VIA MEDICA

REVIEW

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The coincidence of diabetes mellitus and asthma, their probable causal relationships and therapeutic opportunities

Abstract

Both the epidemiological data and the everyday medical practice demonstrate the coincidence of various types of diabetes mellitus (DM) in patients with asthma. Specific correlations between the risk of DM in pregnancy, asthma and the consequences of these diseases to the mother and her baby are also explored. The discussion concerning, on the one hand, the impact of asthma-related inflammatory condition on the metabolism of carbohydrates, and, on the other, the presence of chronic hyperglycemia and inflammatory markers observed in patients with asthma, is still ongoing. In the case of asthma and type 1 diabetes mellitus (T1DM), a correlation with the dysfunction of the immune system and the genetic background has been suggested, and in the case of type 2 (T2DM), the vital role of obesity and insulin resistance (IR) to promote excessive proinflammatory immune response. The data indicate that both asthma and DM affect mutually their clinical presentations, including the prognostic values and therapeutic possibilities. The ongoing controversy concerning the effective and safe anti-asthma and hypoglycemizing therapy does not allow for a definitive therapeutic consensus in this group of patients, despite the suggested role of metformin and hyperglycemizing effects of glucocorticoids. Therefore, the objective of the presented paper is a review of the knowledge in the field of DM and asthma coincidence, their probable causal relationships and therapeutic opportunities.

Key words: diabetes, asthma, epidemiology, immunopathology, treatment

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Introduction

In daily medical practice, either pneumological or diabetological, we are dealing with patients with diabetes mellitus (DM) coexistent with asthma. Due to the pathological and therapeutic heterogeneity of the types of DM, as well as the asthma medications used by the patients, the relationship between these diseases is significant from both theoretical and practical point of view. From the theoretical point of view, the possible etiological mechanisms of the coexistence of both diseases and the factors influencing their mutual course should be sought. Obtaining such information, from the practical point of view, may allow for the development of diagnostic schemes in the direction of DM in patients with asthma, determination of the mutual clinical picture, and selection of the appropriate therapeutic regimens in the case of coexistence of these diseases.

Despite the availability of studies assessing the etiopathological relationship between DM and asthma, there is still an ongoing discussion concerning the impact of inflammatory markers associated with asthma on the metabolism of carbohydrates. On the other hand, the available data suggest a significant effect of the carbohydrate metabolism on the presence of inflammation in the patients' organism. These concerns stem from the lack of a sufficient number of studies exploring the relationship between asthma and the development of DM. Currently, practical

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guidance on the indications to perform diagnostics for DM in asthma patients and the standards of hypoglycemizing and asthma therapy in this group of patients is also missing.

Therefore, the objective of this work is to sum up the knowledge in the field of coexistence of DM and asthma, their probable causal relationship, as well as taking advantage of the opportunities for providing a safe hypoglycemizing and asthma therapy. The presented analysis will seek to harmonize the standards of diagnostic and therapeutic management for the coexistence of these diseases, or their risk factors.

Epidemiology

DM and its complications represent currently an important health problem. In 2017, 424.9 million adult patients aged 20–79 years were estimated to have DM, and the data suggest that by 2045 this number will increase to 628.6 million. It should be noted that type 2 (T2DM) is the most common type of this disease in adults, occurring in approx. 87–91% of diabetic patients. The remaining group consists of patients with type 1 diabetes mellitus (T1DM) (7–12%) and 1–3% of those diagnosed with gestational diabetes (GDM), or secondary diabetes resulting from gene mutation, other chronic diseases (especially of the pancreas), or the used medications. These proportions are reversed in children and adolescents, with the predominance of T1DM and the number of patients reaching currently over one million. It is noteworthy that in this age group, due to the epidemics of obesity, the incidence of T2DM is continually increasing [1]. Notably, DM occurs slightly more frequently in adult men than in women. In 2014, the incidence of this disease amounted to 9.0% and 7.9%, respectively and, according to the predictions, these rates will increase to 12.8% (men) and 10.4% (women) in 2025 [2].

