Diabetes Research and Treatment

Open Access

Received: Oct 21, 2014
Accepted: Dec 12, 2014
Published: Dec 15, 2014

DOI:10.14437/2377-7206-1-116 Research Carl J Ostgren, Diabetes Res Treat Open Access 2014, 1:4

Prevalence of Chronic Kidney Disease in Unselected Swedish Patients with Type 2 Diabetes and its Association with Cardiovascular Disease

Carl J Ostgren[1*], Anders Broijersen[2], Lars Weiss[3] and Maria K Svensson[4]

[1]Department of Medical and Health Sciences, Linkoping University, Linkoping, Sweden

[2]Boehringer Ingelheim, Stockholm, Sweden

[3]Department of Nephrology, Central Hospital, Karlstad, Sweden

[4]Department of Medicine, Sahlgrenska Academy at the University of Gothenburg, Gothenburg, Sweden

Abstract

Aim: To estimate the prevalence of Chronic Kidney Disease (CKD) and albuminuria and its associations to prevalent cardiovascular co-morbidities in patients with type 2 diabetes in a primary care setting in Sweden.

Patients and Methods: Cross-sectional data on demography, laboratory measurements, current medication, previous cardiovascular disease and major events of hypoglycaemia during the last 12 months was consecutively recorded from 53 primary care centers. Stage of CKD was defined based on the presence of albuminuria and estimated Glomerular Filtration Rate (eGFR) according to KDIGO. Albuminuria was measured using the urinary albumin-creatinine ratio.

Results: We included 362 men and 226 women aged 68.5±9.3 years with a mean diabetes duration 9.9±7.2 years. 220 patients (37%) were categorized as having CKD stage 1-5, 105 subjects (18%) CKD 1-2, and 115 subjects (20%) CKD 3-5. In the CKD 1-5 categories, micro albuminuria was prevalent in 128 (58.2%) subjects and macro albuminuria in 27 (12.3%) subjects. The Odds Ratio (OR), adjusted for age and gender, for subjects with CKD 3-5 for having retinopathy was 2.71 (95% CI 1.14 to 6.25, p=0.02) and for myocardial infarction 1.91 (95% CI 1.04 to 3.45, p=0.03) compared with CKD 0-2. Levels of hemoglobin were lower (133 ±14 g/L vs. 143 ±12 g/L) in CKD 3-5 compared to CKD 0-2 (p<0.01). Furthermore, the prevalence of vascular disease (p=0.03) and ischemic stroke (p=0.02) were higher in subjects with albuminuria compared with individuals without.

Conclusion: Chronic kidney disease is common in type 2 diabetes in a primary care setting and associated with prevalent vascular co-morbidities

Keywords: Renal function; Albuminuria; Cardiovascular disease; Type 2 diabetes; Chronic Kidney Disease

***Corresponding Author**: Carl J Ostgren, Department of Medical and Health Sciences, Linkoping University, Linkoping, Sweden; Tel: +46 (0) 13 281698 ;+46 (0)706694225; E-mail: carl.johan.ostgren@liu.se

Introduction

The incidence and prevalence of Type 2 Diabetes (T2D) is increasing worldwide [1] and diabetes increases the risk of developing End Stage Renal Disease (ESRD) 10-12 times [2]. Diabetic nephropathy is currently the main underlying primary disease for renal replacement therapies, i.e. dialysis and kidney transplantation, in many countries [3].Even though T2D is one of the leading causes of ESRD not all patients with T2D

develop renal dysfunction and ESRD during their lifetime [4]. It is estimated that T2D affects approximately 3.5% (350 000 individuals) of the Swedish population [5]. Albuminuria is a well-known risk marker for development of diabetic nephropathy and predicts progression to ESRD [6]. In addition, both albuminuria and reduced renal function are independent predictors of Cardio Vascular Disease (CVD), as well as cardiovascular and all-cause mortality in T2D [7] and thus has a great impact on the cost and burden for the society and quality of life for affected patients and families.

