Chapter

The Risk for the Development of Diabetic Nephropathy: Interplay of Biochemical, Genetic, Nutritional and Lifestyle Factors

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Abstract

The recent unprecedented pandemic COVID-19 has blatantly exposed the healthcare system globally. The increasing rate of mortality and morbidity/co-morbidity were observed due to an interplay of COVID-19 infection with chronic diseases like diabetes, cancers, CVDs, respiratory and mental illness. According to World Health Organization, diabetes kills 1.7 million people annually. The prevalence and incidence of diabetes mellitus, representing >90% of all cases of diabetes and its complications, are increasing rapidly. The International Diabetes Federation has estimated that the number of people with diabetes is expected to rise from 366 million in 2011 to 552 million by 2030 if no urgent action is taken. Diabetes is a leading cause of kidney disease. About one in three adult diabetic patients has kidney disease, that is, diabetic nephropathy. In search for the risk and causes of diabetes and its complications such as diabetic nephropathy, research has now advanced to the molecular level. Genetics, epigenetics, genomics, proteomics, and metabolomics are opening ways to a new and deeper understanding of bodily processes and are providing the tools for more precisely targeted interventions when their function is disturbed. Similarly, tobacco use, physical inactivity, the harmful use of alcohol, and unhealthy diets all increase the risk of developing diabetic nephropathy. This chapter will focus on analyzing recently researched and published biochemical, genetic, nutritional, and lifestyle factors in various populations to ascertain the interplay of a wide variety of modifiable and non-modifiable factors, which will help delay and/or prevent the development of kidney disease in diabetes.

Keywords: diabetes, nephropathy, genetic factors, biochemical factors, nutrition, lifestyle behavior, risk assessment

1. Introduction

1.1 Diabetic mellitus (DM)

Diabetes mellitus (DM) is a global health issue and is on the rise. About 463 million people worldwide have diabetes and 1.7 million deaths are directly attributed

to diabetes each year. The International Diabetes Federation (IDF) estimates that as many as 212 million people, or half of all adults currently living with diabetes, are undiagnosed. Most of these have type 2 diabetes mellitus (T2DM) [1]. Both the number of cases and the prevalence of diabetes have been steadily increasing over the past few decades [2].

DM is a prevalent non-communicable disease worldwide. In most high-income countries as well as middle-income and low-income countries, DM is among the top causes of death [3]. DM is considered a group of metabolic disorders which have multiple etiologies. Chronic hyperglycemia is a characteristic of DM and is related to impaired carbohydrate, protein, and fat metabolism. The etiology of DM is a complex interaction of genetics, biochemical, environmental, nutritional factors, and lifestyle choices [4, 5]. The causes of abnormalities include impaired insulin action or inadequate insulin secretion or both. As a result of chronic hyperglycemia, extensive damage such as abnormal functions and failure of various body organs which especially include blood vessels, eyes, kidneys, nerves, and heart [6].

DM has been classified into four distinctive types [7]:

1. Type 1 diabetes mellitus (T1DM): It leads to a deficiency of absolute insulin due to pancreatic β-cells destruction.

2. Type 2 diabetes mellitus (T2DM): It is a consequence of secretary defects in progressive insulin on the background of insulin resistance.

3. Gestational DM (GDM): It is identified during pregnancy and is not noticeably overt DM.

4. The other types of DM are due to some other reasons which may include genetic defects in insulin action, genetic defects due to abnormal function of pancreatic β-cells, some disorders of the exocrine pancreas, that is, cystic fibrosis, and drug or chemical induction like treatment of organ transplantation or HIV/AIDS.

The risk factors which play a major role in the development of T2DM and the progression of diabetic complications such as diabetic nephropathy (DN) include modifiable behavior risk factors such as unhealthy diet and physical activity which alone is attributed to 1.6 million deaths annually. The leading metabolic risk factor globally is elevated blood pressure to which 19% of global deaths are attributed, followed by overweight and obesity and raised blood glucose [8]. The IDF estimates that as many as 212 million people (or half of all adults) currently living with diabetes mellitus, are undiagnosed. Most of these have T2DM, which is preventable and by knowing the risk score, the chances of developing T2DM can be minimized [9].

