Exploring the impact of chronic obstructive pulmonary disease (COPD) on diabetes control in diabetes patients: a prospective observational study in general practice

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BACKGROUND: Little is known about the association between COPD and diabetes control parameters. The presence of other diseases in addition to an ‘index disease’ is defined as comorbidity. Among patients with mild-to-moderate COPD, the main causes of death are comorbid diseases such as lung cancer and cardiovascular diseases. COPD has a large impact on morbidity and mortality.

Another example of a chronic disease with marked effects on health and health care is type 2 diabetes. Of all patients with COPD, 9–13% of the patients have comorbid diabetes, and 4–13% of patients with diabetes have comorbid COPD. Although these numbers originate from different studies and consequently are not directly comparable, they clearly illustrate that the combination of COPD and diabetes is a rather common one.

In recent years, knowledge and awareness of the importance of patient-specific factors in the treatment of COPD and diabetes has grown, resulting in an increased tendency to individualise disease management. An important characteristic of a patient with a specific chronic disease, such as COPD, is the comorbidity that may also be present. However, current guidelines for COPD and diabetes have limited applicability for patients with comorbid conditions. Very little is known on how the presence of a specific disease, such as COPD, influences the long-term outcomes of another disease, such as diabetes. This type of information is important if health care professionals aim to personalise disease management plans for COPD and diabetes patients. In addition, other characteristics such as age, sex, body mass index (BMI) and socio-economic status (SES) may have well-known effects on COPD and on diabetes, but how they interact if both diseases are present in one and the same patient is unknown. Detailed data on comorbidity, patient characteristics and disease control parameters from a representative patient population may inform us about the interaction between the two diseases and the impact on patients’ prognosis.

The aim of this explorative, hypothesis-generating paper was to investigate the association between COPD as a comorbid condition and longitudinal diabetes control parameters in patients with type 2 diabetes in primary care. We also explored the role of sex, age, BMI and SES in the relationship between COPD and diabetes control.

MATERIALS AND METHODS

Design and study subjects
We used available data from a dynamic prospective cohort of diabetes patients registered in the Continuous Morbidity Registration (CMR), a
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New diagnosis of type 2 diabetes in CMR practice between 1985–2006:
\[ n = 714 \]

HbA1c and SBP unavailable:
\[ n = 30 \]

HbA1c and/or SBP available:
\[ n = 684 \]

No baseline measurement available:
\[ n = 74 \]

Baseline measurement available (included for longitudinal analysis):
\[ n = 610 \]

Patients with pre-existent comorbid COPD:
\[ n = 63 \]

Patients without pre-existent comorbid COPD:
\[ n = 547 \]

Patients with incident comorbid COPD during 5 years of follow-up:
\[ n = 8 \]

Figure 1. Patients with the GP responsible for diabetes treatment.

A patient’s first outcome measurements collected from a diabetes check-up visit within the first 4 months since the diabetes diagnosis was labelled as ‘baseline measurement’. CMR, Continuous Morbidity Registration; COPD, chronic obstructive pulmonary disease; GP, general practitioner; SBP, systolic blood pressure.

general practice registration network in the Nijmegen region, the Netherlands. The four practices constituting the CMR have been recording all morbidities that are presented to the general practitioners (GPs) on a daily basis since 1967. The database reflects the health care system in the Netherlands, where patients are registered with a general practice and have access to specialist care through that practice. In this system, where GPs receive capitation payment, the nature of medical conditions or treatment does not influence the GPs’ performances. Details on the composition of our diabetes cohort are described elsewhere. We selected comorbid COPD as a single disease of particular interest for the analysis of possible associations between comorbid conditions and the course of diabetes control parameters, and we were, in addition, interested especially in comorbid malignancies and cardiovascular, mental and musculoskeletal diseases.

Study outcomes
HbA1c (in %, the current unit during our study period) and systolic blood pressure (SBP, in mmHg) were the primary study outcomes. Measurement of HbA1c is performed at the annual check-up visits. Blood pressure measurement is generally performed at every check-up visit. To include patients with sufficient follow-up starting from the diagnosis, we only included patients with their first measurement performed within the first 4 months after the diabetes diagnosis and labelled these as ‘baseline measurements’. All subsequent measurements were regarded as repeated measurements for individual patients and contributed to the longitudinal analysis. We studied the development of these outcomes during the 5-year follow-up.

