Clinical aspects of the relation between diabetes mellitus and kidney disease: From hyperfiltration to dialysis

Schroijen, M.A.

CHAPTER 1

General introduction

General Introduction

Diabetes mellitus (DM) is characterized by the body's inability to maintain adequate glucose levels, and the hallmark of its diagnosis are therefore increased levels of plasma glucose. Depending on the underlying pathophysiology, diabetes can be classified into different general categories. Type 1 diabetes mellitus (T1DM) is an autoimmune disease in which pancreatic β-cells are destroyed over time and endogenous insulin production is lost. Type 2 (T2DM) diabetes is characterized by progressive loss of β cell insulin secretion, frequently accompanied by insulin resistance. Type 1 and 2 diabetes represent two broad categories, in which clinical presentation and disease progression may vary considerably and the distinction between the two types in clinical practice is not always clear-cut. Besides type 1 and type 2 DM, other etiologic subtypes such as monogenic diabetes (such as neonatal diabetes and maturity onset diabetes of the young (MODY)) have been discovered over the last decades.

The global prevalence of diabetes mellitus has increased dramatically over the past few decades. The total number of adults (20-79 years) with DM increased from 151 million in 2000 to 451 million in 2017[1]. This increase is mainly due to a in T2DM, which is, at least partially, thought to be secondary to the rise in metabolic syndrome and obesity. Between 1980 and 2013, the global prevalence of overweight and obesity combined rose by 27.5% for adults and 47.1% for children[2].

Patients with DM have an increased risk to develop microvascular and/or macrovascular complications due to hyperglycemia and common co-existing conditions such as hypertension and dyslipidemia. Complications, affecting the eyes (retinopathy), kidneys (nephropathy), and peripheral nervous system (neuropathy), are collectively called microvascular complications. Atherosclerotic cardiovascular disease such as coronary heart disease, cerebrovascular disease, or peripheral arterial disease are called macrovascular complications. The risk to develop complications depends on glycemic control, duration and type of DM[3, 4]. About 20-40 % of patients with DM develop chronic kidney disease (CKD)[5-7]. A substantial proportion of patients with DM will develop chronic kidney disease owing to their disease, but also associated conditions, such as hypertension and obesity will contribute. Patients with diabetes and CKD have an even further increased risk of adverse health care outcomes, higher risk of complications, comorbidities and use of polypharmacy and this imposes a huge economic burden on health care systems[8]. As major long-term consequences

of diabetes are the increased risk for cardiovascular, and renovascular disease, the overall management aims to reduce this cardiovascular risk. Furthermore, patients with DM have a reduced quality of life and life expectancy[9, 10].

Excess mortality in type 1 and type 2 DM is largely related to the presence of CKD. Among patients with T2DM younger than 55 years of age, and a normal or only slightly reduced estimated glomerular filtration rate (eGFR of ≥ 90 ml/min/ 1.73 m^2, or 60-90 ml/min/ 1.73 m^2) the excess risk of death from any cause is twice the risks among persons without diabetes. This risk further increases with decreasing kidney function; in DM patients with a clearly compromised renal function (eGFR of ≥ 15 -30 ml ml/ min/ 1.73 m^2), mortality risk is approximately 20 times higher[9]. In line, similar results are shown in patients with type 1 DM[10]**.** Consequently, preventing and management of CKD in patients with DM is a key aim of their overall management.

Pathophysiology of diabetic nephropathy

Kidney disease due to diabetes was first described in 1936 by Kimmelstiel and Wilson, who demonstrated characteristic nodular lesions in patients with diabetes, later termed nodular glomerulosclerosis[11]. Decades further, in the 1980's, it was demonstrated that diabetic kidney disease on average develops more than a decade after diabetes onset in patients with type 1 diabetes[12, 13]. In patients with newly diagnosed T2DM, about 7 % already have diabetic nephropathy at time of diagnosis, which is likely related to a long subclinical period of hyperglycemia; also comorbidities such as obesity and hypertension may play a role[14].

Diabetes related nephropathy is a progressive disease, the earliest sign being microalbuminuria (defined as urine albumin/creatinine ratio >30 mg/g), which can progress to macroalbuminuria (>300 mg/g) and a gradually decline in glomerular filtration rate, eventually leading to end stage renal disease (ESRD). Almost half of patients with established micro-albuminuria will progress to macro-albuminuria, which is associated with a ten foldhigher risk of progression to ESRD than patients with normoalbuminuria[15, 16]. Approximately 50 % of T2DM patients and 30 % of T1DM will develop CKD after 20 years of DM. CKD is defined by the presence of impaired renal function or elevated urinary albumin excretion or both (Table 1)[17-19].

