Review Paper

FEATURES OF GENETIC POLYMORPHISM IN POPULATION WITH DIABETIC NEPHROPATHIA: LITERATURE REVIEW

Abstract

The increasing prevalence of diabetes mellitus has led to a growing number of chronic complications including diabetic nephropathy (DN). In addition to its high prevalence, DN is associated with high morbidity and mortality especially due to cardiovascular diseases. It is well established that genetic factors play a role in the pathogenesis of DN and genetically susceptible individuals can develop it after being exposed to environmental factors. DN is probably a complex, polygenic disease. Two main strategies have been used to identify genes associated to DN: analysis of candidate genes, and more recently genome-wide scan. Great efforts have been made to identify these main genes, but results are still inconsistent with different genes associated to a small effect in specific populations.

Key words: diabetes mellitus; nephropathy; genetics; genetic predisposition, population, polymorphism.

1. INTRODUCTION

Type 2 diabetes mellitus (DM2) is the most common endocrine disease, which is one of the most acute medical and social problems, as it leads to early disability and increased mortality among the population due to the development of various complications [4, 7, 23, 35]. Currently, more than 285 million people in the world suffer from diabetes, in 90% of cases it is type 2 diabetes. There are more than 3 million people with diabetes in Russia, 2.8 million of them with type 2 diabetes. According to WHO forecasts, by 2025 the number of patients with diabetes in the world will increase to 435 million people [2-17, 20]. According to the frequency of disability and mortality, diabetes mellitus is on the 3rd place after cardiovascular diseases and oncologic pathology. Type 2 diabetes is considered a “non-infectious epidemic” [3].

With an increase in the life expectancy of patients with diabetes mellitus (DM), diabetic nephropathy (DN) is becoming an increasingly urgent problem in a series of late complications of diabetes, causing early disability and mortality. A complex issue of diabetology is kidney damage in patients with type 2 diabetes. It has been established that in patients with newly

diagnosed type 2 diabetes, microalbuminuria (MAU) is detected in 15-40% of cases, proteinuria - in 7-10%, uremia - in 1%, which reflects the difficulties of timely diagnosis of type 2 diabetes [1]. Other forms of chronic kidney disease (CKD) can progress under the mask of DN in type 2 diabetes: renal artery stenosis, urinary tract infection, interstitial nephritis, contrast-induced nephropathy, tubulo-interstitial fibrosis and others [2].

As is known, the development of DN is the result of exposure to metabolic and hemodynamic factors. With the same glycemic control and the duration of the disease, DN can have different periods of occurrence and rate of progression in different patients, which made it possible to suggest a significant modulating effect of genetic factors [5, 12, 14].

2. ETIOLOGY AND RISK FACTORS

Diabetic nephropathy (DN) is one of the most formidable vascular complications, the main cause of the development of terminal renal failure. Mortality from uremia in type 1 diabetes reaches 30-50% [7, 8]. Currently, patients with diabetes are in the first place among patients who need treatment with chronic hemodialysis [6, 9, 10].

2.1. Risk factors

The onset and progression of diabetic nephropathy cannot always be explained by traditional risk factors such as hyperglycemia, arterial hypertension or dyslipidemia. It is known that even with ideal compensation characteristic diabetic patients form characteristic lesions in the kidneys [19, 28]. On the other hand, there are cases when patients with long-term decompensation of diabetes can experience only minor changes in the kidneys and, therefore, we can assume the existence of other equally important factors in the development of vascular complications, in particular genetic factors [13, 37].

Currently, thanks to the development of molecular research methods, about 200 tests have been developed that allow the identification of hereditary predispositions to various diseases [11].

2.2. Genetic mutation and its role in DM

The development of molecular genetic methods in modern biology makes it possible to reveal in detail the pathological-biochemical causes of the emergence of diseases (congenital, acquired), to use them in diagnostics and to promote new methods of correction in medical practice. The “genetic markers” of diabetes mellitus have shown that a number of diseases can be inherited, and in some of the population there are prerequisites for the occurrence of a disease [15, 30].

Genetic polymorphism actually occurs as a result of replacing nucleotides with another in different parts of the human genome: introns, exons, and other DNA segments and can be caused by deletion, duplication, triplication, and translocation. This determines a huge number of gene differences [22, 27, 29].

Modern achievements of human genetics indicate the importance of genetic factors in determining the level of health of the population.

It is shown that a number of diseases can be inherited, and a part of the population has prerequisites for the occurrence of a particular disease. The genes and their protein products that are responsible for the development of such diseases were discovered. In laboratory practice, they are sometimes called "genetic markers" [17, 19]. The study of such markers makes it possible to identify groups of various risk of developing diseases, and in particular, diabetes. Such an approach can simplify the early diagnosis of the disease, before the onset of the main clinical features [40].

