



Diabetic Nephropathy and the Relationship between Diabetic Nephropathy and Genetic Polymorphisms

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Authors' contributions

This work was carried out in collaboration between all authors. Authors EMA and FAE wrote the first draft of the manuscript. Author AO revised the information related to genetic polymorphism and author SD revised the information related to diabetic nephropathy. Authors EMA and FAE managed the literature searches. All authors read and approved the final manuscript.

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ABSTRACT

Aims: The aim of this manuscript is to review the pathogenesis of diabetic nephropathy and the relationship between diabetic nephropathy and genetic polymorphisms.

Definition: Diabetic nephropathy is one of the kidney diseases that progresses to harm the capillaries in the glomeruli of the kidneys.

Characterization: Diabetic nephropathy is characterized by diffuse scarring of the glomeruli and nephrotic syndrome.

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Reason: The main reason for diabetic nephropathy is proposed as long-lasting diabetes and in many developed countries it is the main cause of dialysis. Diabetic nephropathy is categorized as one of the microangiopathic complications of diabetes. Several studies present that there is a correlation between diabetic nephropathy and genetic polymorphisms.

Conclusion: The genetic susceptibility may be an important factor in the development of diabetic nephropathy. Several genes, such as TNF- α , eNOS, GLUT1, ACE, FABP2, ADRB2 and ADIPO with some allelic polymorphisms were proposed to be important in the pathogenesis of diabetic nephropathy. In addition, the angiotensinogen M235T and ANP polymorphisms were proposed to be associated with diabetic nephropathy development, but following studies couldn't be able to replicate these observations. On contrary to several successful association studies, there are also numerous contradicting observations too. As a result of this, the relationship between diabetic nephropathy and genetic polymorphisms should be studied in detail for different populations. But while conducting such studies the genetic heterogeneity in populations should be taken into account and also the number of the cases studied should be as high as possible.

Keywords: Diabetes mellitus; diabetes; diabetic nephropathy; genetic polymorphisms.

ABBREVIATIONS

<i>ACE</i>	: <i>Angiotensin-converting enzyme</i>
<i>ADIPO</i>	: <i>Adiponectin gene</i>
<i>ADRB2</i>	: <i>Adrenoceptor beta 2</i>
<i>ANP</i>	: <i>Atrial natriuretic peptide gene</i>
<i>CVD</i>	: <i>Cardiovascular diseases</i>
<i>DM</i>	: <i>Diabetes mellitus</i>
<i>DN</i>	: <i>Diabetic nephropathy</i>
<i>EPHX2</i>	: <i>Epoxide hydrolase 2</i>
<i>FABP2</i>	: <i>Fatty acid binding protein 2</i>
<i>GFB</i>	: <i>Glomerular filtration barrier</i>
<i>GLUT1</i>	: <i>Glucose transporter 1 gene</i>
<i>LADA</i>	: <i>Latent autoimmune diabetes in adults</i>
<i>NDRD</i>	: <i>Nephropathy of non-diabetic origin</i>
<i>PVAT</i>	: <i>Properties of perivascular adipose tissue</i>
<i>RAGA</i>	: <i>Receptor for advanced glycation end products</i>
<i>TNF</i>	: <i>Tumor necrotic factor</i>
<i>VDR</i>	: <i>Vitamin D receptor</i>

1. INTRODUCTION

Diabetes mellitus (DM) is a combination of several metabolic disorders causing chronic lifelong problems triggering sustained high blood glucose levels. It is derived from the Greek word "diabetes" having the meaning of "Siphon-to pass through", where glucose is found in blood as well as in the urine. On the other hand "mellitus", which is originated from a Latin word, means honeyed or sweet. Adding "mellitus" to word "diabetes" is due to finding elevated levels of glucose in blood and urine. DM is the abbreviation used for diabetes mellitus. DM was known in the seventeenth century as "Passing evil" [1].

Today, it is a well-known issue that insulin is the hormone, which is responsible for controlling blood glucose level and it is secreted by pancreas [1].

2. PANCREAS

The pancreas was recognised for European population by an ancient Greek surgeon and anatomist known as Herophilus (335-280 BC) [2]. But several years after the recognition of pancreas, it was named by another ancient Greek anatomist called Rufus of Ephesus, which literally means "all-flesh" most probably due to its composition [3]. It was just in 1889, when Oskar Minkowski discovered that the removal of the pancreas from a dog made it to be diabetic. Insulin was later found by Charles Herbert Best and Frederick Banting in 1921 [4].

