Mechanical Forces in Diabetic Kidney Disease: A Trigger for Impaired Glucose Metabolism

Luigi Gnudi, Stephen M. Thomas, and Giancarlo Viberti
Cardiovascular Division, King’s College London School of Medicine, Guy’s Hospital, London, United Kingdom

ABSTRACT
Nephropathy is one of the major microvascular complications of diabetes, and both hemodynamic and metabolic stimuli participate in its development and progression toward ESRD. There is now a greater understanding of the molecular pathways that are activated by high glomerular capillary pressure and hyperglycemia and how they interplay to produce kidney pathology. The observation that overexpression of glucose transporter 1 (GLUT-1) in mesangial cells could induce a “diabetic cellular phenotype” has led to the postulation that the expression of GLUT-1 could be upregulated in glomeruli that are exposed to high pressure. This review suggests a mechanism by which mechanical forces may aggravate a metabolic insult by stimulating excessive cellular glucose uptake. Proposed is the existence of a self-maintaining cycle whereby a hemodynamic stimulus on glomerular cells induces GLUT-1 overexpression followed by greater glucose uptake and activation of intracellular glucose metabolic pathways, resulting in excess TGF-β1 production. TGF-β1 in turn, maintains overexpression of GLUT-1, perpetuating a signaling sequence that has, as its ultimate effect, increased extracellular matrix synthesis. This mechanical and metabolic coupling suggests a novel pathophysiologic mechanism of injury in the kidney in diabetes and possibly other glomerular diseases.


THE PROBLEM
The “epidemic” of type 2 diabetes—the burden of diabetic chronic vascular complications, together with improvements in patient care and availability of renal replacement therapy and possibly improved patient survival—has given rise to a public health crisis that is seriously challenging health care resources.1–3 Because hyperglycemia and elevated BP interact in the pathogenesis of diabetic kidney disease,4,5 it is imperative that we understand the nature and mechanism(s) of this interplay to develop novel approaches to prevention and treatment.

PATIENTS WITH DIABETES: CLINICAL OBSERVATIONS
When the correlation between urinary albumin excretion and systolic BP was first described in patients with type 2 diabetes,6 the authors made the prescient observation that “the results of hypertension and hyperglycemia combine to increase the degree of albuminuria.” Many investigators have since described the cumulative effect of the parallel perturbations of hypertension and hyperglycemia on the development and progression of diabetes micro- and macrovascular complications.

Prospective, randomized, controlled trials have established the risks of hyperglycemia for the development of kidney disease. The Diabetes Control and Complications Trial (DCCT) in patients with type 1 diabetes demonstrated that intensified insulin therapy with improved glycemic control during approximately 7 yr reduced the risk for development of microalbuminuria by 39%.7 The relationship between glycemia and the risk for microalbuminuria was log-linear with no evidence of a threshold below which improved glycemic control could not further reduce the risk for kidney disease.8 In newly diagnosed type 2 diabetes, the United Kingdom Prospective Diabetes Study (UKPDS) demonstrated that intensive glycemic control reduced the risk for the development of albuminuria also by approximately 33% over 12 yr.9 Similarly strong evidence exists for the importance of raised arterial BP in the development of diabetic kidney disease. In prospective studies, patients who had diabetes and progressed to albuminuria had higher arterial pressure at baseline,10,11 and in intervention studies, BP lowering slowed kidney disease progression and reduced albuminuria in both type 1 and type 2 diabetest.12,13 The interaction of raised BP and hyperglycemia is therefore important in both the initiation and the progression of kidney disease, potentially trebling the rate of loss of GFR and significantly worsening the degree of albuminuria.14

Published online ahead of print. Publication date available at www.jasn.org.

Correspondence: Dr. Luigi Gnudi, Department of Diabetes, Endocrinology and Internal Medicine, 5th Floor Thomas Guy House, Guy’s Hospital, St. Thomas Street, London SE1 9RT, UK. Phone: +44-20-7188-1939; Fax: +44-20-7188-0146; E-mail: luigi.gnudi@kcl.ac.uk

Copyright © 2007 by the American Society of Nephrology
PATHOPHYSIOLOGY OF KIDNEY DISEASE: METABOLIC ALTERATIONS IMPAIR GLOMERULAR MICROCIRCULATION