Even though a population-based Swedish study focusing on renal function recently has been published [8], the prevalence of albuminuria and renal impairment measured with validated methods in an unselected Swedish primary care diabetic population is still unclear. Thus, the present study was undertaken with the primary objective to investigate the prevalence of Chronic Kidney Disease (CKD) in Swedish patients with type 2 diabetes in a primary care setting. Secondary objectives included a description of cardiovascular comorbidity, metabolic profile and current anti-hyperglycaemic treatment in patients with and without CKD.

Patients and Methods

Study centers and Population

In total, 588 patients from 53 primary care centers participated in the trial. The homogeneity of patients was ensured as patients were recruited from all parts of Sweden (Götaland 50%, Svealand 17% and Norrland 33%). Thus, the regions were fairly proportionally represented as compared to the number of inhabitants in the regions (Götaland 48%, Svealand 40% and Norrland 12%), respectively. Patients were eligible for inclusion if they gave their informed consent and had been diagnosed with T2D after the age of 40, and had at least one year duration of the disease. Patients diagnosed with type 1 diabetes or secondary diabetes and patients participating in another clinical study with active drug treatment were excluded. Data were collected between November 2011 and March 2012 from clinical examination and medical charts during single regular outpatient visits. The study protocol was approved by local ethics review committees and conducted in accordance with the guidelines of the declaration of Helsinki.

Measurements and Definitions

From each patient the following parameters were collected from the charts and verbally during the visit; age, gender, height, body weight, office blood pressure, diabetes duration, current glucose lowering therapy, history of micro- or macro-vascular disease, smoking status, antihypertensive and or lipid lowering treatment. History of vascular disease was defined as previous or known; angina pectoris, myocardial infarction, coronary artery bypass surgery, percutaneous coronary intervention, and ischemic stroke. The patients were asked if they had ever been laser-treated for retinopathy and if they had experienced any event of hypoglycaemia requiring assistance during the last 12 months. The latest available laboratory value during the last 12 months for creatinine, HbA1c, total-cholesterol, LDL- and HDL-cholesterol, triglycerides and hemoglobin were collected from charts.

The presence of albuminuria was measured by urinary albumin-creatinine ratio. Sites that were using another method for measuring albuminuria or having urinary data older than 6 months were asked to use the appropriate methodology and/or to collect a new sample. The urinary albumin-creatinine ratio were analysed according to routines at the primary health care centres. The investigators were asked to define whether the collected urinary sample was taken in the morning or as a random spot sample. Patients with a morning urinary albumin-creatinine ratio below 3.0 g albumin/mol creatinine were considered not to have albuminuria, those between 3.0 and 30 to have micro albuminuria and those above 30 albumin/mol creatinine to have macro albuminuria [9]. In those patients where a random spot sample was used, the detection limit for micro albuminuria was defined as 5.0 g albumin/mol creatinine or above [9]. Morning samples were available in 413 (70.2%) cases, random spot samples in 127 (21.6%) subjects, and lost samples in 48 (7.5%) cases. The prevalence of Chronic Kidney Disease (CKD) was determined based on the presence of albuminuria and decreased estimated Glomerular Filtration Rate

(eGFR) measured according to the Modification of Diet in Renal Disease (MDRD) [10].

The CKD stages were categorized based on the classification system established by the Kidney Disease: Improving Global Outcomes (KDIGO) [11].

The CKD stages were defined as follows:

- CKD 0 eGFR ≥60 mL/min/1.73 m^2 without albuminuria
- CKD 1 eGFR ≥90 mL/min/1.73 m^2 with albuminuria
- CKD 2 eGFR 60-89 mL/min/1.73m^2 with albuminuria
- CKD 3 eGFR 30-59 mL/min/1.73m^2
- CKD 4 eGFR 15-29 mL/min/1.73 m^2
- CKD 5 eGFR <15 mL/min/1.73 m^2

Statistical significance was assumed when $p < 0.05$ and borderline statistical significance was assumed when $p < 0.1$.

