INHERITED OR ACQUIRED IN HIPERTENSION AND CRONIC KIDNEY DISEASE IN DIABETES MELLITUS PATIENTS?

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Abstract

Diabetic kidney disease (DKD) is a common and serious microvascular complication of diabetes mellitus (DM), which is characterized by an elevated urinary albumin excretion rate, elevated blood pressure, and declined renal function. Approximately 30-40% of DM patients will develop DKD, which is the leading cause of end-stage renal disease (ESRD) and renal failure. Genetic factors appear critical in DKD pathogenesis based upon the evidence including aggregation in families, variable incidence rates of DKD between different races, and the highly heritable nature of diabetic renal clinic and histologic changes.

Each 10 mmHg increase in mean systolic blood pressure (BP) was associated with a 15% increase in the hazard ratio for development of both micro- and macroalbuminuria and impaired kidney function defined as eGFR <60 ml/min per 1.73 m² or doubling of the blood creatinine level. Broadly, a baseline systolic BP >140 mmHg in patients with DM2 has been associated with higher risk of ESRD and death.

The ACE genes may predict diabetic nephropathy in some groups, the rate of progression and the antiproteinuric response to ACE inhibitors.

Keywords: *diabetic kidney disease, hypertension, genetic susceptibility, ACE genes, diabetes mellitus.*

Rezumat

Boala renală diabetică (BRD) este o complicație microvasculară frecventă și gravă a diabetului zaharat (DZ), care se caracterizează printr-o rată de excreție crescută a albuminei, tensiune arterială crescută și funcție renală scăzută. Aproximativ 30-40% dintre pacienții cu DZ vor dezvolta BRD, care este principala cauză a bolii renale în stadiul final și a insuficienței renale.

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Factorii genetici par să joace un rol critic în patogeneza BRD, fapt demonstrat de agregarea familială, ratele de incidență variabile ale BRD între diferite rase și caracterul ereditar al modificărilor clinice și histologice ale bolii renale diabetice.

Fiecare creștere de 10 mmHg a tensiunii arteriale sistolice medii (TA) a fost asociată cu o creștere de 15% a raportului de risc pentru dezvoltarea atât a micro, cât și a macroalbuminuriei și a deteriorării funcției renale, definită ca eGFR <60 ml/min/1,73 m² sau dublarea nivelului creatininei serice. În general, o TA sistolică inițială >140 mmHg la pacienții cu DZ2 a fost asociată cu un risc mai mare de boală renală în stadiu final și deces.

Genele ECA pot prezice nefropatia diabetică în unele grupuri, rata de progresie și răspunsul antiproteinuric la inhibitorii ECA.

Cuvinte cheie: boală renală diabetică, hipertensiune arterială, susceptibilitate genetică, gene ECA, diabet zaharat.

Diabetic kidney disease definition

Diabetic kidney disease (DKD) is one of the major chronic complications of diabetes, associated with significant morbidity and mortality, with rates of hospitalization three times higher in patients with DKD than in patients without renal complication⁽¹⁾. In diabetic kidney disease, the progressive decline of glomerular filtration rate (GFR) towards to end stage renal disease (ESRD) which is associated with increased mortality, mainly due to cardiovascular causes⁽²⁾. It is postulated that reduced renal function is by itself an indicator of high cardiovascular mortality risk⁽³⁾.

