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REVIEW ARTICLE

Novel Predictors for Personalized Pharmacotherapy in Type 2 Diabetes and COPD

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ABSTRACT
This review aims to identify opportunities to optimize drug therapy in comorbid pathology to increase the effectiveness of pharmacotherapy, improve the prognosis and outcomes of concurrent diseases. One of the ways to individualize pharmacotherapy is to identify polymorphic genes that are responsible for the formation of a pharmacological response to the prescribed pharmacotherapy, thus determining the effectiveness of drug therapy. The key polymorphisms contributing both to the development of diseases –chronic obstructive pulmonary disease and type 2 diabetes mellitus (COPD and T2DM) and potentially forming a pharmacological response to prescribed drug therapy were selected as polymorphisms of the genes of beta -adrenergic receptors, leptin receptors, as well as the gene of endothelial nitric oxide synthase. The polymorphism of these genes determines the development of resistance to leptin and insulin, which, in turn, could be the target of many sugar-lowering drugs. The review reveals potential associations and directions for pharmacogenetics research taking into account the comorbid patients.
Keyword.*T2DM, COPD, gene polymorphism, pharmacotherapy, efficacy, personalized medicine, polypharmacy.*

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INTRODUCTION

According to the International Diabetes Federation (IDF), about 463 million people between the ages of 20 and 79 have diabetes mellitus (DM) worldwide, and it is projected that there will be 578 million adults with diabetes by 2030, and this number will reach 700 by 2045. million people. At the same time, 1 out of 5 people over 65 years old has diabetes, and the share of type 2 diabetes mellitus (T2DM) is steadily growing: 374 million people are at an increased risk of this disease [1].

Comorbid patient often appears to be a difficult problem for rational pharmacotherapy due to the multiple organ damage. The aim is to affect several links of pathogenetic processes leads to a polypharmacy. Polypharmacy is concurrent use of many various medications in one patient. This use becomes less effective, but more toxic and unacceptable at one or another stage of the concurrent diseases. For comorbid patients with long-term T2DM drug interaction issues are as relevant as the selection of optimal glucose-lowering therapy. Relevant studies have shown that nonsteroidal anti - inflammatory drugs (NSAIDs), anticonvulsants, antimicrobials, and most importantly, drugs for the treatment chronic obstructive pulmonary disease (COPD) and asthma have the highest potential for interaction [2].

In patients with concurrent pathologies - chronic obstructive pulmonary disease and type 2 diabetes mellitus(COPD and T2DM) - there are more pronounced clinical manifestations of respiratory disorders: in such patients, shortness of breath is more pronounced, hypoxemia progresses faster, and the participation of auxiliary muscles in the act of breathing is required. In people suffering from both COPD and COPD-related diseases and T2DM it is recommended to pay special attention to pharmacotherapy due

to possible pleiotropic effects of drugs [3]. In one of the studies, it was found that the mortality rate from respiratory tract diseases in patients with T2DM is lower among patients taking metformin. Researchers associate this phenomenon with the anti-inflammatory and antioxidant effect of the drug [4].
Diabetic microangiopathy, as a complication of T2DM, affects small-sized pulmonary vessels in COPD patients accounting to the progression of COPD. T2DMis also associated with a reduction in lung function, a decrease in FEV1 (forced expiratory volume for the first second of the forced expiratory maneuver), which leads to the progression of COPD. Systemic inflammation determines the clinical picture in patients suffering from COPD and T2DM. COPD in diabetic patients is more severe: signs of respiratory failure are more pronounced, exacerbations are more frequent, and the quality of life significantly decreases[5, 6].
It is promising to identify the common components of two pathologies – COPD and T2DM – in order to reveal potential targets of drugs that could simultaneously affect the common pathogenetic links of comorbid pathology. Clinically similar phenotypes of patients suffering from T2DM and COPD have created prerequisites for determining mutations that form a particular picture of diseases and susceptibility. Moreover, the simultaneous presence of several mutations contributes to faster disease progression, severe outcomes, and complications. The detection of gene mutations involved in the common pathogenesis of T2DM and COPD will contribute to applying of personalized pharmacotherapeutic management of both diseases. The determination of a set of mutations associated with severe and rapid progression of comorbid pathology among the population will allow to identifying risk groups of patients with newly diagnosed T2DM and/or COPD. The component of insulin resistance and leptin resistance can be a link in the pathogenesis of two pathologies.