Table 1. Clinical Criteria for the diagnosis of CKD[20]

Clinical Criteria for the diagnosis of CKD*
Estimated glomerular filtration rate of < 60 ml/min/ 1.73 m2
Urinary albumin/creatinine ratio of ≥ 30 mg/g (3 mg/mmol)
Urinary albumin excretion of ≥ 300 mg/g (30 mg/mmol) per 24 hours

*One or more of the following criteria must be present for more than 3 months and validated by repeated testing before a clinical diagnosis of chronic kidney disease can be made.

Many patients with type 1 and type 2 diabetes do not strictly follow this classic course of first developing micro-albuminuria, thereafter progression to macro-albuminuria and only thereafter a decline in eGFR. In the United Kingdom Prospective Diabetes Study (UKPDS) study, 28 % of patients with type 2 DM developed an estimated glomerular infiltration rate (eGFR) < 60 ml/min/ 1.73 m2 after a median of 15 years of follow-up; half of these patients did not show preceding albuminuria[21]. Also, in the Diabetes Control and Complications Trial (DCCT) study, 11 % of patients with type 1 DM developed an eGFR < 60 ml/min/ 1.73 m2 of which 40 % never had preceding albuminuria[22].

Different pathophysiologic pathways seem involved in the development of diabetic nephropathy. Hyperglycemia is essential in the development of diabetic nephropathy as kidney cells are unable to downregulate their glucose transporters in the setting of extracellular hyperglycemia and this subsequently results in an increase in their intracellular glucose concentration[23]. High intracellular glucose levels trigger pathogenic mediators such as reactive oxygen species and protein kinases which lead to cellular dysfunction, inflammation, apoptosis and fibrosis[24]. Although hyperglycemia is essential of the development of diabetic nephropathy, it is rarely the only contributor. Genetic factors influence onset and progression of kidney disease, as genome-wide association studies (GWAS) highlighted genetic variants associated with risk of CKD in large populations independent of actual glucose regulation[25]. Also environmental factors (e.g infections, heavy metals)[26], higher blood pressure[27-29], lipid abnormalities, (especially elevated triglycerides)[30, 31] and adiposity[32] contribute to diabetic nephropathy in type 1 DM as well as type 2 DM.

The "gold standard" for the diagnosis of diabetic nephropathy is a histopathology diagnosis. This invasive diagnostic procedure is however not routinely performed in clinical care settings because of a small risk related to this procedure (bleeding, haematuria) and often the lack of therapeutic consequences. Histopathologically, diabetic nephropathy can be categorized in four stages[33]. The first stage is characterized by isolated glomerular basement membrane thickening, the second phase by mesangial expansion in > 25 % of the total mesangium, the third phase is defined as nodular sclerosis, defined by at least one Kimmelstiel-Wilson lesion and less than 50 % diffuse global glomerulosclerosis and the fourth phase is defined as more than 50 % diffuse global glomerulosclerosis. The clinical relevance of knowing the exact stage in a patient is often limited; staging does not add predictive information regarding the progression of kidney failure, which is the case for other histopathological classifications for other renal diseases such as lupus nephritis[34].

Glycemic control and development of diabetic nephropathy

The importance of treatment of glycemic control in the development of CKD is illustrated by the DDCT/EDIC trial (1375 participants) in which improving glycemic control, reducing the HbA1c level of 9.1 % to 7.3 % in T1DM, lead to a reduction of progression to ESRD in 50 % of patients (16 compared to 8 events) and a slower decline in renal function (eGFR < 60 ml/min/ 1.73 m2 in 46 compared to 24 events) [35]. Moreover, pancreas transplantation in patients with type 1 DM is able to ameliorate the renal histopathological changes associated with diabetes, although this improvement is shown after at least 10 years of normoglycemia[36].