DKD is a clinical syndrome characterizes by: increased urinary albumin excretion rate (UAER) that is confirmed on at least 2 occasions 3 months apart; progressive decline in the glomerular filtration rate (GFR); elevated arterial blood pressure without other renal disease or heart failure^(4,5). UAER is defined as an excretion rate below 20 µg/min or 30 mg/24 hours⁽⁵⁾. An excretion rate between 20-200 µg/min or 30-300 mg/24 hours defines microalbuminuria or more recently named "moderately increased albuminuria"⁽⁶⁾. An excretion rate above 200 µg/min (300 mg/24 hours) is named macroalbuminuria or conform recently recommendations "severe increased

albuminuria^{“(6)}. An alternative method of detecting microalbuminuria is measurement of the albumin/creatinine ratio in a spot urine specimen: a ratio between 30-300 mg albumin/g creatinine is well correlated with 24-hours collections, and is now the preferred screening test for diabetic kidney disease⁽⁷⁾. Microalbuminuria as a marker of glomerular damage predicts the development of overt nephropathy without specific interventions in approximately 80% of insulin-dependent diabetes mellitus, and 20-40% of patients with non-insulin-dependent diabetes mellitus.

Moderately increased albuminuria is also a marker of increased cardiovascular morbidity and mortality in patients with either type 1 diabetes (T1DM) or type 2 diabetes (T2DM). Some evidence also indicates that moderately increased albuminuria may predict cardiovascular events and perhaps early renal damage in patients with essential hypertension⁽⁸⁾. GFR is calculated using MDRD and CKD-EPI equations⁽⁶⁾

Characteristic structural and functional changes in diabetic kidney disease include hyperfiltration, renal and glomerular hypertrophy, mesangial cell hypertrophy and matrix accumulation, glomerular basal membrane thickening, and functional alteration in glomerular filtration barriers. Factors responsible for these typical changes are hyperglycemia, advanced glycosylation end-products (AGEs), growth factors, cytokines, and glomerular hypertension⁽⁹⁾. DKD pathogenesis involves both genetic and environmental factors represented by older age, male sex, smoking status, and ethnic background (African-American, Native American, and Mexican-American people have a much higher risk -3 to 6 fold increase - of developing end-stage renal disease in the setting of diabetes

compared with white Caucasian subjects)⁽¹⁰⁾. The genetic risk of DKD is influenced by the combined effects of variation at an undetermined number of genomic sites, some with a predisposing and some with a protective effect^(11, 12). The screening for DKD should be performed at diagnosis in type 2 diabetes mellitus and 5 years after initial diagnosis in type 1 DM with a urinary albumin/creatinine ratio and serum creatinine. The patients with diabetes mellitus whose GRF decline rate is exceeding 10 ml/min/year or is lower than 30 ml/min should be referred immediately for nephrological exam.

Hypertension in diabetes mellitus

Hypertension in diabetes mellitus may due to one of the following reasons: the metabolic syndrome (hypertension, obesity, atherosclerosis, dyslipidemia); secondary to complications of diabetes mellitus; due to endocrine disorders and drugs and coincidental (essential arterial hypertension, isolated systolic hypertension). The renin-angiotensin-aldosterone system (RAS), natriuretic peptides system (NPS), Endothelin I, Bradykinins and NO are important regulators of fluid and electrolytes homeostasis. The balance between different endogenous vasoconstrictors (angiotensin II, norepinephrine, endothelin-1) and vasodilators (natriuretic peptides, bradykinin, adrenomedullin, NO) is altered in diabetes patients and predisposes to hypertension and microvascular diseases, including diabetic kidney disease. The existence of intricated mechanisms between hypertension and hyperglycemia is sustained by two observations:

- the diabetic patients, especially after onset of chronic complications, have a

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higher prevalence of hypertension than non-diabetic controls⁽¹³⁾;

- the risk of diabetic kidney disease increases in subjects with a family history for hypertension or cardiovascular disease^(14,15).

It is estimated that the risk for loss of renal function is several times higher in hypertensive diabetic patients than in hypertensive nondiabetic patients⁽¹⁵⁾. In patients with newly diagnosed DM2, treating to a target BP of <150/85 mmHg over a median of 15 years resulted in a significant 37% risk reduction of microvascular complications compared with that in patients treated to a target of <180/105 mmHg. Each 10-mmHg increase in mean systolic BP was associated with a 15% increase in the hazard ratio for development of both micro- and macroalbuminuria and impaired kidney function defined as eGFR <60 ml/min per 1.73 m² or doubling of the blood creatinine level⁽¹⁶⁾. Broadly, a baseline systolic BP >140 mmHg in patients with DM2 has been associated with higher risk of ESRD and death^(17,18).

