Frequency and prognosis of end-stage renal disease (ESRD) in diabetes: the Scottish experience

Diabetic nephropathy, mainly due to type 2 diabetes mellitus (T2DM), is becoming the leading cause worldwide of end-stage renal disease (ESRD), while other causes are decreasing. Diabetes is responsible in some countries for as many as half of the cases requiring renal replacement therapy (RRT). Recent data, available from registries from France and from the UK, show that in France, the number of patients with T2DM-related ESRD increased by 21% during the period 2007-2011, mostly explained by an increase in the number of cases. In the United-Kingdom, initiation of RRT in patients with diabetes increased during the period 1995-2009 from 12.3 to 27.6 patients/10^6 population.

Recent data, based on a nationwide study, provide accurate estimates of the prevalence of ESRD, need for RRT, and associated survival in patients with diabetes. Data were obtained and crossed from three Scottish national databases: Renal Registry, Care Initiative-Diabetes Collaboration, and National Records of death data. Survival analyses with Cox regression were performed in a selected cohort of 841 patients who had first received RRT from 2006 to 2011. On 31st May 2008, 187,285 patients with known eGFR status were registered as having type 1 diabetes (T1DM - 10%; n=19,414), or type 2 diabetes (90%; n=167,871). Patients with ESRD (n=1288) were identified by a CKD 5 score (Chronic Kidney Disease score), defined as eGFR less than 15 mL/min/1.73m^2, or on RRT. A minimum of two eGFR <15 mL/min/1.73 m^2 at least 3 months apart were required to eliminate acute kidney injury.

Prevalence of ESRD was 1.63% in T1DM and 0.58% in T2DM, with odds ratios for diabetes type 0.97 (P=0.77) after adjustment for known diabetes duration. Primary renal diagnosis was diabetic nephropathy in 91% of patients with T1DM, and 58% with T2DM on RRT. Among patients with diabetes and a CKD score of 5, 83% of those with T1DM and 61% with T2DM received RRT. RTT was less frequently performed in older patients with diabetes (only 39% of patients aged 75 years or more with diabetes and CKD5), explaining the difference. Prognosis of patients with diabetes at the ESRD stage was poor, with a median survival time after beginning of RRT of 3.84 years (95% CI 2.77-4.62) in T1DM patients, and of 2.16 years (1.92-2.38) in T2DM. For comparison, median survival for the overall population on RRT in Scotland was 4.1 years (95% CI 3.9-4.2).

Early and intensive prevention of diabetic nephropathy in T2DM patients is thus mandatory. The ADVANCE study has provided evidence that nephropathy can be prevented or even reversed in patients with T2DM. After a median 5-year follow-up, in the intensive glucose control group (mean HbA1c level 6.5% vs. 7.3% in control group), risk of ESRD was reduced by 65%, microalbuminuria by 9%, and macroproteinaemia by 30%. Even more promising, five years after the last visit of ADVANCE and cessation of intensive treatment, this significant reduction in the risk of ESRD, as defined by need for dialysis or renal transplant, was maintained (46%) in those patients originally targeting HbA1c to 6.5%.

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A high prevalence of nephropathy in patients with type 2 diabetes (T2D) has been reported in numerous studies, including NHANES IV in the USA,\textsuperscript{1} as well as cohort studies in Korea,\textsuperscript{2} China,\textsuperscript{3,4} and Japan.\textsuperscript{5} However, these data come from prospective studies performed using pre-specified tools in selected populations, and thus may not reflect the prevalence of diagnosed diabetic kidney disease as observed in primary care settings.

A recent Finnish study highlights the gap between the actual prevalence of chronic kidney disease, when screening is performed with appropriate tools, and the diagnosed prevalence of this complication in T2D along with related cardiovascular morbidity.\textsuperscript{6}

For this purpose, an observational cross-sectional population study was performed in patients with T2D treated in 42 primary care centres in Finland. In each site, 10 to 12 patients with T2D, aged 18 years or more, were enrolled between March 2011 and August 2012 at the time of their regular visit. The study population included 625 patients, (53.4 % men, mean age 66.6 years, range 29 to 92 years), with a median diabetes duration of 9.2 years (range 0 to 43 years), mean BMI 32.8 kg/m\textsuperscript{2}, HbA\textsubscript{1c} 7.1 %, and BP 141.8/80.3 mmHg. Dyslipidaemia was present in 73.3 % of patients, and hypertension in 82.7 %. Non-smokers made up 67.4 % and active smokers 10.6 %. The prevalence of laser-treated retinopathy was 13 %.

A diagnosis of diabetic nephropathy was noted in the records of 24.3 % of the patients and decreased estimated glomerular filtration rate (eGFR) (less than 60 mL/min/1.73 m\textsuperscript{2} - chronic kidney disease, CKD 3-5) was present in 16.2 % of patients. Only one patient was classified as CKD5. Increased albuminuria was found in 24.3 % of the study population, with microalbuminuria in 17.1 % and proteinuria in 7.2 %.

Results of the study indicate an overall prevalence of chronic kidney disease (CKD, grade 1-5), or increased albumin excretion of 68.6 %.

In conclusion, while a diagnosis of nephropathy was only documented in the medical records of less than 25 % of patients with T2D regularly followed in primary care centres, about 70 % of them presented with some sign of chronic kidney disease, and nearly half of the whole population had evidence of significant chronic kidney disease.

Thus, it is critical to perform a systematic screening for nephropathy in every patient with T2D at the time of the annual visit by measuring albuminuria and eGFR. Evidence is available that intensive control of both hyperglycemia\textsuperscript{7} and hypertension\textsuperscript{8,9} are effective in preventing and worsening of serious kidney disease, with a reversal in some cases.\textsuperscript{10}

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**Effect of metformin on glucagon-like peptide 1 (GLP-1) and leptin levels in obese non-diabetic subjects**

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**OBJECTIVE:**
To evaluate the effects of metformin on glucagon-like peptide 1 (GLP-1) and leptin levels.