The data indicate a slightly lower incidence of asthma than that of DM. In 2012, the disease was diagnosed in approx. 334 million subjects all over the world, and there have been significant differences between the assessed countries (Austria 21.0% *vs* China 0.2%) [3]. In contrast to DM, the number of asthma cases is believed to remain stable, with its rapid growth in the developing countries, and a reduction in the incidence in the developed countries. It should be noted that male children more often suffer from asthma (approx. 20% higher incidence), whereas cigarette smoking and obesity are among the main risk factors for developing the disease [4].

An increasing number of papers reports the coexistence of various types of DM and asthma. A meta-analysis of 11 clinical studies carried out on a group of more than 550 thousand patients aged 57.23 ± 11.65 years with and without asthma showed that patients who have been diagnosed with the disease suffer from DM more frequently [odds ratio (OR) 1.25, 95% CI 1.08–1.44, $p < 0.00001$] [5]. An analysis of 12-year follow-up in The Women's Health Study, conducted in a group of 38.570 women aged ≥ 45 years with asthma/asthmatic symptoms (8.7%), or with overlap syndrome [asthma accompanying COPD (chronic obstructive pulmonary disease)] (3.2%) without DM showed 2472 new T2DM cases. In the age- and randomized treatment-adjusted model, the presence of asthma and/or COPD was associated with a 1.75-fold increased risk of T2DM as compared with healthy subjects. Moreover, patients with preexisting asthma alone also had a higher risk of T2DM than those in the same control group [the multivariate-adjusted relative risk (RR) 1.37, 95% CI 1.20–1.57]. It should be noted that the risk was independent of the presence of the standard diabetogenic factors, including the lack of adequate physical activity, cigarette smoking, the use of hormone replacement therapy, consuming excessive quantities of alcohol, the family history of DM and hypertension, familial hypercholesterolemia and an improper diet [6]. A study by Finnish researchers showed that previous diagnosis of asthma increased the risk of subsequent T1DM by 41% (95% CI 1.28–1.54), whereas previous diagnosis of T1DM decreased the risk of subsequent asthma by 18% (95% CI 0.69–0.98). It should be emphasized that these findings were independent of the relevant risk factors, such as age at diagnosis, birth decade, sex, the presence of maternal asthma/DM and birth-related factors [7]. A similar observation was made by Chinese scientists in a group of adults, where besides hypertension, myocardial infarction and ischemic stroke, DM was featured as one of the major diseases coexisting with asthma. In addition, statistical analysis demonstrated a significant relationship between the lifestyle affecting carbohydrate metabolism [body mass index (BMI), smoking, alcohol consumption, educational level, watching television and playing computer games] and the risk of the development of asthma [8].

An observational study based on the use of the Austro-German DPV database indicated that 3.4% of patients below 20 years of age with T1DM also had asthma, or received asthma-specific

drugs. It is worth noting that patients with T1DM and asthma were more often males, were older, and had longer DM duration [9]. In turn, a study assessing the presence of post-steroid complications in patients with severe asthma, including subjects from two large databases — the Optimum Patient Care Research Database (OPCRD) and the British Thoracic Society (BTS) Difficult Asthma Registry demonstrated that T2DM occurred in more patients with severe than with mild/moderate form of asthma (10% *vs* 7%, OR 1.46, 95% CI 1.11–1.91, $p < 0.01$) [10].