The natural history of hypertension differs markedly between type 1 and type 2 diabetes mellitus. In insulin-dependent diabetes mellitus patients the blood pressure is usually normal at presentation and remains normal for the first 5-10 years, but increases with

appearance of diabetic kidney disease. To the non-insulin-dependent diabetes mellitus patients, elevated blood pressure is usually present at diagnosis or diabetes, or may develop thereafter⁽¹⁹⁾. Systemic hypertension is an early phenomenon in diabetic kidney disease. Furthermore, nocturnal blood pressure elevation ("non-dippers") occurs more frequently in insulin-dependent diabetes mellitus and non-insulin-dependent diabetes mellitus patients with diabetic kidney disease.

Also, exaggerated blood pressure response to exercise have been reported in long-standing insulin-dependent diabetes mellitus patients with microangiopathy.

Finally, the increase in glomerular pressure consequent to nephron adaptation may be accentuated with concomitant diabetes⁽⁹⁾. The risk for progression for DKD is reduced with reduction of blood pressure to less than 130-140/80-85 mmHg and optimization of HbA1c. In the last twenty five years, the hypothesis that renin-angiotensin system (RAS) inhibitors, either inhibitors of the angiotensin-converting enzyme (ACE-I) or angiotensin receptors blockers (ARB) prevent the development or slow the progression of diabetic kidney disease was intensely studied^(20,21,22,23). Clinical and experimental data relieve that blocking RAS with ACE-Is or ARBs reduces transition from microalbuminuria to proteinuria.

Gene Class	Gene	Location	Loci	Population	Phenotype
Cytokines and growth factors	Adiponectin	3q	ADIPOQ	Danish, Finnish, French	Type 1 DN
	IGF-1	12q23.2	IGF1	White	Type 1 DN
	IGF-binding protein 1	7p14	IGFBP1	White	Type 2 DN
	TGF- β receptor II	3p24.1	TGF β R2	White	Type 1 DN
	TGF- β receptor III	1p22.1	TGF β R3	White	Type 1 DN
Extracellular matrix components	Collagen type IV, α I	7q32.1	COL4A1	White	Type 1 DN
	Laminin, α 4	6q21	LAMA4	White	Type 1 DN
	Laminin, γ 1	1q25.3	LAMC1	White	Type 1 DN
Matrix metalloproteinases and dipeptidases	Tissue inhibitor of metalloproteinase 3	22q12.3	TIMP3	White	Type 1 DN
	Matrix metalloproteinase 9	20q13.12	MMP9	White	Type 1 DN
	Carnosinase	18q22.3	CNDP1	White	Type 2 DN
Transcription factors	HNF1B1/transcription factor 2, hepatic (MODY5)	17q12	HNF1B1/TCF2	White	Type 1 DN
	Neuropilin 1	10p11.22	NRPI	White	Type 1 DN
	Protein kinase C β 1	16p12.1	PRKCBI	White	Type 1 DN
	SMAD, mothers against DPP homolog 3	15q22.33	SMAD3	White	Type 1 DN
Renal function and renin angiotensin system components	Upstream transcription factor 1	1q23.3	USF1	White	Type 1 DN
	Angiotensin II receptor, type 1	3q24	AGTR1	White	Type 1 DN
	Aquaporin 1	7p14.3	AQP1	White	Type 1 DN
	B-cell leukemia/lymphoma 2 (bcl-2) proto-oncogene	18q21.33	BCL2	White	Type 1 DN
	Catalase	11p13	CAT	White	Type 1 DN
	Glutathione peroxidase 1	3p21.3	GPXI	White	Type 1 DN
	Lipoprotein lipase	8p21.3	LPL	White	Type 1 DN
	Cytochrome b, α polypeptide	16q24.3	p22phox	White	Type 1 DN
	Angiotensin-converting enzyme	17q23	ACE	White	Type 1 DN, Type 2 DN
	Engulfment and cell motility factor	7p14	ELMO1	Japanese, Black	Type 2 DN
	Nitric oxide synthase 3	7q36.1	NOS3	Japanese, White	DN, Type 1 DN
	Superoxide dismutase 2	6q25	SOD2	Caucasian, Korean, Japanese	Type 1 DN, Type 2 DN
Lipid metabolism	Apolipoprotein E	19q	ApoE	White	Type 1 DN, Type 2 DN