Results

This cross-sectional study included 588 individuals with T2D. Their mean age was 68.5 ±9.3 years (range 41–92) and 362 (62%) were men. The mean diabetes duration was 9.9±7.2 years (range 1-35). Mean HbA1c was 55±13 mmol/mol (range 29–149). Table 1a and 1b show the baseline characteristics and cardiovascular risk factor status of the study population by CKD stage. No major differences in HbA1c, lipids or blood pressure were found between patients with and without renal impairment. Levels of haemoglobin were lower, 133 ±14 g/L vs. 143 ±12 g/L, in CKD stage 3-5 compared to stage 0-2, $p<0.01$ after adjustment for age and gender.

Table 1a: Baseline characteristics of study the population included in PRIDE: Prevalence of Renal Impairment in Diabetes by CKD stage

	Total (N=588)	CKD 0 (N=368)	CKD 1 (N=46)	CKD 2 (N=59)	CKD 3-5(N=115)
Gender					
Female	226 (38.4)	140 (38.0)	14 (30.4)	21 (35.6)	51 (44.3)
Male	362 (61.6)	228 (62.0)	32 (69.6)	38 (64.4)	64 (55.7)
Age (years)	68.5 (9.3)	66.7 (8.9)	64.2 (8.8)	71.7 (8.0)	74.6 (8.1)
Age group (years)					
40 – 49	19 (3.2)	16 (4.3)	3 (6.5)	-	-
50 - 59	69 (11.7)	52 (14.1)	10 (21.7)	5 (8.5)	2 (1.7)
60 - 69	243 (41.3)	176 (47.8)	20 (43.5)	18 (30.5)	29 (25.2)
70 - 79	177 (30.1)	93 (25.3)	10 (21.7)	25 (42.4)	49 (42.6)
80 +	80 (13.6)	31 (8.4)	3 (6.5)	11 (18.6)	35 (30.4)
BMI (kg/m²)	29.6 (4.8)	29.4 (4.7)	31.4 (6.4)	29.5 (4.7)	29.5 (4.4)
Systolic blood pressure (mmHg)	135.4 (14.9)	133.8 (13.6)	136.9 (13.3)	139.7 (18.2)	137.7 (16.9)
Diastolic blood pressure (mmHg)	77.1 (9.9)	77.1 (9.4)	79.8 (8.7)	77.4 (10.6)	76.0 (11.3)
Duration of diabetes (years) #					
1 - 5	191 (32.5)	145 (39.4)	9 (19.6)	13 (22.0)	24 (20.9)
6 - 10	179 (30.4)	112 (30.4)	23 (50.0)	16 (27.1)	28 (24.3)

	Total (N=588)	CKD 0 (N=368)	CKD 1 (N=46)	CKD 2 (N=59)	CKD 3-5(N=115)
>10	215 (36.6)	110 (29.9)	12 (26.1)	30 (50.8)	63 (54.8)
Smoking					
Non-smoker	305 (51.9)	186 (50.5)	21 (45.7)	31 (52.5)	67 (58.3)
Ex-smoker	221 (37.6)	143 (38.9)	17 (37.0)	20 (33.9)	41 (35.7)
Smoker	61 (10.4)	38 (10.3)	8 (17.4)	8 (13.6)	7 (6.1)

Data are mean (sd) or n (%). CKD stages; see methods section.

Data on diabetes duration were missing in 3 cases

Table 1b: Biochemical characteristics of the study population included in PRIDE: Prevalence of Renal Impairment in Diabetes by CKD stage