Immunopathology

Asthma is a heterogeneous disease associated with the presence of chronic inflammatory condition, leading to remodeling of the airways. A major role in the etiopathogenesis of asthma, in addition to the presence of a polymorphism of many genes responsible for the proper functioning of epithelial barriers, innate and acquired immune responses (including genes for interleukin 33 (IL-33), IL1RL1/IL18R1, HLA-DQ, mothers against decapentaplegic homolog 3 (SMAD3), IL2RB9, zona pellucida binding protein 2 (ZPBP2), GSDMB and ORMDL3), is played by dendritic cells and Th2 cells, producing, inter alia, IL-4, IL-5 and IL-13, and a variety of other cytokines. They all play an important role in the maturation and survival of eosinophils, their recruitment to the pulmonary mucosa, the isotype switching of B-cells and the synthesis of immunoglobulin E (IgE), which activates the mast cells when bound to the appropriate receptors [4, 11].

The etiopathogenesis of the various types of diabetes is somewhat less complex, but also includes the interaction between different genetic and environmental factors resulting in a gradual loss of pancreatic β cell mass and/or their proper functioning. In the case of T1DM, the variants of genes in one large locus– human leukocyte antigen (HLA) are associated with a 50-60% increase in the genetic risk for DM, by affecting the binding of HLA protein with antigen peptides and antigen presentation to T cells. It should be mentioned that these are not the only genes involved in the development of this disease. It has been suggested that there are about ca. 50 such genes, and they all contribute, inter alia, to the modulation of the regulation of immunity. In addition, the suggested association between the environmental factors, such as infections (mainly viral), nutrients (gluten) and the autoimmune process and the risk of the development of T1DM should be emphasized. Notably, in this situation, the presence of autoantibodies reflects the basic immune response of T and B cells to the β cell antigens [12].

Obesity and insulin resistance (IR) are the two main causal factors of T2DM. In the recent years, a close correlation between the presence of excess fat and the functioning of the immune system has been found. This system has been demonstrated to have a significant impact on, inter alia, differentiation of adipocytes and prevention of ectopic deposition of lipids. The dysfunctional adipose cells (due to caloric overload) were found to be characterized by multiple anomalies (including excessive production of leptin and reduced production of adiponectin, hypoxia and excessive deposition of the cellular matrix — collagen and elastin). These changes entail a variety of consequences, including initiation and/or promotion of the immune response in the form of persistent excessive number of immune cells producing proinflammatory cytokines [13]. On the other hand, a study by Carpio *et al*. did not observe the presence of breathlessness sensation during exercise to be dependent on the peak respiratory rate, peak respiratory CO2 equivalent, as well as the proinflammatory cytokines, such as IL-6 and IL-1β in sera [14]. Some authors divide obese patients with asthma into two phenotypes: early atopic Th2-high type asthma with more severe bronchial hyperreactivity and higher concentration of IgE, where asthma is complicated by the presence of obesity and late, non-atopic Th2-low asthma, occurring mainly in women whose development of asthma is the consequence of obesity and is associated with lower incidence of atopy, bronchial hyperreactivity, airway obstruction and the number of exacerbations [15].

The link between obesity, intestinal microbiota and diseases related to the immune system, including asthma, is becoming increasingly popular. This mechanism also seems to be not understood completely, but there are indications that besides the involvement of IgA and calprotectin produced by the mucous membranes, the exposure to lipopolysaccharides (LSP), production of short-chain fatty acids (SCFA), bile acids and intestinal microflora products are involved in this process as well [16]. In a study by Cani *et al*., the animal model demonstrated that mice fed with high-fat carbohydrate-free diet (72% fat, 28% protein and < 1% carbohydrates) had higher concentrations of LPS. Such a diet was observed to change drastically not only the intestinal flora by a significant reduction in the number of Gram-positive and Gram-negative bacteria (*Lacto-*

bacillus spp., *Bifidobacterium* spp., and *Bacteroides-Prevotella* spp.), associated with an increase in the permeability of the intestines caused by decreased expression of epithelial tight junction proteins such as ZO-1 and Occludin (an integral plasma-membrane protein located at the tight junctions), but also the concentrations of mRNA PAI-1, IL-1, tumor necrosis factor-α (TNF-α) and F4/80 in the visceral (mesenteric) adipose tissue. The above correlation was abolished completely by institution of 4-week antibiotic treatment leading to substantial reduction of inflammatory markers in the group fed with the high-fat diet. Moreover, the used high-fat diet was proven to be associated with an increase in blood glucose, which was reduced by the use of antibiotic therapy. Similar observations apply to the carbohydrate diet inducing insulin secretion, the IR indicator, weight gain, total energy consumption and the weight of visceral and subcutaneous adipose tissue [17].