**RESEARCH DESIGN AND METHODS:**
10 obese non-diabetic male patients were studied before and after a 14-day treatment with 2,550 mg/day of metformin and were compared with 10 untreated obese control subjects. On days 0 and 15, leptin and GLP-1-(7-36)amide / (7-37) levels were assessed before and after an oral glucose load during a euglycaemic hyperinsulinaemic clamp to avoid the interference of variations of insulinaemia and glycaemia on GLP-1 and leptin secretion. The effects of metformin on GLP-1-(7-36)amide degradation in human plasma and in a buffer solution containing dipeptidyl peptidase IV (DPP-IV) were also studied.

**RESULTS:**
Leptin levels were not affected by the oral glucose load, and they were not modified after metformin treatment. Metformin induced a significant (P < 0.05) increase of GLP-1-(7-36)amide / (7-37) at 30 and 60 min after the oral glucose load (63.8 +/- 29.0 vs. 50.3 +/- 15.6 μmol/l and 75.8 +/- 35.4 vs. 46.9 +/- 20.0 μmol/l, respectively), without affecting baseline GLP-1 levels. No variations of GLP-1 levels were observed in the control group. In pooled human plasma, metformin (0.1-0.5 μg/ml) significantly inhibited degradation of GLP-1-(7-36)amide after a 30-minute incubation at 37°C; similar results were obtained in a buffer solution containing DPP-IV.

**CONCLUSIONS:**
Metformin significantly increases GLP-1 levels after an oral glucose load in obese nondiabetic subjects. This effect could be due to an inhibition of GLP-1 degradation.

*“Metformin significantly increases GLP-1 levels after an oral glucose load in obese nondiabetic subjects. This could be due to an inhibition of GLP-1 degradation.”*

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**Lifestyle advice is the same for people with diabetes as for general public**

Lifestyle factors that increase the risk of illness and shorten life apply to people with diabetes in the same way as to the general public. This was suggested in a study by German researchers, which was published in "Diabetologia".

Scientists at the German Institute of Human Nutrition Potsdam-Rehbruecke formed a cohort of 6,384 people with diabetes and 258,911 control subjects from the participants in the EPIC-Study (European Prospective Investigation into Cancer and Nutrition). With the aid of computer models, they researched the relationship between mortality and risk factors such as BMI, various food-stuffs and physical activity.

Essentially, the mortality rate was higher among those with diabetes than the general public. However, the association between the different risk factors and mortality took the same direction in both groups. The recommendations given to the general public for a healthy lifestyle were therefore just as valid for people with diabetes. They probably benefitted even more from a healthy diet than the rest, according to the study authors.

*“The recommendations given to the general public for a healthy lifestyle were just as valid for people with diabetes.”*
**Diabetic ketoacidosis still too prevalent**

Diabetic ketoacidosis (DKA), a life-threatening condition caused by a severe lack of insulin, is still a big problem for adolescents in the US suffering from diabetes, US researchers write in *Pediatrics*.

Dana Dabelea and her colleagues at the University of Colorado, Denver, analysed data from more than 5,600 youths with type 1 and more than 1,400 youths with type 2 diabetes newly diagnosed between 2002 and 2010. The study shows that the frequency of DKA at diagnosis in US youth with type 1 diabetes did not decline over the last eight years, but remained high compared with other developed countries.

Specifically, DKA was detected in nearly a third of all young people with type 1 diabetes. Rates were disproportionately high in children younger than five years of age, non-white racial/ethnic groups, youth without private health insurance and those with lower family income. Among youths with type 2 diabetes, DKA was much less common and decreased over time, suggesting improved detection or earlier diagnosis of diabetes.

"Previous research suggests that increased community awareness of type 1 diabetes, including parental education and closer monitoring of signs and symptoms of diabetes, may be effective tools," Dabelea said, adding that improved health care access is also needed to reduce the observed health disparities.

**Possible ‘switch’ for type 2 diabetes discovered**

Canadian researchers may have discovered a ‘switch’ that regulates the insulin resistance seen in type 2 diabetes. Study leader Alexey Pshezhetsky from the Saint Justine University Hospital Research Center in Montreal reports in *Diabetes* that a protein was found that has not previously been associated with diabetes.

Experimenting with cell cultures and mice, the scientists revealed that the protein named after neuraminidase can turn the absorption of sugar on and off in the cells by regulating the amount of sialic acid on the surface of cells.

The researchers are now searching for ways to restore the Neu1-level. "If we can remove sialic acid residues from the cell surface, this will force the insulin receptor do its job of absorbing blood sugar properly", said Pshezhetsky. If this was successful, less insulin therapies would be necessary, the researcher said.

**Omega-3 can reduce diabetes risk**

Omega-3 fatty acids are known to have many beneficial properties. Earlier research results have been contradictory regarding their effect on diabetes, A Finnish study published in *Diabetes Care* now reports that they may reduce the likelihood of developing type 2 diabetes.

In an on-going long-term study, researchers at the University of Eastern Finland in Kuopio determined the serum omega-3 fatty acid concentrations of 2,212 Finnish men aged 42 to 60. During an average follow-up period of 19.3 years, 422 of the participants developed type 2 diabetes.

The participants were divided into four groups according to their omega-3 concentrations. The study showed that men with the highest levels had a 33 percent lower risk of developing type 2 diabetes compared to men with the lowest levels.

This reconfirms how important the consumption of fish is for a well-balanced diet, particularly regarding diabetes, said the authors. A diet should include at least two fish meals per week, especially fatty fish such as salmon, herring, sardine and mackerel.