Table 1. Candidate genes for DKD (adapted after⁽³¹⁾)

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What do we do, now? We think that is rationale to use like anti-hypertensive and renal protective agents a dual blockade; in fact, neither ACE-Is or ARBs can suppress completely the RAS, because of the “escape phenomenon: alternate nonACE-dependent pathways (chymase) for angiotensinogen activation to angiotensin II.

These mechanisms are probably responsible for the return of angiotensin II levels back to baseline after six to nine months of ACE-I treatment⁽²⁴⁾. A multitude of association studies of blood pressure candidate genes was performed; we resume five physiological genes classes: renin-angiotensin-aldosterone system (RAS), sodium volume, sympathetic nervous system, vascular and metabolic systems^(25,26).

Genetic susceptibility to diabetic kidney disease

DKD is a complex is a complex, multifactorial syndrome, which develops when environmental risk factors operate on a pool of genetic variants that confers individual susceptibility to disease. A high number of genes are considered candidates for DKD, an explanation for this high number resides into the intrinsic complexity of the pathophysiology of diabetic renal injury (Table 1, Table 2). The number of DKD candidate genes will increase in the following

years while more data regarding the cellular and molecular pathophysiology of the initial phases of DKD will become available. According to the presumed molecular mechanism of their encoded protein, these genes are grouped into:

- **Blood pressure regulation genes:** Angiotensin Converting Enzyme-*ACE*, Angiotensinogen-*AGT*, Angiotensin Receptors-*AGTR*, Aldosterone Synthetase-*CYP11B2*, Endothelin and Endothelin Receptors, Plasma Kallikrein Bradykinin Receptors, Nitric Oxide Synthetases-*NOS2A*, *NOS3*;
- **Growth factors and angiogenesis factors:** Vascular Endothelial Growth Factor-*VEGF*, Erythropoietin, *TGFβ*;
- **Metabolism genes:** Aldolase Reductase-*AKR1B1*, AGE Receptor-*AGER*, Apolipoproteins, Methylene-tetrahydrofolate reductase-*MTHFR*;
- **Cytokines and inflammation genes:** IL-1, IL6, IL18, ICAM1, MCP1, *TNFα*;
- **Oxidative stress:** Nitric Oxide Synthetases, Glutathione Peroxidase-*GPX*, Catalase-*CAT*;
- Genes with **other functions:** *HSPG2*-Heparan Sulfate Proteoglycan involved in glomerular structure, *GREM1* which is involved in cell growth, *UNC13B* through to be involved in apoptosis).