On observation of the patients already diagnosed with T2DM, the presence of irregularities in the immune system function, associated with the onset and persistence of a chronic inflammatory condition responsible for disturbances of inflammation transduction, is also notable. For example, in a study conducted by Danona *et al.*, it was demonstrated that the expression of inflammatory markers such as IL-4, matrix metallopeptidase 9 (MMP-9), LIGHT (tumor necrosis factor superfamily member 14, TNFSF14), chemokine receptor type 2 (CCR-2) and plasma concentrations of nitric oxide metabolites (NOM) was significantly higher in obese patients, including those with T2DM as compared with healthy, nonobese subjects. It was also found that, except for the concentrations of NOM, these values correlate with The Homeostatis Model Assessment — Insulin Resistance (HOMA-IR) and BMI [18]. In turn, the study by Sindhu *et al*. proved that patients suffering from asthma and T2DM have a higher concentration of monocyte chemoattractant protein-1 (MCP-1) compared to those with and without one of the above diseases, and the concentration of that marker correlated with other exponents of inflammation and respiratory tract remodeling, such as IFN-α2, IL1RA, IL-10, Fractalkine/CX3CL-1 and vascular endothelial growth factor (VEGF). Slightly different correlations of that marker were found in the compared groups of patients with T2DM and asthma (in that group correlation with IL-3, IL-6, IL-9, MIP-1α/CCL-3, MIP-1β/CCL-4, GROα/CXCL-1 i BMI) and those with asthma without T2DM (correlation with IL-1β, IL1RA, MDC/CCL-22, IP-10/CXCL-10, GM-CSF, FGF-2, PDGF-AA, PDGF-BB and glycated hemoglobin — HbA1c) [19].

In the case of patients with T1DM and asthma, the etiopathogenetic link seems to be stronger than in the type of carbohydrate metabolism disorders described above, but there are still controversies. For example, the study by Vaseghi *et al*. showed a significantly lower expression of T-bet and IFN-γ genes in T1DM patient group compared with subjects without DM ($p < 0.05$). There was, however, no significant relationship between the expression of GATA-3 and the presence of DM, while a significant increase in IL-4 mRNAs in peripheral blood mononuclear cells (PBMCs) and plasma concentrations of this cytokine ($p < 0.001$) was reported in the group of patients with T1DM ($p < 0.05$), as well as decreased concentration of another inflammatory marker — IFN-γ ($p < 0.001$) [20]. In the study by Peters *et al*., it was found, however, that notwithstanding the severity of asthma (severe and non-severe), the increased level of IL-6 correlates with the value of BMI ($p < 0.0001$) and the presence of DM ($p = 0.04$) [21].

Clinical picture

Clinical data suggest, however, that DM is one of the least common chronic diseases concomitant in patients with asthma, including controlled/uncontrolled cases. It has been also found that DM is slightly more frequent in asthma patients with correctly controlled disease than in those with poor asthma control (12.5% *vs* 11.1%), as well as in obese ones (18.6 *vs* 13.9, respectively) [22]. It is notable that the presence of obesity in patients with asthma is associated with more severe symptoms, destabilization and loss of control of the disease, as well as deterioration of the quality of life, a different response to the medication to control the disease, the development of steroid resistance and the absence of eosinophilic inflammation [23]. It has also been shown that the diagnosis of IR is associated, like in the case of obesity, with a significantly increased presence of wheezing incidents (OR 1.87, 95% CI 1.38–2.54) and asthma-like symptoms (OR 1.61, 95% CI 1.23–2.10). This correlation has also been proven to be stronger in the case of IR than of obesity and independent of the gender of the patient [24]. It is also worth mentioning that obesity can cause shortness of breath on exertion by reducing the functional residual capacity of the respiratory reserve volume. Obesity in adults, particularly in women, may be associated with treatment-

-resistant asthma with less eosinophilic and more neutrophilic sputum profile [25].