	Total (N=588)	CKD 0 (N=368)	CKD 1 (N=46)	CKD 2 (N=59)	CKD 3-5 (N=115)
S-Creatinine (µmol/L)	81.6 (27.5)	72.4 (14.5)	61.2 (10.5)	81.5 (13.4)	119.2 (34.9)
HbA1c (mmol/mol)	55 (13)	53 (12)	68 (19)	58 (13)	55 (13)
HbA1c (%)	7.2 (1.2)	7.0 (1.1)	8.4 (1.7)	7.5 (1.2)	7.2 (1.2)
P-Cholesterol (mmol/L)	4.68 (1.07)	4.67 (1.00)	5.09 (1.13)	4.63 (1.01)	4.55 (1.22)
P-LDL-cholesterol (mmol/L)	2.65 (0.90)	2.69 (0.86)	2.91 (0.97)	2.58 (0.94)	2.44 (0.93)
P-HDL-cholesterol (mmol/L)	1.25 (0.40)	1.24 (0.38)	1.33 (0.54)	1.28 (0.42)	1.21 (0.39)
P-Triglycerides (mmol/L)	1.91 (1.24)	1.82 (1.20)	2.01 (1.45)	1.97 (1.06)	2.13 (1.37)
Hemoglobin (g/L)	140.7 (13.2)	142.7 (12.2)	145.2 (13.6)	140.0 (12.2)	133.4 (13.7)

Data are mean (sd) or n (%). CKD stages; see methods section.

In subjects without micro albuminuria, mean eGFR, according to MDRD, was 82.7 ±23.2 mL/min/1.73m^2 and 75.0 ±28.7 mL/min/1.73m^2 in subjects with micro or macro albuminuria (data not in table). Data on the prevalence of CKD and micro and macro albuminuria are shown in Table 2. 220 (37.4%) patients had CKD 1-5 and 368 (62.6%) patients were classified as CKD 0. Mean eGFR, according to MDRD, was 80.6 ±25.0 mL/min/1.73m^2 and mean estimated creatinine clearance (eCrCl) was 97.2±39.9 mL/min according to Cockcroft-Gault. In the CKD 1-5 categories, micro albuminuria was prevalent in 128 (58.2%) subjects and macro albuminuria in 27 (12.3%) subjects.

Table 3 displays ongoing medication by CKD stage. Overall, the majority of patients were treated with biguanides as glucose-lowering agent (68%), followed by insulin (33%) and sulphonylureas (14%). In patients with reduced renal function (CKD 3-5) an increase in the use of insulin and sulphonylureas was seen (39 and 20%, respectively), paralleled by a decrease in use of biguanides but, interestingly, 50% of patients with CKD 3-5 had ongoing treatment with metformin.

Table 2: Renal function and prevalence of micro- and macroalbuminuria in the study population included in PRIDE: Prevalence of Renal Impairment in Diabetes

	Total (N=588)	CKD 0 (N=368)	CKD 1 (N=46)	CKD 2 (N=59)	CKD 3-5 (N=115)
eGFR (ml/min/1.73m²) according to MDRD	80.6 (25.0)	88.1 (20.5)	108.7 (20.3)	74.3 (8.4)	48.3 (9.7)
eCrCl (ml/min) according to Cockroft-Gault	97.2 (39.9)	106.6 (35.5)	139.6 (45.7)	86.1 (23.5)	56.1 (16.1)
Albuminuria					
normo	431 (73.3)	368 (100.0)	NA	NA	63 (54.8)
micro	128 (21.8)	NA	39 (84.8)	53 (89.8)	36 (31.3)
macro	27 (4.6)	NA	7 (15.2)	6 (10.2)	14 (12.2)

Data are mean (sd) or n (%). CKD stages; see methods section.