The ADVANCE trial (11,140 participants) showed that intensive glucose control (HbA1c target 6.5% or less) reduced the risk of ESRD in T2DM by 65% (20 compared to 7 events), microalbuminuria by 9% (1298 compared to 1410 patients), and macroalbuminuria by 30% (162 compared to 231 patients)[37]. Also the VDAT trial showed beneficial long term renal outcomes with intensive glycemic control[38]. Nevertheless, a substantial proportion of patients with DM still developed CKD. Furthermore "newer" glucose lowering agents have shown beneficial outcomes on cardiovascular and renal endpoints. Sodium glucose cotransporter-2 (SGLT2) inhibitors, working through inhibition of glucose reabsorption in the proximal kidney tubule and thereby lower plasma glucose levels, prevented the decline in GFR by about 40 % in patients with

type 2DM[39, 40]. Doubling of the serum creatinine level occurred after 2.6 years in 70 of 4645 patients (1.5%) in the empagliflozin (a SGLT2-inhibitor) group and in 60 of 2323 (2.6%) in the placebo group[41]. Mind however that the number needed to treat (that is, the number of patients to be treated to prevent one renal event such as creatinine doubling is substantial: around 100 patients need to be treated 2.9 years to prevent one diabetes related renal event. Several other effects than improvement in glucose control may contribute to renal and cardiovascular protection; lowering of blood pressure, decrease in intraglomerular pressure, reduction in albuminuria, and amelioration of volume overload are all plausible protective mechanisms[42-45]. Also glucagon like peptide receptor agonist (GLP-1ra), lowers plasma glucose levels. GLP-1ra enhances glucose-dependent insulin secretion, delay gastric emptying, and reduce postprandial glucagon secretion and food intake. GLP-1 ra, were associated with a lower risk of developing macro-albuminuria[46, 47]. Similar to the actions of SGLT2 inhibitors on the reno-cardiovascular system, it is likely that the beneficial effects of GLP-1 receptor agonists are also multifactorial, mediated by actions on body weight and blood pressure[48].

While the prevalence of DM (especially T2DM) is dramatically increasing, the incidence rates of ESRD due to diabetes declined from 2006 through 2012, and these rates remained stable in recent years[49]. This suggests improvement in care for patients with diabetes mellitus, which included not only improvement in glucose control, but also improvement in blood pressure treatment and lipid control, with an accompanying reduction in cardiovascular risk and associated mortality[50, 51].

End stage renal disease and diabetes mellitus

Diabetic nephropathy is the leading cause of end-stage-renal disease worldwide, although the majority of patients die from a cardiovascular event before reaching ESRD[52]. Diabetes as the primary cause of renal disease is responsible for 23% of the patients starting renal replacement therapy (RRT) in Europe and almost 50% in the USA[53, 54]. In patients with DM and ESRD the overall mortality risk is twofold higher than in non-diabetic patients with ESRD [55, 56]. In line, survival among dialysis patients with diabetes mellitus is inferior to survival of non-diabetic dialysis[57-59]. Patients with diabetic nephropathy have the largest number of co-morbid conditions within the ESRD population when compared with non-diabetic dialysis patients,

including retinopathy, foot disease including amputation, neuropathy, cognitive decline, mood disorders and cardiovascular disease[60]. The severity of co-morbid conditions and severity of CKD is strongly associated with adverse health related quality of life[61, 62].

Patients with DM have the highest mortality risk within the dialysis population. But this mortality risk might be different within the diabetes population with ESRD and be related to the severity of diabetic complications. It could be that mortality risk differs between patients with diabetes as a primary cause of ESRD and patients with diabetes as a co-morbid condition and a non-diabetic cause of ESRD. In that case a higher prevalence of diabetes related co-morbid conditions, could translate into an increased mortality risk.

Outline of this thesis

The overall aim of this thesis is to contribute to the understanding of the association between diabetes and several clinical aspects of chronic kidney disease.

In the first part of this thesis we describe the association between chronic kidney disease (CKD) and glucose metabolism. In **chapter 2** we estimate the prevalence of chronic kidney disease (CKD) among a Dutch sample of middle-aged adults and examine the association between glucose metabolism, obesity and chronic kidney disease (CKD). Furthermore, we examined the association between measures of glucose metabolism and measures of kidney function.