In daily clinical practice, the existence of an association between the presence of DM and the risk of pneumococcal diseases, including community-acquired pneumonia (CAP) and invasive pneumococcal disease (IPD), in adult patients, especially those aged ≤ 40 years without comorbidities, is also worth keeping in mind. It has been shown that this risk increases with the duration of DM and inadequate glycemic control [26].

In the GEIRD (Gene Environment Interactions in Respiratory Diseases) study conducted on patients aged 45-64 and 65-84 years, including individuals with T2DM, no significant differences as to the incidence of asthma were observed in the analyzed groups of patients with and without DM. It was noticed, however, that people with DM reported slightly more frequently dyspnea limiting the walking pace (modified MRC grade 2 dyspnea) in the respective age groups (7.9% *vs* 23%, $p < 0.001$ and 13.7% *vs* 30.9%, $p < 0.001$). Compared to the general population, patients with DM aged 45–64 years complained more frequently of chronic cough/presence of phlegm ($p = 0.017$) [27].

With respect to patients with T1DM, taking into account the previously cited review of the DPV database, it has been suggested that individuals with this type of DM suffering from asthma, compared to subjects without asthma, are at a similar age at DM diagnosis with similar prevalence of overweight and obesity, diabetic ketoacidosis, as well as similar values of blood pressure and lipid profile. It has also been shown that patients with T1DM and asthma more often use continous subcutaneus insulin infusion, more often have hypoglycemic coma, with almost the same average value of HbA1c (8.28 ± 1.8% *vs* 8.3 ± 1.7%, $p = 0.77$). It seems to be associated with higher doses of insulin that they have to use (0.88 0.3 *vs* 0.84 0.3 U/kg, $p < 0.01$) and specific anti-asthma drugs (62% — asthmatics, including 28% — requiring inhaled glucocorticoids — IGCs, 24% — sympathomimetics, 6% — leukotriene receptor antagonists and 4% — other nonspecific medications). It should also be noted that the subjects using sympathomimetics, compared to patients using IGCs and leukotriene modifiers, had a higher HbA1c (8.42 ± 1.83% *vs* 8.18 ± 1.55% and 8.42 ± 1.55% *vs* 7.97 ± 1.14%). Diabetic ketoacidosis occurred more frequently in subjects using sympathomimetics than IGCs (8.5 *vs* 4.8 per 100 patient-years, $p = 0.0117$) [28].

When discussing the clinical problems associated with the presence of asthma with DM, the impact of these diseases on basic lung function tests should also be mentioned. In their study, Klein *et al*. demonstrated that patients with DM had lower mean forced expiratory volume in 1 second (FEV_1), lower forced vital capacity (FVC) and higher dyspnea scores than those without DM regardless of the presence of chronic lung disease (LD) such as asthma, chronic bronchitis or emphysema [FEV_1 3.00 (95% CI 2.96–3.04) *vs* 3.10 (3.09– 3.11) L, $p < 0.01$, for participants without LD and 2.86 (2.79–2.93) *vs* 2.95 (2.92–2.99) L, $p < 0.05$, for participants with LD, FVC 3.62 (3.59–3.66) *vs* 3.81 (3.79–3.83) L, $p < 0.001$, for participants without LD and 3.56 (3.48–3.63) *vs* 3.74 (3.70–3.77) L, $p < 0.001$, for participants with LD; dyspnea score 0.60 (0.49–0.71) *vs* 0.41 (0.34–0.49), $p < 0.001$, for participants without LD and 1.25 (0.94–1.55) *vs* 0.77 (0.54–1.00), $p < 0.001$, for participants with LD]. There was no significant effect of coexistence of these diseases on CRP activity. It has been shown, however, that the aforementioned indicators of lung damage correlate in patients with T2DM with the value of albumin-to-creatinine ratio (ACR), and the value of FVC was inversely proportional to the HbA1c percentage in patients without LD (a reduction of FVC values of 16 ± 7 L per 1% increase in HbA1c). It should be mentioned that this observation applies to the Spanish/Latino cohort and suggests that alveolar-capillary microangiopathy-related mechanisms play a role in this association [29]. The above study provides the confirmation of the earlier observations concerning the differences in the FVC, FEV_1 and diffusing capacity for carbon monoxide ($T_{L,CO}$) values in spirometry in patients with and without DM, in whom significant differences in the tested aerobic capacity parameters were found. However, this study indicates the presence of a controversy as to the ethnic differences, pointing out the Spanish/Latino race rather than the Caucasians or Afroamericans as more susceptible to pulmonary diabetic complications [30].