Under normal physiologic conditions, autoregulatory mechanisms are in place to protect the glomerular capillaries from changes in systemic arterial BP. A greater understanding of the pathophysiologic interaction between hypertension and hyperglycemia in diabetic kidney disease came from the work of Hostetter et al. who by direct determination of intraglomerular pressure, using a micropuncture technique of superficial renal cortical glomeruli in the diabetic Munich Wistar rat, demonstrated that hyperglycemia altered the normal process of autoregulation within the glomerulus, reducing afferent and, to a much lesser degree, efferent arteriolar tone. This resulted in ready transmission of systemic pressure to the glomerular capillary and higher glomerular transcapillary hydraulic pressure and contributed to an increase in single-nephron and whole-kidney GFR, which was associated with more severe degrees of structural glomerular damage. The use of an angiotensin-converting enzyme inhibitor, which lowered glomerular capillary pressure, resulted in reduction of both albuminuria and glomerular extracellular matrix deposition/accumulation. Thus, hyperglycemia impairs the physiologic mechanism that maintains normal glomerular capillary pressure.

The ways by which hyperglycemia disrupts capillary vasoregulation are complex and beyond the scope of this article. Enhanced production of nitric oxide (NO), leading to both afferent and efferent glomerular arteriolar vasodilation, and increased TGF-β1, which may act through the production of reactive oxygen species, both may be important. In addition, hyperglycemia increases the production of angiotensin II (AngII) particularly by the local tissue renin-angiotensin-aldosterone system (RAAS). The efferent glomerular arteriole is 10 to 100 times more sensitive to the vasoconstrictive action of AngII than the afferent arterioles, and this may contribute to the imbalance in arteriolar tone, which results in higher intraglomerular capillary pressure in diabetes.

GLOMERULAR HYPERTENSION IN EXPERIMENTAL ANIMAL MODELS OF KIDNEY DAMAGE

In hypertensive animal models, in which glomerular vasoregulation is lost, such as the Dahl salt-sensitive rat (DSS), the one-kidney five-sixths nephrectomy model, a rise in intraglomerular pressure results in mesangial matrix expansion and glomerulosclerosis. By contrast, in the spontaneously hypertensive rat (SHR), increased preglomerular arteriolar resistance prevents a rise in capillary pressure, protecting the glomerular circulation from systemic hypertension and resulting in delayed damage. When preglomerular vasoregulation in the SHR is impaired by uninephrectomy or diabetes, capillary hypertension ensues with accelerated albuminuria, increased TGF-β1, mesangial expansion, and glomerulosclerosis. Thus, pathologies that lead to intraglomerular hypertension create the conditions for a mechanical stimulus to induce damage to the glomerular capillary.

EVIDENCE IN HUMANS: GLOMERULAR HYPERTENSION

Intraglomerular pressure is not directly measurable in humans, but glomerular hyperfiltration is common in early diabetes and can be reversed to a large extent by better glycemic control. It has been suggested that hyperfiltration in diabetes is a significant risk factor for progression to microalbuminuria and advanced kidney disease, but the evidence is conflicting. Nevertheless, individuals with higher filtration fraction (FF = GFR/renal plasma flow), an indirect measure of glomerular capillary pressure, may be predisposed to the development of diabetic kidney disease. Thus, glomerular capillary pressure may be elevated in the presence of hyperglycemia even at supposedly “normal” systemic arterial pressure.

The prevalence of kidney damage in individuals with essential hypertension is variable. Ethnicity is an important factor: Individuals of African descent seem more at risk for hypertensive kidney damage, and those who are of both Asian and African descent and develop diabetes are at higher risk for diabetic kidney disease. It is speculated that less effective glomerular autoregulation may be a feature of those with higher predisposition to kidney disease. Phenotypically, this may be represented by higher salt sensitivity, which some authors have suggested may be a surrogate marker for less effective glomerular autoregulation. Certainly, altered response to high salt intake, with a shift of the pressure natriuresis curve to the right, is seen in patients with diabetes and microalbuminuria and in ethnic groups at higher risk for renal disease, such as those of African descent. In salt-sensitive individuals, a salt-rich diet triggers increased RAAS activity, which may lead to increased glomerular capillary pressure. These changes are paralleled by greater degrees of left ventricular hypertrophy, microalbuminuria, and lower insulin sensitivity; the last, in turn, could contribute to higher salt sensitivity in both type 1 and type 2 diabetes. It is intriguing that patients who have both type 1 and type 2 diabetes and develop microalbuminuria have reduced insulin sensitivity.