Statistical analysis
SPSS (version 20.0) and SAS (version 9.02) software supported the analysis. Characteristics of the study population are provided using descriptive statistics. We compared linear trends for both HbA1c and SBP in the 5 years after the diabetes diagnosis between patients with and patients without comorbid COPD. We applied a random intercept mixed model analysis using measurements nested within patients. In this model, the presence of existing COPD, i.e., recorded before the diabetes diagnosis, was the variable of interest. We added an interaction term ‘time’ by ‘COPD’ (absent/present) to the model to explore differences in HbA1c and SBP trends according to the absence or presence of COPD. In this comparison between patients with and without COPD, we entered sex, age at diabetes diagnosis, SES, BMI (handled as ‘last observation carried forward’) and the presence of other comorbidities (as specified above) as potential confounders. Values for age and BMI were handled as continuous variables in the mixed model, but we categorised them as ‘low’, ‘intermediate’ and ‘high’ values to facilitate (graphical) presentation of the results. The categorisation was based on the limits of the first, second (i.e., the median) and third quartiles of the distribution of age and BMI values of the patients who contributed to the analysis.

Furthermore, we performed subgroup effect analyses to test whether potential differences in the HbA1c and SBP trends between diabetes patients with or without comorbid COPD were modified by sex, age, SES or BMI. The confounders in the initial analysis were now tested for potential effect modification separately by adding an interaction term ‘time’ by ‘COPD’ (absent/present) by ‘potential effect modifier’ to the model. Non-significant interaction terms were removed in a stepwise backward elimination procedure. In these subgroup effect analyses, we added the presence of other comorbidities as potential confounders (not as potential effect modifiers). In cases in which no significant results arose from the subgroup effect analysis, the first model (without subgroup effect analysis) defined the results.

Not only comorbid COPD already present at the study start may be associated with the longitudinal diabetes outcomes, the same may be the case for incident COPD after the patient’s diabetes diagnosis. Therefore, we performed sensitivity analyses excluding the patients who did not have COPD at their diabetes diagnosis date but who were diagnosed with COPD during the 5-year follow-up. A P-value < 0.05 was considered statistically significant.
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RESULTS
Study subjects and baseline characteristics
Figure 1 shows a flowchart of our study population. We included 610 patients with a mean age of 63 years (s.d. 12.5, Table 1) for longitudinal analysis. In all, 63 patients (10.3%) had comorbid COPD at the date of their diabetes diagnosis, and another 8 patients were diagnosed with COPD during the 5-year follow-up period. Patients with pre-existing COPD were older and had more additional comorbid conditions, apart from COPD, compared with patients without COPD (i.e., musculoskeletal disease, 31 vs. 30%). Note that in the longitudinal analyses we corrected for the presence of selected comorbidity.

Influence of comorbid COPD on the course of HbA1c and SBP
After correction for covariates, comorbid COPD was not significantly associated with the course of HbA1C (P = 0.54) or SBP (P = 0.33) values over time in the initial analyses. Figure 2 shows the time trends for patients with and without comorbid COPD and the additional effects of covariates. The figure footnotes provide information for the definition of the ‘reference category’.

In the subgroup effect analyses, however, we found a statistically significant association between comorbid COPD and the course of SBP, with effect modification of SES (P < 0.01) and BMI (P = 0.03). To express these complex findings in a comprehensible way, Figure 3 shows a graphical representation of the direction of effects, with separate graphs for combinations of SES and BMI. The figure shows that in the absence of COPD (blue lines), longitudinal SBP values are relatively stable over time, with higher values when BMI is higher (compare panels a, c and e). Diabetes patients with comorbid COPD (red lines) showed a more variable course of SBP over time, with SES more than BMI decreasing SBP values when BMI is higher (compare panels a, c and e).

Characteristics of patients at baseline, i.e., at the date of the diabetes diagnosis.
Abbreviations: BMI, body mass index; DM, type 2 diabetes mellitus; NA, not applicable; SES, socio-economic status.