Referring to the complications and comorbidities, the results of the recently published Swedish study demonstrating that cessation of cigarette smoking in patients with asthma contributes to a reduction of high level of cardiovascular risk factors, including DM (OR 3.87, 95% CI 1.04–14.4, $p = 0.04$) [31].

Treatment

The everyday clinical practice as well as the research data indicate the presence of a contro-

versy concerning the "carbohydrate" safety of anti-asthma medications and the selection of hypoglycemizing drugs in patients with asthma and DM.

The debate on the diabetic safety of anti-asthma medications concerns mainly GCs. A literature review conducted by American scientists points to 4-fold higher risk of developing DM in patients who chronically use this group of drugs [32]. Sullivan *et al.*, based on the MarketScan® data set, found that the use of oral glukocorticosteroids (OGCs) four times per year or more was associated with a significant risk for the development of T2DM (OR 1.28, 95% CI 1.13–1.449, $p < 0.01$). Such a risk was, however, not reported among the patients using this group of drugs less often — 1–3 times per year (OR 1.056, 95% CI 1.015–1.098) [33].

A retrospective study conducted by British researchers using a UK-based Clinical Practice Research Datalink (CPRD) on over 60 thousand patients with severe asthma (stage 4 or 5, according to GINA) also confirmed that the use of OGCS involved a risk of developing DM in this group of patients [1.04 events per 1000 person-(28 day)-periods], and this increase occurred also with small doses (> 0-2.5 mg/day (HR 1.20, 95% CI 1.11–1.30) and correlated with an increase in the administered OGCs dose (for > 2.5 mg/day — HR 1.77, 95% CI 1.44–2.01) [34]. Analyzing other drugs used in the treatment of asthma, it should be noted that there are no detailed data to evaluate the effect of cholinolytics on carbohydrate metabolism. In the case of patients requiring therapy with anti-IgE antibodies, there have been reports suggesting a negative effect of omalizumab on metabolic control of DM, and a positive one of mepolizumab [35].

The choice of drugs in patients with asthma is mainly dependent on the type of DM. In the case of T1DM, the drug of choice is insulin administered in different therapeutic schedules. A study on a small group of 24 patients with more severe asthma exacerbations, requiring the use of OGCs and possibly insulin therapy in the infusion pump or subcutaneously, showed that, regardless of the route of insulin administration, hyperglycemia is associated with the prolongation of the necessary time of hospitalization (8.2 ± 2.4 and 10.2 ± 5.2 *vs* 5.8 ± 1.9 in the group not requiring insulin) [36]. Ahmadizar *et al.*, during their 5-year follow-up study, found a significantly higher rate of the use of asthma medications in patients after the diagnosis of T1DM (23.2% *vs* 18.3% in the control group). However, they did not observe a statistically significant difference between patients with and without DM in the application of the specific anti-asthma medications, except for short-acting muscarinic antagonists, more often used in the T1DM patient group (5.5% *vs* 0.62% of the control group). It is noteworthy that the frequency of use of anti-asthma medications decreased over time, and the peak of the phenomenon was observed in the first year after the onset of DM. It is also worth mentioning that asthma exacerbations reached a peak after the first year, both in the case of T1DM (7.8 per 1000 population per year) and the reference group (6.8 per 1000 population per year) [37].