COOPERATIVITY BETWEEN MECHANICAL AND METABOLIC STIMULI AT THE CELLULAR LEVEL

There is much greater understanding of the molecular mechanisms by which high capillary pressure and hyperglycemia independently lead to altered cellular function and pathology. The intriguing question is whether, at a cellular level, these twin insults interact and, more specifically, whether the hemodynamic perturbation would aggravate the metabolic one magnifying its deleterious impact on glomerular pathology.
The glomerulus is a complex elastic structure, the stability of which depends on the cooperative function of several cell types (endothelial cells, mesangial cells, and podocytes) and the basement membrane. The glomerular volume expands and contracts rapidly as pressure varies. All glomerular cells are hemodynamically responsive, including mesangial cells, which because of their anatomic distribution are exposed to high pressure fluctuations within the capillaries.5,45–48 In the normal glomerulus, capillary pressure is remarkably constant with only minor fluctuations, but once autoregulation is impaired, pressure variations and cell elongation/stretching is seen to a much greater degree. Calculations suggest that the typical rise in glomerular pressure in diabetes is associated with a cell stretching of approximately 10% as compared with the average 4% elongation seen with normal intraglomerular pressure.49,50 We were intrigued by the hypothesis that a hemodynamic perturbation could affect the sensitivity of the cell to a metabolic stimulus and may be changing the way by which the cell “senses” the extracellular glucose level and “controls” cellular glucose uptake.

FACILITATIVE GLUCOSE TRANSPORTER 1: A POTENTIAL MOLECULAR TARGET OF MECHANICAL-METABOLIC INTERACTION IN (DIABETIC) KIDNEY DISEASE

Glucose transporter 1 (GLUT-1) is one of the members of a family of facilitative glucose transporters—proteins that are involved in glucose uptake into the cell.51,52 GLUT-1 is a ubiquitously expressed molecule, residing mostly on the cell plasma membrane, where it mediates the rate of glucose transport into the cell in basal, non–insulin-stimulated, conditions.52 This is particularly relevant for glucose metabolism of cells in the vessel wall and in the glomerular capillaries, where glucose uptake is relatively insulin independent.53

GLUT-1 is highly expressed in the glomerulus.53 As with all facilitative glucose transporters, GLUT-1 is a high-affinity, low-capacity transporter and is at or near saturation at physiologic glucose levels. Therefore, an increase in the number of GLUT-1 molecules would be expected to lead to an increase in basal glucose uptake.53,54

The seminal observation by Heilig et al.55 that GLUT-1 overexpression in mesangial cells that were cultured in “normal” glucose concentrations resulted in both increased basal cellular glucose uptake and extracellular matrix protein expression, thus mimicking a “cellular diabetic phenotype,” highlighted the potential importance of GLUT-1 expression modulation in the pathogenesis of diabetic glomerulopathy. In support of this contention, studies of GLUT-1 expression inhibition, with antisense mRNA in mesangial cells in vitro, showed prevention of both basal glucose uptake and glucose-induced extracellular matrix production.56 Moreover, in vivo evidence suggests that an antisense GLUT-1 transgene in diabetic db/db mice protects against the development of diabetic glomerulopathy,57 whereas normoglycemic animals overexpressing GLUT-1 in glomeruli develop more mesangial expansion and albuminuria.58

Many of the molecules involved in the pathophysiology of glomerular capillary damage in diabetes affect GLUT-1 expression; for example, AngII and TGF-β1 stimulate GLUT-1 protein expression and basal glucose uptake in mesangial cells.5,59–61 Thus, there is experimental evidence linking GLUT-1 upregulation with renal damage. To gain further insight into the molecular pathways of this pathophysiologic mechanism, we asked whether and how hemodynamic forces might interact with GLUT-1 expression and cellular glucose uptake.

We found that mechanical stretch applied to human mesangial cells in vitro significantly upregulated GLUT-1 protein expression, an event coupled with increased transport capacity (Vmax) and basal glucose uptake at normal glucose concentrations. These effects were prevented by neutralization of the action of TGF-β1.5 We then studied whether GLUT-1 expression differed in an animal model of both systemic and glomerular hypertension, the DSS,25,26 as compared with an animal model of systemic hypertension with normal capillary pressure, namely the young SHR.29 DSS that were treated with a high-salt diet developed systemic and glomerular hypertension, with a concomitant 80% increase in glomerular GLUT-1 expression as compared with normotensive DSS (Figure 1).5 By contrast, in the young SHR, a model of normal intraglomerular pressure despite systemic hypertension, GLUT-1 expression was unchanged as compared with the Wistar Kyoto (WKY) normotensive control rat.5 The increased glomerular GLUT-1 upregulation in the hypertensive DSS was associated with a two- to three-fold increase in renal TGF-β1 expression when compared with their DSS normotensive controls. Renal TGF-β1 expression was similar in the young SHR and the WKY.5