1.2 Diabetic nephropathy (DN)

Microvascular complications in DM involve effects on small vessels, arterioles, capillaries, and venules. These complications develop early in the pathogenesis of T2DM and account for morbidity in the form of neuropathy, retinopathy, and nephropathy [10, 11]. The major cause of chronic renal disorder in patients who starts renal replacement therapy is DN [12]. CVD mortality becomes increased in DN patients [13, 14]. The low glomerular filtration rate (GFR) without micro or

macroalbuminuria is observed in 10% of DM and also in type 1 DM and microalbuminuria [15]. A 24-hours urine collection or spot urine measurement of microalbumin may screen microalbuminuria or DN [16]. Urinary tract infections (UTI), hematuria, and exercise may produce falsely elevated urine protein levels. Prevention is the only initial treatment of DN. The development of DN is strongly associated with glucose control like other microvascular complications of DM.

2. Risk factors for the development and progression of diabetic nephropathy

There are various risk factors for developing DM and progression of DN, which include age, gender, obesity, ethnicity, genetics, diet and exercise, abnormal cholesterol level, malnutrition, maternal malnutrition, maternal hyperglycemia, lifestyle and development in childhood, lifestyle in adulthood, physical inactivity, and depression.

2.1 Age

It was generally considered that T2DM patients are above 40 years of age at diagnosis time, but an increased number of children and adolescents are being diagnosed due to increased obesity in childhood. For the incidence of T2DM age is one of the important factors universally. Compared to the western countries DN occurs at lower ages in low- and middle-income countries [17, 18]. An inverse relationship has been observed between potential harm from T2DM and age at diagnosis. The younger you are at the time of diagnosis, the bigger the possible complications such as diabetic nephropathy. As age progresses, it is likely to have multiple medical conditions, including high blood pressure and high cholesterol. That can make it harder to keep the development of T2DM under control. As a result, T2DM can lead to other health problems such as heart disease.

2.2 Gender

Men have double the likelihood of getting T2DM as compared to women. Studies suggested that T2DM is highly prevalent in males than females, while females show high prevalence rates for IGT than males [17, 18]. A noticeable female excess of T2DM was observed in the first half of the last century, but now T2DM prevalence is equal among male and female in most populations, with some evidence of male majority in early middle age [19].

2.3 Ethnicity

A number of sociocultural factors including family history, and environmental factors play a part in developing T2DM, but it is still not clear why people from certain ethnic backgrounds have an increased risk. Various ethnic groups with different lifestyles may account for some of the predisposition to T2DM. The more determinant role may be played by genetic factors. Compared with Individuals of European origin, African-Americans Native Hawaiians, Hispanic/Latino Americans, Asian Americans, American Indians, or other Pacific Islanders are at increased risk for T2DM [20].

2.4 Obesity

One of the thriving predictors of developing T2DM and its complications, such as DN is obesity. Majority of DM that go into the DN are overweight at the time of diagnosis, and they are more expected to have central obesity (fat concentrated around the waist). In different parts of the world, children and women showed higher obesity rates which is associated with the level of insulin and metabolic risk [21].

2.5 Diet and physical inactivity

Excessive susceptibility to DM, mainly through the development of obesity is associated with animal fats and carbohydrates. In the USA and other westernized societies, the main changes in the diet include increased consumption of processed carbohydrates and animal fats while decreased fiber intake [22].

2.6 Malnutrition

Diet should be nutritionally adequate for DM patients. There are various evidence of the strong association between micronutrient deficiencies and risk for DM [23]. The role of undernutrition in the occurrence of type 2 DM in different populations has been established [24].

