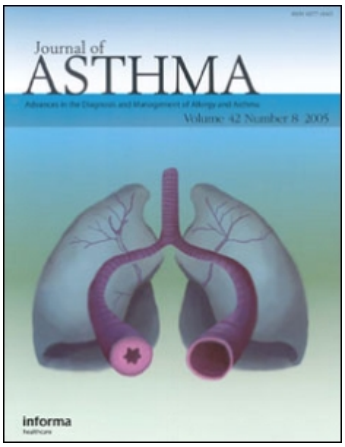
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ORIGINAL ARTICLE

Effect of Insulin on Airway Responsiveness in Patients with Type 2 Diabetes Mellitus: A Cohort Study

Claudio Terzano,[1,*] Susanna Morano,[2] Daniela Ceccarelli,[1] Vittoria Conti,[1] Gregorino Paone,[3] Angelo Petroianni,[1] Elda Graziani,[1] Anna Carnovale,[2] Mara Fallarino,[2] Alessandra Gatti,[2] Elisabetta Mandosi,[2] and Andrea Lenzi[4]

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Background. The correlation between low insulin levels and a decreased sensitivity of the muscarinic receptor has been shown on induced-diabetes animal models. We designed a cohort study with the aim of evaluating the effects of insulin therapy on airway responsiveness (AR) in human patients with type 2 diabetes mellitus. *Methods.* We enrolled 92 patients with type 2 diabetes who had switched from oral anti-diabetic therapy to treatment by insulin subcutaneous injection. Patients were administered the methacholine challenge test (MCT) at time 0 (pre-insulin therapy) and at intervals of 15, 30, 90, 180, and 360 days after insulin treatment. The decline of forced expiratory volume in 1 second (FEV_1)% from baseline (ΔFEV_1) in response to inhaled methacholine (MCH) was determined to assess airway hyper-responsiveness (AHR). *Results.* A total of 81 patients (18 women and 63 men) completed the study. Their mean age was 58 ± 7 years and the mean duration of disease was 13.5 ± 7.7 years. The mean decrease of FEV_1 at pre-insulin assessment was 2.96 ± 2.6%. Compared with the pre-insulin value, a significant increase of ΔFEV_1 was observed at 15, 30, and 90 days after treatment (6.25%, CI 95% 5.4 to 7.2, $p = 0.0005$; 7.64%, CI 95% 6.6 to 8.1, $p < 0.001$; 6.45%, CI 95% 5.5 to 7.3, $p = 0.0004$, respectively), while after 180 and 360 days AR was similar to pre-insulin values (ΔFEV_1, 3.62%, CI 95% 2.7 to 3.5 and 3.11%, CI 95% 7.9 to 9.3, respectively). *Conclusions.* The finding of an increased AR in patients with type 2 diabetes during the first 3 months of insulin therapy may underline the importance of monitoring pulmonary function and respiratory symptoms in patients switching from oral anti-diabetic drugs to insulin therapy, especially in the subset of individuals with respiratory disorders.

Keywords airway responsiveness, asthma, diabetes mellitus, insulin, Methacoline Challenge Test

Introduction

Most of the current literature indicates that the incidence of asthma and atrophic disease is lower in individuals with diabetes mellitus compared to the general population (1, 2). Moreover, the symptoms of asthma appear to be less severe when diabetes is superimposed (3, 4).

The mutual exclusion between asthma and diabetes mellitus reported in many epidemiological studies is still under debate.

The mechanisms of this negative association are still unclear, but a role for inhibitory M_2 muscarinic receptors has been postulated (5, 6).

The inhibitory M_2 muscarinic receptors, which are located within the smooth muscle of airways, inhibit acetylcholine release and may limit vagal-mediated bronchoconstriction (7, 8).

These receptors are dysfunctional in humans with asthma, resulting in increased bronchial constriction in response to vagal stimulation (9). Because the parasympathetic nerves provide the dominant control of airway smooth muscle tone, a lack of the M_2 muscarinic receptor function may be important in the development of hyper-responsiveness in asthmatic patients (10).

Compared with the airway hyper-responsiveness typical of asthma, airways of diabetic patients are characterized by reduced vagal reflex bronchoconstriction (11, 12).

Most of the studies investigating the relationship between insulin and airway responsiveness have been performed on animals.

In such animal models, it has been assumed that insulin may directly decrease the agonists' affinity for M_2 muscarinic receptors and may modify neuronal inhibitory muscarinic receptors function by modulating inflammation (13). Insulin may play an important role in the recruitment of inflammatory cells by promoting their production, or indirectly, through the activation of T lymphocytes [13].