| Patient characteristics | Total included n = 610 | COPD present* n = 63 | COPD absent* n = 547 | P-value* |
|-------------------------|-----------------------|----------------------|----------------------|----------|
| Sex: male, n (%)        | 294 (48.2)            | 34 (54.0)            | 260 (47.5)           | 0.33     |
| Age at DM diagnosis, years; mean (s.d.) | 63.0 (12.3) | 69.0 (11.0) | 62.3 (12.5) | <0.001 |
| Follow-up time, years; mean (s.d., range) | 6.2 (4.6; 0.1–21.9) | 4.1 (3.6; 0.3–15.6) | 6.5 (4.7; 0.1–21.9) | <0.001 |
| Measurements per patient, total number, mean (median; s.d.; range) | 21.8 (17.5; 18.2; 1–106) | 15.7 (10; 14; 9; 1–86) | 22.5 (19; 18; 4; 1–106) | 0.001 |
| BMI at baselineb, mean (s.d.), kg/m² | 29.8 (5.1) | 29.5 (5.2) | 29.8 (5.1) | 0.57 |
| SESc, n (%)             | 315 (52.1)            | 37 (58.7)            | 278 (51.3)           | 0.26     |
| Low                     | 242 (40.0)            | 24 (38.1)            | 218 (40.2)           |          |
| Middle                  | 46 (7.9)              | 2 (3.2)              | 46 (8.5)             |          |
| High                    |                       |                      |                      |          |
| Year of diabetes diagnosis, n (%) | 83 (13.6) | 3 (4.8) | 80 (14.6) | 0.07 |
| 1985–1989               |                       |                      |                      |          |
| 1990–1999               | 235 (38.5)            | 24 (38.1)            | 211 (38.6)           |          |
| 2000–2006               | 292 (47.9)            | 36 (57.1)            | 256 (46.8)           |          |

Comorbidity data
| Comorbid diseasesd, mean number (s.d.; range) | 2.7 (2.3; 0–11) | 4.0 (2.5; 0–11) | 2.6 (2.2; 0–11) | <0.001 |
| Comorbid diseasesd, (categorised), n (%) |                      |                      |                      |        |
| 0                                      | 100 (16.4)          | 4 (6.3)             | 96 (17.6)            | 0.002   |
| 1 or 2                                 | 227 (37.2)          | 17 (27.0)           | 210 (38.4)           |          |
| 3 and more                             | 283 (46.4)          | 42 (66.7)           | 241 (44.1)           |          |
| Cardiovascular comorbidity, present, n (%) | 390 (63.9) | 44 (69.8) | 346 (63.3) | 0.30 |
| Musculoskeletal comorbidity, present, n (%) | 197 (32.3) | 32 (50.8) | 165 (30.2) | 0.001 |
| Mental comorbidity, present, n (%)     | 140 (23.0)          | 18 (28.6)           | 122 (23.3)           | 0.26     |
| Comorbid malignancyd, present, n (%)   | 42 (6.9)            | 4 (6.3)             | 38 (6.9)             | 0.86     |
| Incident COPD after DM diagnosisd, n (%) | 12 (2.0)           | NA                  | 12 (2.2)             | NA       |
| Incident COPD in the first year after DM diagnosis, n (%) | 1 (0.2) | NA | 1 (0.2) | NA |
| Incident COPD in the first 5 years after DM diagnosis, n (%) | 8 (1.3) | NA | 8 (1.5) | NA |

Table 1. Baseline characteristics of patient population, according to the presence/absence of COPD

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**DISCUSSION**

Main findings

In the current study, we explored the association between comorbid COPD and the longitudinal development of HbA1C and SBP in a representative cohort of newly diagnosed type 2 diabetes patients in primary care during 5 years of follow-up. The initial analyses showed no significant associations between COPD and these outcomes, but subgroup effect analysis indicated that, in the presence of COPD, the development of SBP was different for patients from different SES and BMI subgroups. This suggests that comorbid COPD, in relation with these particular patient characteristics, may influence long-term diabetes control parameters.

Strengths and limitations of this study

In this dynamic cohort study, we used data from robust datasets that originate from decades of experience in morbidity recording in a practice-based research network from our department and good quality of diabetes care. We studied relevant diabetes control parameters as study outcomes (not treatment intensification) over a follow-up period that was long enough to assess potential associations with comorbid COPD. Comparison of outcomes over time between patients was meaningful, as we included only newly diagnosed diabetes patients. Another strength is that we studied an unselected population with ‘real patients’ receiving regular primary health care, i.e., a representative sample of the type 2 diabetes patient population.

It is important to realise that, within our study period, the criteria for the diagnosis of COPD and diabetes have changed. The current criteria for diagnosing COPD were introduced in Dutch general practice in 2001. Towards the end of our observation period, there was a higher rate of diabetes diagnoses. This implies that COPD and diabetes data from early in the observation period may not be fully comparable to similar data at the end of the period. This type of limitation is inherent to working with longitudinal data. In general, the CMR has shown to record diagnoses with high validity.

One limitation of this study is that we were unable to account for smoking in the analyses, because this has not been consistently recorded in the CMR and NMP databases, nor did we have data available on the severity of COPD (i.e., degree of airflow obstruction, exacerbation rate, severity of dyspnoea). From a previous study, we know that the majority of COPD patients in the NMP registry have mild or moderate COPD, but from our current work we cannot tell whether and how the severity of underlying COPD may be associated with the course of diabetes outcomes.