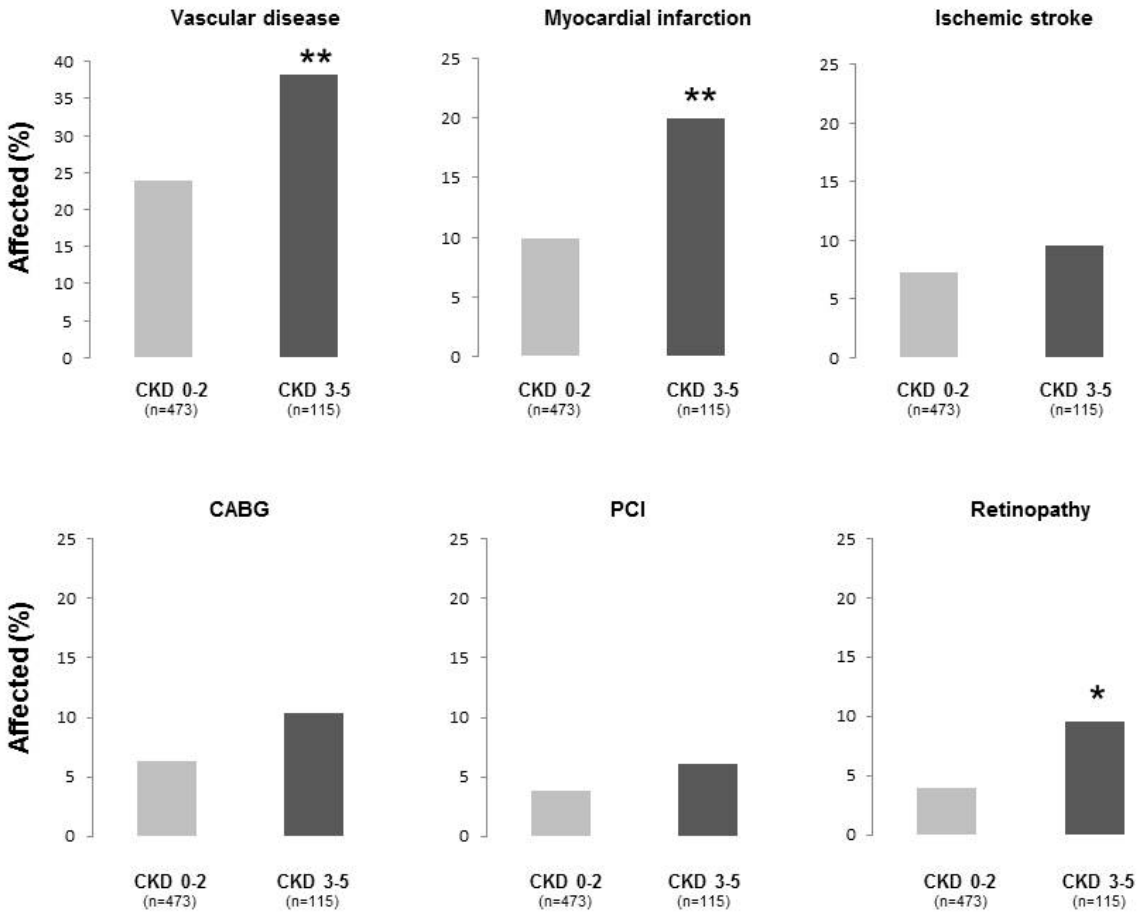
Table 3: Ongoing medication in study population included in PRIDE: Prevalence of Renal Impairment in Diabetes

Glucose lowering treatment[1]	Total (N=588)	CKD 0 (N=368)	CKD 1 (N=46)	CKD 2 (N=59)	CKD 3-5 (N=115)
Insulins and analogues	193 (32.8)	103 (28.0)	17 (37.0)	28 (47.5)	45 (39.1)
Biguanides	397 (67.5)	258 (70.1)	39 (84.8)	42 (71.2)	58 (50.4)
Sulfonamides, urea derivatives	84 (14.3)	43 (11.7)	9 (19.6)	9 (15.3)	23 (20.0)
Fixed dose combinations of oral blood glucose lowering drugs	12 (2.0)	5 (1.4)	1 (2.2)	3 (5.1)	3 (2.6)
Alpha glucosidase inhibitors	1 (0.2)	-	-	-	1 (0.9)
Thiazolidinediones	8 (1.4)	2 (0.5)	1 (2.2)	2 (3.4)	3 (2.6)
Dipeptidyl peptidase 4 (DPP-4) inhibitors	38 (6.5)	20 (5.4)	7 (15.2)	3 (5.1)	8 (7.0)
Repaglinide	14 (2.4)	9 (2.4)	3 (6.5)	1 (1.7)	1 (0.9)
Exenatide	3 (0.5)	3 (0.8)	-	-	-
Liraglutide	22 (3.7)	11 (3.0)	6 (13.0)	2 (3.4)	3 (2.6)
Antihypertensive treatment					
ACE / ARB	405 (68.9)	243 (66.0)	32 (69.6)	45 (76.3)	85 (73.9)
Other	87 (14.8)	49 (13.3)	6 (13.0)	7 (11.9)	25 (21.7)
No treatment	96 (16.3)	76 (20.7)	8 (17.4)	7 (11.9)	5 (4.3)
Lipid treatment					
Statins	393 (66.8)	245 (66.6)	29 (63.0)	42 (71.2)	77 (67.0)
Other	38 (6.5)	18 (4.9)	4 (8.7)	5 (8.5)	11 (9.6)
No treatment	157 (26.7)	105 (28.5)	13 (28.3)	12 (20.3)	27 (23.5)