The pancreas is one of the endocrine organs, which is around stomach area, particularly on the left hand side of the upper abdomen.

Anatomically three main areas can be defined on pancreas, namely the head, the body and the tail. The head part mainly fills the duodenum's curve and the tail is close to the spleen, where the body is the area between the head and the tail, in which the superior mesenteric artery and vein flow through. The splenic vein flows into the head and the body section of pancreas, where the superior mesenteric artery and vein flows firstly into the head section of the pancreas [5].

The tissues, which form the pancreas have both exocrine and endocrine roles. In addition, this separation is observable as they are examined

by any type of microscope, too. The tissue presenting the endocrine function are observed as slightly coloured cell groups after staining, known as pancreatic islets, which are also called Islets of Langerhans. In each acinus, tiny ducts are surrounded by the cells serving the secretion function. Due to such a role, the secretory cells contain observable zymogen granules [6,7].

The tiny ducts surrounded by the cells serving the secretion function are then run into greater ducts in the lobule, and lastly into interlobular ducts. These ducts are surrounded by one layer of cell, which is known as columnar cells. The size of the pancreas varies considerably, linked to the growth of the parts of the pancreas during the embryonic period [7].

It is known that the section of the pancreas serving an endocrine role consists of around 3 million cells known as pancreatic islets. They can be classified by their secretion [8,9].

- α (alpha) cells: Produce glucagon, which is responsible to increase blood glucose level,
- β (beta) cells: Produce insulin, which is responsible to decrease blood glucose level,
- δ (delta) cells: Produce somatostatin, which controls alpha and beta cells and
- γ (gamma) cells or PP cells: Produce pancreatic polypeptide.

Utmost cells having endocrine function are known to have direct interaction with a vessel carrying blood.

3. INSULIN

The term insulin is rooted from the Latin word "insula", which means island. Insulin is one of the hormones synthesised in the human body having peptide structure. As it was mentioned previously, β cells are the cells, which are responsible for the production of insulin in the pancreas. It has a role especially in carbohydrate metabolism by directing the glucose absorption through the blood to skeletal muscles. In addition, it takes an important role in lipid metabolism, in which directing glucose to form lipids to be stored in adipose tissues. Furthermore, the insulin is also important in inhibiting gluconeogenesis in the liver [10,11]. Some different mechanisms take important roles in keeping the glucose level of blood in healthy ranges. Production of glucagon and insulin,

which are secreted by the pancreas are one of the mechanisms for managing the glucose levels of blood [10,11]. Glucagon is known to be secreted by the α cells of pancreas to increase the low glucose level of blood, whereas insulin is secreted by the β cells to decrease the high glucose level of blood [12].

The over-all effect of insulin on the metabolism could be:

- Regulating mostly the glucose uptake of adipose and muscle tissues.
- Directing an increase in protein synthesis and the replication of DNA by controlling absorption of amino acids.
- Altering the activities of several enzymes.

It is known that insulin is the major hormone that adjusts the intake of glucose from the blood not only into muscle and liver, but also adipose tissue cells as well. Thus, lack of insulin production in the body or the insensitivity of insulin receptors against the insulin produced in the body is known to play a key role in any types of diabetes [13].

4. DIABETES

Diabetes may appear mainly for two reasons; due to the failure to produce enough insulin for body cells and fail to respond to the insulin produced by pancreas accurately. The two main types of diabetes mellitus (DM) are type 1 and type 2 DM [14].

4.1 Diabetes Mellitus Type 1

Type 1 DM is appeared due to the absence of insulin in the blood as a result of a damage in β cells, which are responsible for producing insulin in the pancreas. The type 1 DM is an autoimmune disease, in which the cells responsible for immunity attack and destroy the β cells. In type 1 DM, the destruction of β cells could appear in years, but symptoms start usually to progress in a shorter period of time. Although type 1 DM may develop at any age, it usually appears in young adults and children. In the past, type 1 DM was also known as juvenile diabetes, since it is common in children. It is also known as insulin-dependent DM [15,16].

