

## Onset of End-Stage Renal Disease and Prevalence of Vascular Diseases at the Start of Dialysis in Type 2 Diabetic Patients with Diabetic and Vascular Nephropathy

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### Abstract

**Background:** End-Stage Renal Disease (ESRD) in type 2 diabetic patients with renal disease can be observed after a varying duration of diabetes. The aim of the study was to investigate differences between type 2 diabetic patients with diabetic nephropathy (dNP) versus Vascular Nephropathy (vNP).

**Patients and Methods:** We investigated 90 uremic type 2 diabetic patients before start of dialysis. According to clinical diagnosis 66 patients had dNP (72%) and 20 patients vNP (24%) and four patients a chronic glomerulonephritis was diagnosed (4%). The clinical diagnosis was confirmed by histological findings in 40 patients, of them in 28 patients with dNP and in 12 subjects a histological finding was available. In 14 cases a kidney biopsy performed and in 26 patients a post-mortem biopsy at autopsy.

Differences in the onset of ESRD in the presence of dNP and vNP were evaluated. Additionally, at the start of dialysis we investigated the prevalence of vascular diseases in relation to renal disease and diabetes duration.

**Results:** The patients were divided into 3 groups, depending on the duration of diabetes. In group 1 diabetes duration was <15 years (n=30), In group 2 duration was 15-20 years (n=44), and in group 3 >20 years (n=16). The majority of the patients with dNP had diabetes for 15-20 years (50%) while most of those with vNP usually had diabetes for <15 years (55%). The prevalence of vascular diseases was similar in both groups. The prevalence of coronary artery disease was slightly higher in patients with dNP but not significant.

**Conclusion:** In patients with dNP the duration of diabetes until onset of ESRD was longer than in patients with vNP, however, marked variations were found. At onset of ESRD the prevalence of vascular diseases was similar in patients with dNP and vNP, though in the vNP group the diabetes duration was significantly longer. This can be explained by a higher age of the patients with vNP. Diabetes – end-stage renal disease – diabetic nephropathy – vascular nephropathy – vascular diseases.

### Introduction

In type 2 diabetics, End-Stage Renal Disease (ESRD) commences after diabetes varying duration. In the published literature ESRD has been largely reported in diabetic patients after a disease duration of 20 years [1]. Histological investigations have shown diabetic nephropathy (dNP) to be the cause of renal failure only in 70-80% of type 2 diabetic patients [2]. The remaining 20-30% are related to non-diabetic renal disease, most of these patients have vNP, in rare cases a glomerulonephritis is the cause of ESRD [3].

The aim of the present study was to investigate the relationship between the duration of diabetes and the onset of ESRD in type 2 diabetic patients with dNP versus vNP. Additionally, at the start of dialysis therapy we evaluated the prevalence of vascular disease in relation to the duration of diabetes in patients with dNP as well as those with vNP.

### Patients and Methods

All type 2 diabetic patients with ESRD who had started dialysis therapy at our dialysis centre between 2004 and 2009, were screened for this study (114): Patients with inaccurate diagnosis of renal disease (n=8), heart insufficiency and NYHA IV (n=8) as well as malignant or severe systemic diseases (n=8) were excluded. Thus a total of 90 patients were included in this retrospective study. According to clinical diagnosis dNP was present in 66 patients (73%), and vNP in 20 patients (23%). Four patients (4%) had chronic glomerulonephritis.

Diagnosis of type 2 diabetes was assumed in patients with onset of diabetes after age 35 years and no insulin requirement during the first 3 years diabetes duration.