To investigate the effects of insulin on airway responsiveness (AR) in humans, we designed a cohort study using a group of non-asthmatic diabetic insulin-treated patients and measured their response to treatment by administering the methacoline challenge test (MCT) at various post-treatment intervals.

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Patients and Methods

Using a cohort study, between March 2006 and September 2007, we recruited a sample population of 92 patients with type 2 diabetes, (as defined by the American Diabetes Association guidelines [14]). These patients were undergoing treatment with oral agents but needed to switch to insulin treatment owing to worsening glycaemic control. The inclusion criteria for subjects were as follows: age between 18 and 75 years; duration of diabetes > 5 years; previous treatment with oral hypoglycaemic drugs. The exclusion criteria were history of asthma, atopy or chronic obstructive pulmonary disease (COPD) and/or a positive bronchodilator response to inhaled salbutamol; current treatment with corticosteroids and/or antibiotics; the presence of serious medical disorders (recent myocardial infarction, stroke, dementia, peptic ulcer, cancers, drug or alcohol addiction, major depression, heart failure, arrhythmias, severe neuromuscular diseases); glicosilated hemoglobin more than 12%; and insufficient adherence to therapy.

The study was approved by the local ethics committee, and informed signed consent was obtained from all participants.

Enrollment Phase

At recruitment (visit 0), demographic data, personal medical histories, and last measurements of blood glucose and glycerinated hemoglobin (HbA1c) of all participants were collected. In addition, subjects underwent a complete physical examination (including measurements of height, weight, body mass index [BMI], blood pressure, and heart rate). Pulmonary function tests (PFT) and post-bronchodilator reversibility tests were performed with a Spiro meter Quark PFT4 (Cosmed, Pavona, RM, Italy) by experienced personnel following the American Thoracic Society (ATS) and European Respiratory Society (ERS) recommendations (15).

To assess basal airway responsiveness the Methacoline Challenge Test (MCT) was performed using a dosimeter Mefar MB3 (Markos Mefar S.R.L. Bovezzo (BS), Italy) according to ATS/ERS guidelines (16). A dosing schedule using methacholine concentrations of 12.5–25–50–100–200–400–800–1,600 μg/mL (9 steps, with the diluents step as the first one) was applied. A spirometry was performed at the beginning of the test (baseline) and at 30 and 60 seconds (in any case less than 3 minutes) after any step, to assess any variation of FEV_1. Decline of FEV_1 % (ΔFEV_1) at 1,600 μg of inhaled methacholine was determined to assess airway hyper-responsiveness (AHR).

Technicians were instructed to stop the test when the decline of FEV_1 was $\geq$ 20% (PD20 FEV_1).

In consideration of the demonstrated relationship between asthma and atopy, the dosage of total immunoglobulin E (IgE) blood levels was obtained in each patient by radioimmunologic methods Paper Radio Immuno Sorbent Test (PRIST).

Follow-Up

Patients who successfully switched from treatment by oral anti-diabetic drugs to Neutral Protamine Hagedorn (NPH) insulin therapy were instructed to attend a follow-up visit after 15 (visit 1) –30 (visit 2) – 90 (visit 3) – 180 (visit 4), and 360 (visit 5) days of insulin therapy. During each visit, subjects underwent a complete physical examination. Measurements were taken of blood glucose and HbA1c, PFT, and MCT with the same dosing schedule applied at visit 0. The dosage of total IgE blood levels was repeated at visit 5.

Statistical Analysis

Data are shown as mean $\pm$ standard deviation of mean.

A two-tailed, paired t test, with 95% confidence intervals was performed to analyze the difference in FEV_1 decline and in IgE levels; a one-way analysis of variance (ANOVA) with repeated measure test and Bonferroni post-test were also performed to compare all the variables. Correlation coefficients between insulin dosages and ΔFEV_1 were determined by Pearson's test.

p values less than 0.05 were considered significant. Statistical analyses were performed by using SPSS (Statistical Package for the Social Sciences, Chicago, IL) V13.0 for Windows.

Results

From the 92 subjects eligible to participate, 81 completed the study, 6 were excluded due to scheduling difficulties, 2 were excluded due to insufficient adherence to therapy, and 3 subjects declined to participate in a complete follow-up.

Clinical characteristics of the patients included in the study are summarized in Table 1.

Table 2 provides the patients' mean blood glycemic, glyated hemoglobin (HbA1c), and IgE blood levels at visit 0 and at the end of the 12-month insulin treatment and the mean daily dosages of insulin administered.

At visit 0, none of the subjects showed airway hyperresponsiveness and features of atrophic disease as assessed by MCT, skin prick tests, and total IgE.

The mean decline of FEV_1 during pre-insulin assessment was 2.96%, 95% CI 2.3 to 3.5.