Importantly in hypertensive DSS, blockade of the RAAS was found to reduce intraglomerular pressure and prevent glomerular TGF-β1 upregulation.52 Studies in the Milan rat strain also suggest that susceptibility to renal lesions is associated with upregulation of GLUT-1. In this rat model, the normotensive strain with defective afferent arteriolar vasoregulation develops glomerular injury, whereas the hypertensive strain, which maintains the ability to vasoconstrict the afferent arteriole, is protected from renal damage. In the first case, there is increased glomerular GLUT-1 and TGF-β1 expression that is absent in the hypertensive strain.63

The mechanical GLUT-1–mediated elevated cellular glucose transport would result in activation of different intracellular metabolic pathways: the polyl and hexosamine pathway, increased production of advanced glycation end products, activation of protein kinase C and p38 mitogen-activated protein kinase, and increase in oxidative stress.64 All of these pathways when activated would lead to glomerular TGF-β1 upregulation with increased glomerular extracellular ma-
tissue deposition and progressive impairment of glomerular function. Similarly, stretch-induced upregulation of local AngII and the angiotensin type 1 receptor will lead to activation of TGF-β-mediated GLUT-1 upregulation, thus triggering a vicious cycle that results in higher cellular glucose uptake. Thus, a hemodynamic stimulus, via GLUT-1 upregulation, may magnify intracellular glucose metabolism. Stretching of a mesangial cell would result in higher intracellular glucose concentration relative to actual ambient glucose, in as far as GLUT-1 transporter abundance alone should be sufficient to alter cellular glucose uptake/metabolism, although other mechanisms may also operate. Because all glomerular cells are to some degree capable of responding to hemodynamic stimuli, this process may apply not just to the mesangium. These observations help to explain how a metabolic disturbance is potentiated by a hemodynamic insult.

Rats with streptozotocin-induced diabetes display a greater abundance of renal cortical GLUT-1 as compared with nondiabetic counterparts. In diabetes, GLUT-1 expression is downregulated by 50% in heart tissue and in the retinal microvasculature. High glucose concentrations in mesangial cells counterintuitively increase GLUT-1 expression via a TGF-β1–dependent mechanism. This may be peculiar to mesangial cells as opposed to other cell types; for example, GLUT-1 levels downregulate in mouse vascular smooth muscle cells when cultured in high-glucose conditions. Similarly, in ex vivo work, mesangial cells, obtained from microdissected glomeruli of patients with type 2 diabetes and cultured in vitro, showed enhanced GLUT-1 transporter expression, increased basal glucose uptake, and excessive flux of glucose metabolism through the hexosamine pathway, paralleled by increased extracellular matrix deposition and mesangial cell hypertrophy. In contrast skeletal muscle GLUT-1 protein expression as well as basal glucose uptake is reduced in patients with type 2 diabetes. Various stimuli may therefore modulate GLUT-1 overexpression in the glomerulus in diabetes, an event that we suggest plays a central role in the sequence of molecular pathways responsible for glomerular damage (Figure 2).

It is plausible that mechanical forces alter intracellular glucose transport/metabolism via GLUT-1 overexpression in other nondiabetic glomerular diseases at “normal” glucose levels. In human obesity, where alterations in plasma glucose are modest and below the “diabetic” range, high arterial pressure and activation of the RAAS are important risk factors for the development of glomerular damage, and in obesity-related glomerulopathy, renal cortical GLUT-1 levels are upregulated.

**GENETICS OF GLUT-1 IN DIABETIC KIDNEY DISEASE**

Multiple genes have been implicated in the pathogenesis of diabetic kidney disease, including polymorphisms of the angiotensin-converting enzyme and aldose reductase gene. Reports have also linked an XbaI polymorphism, located on the second intron of the GLUT-1 gene, with a greater risk for diabetic kidney disease. Data on this polymorphism are conflicting, and a recent meta-analysis was not able to support a clear association between this polymorphism and diabetic kidney disease. Two large studies conducted in white patients with type 1 diabetes failed to show an association, whereas two smaller studies (white