In the group of patients with T2DM, the situation seems to be more complicated, because the availability of hypoglycemizing drugs is increasing. According to the diabetological recommendations, the drug of choice is metformin (MET), which each patient without contraindications and tolerant to this medicine should receive [38]. A study by Li *et al.* in 1332 asthma and DM patients (including 33.3% of the patients on MET) demonstrated that the use of MET reduces the risk of hospitalization for asthma (OR = 0.21, 95% CI 0.07–0.63) and the risk of asthma exacerbations (OR = 0.39, 95% CI 0.19–0.79), but not emergency room visits (OR = 0.62, 95% CI 0.26–1.44). It was found that the subjects treated with MET use more often short-acting β2-agonists (30.2% *vs* 24.1%, $p < 0.05$) and methylxanthine (42.8% *vs* 32.8%, $p < 0.01$). It should be noted that patients who used MET less frequently required insulin (6.1% *vs* 13.5%, $p < 0.01$) and hospitalization for asthma (0.9% *vs* 3.3%, $p < 0.01$) than those not treated with MET [39]. It has been suggested that the mechanism underlying these properties of MET beneficial to protect the lungs is LPS-evoked TLR4 activation and the protective effect can be related to the activation of AMPK [40]. In contrast to insulin therapy, it was concluded that the use of MET by patients with DM reduces the risk of the development of asthma (for insulin OR 2.23, 95% CI 1.52–3.58, for MET OR 0.75; 95% CI 0.60–0.95, respectively) [41].

In the case of patients with T2DM and coronary heart disease coexisting with asthma, the use of pioglitazone in this group was demonstrated to improve the clinical course of DM and its proper control, reduce inflammation and ameliorate the epithelial function [42]. A study carried out with the use of pioglitazone in the group of 23 patients did not confirm the difference in the amount of exhaled nitric oxide, asthma control and lung function during the 12-week administration of

the drug (the median airway reactivity, measured by PC20 methacholine was 1.99 (IQR 3.08) and 1.60 (5.91) mg/mL in the placebo and pioglitazone group at the baseline, and 2.37 (15.22) and 5.08 (7.42) mg/mL after 12 weeks, p = 0.38) [43]. In turn, a 12-week study conducted on a group of 68 patients with mild asthma (with 55 patients ultimately assessed) showed that the use of this drug in the dose of 30 mg for 4 weeks, and then 45 mg for 8 weeks, does not significantly affect the FEV_1 value (0.014 L, 95% CI 0.15–0.12, p = 0.84), as well as the assessed secondary endpoints such as mean peak expiratory flow (PEF), scores on the Juniper Asthma Control Questionnaire (ACQ) and Asthma Quality of Life Questionnaire (AQLQ), fractional exhaled nitric oxide (FeNO), bronchial hyperresponsiveness (PD20), induced sputum counts, and sputum supernatant interferon gamma-inducible protein-10 (IP-10), VEGF, monocyte chemotactic protein-1 (MCP-1), and eosinophil cationic protein (ECP) levels [44].

A retrospective, observational cohort study conducted on the basis of American commercial databases, covering the years 2006–2014 and patients with T2DM and asthma, demonstrated that the use of the DPP4 inhibitors, such as alogliptin, linagliptin, saxagliptin, sitagliptin or mixed products containing these agents for a year did not affect significantly the risk-domain asthma control (RDAC), defined as no asthma hospitalizations, no lower respiratory tract infections, and no OGCs prescriptions (OR 1.05, 95% CI 0.964–1.147), total control AS (OR 1.04, 95% CI 0.956–1.135), stability of the therapy (OR 1.04, 95% CI 0.949–1.115) and the number of severe exacerbations (mean = 0.32 *vs* 0.34 exacerbations per subject-year, respectively; p = 0.064) [45].