The clinical diagnosis of dNP was based on long-acting diabetes (10 years and more) the presence of proteinuria, normal urine sediment as well as a normal kidney size in the renal sonogram and diabetic retinopathy. The clinical diagnosis of vNP was based on long acting diabetes, normal urine (no proteinuria), normal urine sediment; and

severe atherosclerosis and/or a shrinkage of a kidney in the sonogram. The clinical diagnosis was confirmed by histological investigation in 40 patients, of them in 28 patients with dNP and in 12 patients with vNP : (histological findings by renal biopsy (n=14) and by post-mortem biopsy at autopsy (n=26). In each group only one false clinical diagnosis could be observed, the sensitivity of the clinical diagnosis was high ( 95% in the dNP and 83% in the vNP group). We measured creatinine (Cr), BUN, Cr-clearance and protein (24-hour urine), estimated urine sediment, and performed an electrocardiogram, a sonogram of the kidneys, a Duplex scan of the carotids artery, and a Doppler ultrasound investigation of leg arteries. We investigated differences in the onset of dNP and vNP as well as we evaluated the prevalence of vascular diseases at the start of dialysis. These vascular diseases included cerebrovascular disease (CVD), coronary artery disease (CAD) and peripheral artery disease (PAD) have been defined in the published literature [3].

### Statistics

The Student's t-test was used to compare continuous variables and the Qui-test for dichotomous variables. Wilcoxon's test was used to compare differences between groups with not normally distributed data. A p-value less than 0.05 was considered statistically significant. The SPSS for Windows statistical (software) was used for statistical calculations.

### Results

The clinical diagnosis (dNP in 66 and vNP in 20 patient) was confirmed by histological findings in 40 patients. Histological findings were available in 28 patients with dNP and 12 patients with vNP. The 90 patients were divided into three groups according to the duration of diabetes: group I had diabetes <15 years (n=30), group II had diabetes for 15-20 years (n=44) and group III had diabetes for >20 years (n=16). Baseline data presented in Table 1.

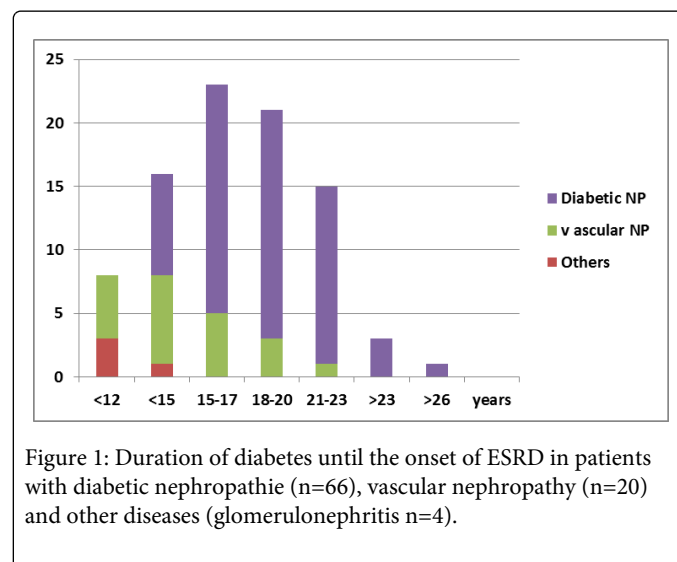
The prevalence of NP and vNP in relation to the duration of d50 diabetes is shown in Table 2. The majority (50%) of the patients with dNP had a diabetes duration of 15 to 20 years, in the majority (55%) of the subjects with vNP diabetes duration was <15 years. In the same group onset of ESRD was observed in the four patients with glomerulonephritis.

|   | dNP(n=66) | vNP(n=20) | Others(n=4) |
|---|-----------|-----------|-------------|
| Age (years)                               | 59+9*     | 66+8*     | 52-6        |
| Sex (% fem)                               | 48%       | 55%       | 50%         |
| Caucasian (%)                             | 100%      | 100%      | 100%        |
| HbA1c (%)                                 | 7.8+1.2   | 7.9+1.2   | 7.6+0.9     |
| Antidiabetic therapy (n/%)                |           |           |             |
| Sulfonylurea oral                         | 12 (18%)  | 4 (20%)   | 0           |
| Insulin conventional                      | 24 (36%)  | 10 (50%)  | 0           |
| Insulin intensified                       | 24 (36%)  | 6 (30%)   | 0           |
| Diet alone                                | 6 (10%)   | 2 (10%)   | 4 (100%)    |
| Serum Creatinine (mg/dl)                  | 6.8 ± 1.2 | 7.2 ± 1.4 | 6.2 ± 1.2   |
| Cr-clearance (ml/min/1.73m <sup>2</sup> ) | 12 (4-16) | 8 (2-12)  | 7 (6-14)    |