---

**Figure 1.** Glomerular hypertension stimulates glucose transporter 1 (GLUT-1) expression in glomeruli. (A) GLUT-1 immunohistochemistry in kidney cortex from Dahl salt-sensitive rats (DSS) on high-salt diet (DSH), DSS on low-salt diet (DSN), spontaneously hypertensive rat (SHR) and Wistar Kyoto (WKY) rats. Intense GLUT-1 staining (brown) was seen in the DSH glomeruli but not in DSN, SHR, or WKY rats. (B) GLUT-1 protein levels in glomeruli isolated from WKY rats, SHR, DSN, and DSH. (Top) Representative Western immunoblotting. (Bottom) Densitometry analysis for GLUT-1 expressed as percentage change over controls (WKY and DSN, respectively). *P = 0.004, DSH versus DSN (n = 4 to 5 rats per group). Reprinted with permission from Gnudi et al.: “GLUT-1 Overexpression: Link between Hemodynamic and Metabolic Factors in Glomerular Injury?” Hypertension 42:19–24, 2003.
injury in diabetes and possibly other glomerular diseases. Strategies that interrupt pressure-induced metabolic injury may provide new targets for treatment.

DISCLOSURES
None.

REFERENCES

CONCLUSION
Much more is known about the independent pathways of both glucose- and pressure-induced renal injury; much less is known about how they combine. Hemodynamic–metabolic coupling, whereby a mechanical stimulus enhances glucose transport and metabolism, suggests a novel pathophysiological mechanism of...