[1] One or more combinations possible. Data are n (%). CKD stages; see methods section.

The prevalence of micro and macro vascular disease by CKD stage is shown in Figure 1. The Odds Ratio (OR), adjusted for age and gender, for subjects in CKD stages 3-5 for having retinopathy was 2.71 (CI 1.14 to 6.25, p=0.02) and for myocardial infarction 1.91 (CI 1.04 to 3.45, p=0.03) compared with CKD stages 0-2. The difference in previous cardiovascular disease between the groups in CKD stage 0-2 vs. 3-5 did not remain statistically significant when adjusted for age and gender, p=0.18.The prevalence of vascular disease (p=0.03) and ischemic stroke (p=0.02) were higher in subjects with albuminuria compared with individuals without. However, only the OR for previous stroke remained borderline statistically significant 1.87 (CI 0.98 to 3.52, p=0.054) when adjusted for age and gender. Previous experience of hypoglycaemia was more common in CKD stage 3-5 (n=3; 2.6%) compared to stage 0-2 (n = 2; 0.4%) and the OR, adjusted for age and gender, for subjects in CKD stages 3-5 for having hypoglycaemia was 8.71 (CI 1.19 to 80.11, p=0.03). However, this observation must be interpreted with caution due to the small numerical difference and the clinical relevance of the finding could be questioned.

Figure 1: Micro- and macrovascular disease according to CKD stage (CKD 0-2 vs 3-5) in the study population included in PRIDE: Prevalence of Renal Impairment in Diabetes



Vascular disease was defined as a composite of; myocardial infarction, ischemic stroke, Coronary Artery Bypass surgery (CABG) and Percutaneous Coronary Intervention (PCI).

Discussion

In this cohort of unselected patients with T2D were studied at their annual out-patient control visit in the primary care setting one-third of patients had some degree of chronic kidney disease and one-fifth had reduced renal function (eGFR<60 mL/min/1.73m^2). Furthermore, both albuminuria and renal impairment were associated with an increased risk of prevalent vascular co-morbidities. To the best of our knowledge this is the first study exploring the prevalence of chronic kidney disease by using urinary albumin-creatinine ratio for defining albuminuria and in an unselected Swedish primary care diabetic population. One limitation of the study is that the stratification for albuminuria and eGFR were based on only one reported value as both the levels of urinary albumin and serum creatinine have well known within-person day-to-day variations. In this study we used the MDRD equation to estimate renal function since this currently is the most commonly used equation although other renal markers and equations could have been considered [12]. However, the strengths of this study are that the same method to measure absence or presence of albuminuria was used and that clinically relevant co-morbidities endpoints for retinopathy (laser-treated) and hypoglycemia (major-requiring assistance) were reported and are presented.

In this study the majority (55%) of patients with renal impairment was normoalbuminuric which is in accordance with results from different populations with T2D [13-16]. This finding is important since patients with reduced renal function have a CV mortality that is 10-20-fold compared to age-matched subjects in the general population [17] and is strongly accentuated when renal function is lower than eGFR <45 mL/min/1.73m^2 [18]. In addition, an increased level of albuminuria is associated with increased risk of CV events, CV mortality and all-cause mortality in patients with T2D in any significant CKD stage [7].