2.7 Maternal malnutrition

Pregnant mothers are commonly malnourished, due to this reason offspring are exposed to intrauterine growth retardation (IUGR) and compromised metabolic potential during the prenatal period. Maternal malnutrition ultimately results in maternal mortality rate and low birth weight [25].

2.8 Lifestyle and growth in childhood

Growth of malnourished children may result in increased body fat than bone length and muscle mass, it may expose these children to higher risk of developing DM. One of the indications of early malnutrition is stunting and accumulation of fat in the child is indicated by stunting and overweight among children who have been malnourished in early life [26]. Central obesity and type 2 DM as a result of higher body fat percentage were found to be higher in stunted children even at body weight falling within the normal range [27, 28]. Higher frequency of various risk factors which include physical inactivity and overweight were observed in children with positive family history of DM, upper income group, and children living in urban areas. The risk of DM increases in children from lower income group because they have poor nutrient density of diets [29] and those low birth weights were also common in these children. Children from urban areas show low activity levels [30].

2.9 Lifestyle in adulthood

The risk of developing DM is increased in the population, who have a high intake of carbohydrates, as a result of which insulin resistance is developed. An increased oxidative stress is developed as a result of low intake of vitamins and minerals as well as decreased immunity. The dietary pattern of society, in general, favors diabetic

conditions, so-called pro-diabetic. The risk of diabetes would therefore be high in those who are taking lower than average proteins and micronutrients. The levels of toxicities caused by minerals are found higher among diabetic patients as compared to non-diabetics which will certainly cause higher levels of oxidative stress [31, 32]. The incidence of T2DM development decreases in people who are used to physical activity which includes 30 minutes walking or cycling regularly [33].

2.10 Depression

There is a significant association between newly diagnosed DM with depression [34]. Depression affects all aspects of a person's life being a common public health problem. It has been recognized as an important co-morbid condition in DM [35]. Depression frequently co-exists with DM and DM-related complications. Abnormal glucose level and increased rates of DM complications along with disabilities are observed in depressive patients [36].

3. Genetic susceptibility

The high risk of developing DN in T2DM is associated with a positive family history of T2DM and/or DN. Genetics is an important factor for the predisposition of South Asians to T2DM and its complications. Pathogenesis of DN depends on genetic factors as well and genetically susceptible individuals can develop DN after environmental interaction DN is a complex, polygenic disease. For the identification of associated genes for the development of DN, two main strategies have been used which include analysis of candidate genes and more recently genome-wide scan [37].

For the identification of these main genes efforts have been made, but due to different genes associated with small effects in the specific population, results are inconsistent. Detection of the individual at high risk of developing DN and understanding the pathophysiology of DN is possible after the identification of candidate genes. Identification of those genes associated will allow the recognition of individuals at high risk and an understanding of mechanism and progression of DN is also possible. Disease burden and mortality can be reduced by providing earlier and more aggressive therapies to the individual at high risk. Advances in pharmacogenetic research may help treatment choices by selecting renoprotective drugs according to individual haplotypes [38–40]. Candidate genes involved in different metabolic functions of the body, responsible for DN development in type 2 DM are illustrated in **Table 1**.

3.1 Renin angiotensin aldosterone system

Blood pressure and water (fluid) balance is being regulated by the hormonal system known as renin-angiotensin system (RAS) or the renin-angiotensin-aldosterone system (RAAS). Juxtaglomerular cells in the kidneys secrete renin directly into circulation when blood volume is small. The angiotensinogen which is being released by the liver is converted into angiotensin I by plasma renin. ACE which is found in the lungs converts angiotensin I into angiotensin II. Blood vessel constriction is caused by angiotensin II which is a potent vaso-active peptide, it results in high BP. It also stimulates the secretion of the hormone aldosterone from the adrenal cortex. Aldosterone causes the reabsorption of sodium and water into the blood by the kidney tubules. It increases the fluid volume in the body, which increases BP [41].