63. Ricci C, Iacobini C, Oddi G, Amadio L, Me-
GLUT1 axis in susceptibility vs resistance to 
diabetic glomerulopathy in the Milan rat 
64. Brownlee M: Biochemistry and molecular 
cell biology of diabetic complications. Na-
ture 414: 813–820, 2001
65. King GL, Kunisaki M, Nishio Y, Inoguchi T, 
Adhikary L, Chow F, Nikolic-Paterson DJ,
Igarashi M, Wakasaki H, Takahara N, Ishii H,
Burt DJ, Gruden G, Thomas SM, Tutt P,
Koya D, King GL: Protein kinase C activation 
mediated by the hexosamine pathway in 
porcine glomerular mesangial cell. J Cell 
66. Adhikary L, Chow F, Nikolik-Paterson DJ, 
Stambe C, Dowling J, Atkins RC, Tesch GH: Abnor-
mal p38 mitogen-activated protein kinase 
signaling in human and experimental 
diabetic glomerulopathy. Diabetologia 45(Suppl 
Schleicher ED: High glucose induced trans-
forming growth factor beta 1 production is 
mediated by the hexosamine pathway in 
porcine glomerular mesangial cell. J Clin 
68. Burt DJ, Gruden G, Thomas SM, Tutt P, 
Dell’Anna C, Viberti GC, Gnudi L: P38 mito-
gen-activated protein kinase mediates hex-
osamine-induced TGFbeta1 mRNA expres-
69. Igarashi M, Wakasaki H, Takahara N, Ishii H, 
Jiang ZY, Yamauchi T, Kuboki K, Meier M, 
Rhodes CJ, King GL: Glucose or diabetes 
activates p38 mitogen-activated protein ki-
70. Koya D, King GL: Protein kinase C activation 
and the development of diabetic complic-
71. Henry DN, Busk JV, Brosius FC 3rd, Heilig 
CW: Glucose transporters control gene ex-
pression of aldose reductase, PKCalpha, 
and GLUT1 in mesangial cells in vitro. Am J 
Physiol 277: F97–F104, 1999
72. Becker BN, Yasuda T, Kondo S, Vaikunth S, 
Homma T, Harris RC: Mechanical stretch/ 
relaxation stimulates a cellular renin-angio-
tensin system in cultured rat mesangial cells. 
73. Weigert C, Brodbeck K, Klopfer K, Haring 
HU, Schleicher ED: Angiotensin II induces 
human TGF-beta 1 promoter activation: 
74. D’Agord SB, Lacchini S, Bertoluci MC, 
Irigoyen MC, Machado UF, Schmid H: In-
creased renal GLUT1 abundance and urinary 
TGF-beta 1 in streptozotocin-induced dia-
abetic rats: Implications for the development of 
neurophyopathy complicating diabetes. 
75. D’Agord Schaan B, Lacchini S, Bertoluci MC, 
Irigoyen MC, Machado UF, Schmid H: Im-
port of renal denervation on renal content of 
GLUT1, albuminuria and urinary TGF-beta1 in 
streptozotocin-induced diabetic rats. Au-
76. Depre C, Young ME, Ying J, Ahuja HS, Han 
Q, Garza N, Davies PJ, Taegtmeyer H: Streptozotocin-induced changes in cardiac 
gene expression in the absence of severe 
contractile dysfunction. J Mol Cell Cardiol 
32: 985–996, 2000
77. Hirsch E, Rosen P: Diabetes mellitus induces 
long lasting changes in the glucose trans-
porter of rat heart endothelial cells. Horm 
Metab Res 31: 645–652, 1999
78. Badr GA, Tang J, Ismaiel-Beigi F, Kern TS: 
Diabetes downregulates GLUT1 expression 
in the retina and its microvessels but not in 
the cerebral cortex or its microvessels. Dia-
79. Heilig CW, Liu Y, England RL, Freytag SO, 
Gilbert JD, Heilig KO, Zhu M, Concepcion 
LA, Brosius FC 3rd: D-glucose stimulates 
mesangial cell Glut1 expression and basal 
and IGF-I-sensitive glucose uptake in rat 
mesangial cell. Diabetes 46: 1030–1039, 
1997
80. Howard RL: Down-regulation of glucose 
transport by elevated extracellular glucose 
concentrations in cultured rat aortic smooth 
muscle cells does not normalize intracellular glucose concentrations. J Lab 
81. Liu Z, Chen Z, Li Y: Phenotypic and func-
tional alterations of mesangial cells in pa-
tients with diabetic nephropathy. Zhonghua 
Yi Xue Za Zhi 81: 1369–1373, 2001
82. Ciaraldi TP, Mudalair S, Barzin A, Macievic 
JA, Edelman SV, Park KS, Henry RR: Skeletal 
muscle GLUT1 transporter protein expres-
sion and basal leg glucose uptake are re-
duced in type 2 diabetes. J Clin Endocrinol 
Metab 90: 352–358, 2005
83. Praga M, Morales E: Obesity, proteinuria 
and progression of renal failure. Curr Opin 
84. Wu Y, Liu Z, Xiang Z, Zeng C, Chen Z, Ma X, 
Li L: Obesity-related glomerulopathy: In-
sights from gene expression profiles of the 
glomeruli derived from renal biopsy sam-
85. Rich SS: Genetics of diabetes and its com-
2006
86. Zintzaras E, Stefanidis I: Association be-
tween the GLUT1 gene polymorphism and 
the risk of diabetic nephropathy: A meta-
87. Hodgkinson AD, Page T, Millward BA, De-
maine AG: A novel polymorphism in the 5’ 
flanking region of the glucose transporter 
(GLUT1) gene is strongly associated with di-
abetic nephropathy in patients with type 1 
diabetes mellitus. J Diabetes Complications 
19: 65–69, 2005
88. Liu Z, Guan T, Chen Z: Insulin receptor sub-
strate-1 and glucose transporter gene poly-
morphisms in noninsulin-dependent dia-
betes mellitus. Zhonghua Yi Xue Za Zhi 78: 
662–665, 1998
89. Imperatore G, Hanson RL, Pettitt DJ, Kobes 
S, Bennett PH, Knowler WC: Sib-pair linkage 
analysis for susceptibility genes for micro-
vascular complications among Pima Indians 
with type 2 diabetes. Pima Diabetes Genes 
90. Iyengar SK, Fox KA, Schachere M, Manzoor 
F, Slaughter ME, Covic AM, Orlloff SM, Hay-
den PS, Olson JM, Schelling JR, Sedor JR: 
Linkage analysis of candidate loci for end-
stage renal disease due to diabetic ne-
S195–S201, 2003
91. Lindner TH, Monks D, Wanner C, Berger M: 
Genetic aspects of diabetic nephropathy. 
92. Moczulska DK, Rogus JJ, Antonellis A, War-
ram JH, Krolewski AS: Major susceptibility 
locus for nephropathy in type 1 diabetes on 
chromosome 3q: Results of novel discordant 
sib-pair analysis. Diabetes 47: 1164–1169, 
1998
93. Varadar I, Baier LJ, Hanson RL, Akkoyun I, 
Fischer C, Rohmeiss P, Basci A, Bartram CR, 
von der Woude FJ, Janssen B: Gene for 
susceptibility to diabetic nephropathy in 
type 2 diabetes maps to 18q22.3-23. Kidney 
Int 62: 2176–2183, 2002