In the second part of this thesis we studied survival in patients with diabetes mellitus and ESRD. In **chapters 3 and 4** we compared survival in a dialysis population between patients with diabetes as primary renal disease and patients with diabetes as a co-morbid condition. Previous studies assessing survival made no distinction between patients with diabetes as primary renal disease and as a co-morbid condition. In patients with diabetic nephropathy, organ damage is likely not limited to the kidney but may also involve other organs resulting in retinopathy, neuropathy, diabetic foot disease and cardiovascular complications. In contrast, patients on dialysis with diabetes only as a co-morbid condition may have less pronounced organ damage. Therefore, we hypothesized that survival in patients on dialysis with diabetes as co-morbid condition may be better compared to patients with ESRD due to diabetic

nephropathy. In **chapter 3** we assessed and compared survival in a relatively small cohort of Dutch dialysis patients and in **chapter 4** we assessed and compared survival in a large sample of dialysis patients from 7 different European countries. In **chapter 5** we made a prediction model in order to predict 1-year mortality for diabetic incident dialysis patients. Survival among dialysis patients with diabetes mellitus is inferior to survival of non-diabetic dialysis patients and this might be related to the higher prevalence of diabetes related complications. Therefore, in **chapter 6** we assessed survival after amputation in diabetic patients compared to non-diabetic patients on dialysis. We hypothesized that these co-morbid conditions also contribute to a decreased survival in diabetic patients compared to non-diabetic patients on dialysis.

The results of the studies described in this thesis are summarized, discussed and put into clinical context in **chapters 7 and 8.**

References

1. IDF Diabetes Atlas - 8th Edition, Diabetes Atlas www.diabetesatlas.org 2017.
2. Ng, M., et al., Global, regional, and national prevalence of overweight and obesity in children and adults during 1980-2013: a systematic analysis for the Global Burden of Disease Study 2013. Lancet, 2014. 384(9945): p. 766-81.
3. Diabetes, C., et al., The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. N Engl J Med, 1993. 329(14): p. 977-86.
4. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). UK Prospective Diabetes Study (UKPDS) Group. Lancet, 1998. 352(9131): p. 837-53.
5. Afkarian, M., et al., Clinical Manifestations of Kidney Disease Among US Adults With Diabetes, 1988-2014. JAMA, 2016. 316(6): p. 602-10.
6. de Boer, I.H., et al., Temporal trends in the prevalence of diabetic kidney disease in the United States. JAMA, 2011. 305(24): p. 2532-9.
7. de Boer, I.H. and D.E.R. Group, Kidney disease and related findings in the diabetes control and complications trial/epidemiology of diabetes interventions and complications study. Diabetes Care, 2014. 37(1): p. 24-30.
8. US Renal Data System: 2017 USRDS annual data report: Epidemiology of kidney disease in the United States, Bethesda, MD, National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases. 2017.
9. Tancredi, M., et al., Excess Mortality among Persons with Type 2 Diabetes. N Engl J Med, 2015. 373(18): p. 1720-32.
10. Lind, M., et al., Glycemic control and excess mortality in type 1 diabetes. N Engl J Med, 2014. 371(21): p. 1972-82.
11. Kimmelstiel, P. and C. Wilson, Intercapillary Lesions in the Glomeruli of the Kidney. Am J Pathol, 1936. 12(1): p. 83-98 7.
12. Mogensen, C.E. and C.K. Christensen, Predicting diabetic nephropathy in insulin-dependent patients. N Engl J Med, 1984. 311(2): p. 89-93.
13. Mogensen, C.E., Microalbuminuria predicts clinical proteinuria and early mortality in maturity-onset diabetes. N Engl J Med, 1984. 310(6): p. 356-60.
14. Adler, A.I., et al., Development and progression of nephropathy in type 2 diabetes: the United Kingdom Prospective Diabetes Study (UKPDS 64). Kidney Int, 2003. 63(1): p. 225-32.
15. Berhane, A.M., et al., Albuminuria and estimated glomerular filtration rate as predictors of diabetic end-stage renal disease and death. Clin J Am Soc Nephrol, 2011. 6(10): p. 2444-51.
16. Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney diseaseKidney Int Suppl, 3, 2013: p. 1-150.
17. Thomas, M.C., et al., The burden of chronic kidney disease in Australian patients with type 2 diabetes (the NEFRON study). Med J Aust, 2006. 185(3): p. 140-4.