More than 30 thousand genes have already been identified on the physical map of the human genome, about 10–11 thousand have been studied functionally [16, 18, 31]. There is a growing list of hereditary diseases for which molecular genetic diagnostic methods can be used [21, 25]. This enables the development of methods for the prevention of these diseases [7].

By its nature, T2DM is a genetically determined disease with a polygenic type of inheritance. Today, due to the active introduction of the technological advances of modern medical science into clinical practice, in particular, molecular genetic analysis methods, it becomes possible to develop approaches to the prevention and preclinical diagnosis of diabetes mellitus based on an understanding of the molecular basis of its etiology and pathogenesis [20, 33].

Genetic predisposition to diabetes is familial, and often with concomitant obesity. A number of detected polymorphisms in genes is a predisposing risk factor for the development of type 2 diabetes. The products of these genes (proteins) are regulators of glucose metabolism. The structure of proteins encoded in the genes is mediated by those responsible for glucose homeostasis. Some polymorphisms in these genes can lead to disruption of the normal glucose metabolism. For example, polymorphism in the ADAMTS9 gene leads to a decrease in the sensitivity of peripheral tissues to insulin, and increased expression of the TCF7L2 gene product leads to impaired glucose tolerance and is mediated to a decrease in insulin secretion [22, 36]. The KCNJ11 and KCNQ1 genes contain information about the structure of proteins, mediated by participating in the regulation of insulin secretion. Disruption of the structure of these proteins (version 23K of the KCNJ11 gene) leads to a decrease in insulin release with an increase in glucose concentration [22].

2.3. Association between DM and HLA system

In assessing the possibility of the development of diabetes mellitus, a study of polymorphisms in the HLA (human leucocyte antigens) system has a definite role. Histocompatibility antigens (HLA-complex) - a human system consisting of a complex of genes and their products (proteins) that perform various biological functions, and first of all, provide genetic control of the immune response and the interaction between cells that implement this response [23, 25].

The HLA genes of the second class include several dozen genes found in humans. HLA class II genes are located on B-lymphocytes, activated T-lymphocytes, monocytes. These cells produce proteins with certain properties that are necessary in regulating the recognition of foreign molecules [23, 34].

In the study of the alleles of a number of HLA genes, especially with the frequency of occurrence of HLA genes of the second class, a relationship was found between their presence and an increased risk of the occurrence of such diseases as diabetes mellitus and autoimmune diseases. It was found that part of the allelic variants of the HLA class II genes are associated with an increased risk of developing type 1 diabetes mellitus [25, 31].

Three genes, DQA1, DQB1 and DRB1, belong to the HLA class II genes that have the greatest clinical significance. DQA1, DQB1 and DRB1 are the so-called genes encoding class II tissue compatibility proteins – DQ and DR. Many people with diabetes are carriers of some HLA-DR3 and HLA-DR4 alleles. Since diabetes is a disease with a genetic predisposition, the study of combinations of these genes is a method of preliminary assessment of the possibility of the development of this disease [18, 35, 36].

Molecular biological methods for diagnosing diabetes mellitus are constantly being improved and introduced into clinical practice [30].

3. GENOTYPE OF DM AND POLYMORPHIC MARKERS

From a molecular genetic perspective, type 2 diabetes mellitus is not well understood. The overwhelming number of studies on the role of various candidate genes in the formation of T2DM and its complications have been carried out abroad [32]. In the Russian Federation, only a few papers are devoted to molecular genetic aspects of type 2 DM [28]. For instance, according to S.V. Berstneva et al., genetic aspects of diabetic nephropathy in patients with type 2 DM was studied with its frequency, which was that alleles and genotypes distribution. They identified the association of polymorphic markers I/D of ACE gene, M234T of AGT gene, T-786C of NOS3 gene, and Lys198Asp of EDN 1 gene in patients with 2 type DM with a high risk of developing

diabetic nephropathy. In results and their discussion, association between the D-allele carriage (genotype ID and DD) of the ACE gene and diabetic nephropathy in patients with type 2 diabetes has been identified [26, 39].

The obtained results are consistent with the data of domestic and foreign authors, who showed that the D-allele carrier is an independent risk factor for DN in patients with diabetes type 1 and type 2 in different ethnic groups [3]. Significant association of the I/D ACE gene with the risk of end-stage renal failure in patients with type 2 diabetes in the Asian population were showed in a data from meta-analysis published in 2011 [4]. However, in the study which was conducted over Moscow population, there were no found an association of this polymorphic marker with the development of DN and CKD in patients with type 2 diabetes was obtained [5].

A comparative analysis of the frequency distribution of alleles and genotypes of the M235T polymorphism of the AGT gene carried out by the authors who did not reveal significant differences in patients with and without DN in the examined population [33]. As mentioned above, the literature data on this issue are rather contradictory and probably depend on the ethnic characteristics of the sample. According to some authors, synergism of the ACE and AGT genes: a joint analysis of the markers of the ACE gene and M235T of the AGT gene indicated a predominance of more severe kidney damage in individuals with the TT genotype with their U and DD genotypes. Based on this, it was concluded that the TT genotype has a modulating effect on the negative role of the D allele in the progression of renal pathology [37], but this is not confirmed in all publications. In our study, the association of the indicated genetic polymorphisms with DN in the groups of examined patients was also not detected.