Compared with the pre-insulin value, a significant increase of AR was observed at t15, t30, t90 (6.25%, 95% CI 5.4 to 7.2, $p = 0.0005$; 7.64%, 95% CI 6.6 to 8.1, $p < 0.001$; 6.45%, 95% CI 5.5 to 7.3, $p = 0.0004$, respectively), while after 180 and 360 days AR was similar to pre-insulin values (3.62%, 95% CI 2.7 to 3.5 and 3.11%, 95% CI 7.9 to 9.3) (Figure 1).

At visit 3 (after 90 days) a significant correlation was observed between insulin administered and ΔFEV_1 ($p = 0.0157$).

A significant increase of total IgE blood levels was observed after 12 months of insulin therapy (PRIST-V0 61 $\pm$ 24 KU/L, PRIST-V5 96 $\pm$ 20 KU/l, $p < 0.0001$; Figure 2).

Table 1.—Clinical characteristics of the patients included in the study.

Number of patients	81 (63 M; 18 F)
Age (years)	58 $\pm$ 7
Height V0 (meters)	1.68 $\pm$ 0.07
Weight V0 (kg)	77 $\pm$ 5
BMI V0 (kg/m^2)	27 $\pm$ 2.7
Weight V5 (kg)	76.58 $\pm$ 4.8
BMI V5 (kg/m^2)	27 $\pm$ 2.8
Duration of diabetes (years)	13.5 $\pm$ 7.7

Values are expressed as means $\pm$ SD. BMI = body mass index.

TABLE 2.— Mean daily dosages of insulin administered and mean blood glycemic, glycated hemoglobin (HbA1c), and IgE blood levels at visits 0 and 5.

Insulin (IU/day)	8 ± 2
HbA1cV0	8.75 ± 0.7
HbA1cV5	7.08 ± 0.69
Blood glucose V0 (mg/dL)	200 ± 51
Blood glucose V5 (mg/dL)	150 ± 40
IgE V0 (KU/L)	61 ± 24
IgE V5 (KU/L)	96 ± 20

DISCUSSION

To our knowledge, this is the first study that investigates the effects of insulin on airway smooth muscle tone in human patients using the MCT.

To investigate insulin effects on airways muscarinic receptors, we decided to include patients with type 2 diabetes mellitus rather than those with type 1. The reasons for this decision are varied. First, type 1 diabetes (insulin-dependent diabetes mellitus [IDDM]) results from the autoimmune destruction of insulin-producing ß cells in the pancreas by CD4+ and CD8+ T cells, so the immunological and inflammatory phenomena typical of IDDM could influence the pro-inflammatory effects of insulin on the broncho-motor tone. Additionally, immune-mediated diabetes commonly occurs early in life, so the timely beginning of insulin therapy prevents the possible functional evaluation of patients before treatment (14).

Despite an impaired glucose tolerance caused by inflammation-induced insulin, resistance may occur in asthmatic patients (17). A lower prevalence of asthma and atopia has been demonstrated in patients with IDDM in several epidemiological studies (1–5). The observation that insulin induces a shift towards a state of muscle hyper-contractility suggests that patients with poorly controlled diabetes could have a reduced muscular bronchial tone.

Moreover, an abnormality in β-adrenergic receptor function or circulating catecholamine levels has been postulated to explain the airway hyper-responsiveness typical of asthma (18, 19). Since β-stimulation is able to increase blood glucose levels, this could represent a further possible explanation of the inverse relationship between diabetes and asthma.

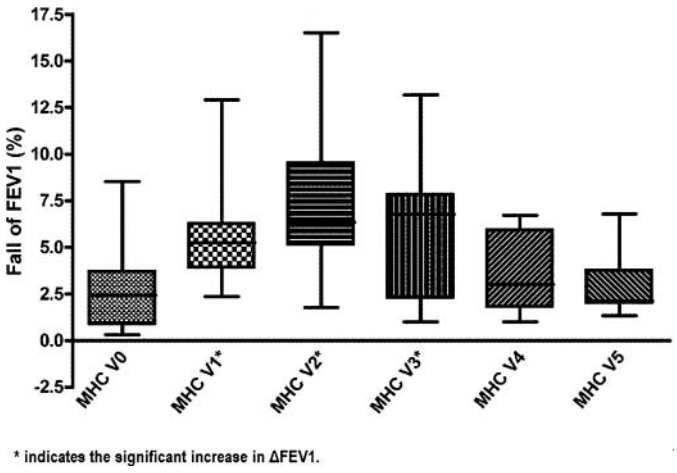


FIGURE 1.—Fall of FEV1 (ΔFEV1) after 15, 30, 60, 180 and 360 days of insulin treatment.