|                      |          |          |          |
|----------------------|----------|----------|----------|
| Hypertention (n/%)   | 62 (93%) | 19 (95%) | 1 (25%)  |
| ACE inhibitors (/%)  | 41 (62%) | 12 (60%) | 0        |
| Cholesterol (mg/l)   | 146 ± 26 | 142 ± 29 | 165 ± 32 |
| Trglycerides (mg/dl) | 152 ± 30 | 148 ± 38 | 145 ± 34 |
| Smoking (n/%)        | 24 (36%) | 7 (35%)  | 1 (25%)  |
| *p>0.05              |          |          |          |

**Table 1:** Baseline data of patients with diabetic nephropathy (cNP) and vascular nephropathy (vNP) as well as other renal diseases with ESRD.

The mean duration of diabetes until the onset of ESRD was 21+6 (range, 12-28) years in patients with dNP and 15+5 (range: 11-22) years in those with vNP (p>0.05). The different diabetes duration before the occurrence of ESRD in patients with dNP and vNP is shown in Figure 1.



**Figure 1:** Duration of diabetes until the onset of ESRD in patients with diabetic nephropathie (n=66), vascular nephropathy (n=20) and other diseases (glomerulonephritis n=4).

|                                  | Duration of diabetes |                   |                   |
|----------------------------------|----------------------|-------------------|-------------------|
|                                  | < 15 years(n=30)     | 15-20 years(n=44) | > 20 years (n=16) |
| Diagnosis of renal disease (n/%) |                      |                   |                   |
| Diabetic nephropathy             | (12%)                | 33 (50%)          | 5 (30%)           |
| Vascular nephropathy             | 11 (55%)             | 8 (40%)           | 1 (5%)            |
| Other renal disease              | 4 (100%)             | 0                 | 0                 |
| *p<0.05                          |                      |                   |                   |

**Table 2:** Onset of ESRD of renal diseases depends on the duration of diabetes

At the start of dialysis the prevalence of vascular disease in relation to renal disease was slightly higher in patients with dNP and also slightly higher in patients with a longer duration of diabetes (NS). The highest prevalence was seen in patients with CAD, dNP and a long duration of diabetes (53%).

The prevalence of vascular diseases (%) at the start of dialysis in relation to renal disease a duration of diabetes can be seen in Table 3.

|              | dNP   |        |        | vNP    |       |       | Others |
|--------------|-------|--------|--------|--------|-------|-------|--------|
|              | <15   | 15-20  | >20    | <15    | 15-20 | >20   |        |
| Patients (n) | (n=8) | (n=42) | (n=16) | (n=16) | (n=3) | (n=1) | (n=4)  |
| CVD (%)      | 38    | 40     | 42     | 32     | 36    | 40    | 25     |
| CAD (%)      | 44    | 48     | 53     | 42     | 46    | 48    | 25     |
| PAD (%)      | 36    | 42     | 48     | 35     | 38    | 44    | 25     |

Table 3: Prevalence of vascular diseases (%) at the start of dialysis in relation to renal disease and duration of diabetes

## Discussion

We compared the diabetes duration till onset of ESRD. In uremic type 2 diabetic patients with dNP and/or vNP as well as other renal diseases. The published literature provides accurate data about the duration of diabetes until the onset of ESRD for type I diabetics. In a Swedish cohort study on childhood-onset diabetes, the median duration of diabetes was 21 years. Pre-pubertal onset of diabetes appears to prolong the time until the development of ESRD [4].