In this study we found an increased risk for having a previous myocardial infarction in patients with reduced renal function compared to those with normal function. In addition, the prevalence of previous cardiovascular disease including ischemic stroke seemed to be higher in patients with albuminuria compared with individuals without albuminuria, but when adjusting for age and gender only previous stroke remained borderline statistically significant.An interesting finding in this study was that 50% of the patients with an eGFR < 60ml/min/1.73m^2 had biguanide/metformin treatment despite the risk of lactic acidosis. The National Institute for Health and Clinical Excellence (NICE) U.K has recently updated the guidelines on the use of metformin such that metformin may be continued (or initiated) in patients with eGFR <60 mL/min per 1.73 m^2 but the dose should be reduced in those with eGFR <45 mL/min per 1.73 m^2 and metformin should be discontinued at eGFR <30 mL/min per 1.73 m^2 [19]. The safety of metformin at different levels of renal function has also been evaluated in a Swedish population-based study [20]. Concomitant retinopathy is clinically often considered to be a concomitant finding with in patients with diabetic nephropathy. However, it has previously been shown that the association between retinopathy and nephropathy in T2D is weak and recent studies has shown that only around 40% of T2D patients with renal impairment and micro albuminuria have concomitant retinopathy [21, 22]. In this study, the risk of having diagnosed laser-treated retinopathy increased in patients with both albuminuria (non-significantly) and renal impairment (significantly). It is therefore important to highlight that up to one third of patients with T2D may have other primary underlying renal diseases as previously shown in renal biopsy studies [23]. Alterations in the coagulation/fibrinolytic system with a balance towards a more coagulant state could contribute to the increased risk for venous thromboembolism found in patients with diabetes [24] and renal impairment [25]. We conclude that the occurrence of chronic kidney disease, as measured by the presence of significantly decreased GFR (< 60 ml/min/1.73m^2) with or without albuminuria, is very common in Swedish patients with type 2 diabetes in primary care. The majority of patients with mild to moderate renal impairment were normoalbuminuric. However, both albuminuria and renal impairment were associated with an increased risk of prevalent vascular co-morbidities.