RESULTS

Currently, many studies are being conducted on the search for associations of single-nucleotide polymorphisms(SNPs) genes with a risk of developing a particular disease [7]. Thanks to the rapid introduction of innovative technologies and the improvement of the polymerase chain reaction (PCR)methodin real time, such studies have become available and are being implemented in general clinical practice[8]. Thus, a clear example of pharmacogenetic typing for personalization of pharmacotherapy is the determination of the SNPs gene for individual dosing of warfarin [9].
However mostchronic diseases do not have a strictly genetically determined nature, and the origin and developing of such diseases are explained by the polygenomic nature of pathogenetic processes, which, in turn, can form the clinical type of pathological manifestations. A significant contribution is made by the individual characteristics of the patient's organism, especially in comorbid pathology. Moreover, combinations of gene mutations distort the pharmacological effects of prescribed drug therapy, or lead to its absolute ineffectiveness. Nowdays medical practitioners have an opportunity to gain the pharmacogenetic information from specified recourses such as Pharmacogene Variation Consortium [https://www.pharmvar.org/] and Clinical pharmacogenetics implementation consortium [https://cpicpgx.org/]. The data on these portals is in updating in conformity with contemporaneous clinical researches.
It is known that the so-called average «inefficiency» of prescribed pharmacotherapy in many socially significant chronic non-communicable diseases can reach 75%. For example, from 10 to 30% of patients have a variable pharmacological response to antihypertensive drugs (ACE inhibitors, beta-blockers), up to 50% of patients respond differently to taking antidepressants. Inadequate effectiveness of drugs used for broncho-obstructive pathologies and type 2 diabetes mellitus reaches 40% [10]. When these two pathologies are combined, the effects of prescribed pharmacotherapy can be unpredictable.
Therefore, there is a need for a comprehensive assessment of the contribution of mutations of target genes for drug exposure, which can be involved in the pathogenetic process of COPD andT2DM [11-13].
Two most studied functional SNPs genes of ADRB2 (β2-adrenergic receptor) are rs1042713 (Arg16Gly, 46GA) and rs1042714 (Gln27Glu, 79CG). Studies have shown that these polymorphisms mediate a wide range of effects due to the regulation of vascular reactions, the functioning of the pulmonary, endocrine and central nervous system (CNS). The polymorphism of the β_2-adrenergic receptor geneis essential for explaining the mechanism of simultaneous occurrence of COPD and T2DM [14]:participating in the relaxation of bronchial smooth muscle [15] and insulin secretion[16]. Another SNP ADRB 2 gene polymorphism(R16G) correlates with COPD severity, glucose tolerance, and insulin sensitivity in postmenopausal obese women [17]. SNPS (rs1042714 C79G, Gln27Glu) encodes a beta-adrenergicreceptor that provides vasodilation and bronchodilation, as well as increasing heart rate and force of contraction. ADRB2 is a target for agonists in the treatment of asthma and blockers in the treatment of hypertension.ADRB2 is involved in the control of glucose homeostasis, as it inhibits the release of histamine by mast cells, increases the releaseof insulin into the blood and activates