Controversial data have been reported for type 2 diabetic patients (1). In type 2 diabetes with diabetic nephropathy, ESRD occurs after varying durations of diabetes. It may be assumed, however, that diabetes and micro-albuminuria existed long before it was diagnosed. The main reason for the varying duration of diabetes until the onset of ESRD in type 2 diabetes is probably genetic predisposition [5]. In a recent study it was reported that early-onset type 2 diabetes mellitus is associated with substantially higher prevalence of ESRD and mortality in middle age due to the longer duration of diabetes (5). Moreover, ethnic differences have been registered in susceptibility to renal disease.

Pima Indians show a higher cumulative incidence of ESRD 15 years after the onset of proteinuria (61%) than do Caucasians [6,7]. The duration of diabetes until the onset of ESRD is also dependent on the rate of decline in GFR during the pre-dialysis period, which can be influenced by ACE inhibitor therapy [8,9]. However, in patients with already deteriorating renal function, the rate of decline in GFR is similar in type 1 and type 2 diabetic subjects [9,10]. There is substantial evidence to show that early treatment delays the onset of diabetic nephropathy as well as the onset of ESRD [11,12] During the last years the incidence of uremia in type 1 diabetes remained unchanged, in contrast to the subjects with Type 2 diabetes [13]. In type 2 diabetic patients the onset of ESRD also depends on the primary renal disease (dNP) and non diabetic renal diseases. Especially vascular nephropathy (20-30%), other non-diabetic diseases are rare cases. In our study we compared risk factors for vascular diseases in the patients with ESRD due to diabetic or vascular NP or other renal diseases.

The patients showed no significant differences, only the mean age was higher in the vNP patients. Further more, we evaluated the onset of ESRD of each patient and divided the groups in those with onset of ESRD after 15-20 or <15 or >20 years.

The differential diagnosis of dNP and vNP is clinically and histologically possible. In the published literature, diverse histological findings have been reported in uremic patients with type 2 diabetes:

dNP (nodular and diffuse glomerulosclerosis) was reported in 70-80%, vascular (ischemic) nephropathy (vascular change without evidence of glomerulosclerosis) in 10 to 15 %non-diabetic renal disease superimposed on diabetic superimposed on diabetic glomerulosclerosis in 5 to 10% [2]. Histological findings in dNP are diffuse and nodular glomerulosclerosis, including mesangial expansion, interstitial fibrosis and inflammation, arteriolar hyalinosis, and tubular atrophy.

In vascular disease one finds vascular changes. Vascular (ischemic) nephropathy has not been conclusively established as the cause of ESRD. Its incidence has increased in the last few years. It should be noted that a number of functional and anatomic tests are needed to diagnose this pathology [12,13].

We evaluated the onset of dNP and vNP in relation to the duration of diabetes. In diabetic patients, ESRD has been reported to occur 15 to 20 years after manifestation of diabetes [8] In our patients with dNP, the onset of ESRD was most commonly (50%) observed in group 2(15-20 years of diabetes duration). In patients with vNP the onset of ESRD was most commonly (55%) registered in group 1 (<15 years of diabetes duration). The data are summarised in Table 2. The mean duration of diabetes until the onset of ESRD was 21+6 (range, 12-24) years in patients with dNP and 15+5 (range, 11-22) years in those with vNP. The duration of diabetes until the onset of ESRD is shown in Figure 1.

As regards the prevalence of vascular disease at the start of dialysis in dNP versus vNP) and in relation to the duration of diabetes, the mean prevalence of vascular disease was slightly higher in dNP, and tended to increase with the duration of diabetes (NS) These data are similar to those reported in the published literature [14,15]. The difference can be explained by the higher age of patients with vNP and the longer duration of diabetes in dNP patients.

## Conclusion

The onset of ESRD in patients with dNP was in the majority (50%) 15-20 years after the diagnosis of diabetes. In patients with vNP, the duration of diabetes was in a majority (50%) below 15 years. The prevalence of vascular disease was only slightly higher (NS) in patients with dNP, though the diabetes duration was significantly higher in the dNP group. This could be explained by a higher mean age in the group with vNP.

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