A study by Toki Si *et al*. carried out on an animal model showed that liraglutide used for two days before exposure to *Alternaria alternata* — an airborne allergen responsible for severe exacerbations of asthma – reduces the number of lung epithelial cells expressing IL-33 and the level of IL-33 expression by individual cells as well as the level of IL 33 in BAL fluid. It should be noted that IL-33 is one of the most consistently associated gene candidates for asthma identified by GWAS. Studies in animal and human cells have confirmed the importance of IL-33 in inducing type-2 cytokine production from both group 2 innate lymphoid cells (ILC2) and Th2 cells. There was, however, no significant correlation between the use of liraglutide and reduction of lactate dehydrogenase (LDH) activity in BAL fluid, extract-induced CysLT and PGD_2 levels. Further, a GLP-1R agonist significantly decreased the number of ILC2 expressing IL-5 and IL-13, the lung protein expression of type-2 cytokines and chemokines, the number of perivascular eosinophils, the mucus production, and the airway responsiveness compared with vehicle treatment. GLP-1R agonist treatment instituted one day after the first *Alternaria* extract challenge also significantly decreased eosinophilia and type-2 cytokine and chemokine expression in the airway after 4 days following *Alternaria* extract challenge [46].

Pregnancy

The coincidence of asthma and GDM is still being discussed. In a study by Iranian scientists, a higher prevalence of GDM was found in a group of patients with asthma (adjusted OR 2.64, 95% CI 1.45–4.78). Such a correlation was not observed in the case of DM diagnosed prior to pregnancy (4% *vs* 2.6%) [47]. The data coming from the Finnish Medical Birth Register (MBR) (over 1 million children followed up within 7 years after birth) indicate the predictive value of the presence of DM in the mother for the later application of anti-asthma medications in children born between 32-33 weeks of gestation (HR 1.62, 95% CI 1.02–2.58) and/or between 34–36 weeks (HR 0.78, 95% CI 0.63–1.11) [47].

Data from the Quebec Asthma and Pregnancy Database (QAPD) based on a cohort of pregnant patients with asthma indicate that the use of inhaled GCs (IGCs) is not associated with the risk of GDM, regardless of whether the patients use LABA additionally. There was also no significantly greater risk in the case of average IGCS doses without LABA compared to low IGCs doses used with LABA, and this risk was comparable in the groups of patients who used high IGCs doses without LABA or average IGCs doses with LABA [48]. A meta-analysis carried out in 14 European countries with the participation of 85,509 children born, assessing the presence of wheezing of various severity (at least one, or recurrent episodes in the offspring within 12-24 months after birth) showed no relationship between this clinical symptom and the presence of GDM. It should be emphasized that in the case of recurrent wheezing, aRR of 1.25 was obtained (95% CI 0.86–1.79) [49]. On the other hand, data from the Swedish Hospital Discharge Register evidence an increased risk of developing asthma in children over 2 years of age whose mothers had GDM (OR 1.20, 95% CI 1.02–1.42) [50].

Discussion

Epidemiological studies indicate a significant relationship between the different types of diabetes and bronchial asthma. Regardless of the pathomechanism leading to chronic hyperglycemia, it has been found to be associated with the activation of the inflammatory response that is closely correlated with the presence of asthma and its severity. Due to that correlation, each patient diagnosed with asthma should also be diagnosed for diabetes. Currently, there are no hypoglycemizing therapeutic standards for patients with concurrent asthma and DM, due to the controversy concerning the cause and effect relationship between the anti-asthma medications and hyperglycemia. In this case, metformin is still the drug of choice, but high hopes are associated with the novel hypoglycemizing drugs, such as DPP4 inhibitors.

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Conflict of interest:

None declared.

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