Blurred vision, weight loss, polydipsia and polyuria are some of the symptoms of an obvious hyperglycemia. In addition, deficiency in development and vulnerability against some infections may also be observed in chronic

hyperglycemia. On the other hand, the main long-term problems of DM are mostly linked to the macrovascular complications, especially cardiovascular disease. Because it is known that DM increases the risk of cardiovascular diseases; in addition, the risk of peripheral vascular and other "macro vascular" diseases are also increased [16].

4.2 Diabetes Mellitus Type 2

Type 2 DM is characterized by insulin resistance. A decreased secretion of insulin hormone may also accompany with the insulin resistance. The decreased sensitivity of cells to insulin is accepted to be a result of decreased sensitivity of the insulin receptor. Type 2 DM is the most common type of diabetes mellitus that is primarily related to lifestyle factors and genetics [17].

It is a very well-known issue that several parameters related to the lifestyle have a great influence on the development of type 2 DM, such as urbanization, stress, lack of physical activity and obesity. Nutritional parameters are also known to affect the risk of type 2 DM development. Several studies show that consuming drinks high in sugar are found to be related to a high risk of type 2 DM development. On the other hand, it was also proven that consuming foods high in trans-fatty acids and saturated fats, where monounsaturated fat and polyunsaturated fat are low, also increase the risk. In addition, excluding exercise from daily life found to cause about 7% of the type 2 DM cases [17].

4.2.1 The reason of type 2 diabetes

The most common type of DM is known to be type 2 DM and it is proposed to be triggered by a combination of several parameters, such as a disorder that cause liver, adipose and muscle cells not to recognise insulin properly and the insulin resistance. Type 2 DM develops when the body can no longer produce enough insulin to compensate for the impaired ability to use insulin. Symptoms of type 2 DM may develop gradually and can be subtle. Some people with type 2 DM remain undiagnosed for years. Type 2 DM develops most often in middle-aged and older people, who are also overweight or obese [18-20].

4.2.2 Genetic susceptibility

Type 2 DM is proven to be significantly related to genetic variations, which may increase the

susceptibility to DM. It is shown that genetic variations may decrease or increase the risk of DM progression. The effect of genetic composition was proven by conducting research on families of different races; in which DM is observed at a high rate and on identical twins [21].

4.2.3 Obesity and physical inactivity

Obesity and inadequate physical activity are found to be highly correlated with type 2 DM progression. When any factors increasing the risk of DM, such as inadequate physical activity and obesity are present, genetic composition play a key role in the risk of type 2 DM development [22].

In addition, if calorie intake is higher than energy expenditure, the resultant obesity may lead to insulin resistance, which is frequently observed in type 2 DM [22-25].

Abdominal obesity in a patient with excessive fat in abdominal area is also the main risk not only for Type 2 DM and insulin resistance, but for cardiovascular diseases (CVD), too [22-25].

Type 2 DM and obesity have a very complicated connection. Although obesity increases the risk of being type 2 DM, there are also some cases where Latent Autoimmune Diabetes in Adults (LADA) develops when the subjects are not obese. Obesity can be accepted to be a precursor in the development of type 2 DM after leading to an insulin resistance. The majority of the scientists emphasize that this relation could be diverse in different types of obesity and type 2 DM [22-25].

4.2.4 Insulin resistance

Visceral obesity can be a key factor in the development of insulin resistance by producing inflammatory cytokines. Such inflammatory cytokines cause an increase in cardiovascular risk especially in the patients, who are accepted to be obese, regardless of their function in insulin resistance [26-29].

Inflammation can be elevated by concurrent nitric oxide deficiency, too. This also reduces the vasodilatory properties of perivascular adipose tissue (PVAT), which leads to oxygen insufficiency, oxidative stress and inflammation. Hyperinsulinaemia and visceral obesity also cause hypertension in arteria. Therefore, in

patients with visceral obesity, a vicious circle probably arises between weight gain, hyperinsulinemia and sympathetic activation [26-29].

5. DIABETIC NEPHROPATHY

Diabetic nephropathy (DN) is one of the kidney diseases that progresses to harm the capillaries in the glomeruli of the kidneys. DN is characterized by diffuse scarring of glomeruli and nephrotic syndrome. The main reason for DN is proposed as long-lasting DM and in many developed countries, it is the main cause of dialysis. DN is categorized as one of the blood vessel complications of diabetes [30-32].