Chromosome	Region	Maximum LOD	Population	Study	Phenotype	Characteristics
3q	13	4.55	Black	Sibling pairs	Type 2 DN	Age at ESRD onset
	21.3	2.67	Finnish	Discordant sibling pairs	Type 1 DN	
	25.1	3.1	White	Discordant sibling pairs	Type 1 DN	
7q	12.3	1.84	West African	Sibling pairs	Type 2 DN	CC
	21.1	(6.0×10^{-4})	White	90% sibling pairs	Predominantly type 2 DN	ACR
	21.3	(6.0×10^{-5})	Black	90% sibling pairs	Predominantly type 2 DN	Nephropathy
	33	2.04 to 2.73	Pima Indian	Sibling pairs	Type 2 DN	Nephropathy and retinopathy
	36.2	3.1	94% white	Families	Type 2 DN	ACR
	(99 cM)	(1.1×10^{-4})	White	90% sibling pairs	Predominantly type 2 DN	Nephropathy
7p	21.3	4	94% white	Sibling pairs	Type 2 DN	CC-GFR
	32.1	3.59	Black	Sibling pairs	Type 2 DN	Age at diabetes onset
	(12 cM)	(1.6×10^{-4})	American Indian	90% sibling pairs	Predominantly type 2 DN	ACR
	(78 cM)	(1.0×10^{-3})	Mexican American	90% sibling pairs	Predominantly type 2 DN	GFR
10q	23.31	3.1	94% white	Sibling pairs	Type 2 DN	Diabetic/nondiabetic ; CC-GFR
	26	2.47	Black	Sibling pairs	Type 2 DN	Age at ESRD onset
18q	22.1	3.72	Black	Sibling pairs	Type 2 DN	Age at diabetes onset
	22.1	(3.15×10^{-2})	White	Discordant sibling pairs	Predominantly type 2 DN	Nephropathy
	22.3-23	6.1	Turkish	Families	Type 2 DN	Nephropathy

Table 2. Genome-wide linkage scans for diabetic kidney disease (adapted after^[31])

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In the last two decades, the attention has focused on genetic susceptibility to renal injury from elevated blood pressure. According to Churchill et al⁽²⁷⁾, an experimental animal model of renal injury caused by hypertension suggests that nephropathy susceptible genes exist, but genes have not yet been identified. In humans, the familial clustering of hypertensive renal disease and the identification of polymorphism in the renin-angiotensin-aldosterone system gene components support the idea of genetic susceptibility to hypertensive renal injury in diabetic nephropathy⁽²⁸⁾.

Krolewski et al⁽²⁹⁾ identified a region on the long arm of chromosome 3 in the vicinity of the angiotensin II type-1 receptor gene that harbors a locus with major effects. In addition, they have demonstrated minor effects of the insertion allele in the ACE gene and the T-allele at position 235 in the angiotensinogen gene on the development on diabetic nephropathy; this finding must be confirmed in other family-based studies.

Is susceptibility to diabetic nephropathy the same as susceptibility to essential hypertension? Krolewski et al⁽²⁹⁾ identified some overlap. Essential hypertension has a significant genetic component with minor gene effects and these authors postulated that the expression and penetrance of one of these minor genes for essential hypertension

is changed in the presence of hyperglycemia in such a way that carriers of that disease allele, which must be a common one, would develop diabetic nephropathy together with their hypertension. Overactivity of the sodium/potassium exchanger in the pathogenesis of diabetic nephropathy remains uncertain. Demanine et al⁽³⁰⁾ presented the results of an analysis of polymorphism in two areas of the aldose reductase gene in normal healthy controls and in insulin-dependent diabetes mellitus patients with nephropathy; this finding is incert by others authors⁽²⁹⁾.

The kidney also plays a critical role in the development of systemic hypertension. The major alterations are sodium retention and increased peripheral vascular resistance⁽²⁸⁾. The molecular aspect of this phenomenon in patients with diabetic nephropathy is not completely understood.

Conclusion

Hypertension and microalbuminuria play a critical role in initiation and progression of diabetic kidney disease. The ACE genes may predict diabetic nephropathy in some groups. Insulin resistance contributes to diabetic nephropathy but mostly indirectly. ACE genes may predict the rate of progression and the antiproteinuric response to ACE inhibitors. Diabetic kidney disease does not develop in

the absence of hyperglycemia but other factors exist that interact with poor glycemic control to produce nephropathy and hypertension. Genetic susceptibility is one of the most important factors. The detection of genetically predisposed subjects will improve the results of the preventive strategies

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