Gene and biological system		Symbol	Location
Cytoskeleton gene	Caldesmon	CALD	7q35
	Beta-adducin	ADD2	2p14
Glucose metabolism	Aldose reductase	AKR1B1	7q35
	Glucose transpoter-1	SCL2A1	1p35
	Receptor for advanced glycosylation end-products	RAGE	6p21.3
Growth factor	Transforming growth factor-B1	TGFB1	19q13.1
	Transforming growth factor-B, receptor I–III	TGFBR1/2/3	9q22, 3p22, 1p33
	Vascular endothelial growth factor	VEGF	6p12
Inflammation	Intracellular adhesion molecule-1	ICAM1	19p13.3
	Regulated upon activation, normal T-cell expressed and secreted gene receptor	CCR5	3p21
	Interleukin-I	IL1B	2p14
Lipid metabolism	Apolipoprotein	APOE	19q13.2
	Adiponectin	ADIPOQ	3q27
	Peroxisome proliferator activated receptor gamma	PPAR	3p25
Oxidative stress	Superoxide dismutase 1 and 2	SOS1/2	21q22, 6q25.3
	Haptoglobin	HP	16q22
	Paraoxonase 1 and 2	PON ½	7q21–22
	Catalase	CAT	11p13
	Glutathione peroxidase 1	GPX1	3q21.3
Renin-angiotensin system	Angiotensin-converting enzyme 1	ACE 1	17q23
	Angiotensinogen	AGT	1q42–43
	Angiotensin II receptor, type 1 and 2	AGTR1	3q21–25
Other	Unc-13 homolog B	UNC13B	9p11–12
	Endothelial nitric oxide synthase	NOS3	7p36
	Protein kinase C, B1	PRKCB1	16p11.2

Table 1.
Genes involved in the progression of T2DM complications such as DN.

3.2 Angiotensin converting enzyme gene

ACE gene is localized on the long arm of chromosome 17 (17q23). It is 21 kb long and consists of 26 exons and 25 introns. In the National Center for Biotechnology Information (NCBI) records, greater than 160 ACE gene polymorphisms are enlisted, most of these polymorphisms are SNPs. Only 34 of those are located in coding regions of the gene while 18 are missense mutations. ACE is a zinc metallopeptidase, which is dispersed on the surface of endothelial and epithelial cell surfaces [42].

ACE gene has received substantial attention as a possible candidate for DM and its complications like hypertension, cardiovascular diseases, and nephropathy. The insertion–deletion (I/D) polymorphism of 287-bp alu repetitive sequences at intron 16 of the ACE gene is the frequently occurring variant that results in three different genotypes; II, ID, and DD. The II and DD are homozygotes and ID is heterozygote. This polymorphism is responsible for the variability in the activity of ACE in serum and various tissues as well as deletion is found to be associated with the raised activity of the enzyme. On the other hand, the low ACE activity increases insulin-stimulated hexose transport in adipocytes and insulin suppression of non-esterified fatty acid flux [43, 44].

3.3 ACE insertion/deletion polymorphism

The possible genetic factors for the development and progression of nephropathy in DM are the ACE gene insertion (I) and deletion (D) mutation or polymorphism (rs1799752). Based on the presence or absence of 287 bp alu-repetitive sequences in intron 16, three genotypes II (homozygous for I), and ID (heterozygous for ID) and DD (homozygous for D) are found. ACE mediates the regulation of blood volume, arterial pressure, cardiac and vascular functions, and electrolyte metabolism [45].

Conflicting findings in different populations on the association between ACE I/D gene polymorphism and DN development led us to investigate the ACE I/D gene polymorphism as an important risk factor for the development of hypertension and nephropathy in DM [46]. Wide inter-ethnic allelic variations of the ACE, I/D gene polymorphism were thought to be responsible for the conflicting gene-diabetic nephropathy disease association worldwide. The I/D polymorphism of the ACE gene and association of diabetic nephropathy was positively identified in Japan, South India [47, 48].