18. Dwyer, J.P., et al., Renal Dysfunction in the Presence of Normoalbuminuria in Type 2 Diabetes: Results from the DEMAND Study. Cardiorenal Med, 2012. 2(1): p. 1-10.
19. Hasslacher, C., et al., Similar risks of nephropathy in patients with type I or type II diabetes mellitus. Nephrol Dial Transplant, 1989. 4(10): p. 859-63.
20. Stevens, P.E., A. Levin, and M. Kidney Disease: Improving Global Outcomes Chronic Kidney Disease Guideline Development Work Group, Evaluation and management of chronic kidney disease: synopsis of the kidney disease: improving global outcomes 2012 clinical practice guideline. Ann Intern Med, 2013. 158(11): p. 825-30.
21. Retnakaran, R., et al., Risk factors for renal dysfunction in type 2 diabetes: U.K. Prospective Diabetes Study 74. Diabetes, 2006. 55(6): p. 1832-9.
22. Molitch, M.E., et al., Development and progression of renal insufficiency with and without albuminuria in adults with type 1 diabetes in the diabetes control and complications trial and the epidemiology of diabetes interventions and complications study. Diabetes Care, 2010. 33(7): p. 1536-43.
23. Brasacchio, D., et al., Hyperglycemia induces a dynamic cooperativity of histone methylase and demethylase enzymes associated with gene-activating epigenetic marks that coexist on the lysine tail. Diabetes, 2009. 58(5): p. 1229-36.
24. Brownlee, M., Biochemistry and molecular cell biology of diabetic complications. Nature, 2001. 414(6865): p. 813-20.
25. Sandholm, N., et al., New susceptibility loci associated with kidney disease in type 1 diabetes. PLoS Genet, 2012. 8(9): p. e1002921.
26. Obrador, G.T., et al., Genetic and environmental risk factors for chronic kidney disease. Kidney International Supplements, 2017. 7(2): p. 88-106.
27. Derby, L., et al., Elevated blood pressure predicts the development of persistent proteinuria in the presence of poor glycemic control, in patients with type I diabetes. Diabete Metab, 1989. 15(5 Pt 2): p. 320-6.
28. Schmitz, A., M. Vaeth, and C.E. Mogensen, Systolic blood pressure relates to the rate of progression of albuminuria in NIDDM. Diabetologia, 1994. 37(12): p. 1251-8.
29. Tanaka, Y., et al., Role of glycemic control and blood pressure in the development and progression of nephropathy in elderly Japanese NIDDM patients. Diabetes Care, 1998. 21(1): p. 116-20.
30. Tolonen, N., et al., Lipid abnormalities predict progression of renal disease in patients with type 1 diabetes. Diabetologia, 2009. 52(12): p. 2522-30.
31. Thomas, M.C., et al., Serum lipids and the progression of nephropathy in type 1 diabetes. Diabetes Care, 2006. 29(2): p. 317-22.
32. de Vries, A.P., et al., Fatty kidney: emerging role of ectopic lipid in obesity-related renal disease. Lancet Diabetes Endocrinol, 2014. 2(5): p. 417-26.
33. Tervaert, T.W., et al., Pathologic classification of diabetic nephropathy. J Am Soc Nephrol, 2010. 21(4): p. 556-63.
34. Weening, J.J., et al., The classification of glomerulonephritis in systemic lupus erythematosus revisited. J Am Soc Nephrol, 2004. 15(2): p. 241-50.
35. Group, D.E.R., et al., Intensive diabetes therapy and glomerular filtration rate in type 1 diabetes. N Engl J Med, 2011. 365(25): p. 2366-76.

