The strengths of this study lay in its large sample size and the laboratory-measured response with complete data. Additionally, a retrospective cohort design was used; this is a very strong design in epidemiology, in which robust data are collected and stored over time. A large amount of data that had been collected and stored in the past was analysed using a cohort design; by doing this, information collected *tempore non suspecto* could be used, avoiding the main risks of bias, especially selection and recall bias, that often occur in retrospective studies.

Weaknesses were also noted. No details were available about each comorbidity and comedication, which could include disorders or drugs with different characteristics. The categorisation employed in this study was a compromise between specificity and practicality. Only date of diagnosis or first prescription was recorded. Severity of the comorbidities are potential confounders,²⁸ although use of corticosteroids, for example, may be a proxy for disease severity in respiratory and joint disorders.

The effect of five comorbidities and three groups of medication, which to the authors' knowledge is more than has ever been done before, were examined. However, more chronic diseases and more groups of medication that may also influence glycaemic control exist; if related to the predictors used, these might confound these results. Smoking status and other lifestyle behaviours that influence glycaemic control were insufficiently captured and,

therefore, not used in the analysis. In addition, although a generic measure of the outcome status of the patients would have been helpful, such information is not available in the Intego database.

The derivation of the response used in this study is susceptible to random variation in the HbA1c levels at the end of the study. To check for the possible effect of this phenomenon, these data were initially recalculated, taking into consideration only an increase in HbA1c level larger than the standard deviation of the overall mean as a worse outcome. In addition, only a difference between the initial and the last observation of >1 unit of HbA1c was considered as evidence of elevated HbA1c. As the results from modelling did not differ a great deal, the initial response was maintained. In an alternative approach, a repeated-measures analysis on each subject, rather than the change in HbA1c level from the initial to the last available level, was performed. Two techniques taken into consideration were the linear mixed models for continuous HbA1c level and the generalised estimating equations for the dichotomised HbA1c level, based on the 7% stable cut-off point. Both analyses gave largely similar results to those reported in this article.

A further point to note is that some of the patients had been diagnosed with diabetes before the start of the registration period. This could bias the results as incident and prevalent cases were considered together so the second year of follow-up was considered the initial year into the study for each patient and the response was derived in a similar fashion. In this way, only patients who had had diabetes for at least 1 year were considered. There were no significant changes in results.

Differences between treatment groups in age at baseline and sex subgroups were significant, as was the absence of any comorbidity or comedication. However, this has no real influence on the study conclusions as all analyses were adjusted for treatment group, age, and sex.

This study did not find any association between depressive disorders and worsening HbA1c levels: a finding that contradicts those of several other studies that did find such an association.^{29,30} In addition, a recent trial showed that, in patients who were simultaneously treated for both type 2 diabetes and depression, medication compliance, blood-sugar, and depression levels significantly improved, compared with patients receiving usual care.³¹ A possible explanation is that coded depressive disorders in primary care may

differ from the diagnosis of major depression in patients selected for prospective cohort studies.

Comparison with existing literature

No effect was found relating to malignancy or anaemia; this could be a result of complex mechanisms either increasing (for example, some drug treatment) or decreasing (for example, weight loss) HbA1c levels in interactions with routine diabetes care.

Few studies have reported on the effect of comedication. Faul *et al*²² did not find a significant impact of corticosteroid use on changes in HbA1c levels, despite suggesting careful monitoring of blood glucose levels for patients initiating use of corticosteroids. It seems sensible that, although starting corticosteroids or a change in dosage can lead to short periods of increased glycaemia, chronic corticosteroid use is easily controlled by adapting the treatment prescription. These results also pointed to treatment with NSAIDs being associated with an increased risk of elevated HbA1c levels. It is interesting to note that the comorbidities and NSAID treatments seemed to have an independent effect without meaningful interaction; in fact, the effect of each of them separately seemed to have a magnitude that was, more or less, similar; this was not cumulative

when the treatments were combined. This may be important as the population under consideration is ageing and, hence, most patients with diabetes are likely to be prescribed more than one medication for a chronic condition.

Implications for research and practice

This study once more confirms the need for comprehensive guidelines to effectively care for patients with multiple diseases; these guidelines should be as generic as possible but could include adapted metabolic targets discussed on the basis of patient-specific treatment goals. The findings of this study could add to the body of evidence underpinning such new guidelines.

This study was performed in a population of patients with type 2 diabetes. However, in the future, a generic set-up must be developed to study all combinations of chronic diseases and chronic drug therapy. Ongoing databases of routinely collected information — such as the General Practice Research Database (UK), Intego (Belgium), RegistratieNet Huisartsgeneeskunde (The Netherlands) — seem to be a good framework for such studies. However, for most chronic disorders it may be difficult to identify good-quality outcome indicators that are routinely recorded in these databases.

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Ethical approval

The Intego procedures have been approved by the ethical review board of the Medical School of KU Leuven (reference number: ML1723).

Provenance

Freely submitted; externally peer reviewed.

Competing interests

The authors have declared no competing interests.

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