3.4 ACE G2350A polymorphism

In the ACE gene, the exonic polymorphism G2350A (rs4343) is located in exon 17. It has been revealed to exert the most significant effect on plasma ACE levels. Dimorphism was found to be significantly associated with SBP with an average increase of 3.2 mmHg. There are three genotypes on the basis of such polymorphism which include AA (homozygous for adenine), AG (heterozygous for adenine and guanine), and GG (homozygous for guanine) [49].

ACE G2350A polymorphism association with hypertension showed inconclusive results of either null or positive associations [50]. Another study revealed that in Muslims from the Arab Gulf and Pakistan the ACE 2350A allele is associated with significantly reduced hypertension while elevated risk among Chinese [51]. The allele A of the G2350A polymorphism is considered to be an independent risk factor for susceptibility to ESRD among Malays [52]. Another study has also shown the positive association of I/D and G2350A polymorphism with the development of ESRD [53].

Several factors are responsible for the lack of reproducibility which might include sample size, study design, power issues, and true variability among different populations [54].

3.5 Angiotensinogen gene

The AGT gene is localized on the long arm of chromosome 1(1q42–43), which consists of five exons. More than 23 variants of the AGT gene have been linked with hypertension [55]. However, whether or not the genetic variations of the AGT gene contribute to the risk of developing T2DM remains to be confirmed.

3.6 AGT M268T polymorphism

M268T polymorphism of the AGT gene was previously recognized as M235T. About 78 molecular variants of the human ACE gene have been reported, since the identification of its gene sequence [56]. The association between AGT M268T (M235T) gene polymorphisms and CVD has been identified in various studies [57]. Increase in levels of angiotensinogen in T268 homozygous variant leads to an increase

in BP. The AGT M268T polymorphism was found to be in linkage disequilibrium with T207M and promoter region A-6 G polymorphisms [58]. Haplotype analysis of AGT T207M and M268T revealed a significant association with hypertension among the Caucasian and Taiwan Chinese population [59]. The response of different variants of the AGT and other members of RAAS is different to different antihypertensive treatments. The role of AGT variants has been studied in different ethnic groups and variable results were identified [60].

3.7 Fat mass and obesity (FTO) gene

FTO-Gene variants are found to be associated with food intake, obesity, and metabolic risks. This study explored the differences in food intake and a possible association between diet and metabolic risk markers in T2DM having different FTO gene alleles. Metabolism of AA variants appears to be more sensitive to dietary components and supports the application of nutrigenomics in the management of T2DM. A linear correlation was observed between diet and metabolic profile markers such as BMI, waist circumference, blood pressure, and lipid profile among high-risk alleles AA. The associations of energy intake and percent level of carbohydrate and protein intake with metabolic syndrome were significantly higher among risk alleles AA. Studies suggest that the genetic profile is likely to affect both dietary habits as well as the association between diet and metabolic syndrome markers. Therefore, it can be concluded that the diet-disease associations are more prominent in individuals having risk alleles AA as compared to protective alleles TT and heterozygous alleles AT as far as FTO gene is concerned [61, 62].

4. Conclusions

A number of genetic, biochemical, nutritional, and lifestyle factors are found to be involved in the progression of type 2 diabetes mellitus and its complications such as diabetic nephropathy. Many genes including ACE, AGT, and FTO polymorphisms are significantly associated with the development and progression of diabetes nephropathy. ACE gene D-allele and DD-genotype are significantly correlated with abnormal metabolism and progression of diabetic nephropathy. Studies show that the distribution of T-allele and TT-genotype in the AGT gene were significantly different in diabetic patients with and without complications, nephropathy, for example.

Similarly, FTO rs9939609 SNP was found to be associated with an increased risk of metabolic syndrome in diabetic patients. AA-allele and A-genotype appear to be sensitive to dietary components and support the application of nutrigenomics in the management of diabetes and its complications. Future studies with a larger number of population and a variety of samples are recommended to confirm the findings and susceptibility to inform and progress the prevention and better management of the disease.

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