References

1. Wild S, Roglic G, Green A, Sicree R, King H (2004) Global prevalence of diabetes: estimates for the year 2000 and projections for 2030. Diabetes Care 27:1047-53
2. Brancati FL, Whelton PK, Randall BL, Neaton JD, Stamler J et al (1997) Risk of end-stage renal disease in diabetes mellitus: a prospective cohort study of men screened for MRFIT. Multiple Risk Factor Intervention Trial. JAMA 278:2069-74
3. Williams ME. Diabetic CKD/ESRD: a progress report? (2010) Semin Dial. 23:129-33
4. Adler AI, Stevens RJ, Manley SE, Bilous RW, Cull CA et al; UKPDS GROUP (2003) Development and progression of nephropathy in type 2 diabetes: the United Kingdom Prospective Diabetes Study (UKPDS 64). Kidney Int. 63:225-32
5. Gudbjornsdottir S, J. Cederholm J, Nilsson PM, Eliasson B (2003) The National Diabetes Register in Sweden: an implementation of the St. Vincent Declaration for Quality Improvement in Diabetes Care. Diabetes Care 26:1270-6
6. de Zeeuw D, Remuzzi G, Parving HH, Keane WF, Zhang Z et al (2004) Proteinuria, a target for renoprotection in patients with type 2 diabetic nephropathy: lessons from RENAAL. Kidney Int. 65:2309-20
7. Sasso FC, Chiodini P, Carbonara O, De Nicola L, Conte G et al (2011) High cardiovascular risk in patients with Type 2 diabetic nephropathy: the predictive role of albuminuria and glomerular filtration rate. The NID-2 Prospective Cohort Study. Nephrol Dial Transplant 2012;27:2269-74. doi: 10.1093/ndt/gfr644
8. Afghahi H, Miftaraj M, Svensson AM, Hadimeri H, Gudbjörnsdottir S, Eliasson B et al (2013) Ongoing treatment with renin-angiotensin-aldosterone-blocking agents does not predict normoalbuminuric renal impairment in a general type 2 diabetes population J Diabetes Complications: 27:229-34
9. The European Confederation of Laboratory Medicine (2000). European Urinalysis Guidelines. Scand J Clin Lab Invest 60:1-96
10. Levey AS, Coresh J, Greene T, Stevens LA, Zhang YL et al (2006) Using standardized serum creatinine values in the modification of diet in renal disease study equation for estimating glomerular filtration rate. Ann Intern Med.145:247-54
11. Levey AS, Eckardt KU, Tsukamoto Y, Levin A, Coresh J et al (2005) Definition and classification of chronic kidney disease: a position statement from Kidney Disease: Improving Global Outcomes (KDIGO). Kidney Int. 67:2089-100
12. Rigalleau V, Beauvieux MC, Gonzalez C, Raffaitin C, Lasseur C, Combe C et al (2011) Estimation of renal function in patients with diabetes Diabetes Metab 37 359-66
13. Yokoyama H, Sone H, Oishi M, Kawai K, Fukumoto Y et al (2009) Prevalence of albuminuria and renal insufficiency and associated clinical factors in type 2 diabetes: the Japan Diabetes Clinical Data Management study (JDDM15). Nephrol Dial Transplant 24:1212-9
14. Rigalleau V, Lasseur C, Raffaitin C, Beauvieux MC, Barthe N et al (2007) Normoalbuminuric renal-insufficient diabetic patients: a lower-risk group. Diabetes Care 30:2034-9
15. Penno G, Solini A, Bonora E, Fondelli C, Orsi E et al (2011) Clinical significance of nonalbuminuric renal impairment in type 2 diabetes. Journal of hypertension 29:1802-9
16. Thomas MC, Macisaac RJ, Jerums G, Weekes A, Moran J et al (2009) Nonalbuminuric renal impairment in type 2 diabetic patients and in the general population (national evaluation of the frequency of renal impairment cO-existing with NIDDM [NEFRON] 11). Diabetes Care 29:1497-502

17. Foley RN, Parfrey PS, Sarnak MJ. (1998) Epidemiology of cardiovascular disease in chronic renal disease, J Am Soc Nephrol 9:S16-23
18. Go AS, Chertow GM, Fan D, McCulloch CE, Hsu CY (2004) Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization, N Engl J Med 351:1296-305
19. Lipska KJ, Bailey CJ, Inzucchi SE (2011) Use of Metformin in the Setting of Mild-to-Moderate Renal Insufficiency. Diabetes Care 34:1431-1437
20. Ekström N, Schiöler L, Ekström N1, Schiöler L, Svensson AM et al (2012) Effectiveness and safety of metformin in 51 675 patients with type 2 diabetes and different levels of renal function: a cohort study from the Swedish National Diabetes Register. BMJ Open.13;2(4). pii: e001076. doi: 10.1136/bmjopen-2012-001076
21. Manaviat MR, Afkhami M, Shoja MR (2004) Retinopathy and microalbuminuria in type II diabetic patients. BMC Ophthalmol. 4:9
22. Chen H, Zheng Z, Huang Y, Guo K, Lu J et al (2012) A microalbuminuria threshold to predict the risk for the development of diabetic retinopathy in type 2 diabetes mellitus patients. PloS one 7:e36718
23. Mazzucco G, Bertani T, Fortunato M, Bernardi M, Leutner M et al (2002) Different patterns of renal damage in type 2 diabetes mellitus: a multicentric study on 393 biopsies. Am J Kidney Dis 39:713-20
24. Petrauskiene V, Falk M, Waernbaum I, Norberg M, Eriksson JW (2005) Diabetologia. 48(5):1017-21
25. Wattanakit Cushman M, Stehman-Breen C, Heckbert SR, Folsom AR (2008) J Am Soc Nephrol.19(1):135-40