In the Mexican population, it would be important to study the association of the ELMO1 and TJP1 genes with diabetic nephropathy (determinants of filtration barrier homeostasis), given that they are polymorphic markers in this population, and these have already been established as risk markers for renal diseases [16, 17]. At the level of carbohydrate metabolism regulators, the ATXN2 gene is also associated with diabetes and determines the filtration rate (18,19). In this sense, MAGI1gene is a prospective candidate. This gene is involved in glucose homeostasis and is part of the cytoskeleton podocyte. The c.12345C>T variant is polymorphic and is associated with an elevated fasting glucose level, which determines the progression of kidney damage, for these reasons it may be due to DN [20]. It would be worthwhile to pick up the DRB1*1502 allele from the MHC class II genes, which in Mexican has long been established that the population is associated with the terminal stage of renal failure and to analyze the connection with albuminuria (21). Given the genetic diversity of the Mexican population and the complexity of type 2 diabetes, it is necessary to look for more candidate genes that explore the risk of developing diabetic nephropathy [40].

In the European population, the detectability of the TT, TC and CC variants of the promoter in position 786 of the N0S3 gene varies considerably: 29.9-40.6%; 41.3-52.3% and 13.5-17.8%, respectively [7].

A molecular genetic study of the polymorphic variants of four genes was carried out in the Azerbaijani population by Sardarly F.Z. et al., c-233+8274C>T g.4682G>A, and adiponectin gene ADIPOQ (g.93054571A>G) (rs4994).

It can be concluded that the patients with DM in Azerbaijani nationality showed a high incidence of the AG genotype (62.5%) leptin gene (relative risk (RR)=2.50 (1.09-5.72)), GG genotype (100%) of the gene TNF-α (RR=20.71 (1.08-396.39)), AA genotype (97.2%) of the adiponectin gene (RR=3.28 (0.52-20.51)), (RR=20.71 (1.08–396.39)) and the CC genotype (97.0%) of the polymorphic Pro12Ala marker of the PPARG2 gene (RR=1.23 (0.23–6.47)). In patients with type 2 diabetes of the Azerbaijani population, single-nucleotide polymorphism rs1800629 of the FNO-α gene should be considered as a marker for the development of diabetic nephropathy [24].

Bondar I.A. et al. have studied the associations of the polymorphic markers rs7903146 of the TCF7L2 gene and rs1801282 of the PPARG Pro12Ala gene with type 2 diabetes mellitus (SD2) in the Novosibirsk region. The study demonstrated that the carrier of the 12Pro allele of the polymorphic rs1801284 marker of the PPARG gene and the T allele of the polymorphic rs7903146 marker of the TCF7L2 gene is associated with the development of T2DM in the Novosibirsk Region. The combination of risk genotypes of the polymorphic markers rs1801282 of the PPARG gene and rs7903146 of the TCF7L2 gene in patients with type 2 diabetes in the Novosibirsk region reaches 74.4% [12].

Using genetic markers, you can identify groups of people with a risk of developing diabetes. This is an important step in the diagnosis of diabetes, because in combination with traditional methods (determination of glucose, glycated hemoglobin, hormones, detection of autoantibodies) leads to improved diagnosis of the disease before the manifestation of pronounced clinical symptoms of the disease and helps to develop human behavior and take preventive measures [38].

4. CONCLUSION

In recent years, genetic aspects of the development of type 2 diabetes, its complications and associated metabolic disorders in many populations have been actively studied. Currently in French (Sladek et al, 2007). Finnish and Swedish (Saxena et al., 2007), British (Zeggini et al, 2007). Icelandic (Steinthoarsdottir et al, 2007), Chinese (Tsai et al, 2010), Japanese (Yama ucli

et. al, 2010) and other populations, groups of polymorphic genetic markers associated with the development of type 2 diabetes were established.

However, in the Uzbek population, genetic markers of type 2 diabetes with DN were not studied. Despite the understanding of the significant role of hereditary factors in the formation of T2DM, the genetic component responsible for its development has not yet been fully established. Obviously, this is due to its complex nature, as a multifactorial disease, that is, with the need to study the role of a large number of polymorphic genetic markers and their interactions, as well as the relationship between hereditary predisposition and environmental factors. A variety of genetic markers characteristic of different population groups confirms the special significance of the ethnic component for identifying hereditary risks, which determines the relevance and need for a detailed, comprehensive study of the genetic basis of type 2 diabetes. Therefore, it was interesting for us to study the genetic predispositions of DN in type 2 diabetes in the Uzbek nation.

CONSENT

It is not applicable.

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