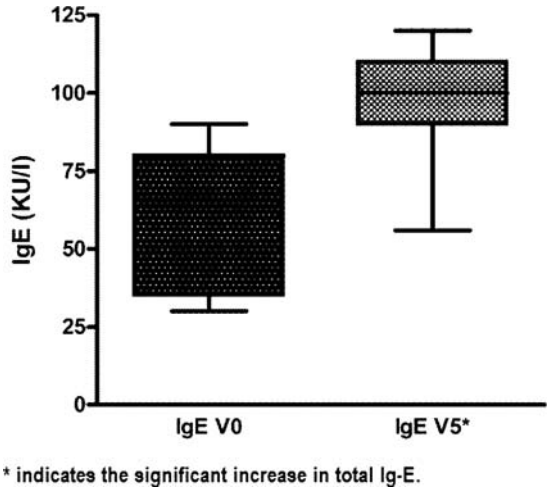


FIGURE 2.—Ig-E blood levels at V0 and V5.

Douek et al. (20) and the EURODIAB substudy group (5) also suggest that the low incidence of asthma among patients with IDDM is more than accidental. Asthma is generally regarded as a disease with strong Th2 type cytokine expression (21), whereas in autoimmune disorders, such as insulin-dependent diabetes mellitus, a Th1 type expression has been observed [14].

The T-helper model proposes that the two diseases are unlikely to coexist in the same individual, which is in accordance with the immunologic concept of Th1 (type 1 diabetes) and Th2 (atopy) diseases being mutually exclusive (22, 23).

These observations have prompted further studies using animals to investigate the biochemical effects of insulin on airway responsiveness (24–28).

Using murine models, Belmonte et al. have demonstrated a positive association between low insulin levels and decreased sensitivity of the muscarinic receptor, with a reduction of the bronchoconstriction induced by cholinergic system. Their study also showed that the administration of insulin was able to restore the normal sensitivity of the muscarinic receptor, causing an increase in airway responsiveness (29, 30).

These findings demonstrate that insulin may remove the protective effects provided by diabetes.

To investigate the mechanisms involved in the interaction between insulin and airway smooth muscle, Schaafsma et al. (24) studied the effects of insulin on muscle contraction, discovering that the long-term exposure of bovine tracheal smooth muscle strips to insulin stimulation induces a functional hyper-contractile phenotype.

In contrast with the hyper-reactivity observed in asthma, the airways of patients with diabetes are characterized by a reduced vagal reflex bronchoconstriction [11, 12]. In accordance with research literature, our study suggests that the modulation of the airway's reactivity is due to changes in the functioning of the parasympathetic autonomic nervous system [10, 29]. Since the M_2-receptors limit the release of Acetylcholine (Ach), alterations of these receptors might explain the modifications in the airway vagal responsiveness.

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The importance of our study lies in the observation that insulin caused a significant increase of airway responsiveness during the first 3 months of therapy, with a tendency towards pre-insulin values after 1 year of treatment. Further studies are needed to understand why the heightened reactivity disappears towards the end of the follow-up period. A possible explanation could be found in the restored M_2 receptor function, which was absent during the first 3 months of therapy.

Our results raise several considerations. Although the observed reduction in FEV_1 could be irrelevant in healthy subjects, the possibility of a decline in pulmonary function at the start of insulin therapy should be considered. Therefore, it would be of clinical significance to monitor the spiro metric parameters and perform an MCT before and after initiation of treatment to identify at an early stage the subset of patients at risk of developing bronchial hyper-responsiveness, especially in those with persistent impaired pulmonary function.

Considering that the use of aerosol insulin formulations has recently been approved in the United States and Europe for the treatment of diabetes mellitus type 1 and 2 (31, 32), our observations may have clinical relevance.

Previous studies (33, 34) have shown that inhaled insulin causes an insignificant decrease in FEV_1 of healthy individuals. Subjects with asthma and COPD were not included in this study, therefore we cannot rule out the possibility that those stimuli that do not alter pulmonary function in normal subjects could determine a significant decline of spirometric parameters in patients with obstructive lung disease.

In our study, a significant increase of total IgE blood levels was observed at the end of the follow-up period, and although it was within the range of normality, we cannot rule out a direct effect of insulin treatment on IgE synthesis.

A limitation of this study is the absence of a control group, which would have been useful to support the clinical significance of our results. Our aim was to use the same study subjects before the beginning of insulin treatment as the control group.

In light of these observations it would be interesting to investigate the acute and chronic effects of insulin on airway smooth muscle in the subset of individuals with specific disorders such asthma and chronic obstructive pulmonary disease.

Further studies, perhaps using osmotic challenge tests such as inhaled mannitol, are needed to confirm our results and to evaluate the possible benefits of a prophylactic therapeutic support in diabetic patients at risk of developing a decline in pulmonary function.

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