Clearly, the development of HbA1C and SBP over time as observed will have been influenced by the diabetes treatment as provided by GPs. This treatment may include stimulation of physical exercise (which is beneficial not only for the diabetes but also for the COPD) and prescription of glucose-lowering medication. Medication prescribed for COPD (e.g., oral or inhaled corticosteroids) may increase the glucose level and SBP in patients with diabetes. In this dynamic cohort study, it was
not possible to compare therapeutic regimes between diabetes patients with and without COPD. Differences in medication or lifestyle regimes may have contributed to the observed differences.

Twenty-eight cases with missing data for SES or BMI throughout the follow-up period (variables included in the linear model) dropped out. Their numbers were relatively low, which makes it unlikely that they introduced bias.

The percentage of diabetes patients with comorbid COPD in our cohort corresponds with prevalence numbers described in the literature. Although the absolute number of patients with COPD (n = 63) was relatively low, one of the subgroup effect analyses did show significant results. In a larger sample of diabetes patients with comorbid COPD, it would have been possible that some nonsignificant trends observed would have reached statistical significance.

The current paper is one result of a larger project with an explorative design aimed at investigating associations between several types of comorbidities on diabetes control parameters. These results generate new hypotheses and may guide further research elaborating on the early findings. It helps increase the evidence base for the complex care to patients with multimorbidity. We believe that the most important strength of the current work is precisely this novelty. To the best of our knowledge, this is the first study exploring longitudinal associations between COPD and another common chronic disease, in this case diabetes. Because the combined occurrence of diabetes and COPD is common, assessing possible interactions in terms of long-term outcomes is important. Our observation that, in some subgroups, comorbid COPD was associated with altered diabetes outcomes warrants further research in this area. Our study may serve as an example of how to investigate the complex relationships between two or more chronic conditions (i.e., multimorbidity) on patients’ prognoses for the diseases involved.

Interpretation of findings in relation to previously published work

The unfavourable effect of increasing BMI on systolic blood pressure is not surprising. Our observations indicate that for diabetes patients with comorbid COPD, patient characteristics that predict long-term outcomes may be different from those without COPD. Our study design had an explorative nature in which we tested several associations; hence, care needs to be taken in the interpretation of our findings. We did not find significant associations between comorbid COPD and all study outcomes tested. It is possible that the significant associations between longitudinal SBP and comorbid COPD among diabetes patients may not be replicated in a future study. It cannot be concluded from observational research only whether and how our findings should be translated into therapeutic consequences. One could reason that, in patients with diabetes and comorbid COPD, factors related to a patient’s SES are more important in achieving long-term SBP control than just reducing BMI. Our finding that among COPD patients the lower SES group had the best long-term SBP control is consistent with previous studies, as patients with lower SES are more likely to have other comorbidities.
The majority of practitioners caring for patients with either COPD or diabetes will see several patients with these diseases combined, and our findings may help raise awareness on the importance of formulating personalised management plans that aim for sensible outcomes taking into account both diseases. The current explorations do not yet allow for concrete recommendations for daily practice changes—our findings need to be replicated in larger diabetes cohorts.

Knowledge of the impact of comorbidity on disease outcomes is also important to support pay-for-performance initiatives that facilitate patient-centred care. Therefore, ongoing research in this area should be prioritised by funding bodies and policymakers.

Conclusions

Comorbid COPD was associated with longitudinal control parameters of newly diagnosed type 2 diabetes patients in general practice. This association was observed on SBP (but not on HbA1C) and was modified by SES and BMI. Although these results need to be verified first, this exploratory study provides new information on the interaction between multiple chronic diseases, and may guide further development of personalised care that accounts for patients’ comorbidity.

ACKNOWLEDGEMENTS

We thank all GPs and practice assistants in the CMR-NMP practices for their years of consistent morbidity and outcome recording.

CONTRIBUTIONS

TS is an Associate editor of npj Primary Care Respiratory Medicine, but was not involved in the editorial review of, nor the decision to publish, this article. HL and TS conceived and designed the study, with contributions from WdG, MB, AL-J and CvW. HL and JB acquired the data. HL and TS drafted the manuscript and WdG, MB, CvW, AL-J and JB critically revised it. Statistical analysis was performed by HL and HB, with contributions from TS, WdG and MB. WdG, CvW and AL-J supervised the study. JB is a statistician. HL is the guarantor of the study. The other authors declare no conflict of interest.

COMPETING INTERESTS

The authors declare no conflict of interest.

FUNDING

There was no specific funding for the current work. Hilde Luijks received a personal research development grant to combine her general practice specialty training with a research training from SBOH, employer of general practitioner trainees in the Netherlands.

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