36. Fioretto, P., et al., Reversal of lesions of diabetic nephropathy after pancreas transplantation. N Engl J Med, 1998. 339(2): p. 69-75.
37. Perkovic, V., et al., Intensive glucose control improves kidney outcomes in patients with type 2 diabetes. Kidney Int, 2013. 83(3): p. 517-23.
38. Agrawal, L., et al., Long-term follow-up of intensive glycaemic control on renal outcomes in the Veterans Affairs Diabetes Trial (VADT). Diabetologia, 2018. 61(2): p. 295-299.
39. Neal, B., V. Perkovic, and D.R. Matthews, Canagliflozin and Cardiovascular and Renal Events in Type 2 Diabetes. N Engl J Med, 2017. 377(21): p. 2099.
40. Wanner, C., S.E. Inzucchi, and B. Zinman, Empagliflozin and Progression of Kidney Disease in Type 2 Diabetes. N Engl J Med, 2016. 375(18): p. 1801-2.
41. Wanner, C., et al., Empagliflozin and Progression of Kidney Disease in Type 2 Diabetes. N Engl J Med, 2016. 375(4): p. 323-34.
42. Cherney, D.Z., et al., Renal hemodynamic effect of sodium-glucose cotransporter 2 inhibition in patients with type 1 diabetes mellitus. Circulation, 2014. 129(5): p. 587-97.
43. Lv, J., et al., Effects of intensive blood pressure lowering on the progression of chronic kidney disease: a systematic review and meta-analysis. CMAJ, 2013. 185(11): p. 949-57.
44. Vallianou, N.G., E. Geladari, and C.E. Kazazis, SGLT-2 inhibitors: Their pleiotropic properties. Diabetes Metab Syndr, 2017. 11(4): p. 311-315.
45. Baartscheer, A., et al., Empagliflozin decreases myocardial cytoplasmic Na(+) through inhibition of the cardiac Na(+)/H(+) exchanger in rats and rabbits. Diabetologia, 2017. 60(3): p. 568-573.
46. Mann, J.F.E., D.D. Orsted, and J.B. Buse, Liraglutide and Renal Outcomes in Type 2 Diabetes. N Engl J Med, 2017. 377(22): p. 2197-2198.
47. Marso, S.P., et al., Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes. N Engl J Med, 2016. 375(19): p. 1834-1844.
48. Sarafidis, P., et al., SGLT-2 inhibitors and GLP-1 receptor agonists for nephroprotection and cardioprotection in patients with diabetes mellitus and chronic kidney disease. A consensus statement by the EURECA-m and the DIABESITY working groups of the ERA-EDTA. Nephrol Dial Transplant, 2019. 34(2): p. 208-230.
49. Saran, R., et al., US Renal Data System 2017 Annual Data Report: Epidemiology of Kidney Disease in the United States. Am J Kidney Dis, 2018. 71(3S1): p. A7.
50. Emdin, C.A., et al., Blood pressure lowering in type 2 diabetes: a systematic review and meta-analysis. JAMA, 2015. 313(6): p. 603-15.
51. Griffin, S.J., et al., Effect of early intensive multifactorial therapy on 5-year cardiovascular outcomes in individuals with type 2 diabetes detected by screening (ADDITION-Europe): a cluster-randomised trial. Lancet, 2011. 378(9786): p. 156-67.
52. Navaneethan, S.D., et al., Diabetes Control and the Risks of ESRD and Mortality in Patients With CKD. Am J Kidney Dis, 2017. 70(2): p. 191-198.
53. Noordzij, M., et al., Renal replacement therapy in Europe: a summary of the 2011 ERA-EDTA Registry Annual Report. Clin Kidney J, 2014. 7(2): p. 227-38.
54. Saran, R., et al., US Renal Data System 2016 Annual Data Report: Epidemiology of Kidney Disease in the United States. Am J Kidney Dis, 2017. 69(3 Suppl 1): p. A7-A8.

55. Villar, E., S.H. Chang, and S.P. McDonald, Incidences, treatments, outcomes, and sex effect on survival in patients with end-stage renal disease by diabetes status in Australia and New Zealand (1991 2005). Diabetes Care, 2007. 30(12): p. 3070-6.
56. Karame, A., et al., The Impact of type 2 diabetes on mortality in end-stage renal disease patients differs between genders. Nephron Clin Pract, 2009. 112(4): p. c268-75.
57. Liem, Y.S., et al., Comparison of hemodialysis and peritoneal dialysis survival in The Netherlands. Kidney Int, 2007. 71(2): p. 153-8.
58. Vonesh, E.F., et al., The differential impact of risk factors on mortality in hemodialysis and peritoneal dialysis. Kidney Int, 2004. 66(6): p. 2389-401.
59. Van Dijk, P.C., et al., Renal replacement therapy for diabetic end-stage renal disease: data from 10 registries in Europe (1991-2000). Kidney Int, 2005. 67(4): p. 1489-99.
60. Lok, C.E., et al., The growing volume of diabetes-related dialysis: a population based study. Nephrol Dial Transplant, 2004. 19(12): p. 3098-103.
61. Dukes, J.L., et al., Health-related quality of life in kidney transplant patients with diabetes. Clin Transplant, 2013. 27(5): p. E554-62.
62. Campbell, K.H., et al., Association between estimated GFR, health-related quality of life, and depression among older adults with diabetes: the Diabetes and Aging Study. Am J Kidney Dis, 2013. 62(3): p. 541-8.