5.1 Signs and Symptoms of Diabetic Nephropathy

In the early stages of diabetic nephropathy, there are usually no symptoms. Symptoms may be seen 5 to 10 years after the starting of the kidney damage. These symptoms, which are also known as late symptoms include swollen legs, itchy skin, loss of appetite, vomiting, a general sickness, headache and severe fatigue [33].

5.2 Causes of Diabetic Nephropathy

The main reason for development of DN is believed to be high sugar level in blood. High blood glucose level results in production of advanced glycation end products and cytokines, which may lead to development of DN [34].

If one or more of the following conditions are present, kidney damage is likely to occur.

- Familial kidney disease history
- Smoking history
- Occurrence of type 1 DM before the age of 20
- High blood pressure
- A weak control of blood glucose level [34].

5.3 Mechanism of Diabetic Nephropathy Progression

It is thought that the progression of DN is related to oxidative stress. There are some mechanisms that induce oxidative stress, such as receptor for advanced glycation end products (RAGE) and NADPH oxidase [35].

Diabetes leads some changes in the metabolism of the body and in the circulation of blood that cause the formation of excess reactive oxygen

metabolites, which are chemically reactive molecules that contain oxygen. An injury in the glomeruli secondary to DM destroys the glomerular filtration barrier (GFB) results in albuminuria. There are three layers in the structure of GFB, which are epithelial podocytes, glomerular basement membrane and fenestrated endothelium. The main function of GFB is to filtrate the blood that enters into glomeruli with a highly selective filtration, so that only very small proteins, small molecules and water can pass through, while albumin can't [36,37].

6. THE RELATION BETWEEN DIABETIC NEPHROPATHY AND GENETIC POLYMORPHISMS

As it was stated previously, several conditions such as high blood pressure, smoking, weak control of blood glucose level and occurrence of type 1 DM before the age of 20 may lead to progression of DN. But the aim of this review is to mainly focus on one parameter, namely genetic polymorphisms, which may potentially be related to DN progression.

Several studies suggested that there is a correlation between diabetic nephropathy and genetic polymorphisms apart from the environmental factors involved. This relation is clearly shown especially for type 1 DM, in which DN is developed in the first 15 years, but the frequency of DN decreases after this period. This proposes that children are more vulnerable to developing DN [38].

The relationship between DN and type 2 DM has not been clearly demonstrated as in type 1 DM, since most patients with type 2 DM possibly die as a result of cardiovascular disease before reaching to an age to develop DN. Numerous studies have shown that there are different genetic risk factors associated with the development of DN in type 1 and 2 DM patients [38].

The significant variability in the prevalence and incidence of DN is important in showing the multigenetic vulnerability to the development of DN. Some genes that are likely to cause DN also known to cause some cardiovascular system diseases, familial hypertension, familial hyperlipidemia and problems in the regulation of blood pressure. Some previous studies have shown that some polymorphisms such as the G894T polymorphism in the eNOS gene [39], XbaI (the G/T polymorphism) in the intron 2 of

glucose transporter 1 (GLUT) gene [40] and the insertion/deletion (I/D) polymorphism in the gene for angiotensin-converting enzyme (ACE) are related with DN [41], nephropathy of non-diabetic origin (NDRD) and hypertension in patients having DM. It has also been confirmed that the G894T polymorphism in the eNOS gene is associated with type 2 DM [42]. But another study showed that the association between eNOS gene G894T polymorphism and DN is failed for Arab population [43].

Angiotensin I converting enzyme has been shown to be a key factor in the progression of arterial hypertension. Polymorphisms in this gene were previously shown to be associated with the high levels of circulating angiotensin I converting enzyme (ACE) levels [44]. Several studies presented that there is a positive association between the ACE D allele and DN [45-48]. On the other hand, the I/D polymorphism in Central European diabetic patients has not been associated with DN [49]. Also, it was previously shown that neither the DD genotype nor the D allele was observed to be associated with DN in Iranian population [50].

Some studies in the Japanese population have examined the relationship between RAGE G1704T and NADPH oxidase p22 phox C242T polymorphisms and diabetic nephropathy development in patients having type 2 DM. The observations in these studies have shown that the combination of RAGE G1704T and NADPH oxidase p22 phox C242T polymorphisms can be useful in determining the risk of DN development in type 2 DM patients [51,52].