glycogenolysis. In variant 27Glu, sensitivity to agonists is increased and hyperinsulinemia occurs, while in variant 27Gln, sensitivity to agonists and of insulin production is reduced [18].
In the conducted studies, the association of Arg16Gly and Gln27Glu polymorphisms of the ADRB2 gene with an increased risk of obesity, abdominal obesity, and obesity caused by a high-carbohydrate diet was confirmed [19].
Adrenoreceptors as they belong to the sympathetic nervous system (SNS), directly depend on its functional state. It was found that an excessive increase in the activity of the sympathetic nervous system is observed in increased insulin resistance (IR).SNA override in IR is associated with reduced production of nitric oxide (NO) [20]. Researchers have noted that SNP e*NOS3* C786T gene is associated not only with the regulation of vascular tone – vasodilation, but also the tone of the bronchi.
It is no coincidence that the risk of developing comorbid pathology of bronchial asthma and hypertension in comparison with isolated bronchial asthma is 2.4 times higher in carriers of the T -allele polymorphism eNOS3 786C/T [21]. On the other hand, the study found a higher risk of COPD with the carrier of the C-allele [22].
The common pathogenetic link that unites the functioning of these polymorphic genes in T2DMand COPD is IR, leading to an increase in body weight, which negatively affects the course of both diseases and reduces the effectiveness of pharmacotherapy. Excess adipose tissue promotes increased insulin production and hyperinsulinemia, which, in turn, leads to a decrease in the number of insulin receptors in peripheral tissues and insulin resistance. Normally, leptin, regardless of the effect of insulin, increases the utilization of glucose by peripheral tissues and the oxidation of fatty acids in the liver, increases the sensitivity of peripheral tissues to insulin and reduces its secretion by beta cells of the pancreas.
Leptin is a hormone of adipose tissue that regulates energy, neuroendocrine, and metabolic processes in the body. It serves as a clinical and laboratory risk markerT2DM [23-24]. Leptin resistance, including through mutation of the leptin receptor, and increased leptin levels can account to the T2DM, to the functioning of the respiratory system[25]. There is an increasing interest in the functioning of leptin receptors in the lung tissue. Leptin performs its biological function by binding to the leptin receptor, which is present in many tissues, including the pulmonary epithelium. Leptin is mainly secreted by adipocytes, but it is also expressed in alveolar macrophages and lung tissue epithelium. While leptin was originally identified as a satiety signaling molecule that regulates food intake and energy expenditure, today it is considered a pluripotent protein that is involved in a wide range of body functions, including the inflammatory response and angiogenesis. For example, leptin has been shown to induce cytokine production of monocytes / macrophages and increase the cytotoxicity of natural killers. Leptin plays a rolein systemic inflammation in COPD. It was found that the bronchial expression of leptin increases in COPD, and the pulmonary epithelium contains an active leptin receptor[26-27].
SNPin the leptin receptor gene (*LEPR*) were associated with a decrease in forced expiratory volume (FOV_1) in COPD patients, indicating that leptin receptor gene polymorphisms may be associated with insufficient control of bronchial obstructive diseases [28].There is data determining the significance of some SNPs for example, beta-receptor mutations in the use of bronchodilators and glucocorticoids [22]. However, none of the published studies have studied the effect of polymorphic genes of endothelial nitric oxide synthase, adrenoreceptors and leptin receptors on the course and pharmacotherapy of comorbid condition COPD and T2DM.Studying SNPs.LEPR Gln223Arg (rs1137101) ADRB2 Arg16Gly (rs1042713) Gln27Glu (rs1042714). One study conducted on patients without diabetes (Brazil, Japan) found the following associations [29]: SNP LEPR (Gln223Arg) - and NSAIDs ADRB2 (Arg16Gly) are associated with and potentiate the risk of obesity, especially in male smokers.
The concentration of leptin is increased in both COPD and T2DM. However, in comorbid patients, changes in the balance between leptin and pro-inflammatory cytokines are more persistent and pronounced. However, no similar studies were conducted among patients with T2DM.Low sensitivity to leptin in preexisting insulin resistance can serve as a target for pharmacological management both inCOPD and diabetic patients. The study of IR in patients with arterial hypertension and COPD has showed high adipokine (increased leptin and reduced level of adiponectin along with mutations of leptin-binding receptor) and cytokine (increasing the concentration of mediators of inflammation) activity of adipose tissue [30].
It has been found that gene polymorphisms contribute to the formation of individual differences in response to pharmacotherapy in smokers, which could lead to more targeted actions against smoking. It is very promising to study the influence of SNP on the effectiveness of antidiabetic pharmacotherapy and consider them. They can be used for predicting the outcome of the disease and further complications [31].
In the study of the contribution of polymorphic genes to the assessment of the effectiveness and sugar-lowering therapy, the main focus is on gene mutations, the participation of which in the pathogenesis of

T2DMhas been proveno with a high degree of probability. For example, the polymorphism of PPARG Prol2Ala gene is responsible for the high effectiveness of the effect of rosiglitasone on glycemic control.It is hypothesized that GLP-1R is a t149m gene that is responsible for the effect of natural GLP-1 (a glucagon-like peptide – 1-the main one of the incretins) and contributes to the response to the use of exogenous GLP-1 agonists [32]. One of the most explored pharmacogenetic properties is metformin pharmacokinetic variations [33], but there are many other options likely to change the pharmacological response to the drug.

CONCLUSION

Thus, the «failure phenotype» and a «response phenotype» [34-35]to pharmacotherapy in comorbid pathology is a way to individualize drug prescriptions, reduce the toxicity of therapy and polypharmacy in comorbid conditions (COPD and T2DM).

Current research in the field of studying genetically determined risk factors and predisposition to T2DMCOPDhas significant limitations and a very small number of studies devoted to the influence of polymorphic genes on the effectiveness of prescribed pharmacotherapy. Nevertheless, the identification of «response phenotypes» and «failure phenotypes» of patients with comorbid pathology is extremely promising and justified [36]. This approach enables to predict the effectiveness of drug therapy in this patient and avoid the consequences of a therapeutic strategy of «treatment till failure», when insufficient disease control leads to a deterioration of the patient's condition and this is registered post factum. This, in turn, may lead to the need to intensify therapy, which is sometimes impossible due to poor drug tolerance, age – related features and deep structural and functional changes that occur as a result of disease progression.

CONFLICT OF INTEREST

None

SOURCE OF SUPPORT

Nil

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