In another study, Hameed et al. analysed the association between DN and TNF- α rs1800629 in Indian population and found that TNF- α rs1800629 have strong association with DN [53].

The Ala54Thr polymorphism in the FABP2 gene and Arg16Gly polymorphism in the ADRB2 gene were also proven to have a visible effect on the renal functions in DN patients from Chinese population [54].

Adiponectin (ADIPO) has anti-inflammatory properties and it modulates dyslipidemia and insulin resistance. It was previously shown that

the minor allele (A) in intron 1 (rs182052) of adiponectin gene is associated with DN in an African American population [55]. It was also shown that there is a strong association between the polymorphism rs17300539 G>A in the promoter region of ADIPO gene and DN. It was observed that the A-allele increases the risk for DN. This association was observed to be significant in a population from Denmark, but was not significant in a population from Finland [56].

TaqI (rs731236), ApaI (rs7975232), BsmI (rs1544410) and FokI (rs10735810) are four commonly observed polymorphisms of VDR gene. The relation between these polymorphisms and DN were analysed for several populations from different ethnicities living in different countries and possible relation between TaqI and DN susceptibility was observed for only Asians [57-59].

In addition to some studies showing that genetic polymorphisms may lead to DN, there are several studies proving that some genetic polymorphisms may have a protective effect against DN. For example, a study conducted for Iranian population to observe the association between apolipoprotein E polymorphism and DN showed that especially Apo ϵ 4 allele has a protective effect against DN in DM patients [60].

Ma et al. were examined the association between DN and EPHX2 rs751141 (R287Q polymorphism) for type 2 DM patients from Chinese population. As a result it was observed that especially A allele frequency in EPHX2 rs751141 was considerably lower in DN patients, thus the A allele was concluded to lower the risk for DN. In addition, in the same study a significant association was also found between homocysteine level and EPHX2 rs751141. As a result, it was proposed that EPHX2 rs751141 polymorphism is negatively related to the incidence of DN in Chinese population presenting type 2 DM, which is possibly controlled by homocysteine levels [61]. Table 1 shows a summary of the relation between diabetic nephropathy and genetic polymorphisms.

As it can be seen from the information given above, although several successful association studies are present in the literature, there are

Table 1. The relation between diabetic nephropathy and genetic polymorphisms

Gene	Polymorphism	Population	Relation	Reference
eNOS	G894T	Asian	DN association	[39]
		Arab	No association	[43]
GLUT1	XbaI	Caucasian	DN association	[40]
ACE	Insertion/Deletion	Caucasian	DN association	[41]
		Central European	No association	[49]
	D allele	Brazilian	DN association	[45-48]
		Iranian	No association	[50]
RAGE	G1704T	Japanese	DN association	[51,52]
NADPH oxidase	p22 phox C242T	Japanese	DN association	[51,52]
TNF- α		Indian	DN association	[53]
FABP2	Ala54Thr	Chinese	DN association	[54]
ADRB2	Arg16Gly	Chinese	DN association	[54]
ADIPO	minor allele (A)	African American	DN association	[55]
	prom2 G > A	Denmark	DN association	[56]
		Finland	No association	[56]
VDR	TaqI	Asian	DN association	[57-59]
Apo	Apo ϵ 4 allele	Iranian	Protective	[60]
EPHX2	R287Q A allele	Chinese	Lower the risk	[61]

also numerous contradicting observations, too [56].

In addition to the polymorphisms given above, for example, the initial studies for the angiotensinogen M235T polymorphism, atrial natriuretic peptide gene (ANP) polymorphisms were proposed to be associated with diabetic nephropathy development, but following studies couldn't be able to replicate these observations [56,62-68].

The reason for these contradictions is explained as a reason of the genetic heterogeneity by relatively small gene effects in populations with relatively small number of cases, which is not higher than 200. In addition, it can be seen that most of the studies did not observe functional effects of their associated variants [56].

7. CONCLUSION

The genetic susceptibility may be an important factor in the development of diabetic nephropathy. Several genes with some allelic polymorphisms were proposed to be important in the pathogenesis of diabetic nephropathy. As a result of this, the relationship between diabetic nephropathy and genetic polymorphisms should be studied in detail for different populations. But while conducting such studies the genetic heterogeneity in populations should be taken into account and also the number of the cases studied, should be as high as possible.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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