Strict glycaemic control in diabetic patients with CKD or ESRD: beneficial or deadly?

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The evidence that strict glycaemic control is beneficial

Several large randomized controlled trials including the Diabetes Control and Complications Trial in type 1 diabetes [1] and the UK Prospective Diabetes Study [2] as well as the Kumamoto Study [3] in type 2 diabetes indicate that good glycaemic control can reduce the risk of nephropathy. More recently, the ADVANCE trial [4] documented in subjects with type 2 diabetes (T2DM) that strict glycaemic control (mean HbA1c: 6.5\%) in comparison with the standard control (mean HbA1c: 7.3\%) is associated with a significant reduction in renal events, including onset of or worsening of nephropathy [hazard ratio (HR) 0.79; \( P = 0.006 \)] and, in particular, development of macroalbuminuria (HR 0.70; \( P < 0.001 \)). Moreover, patients with macroalbuminuria and chronic kidney disease (CKD; eGFR 60 mL/min/1.73 m\(^2\) at baseline) had a 3.2-fold higher risk for cardiovascular (CV) events and a 22.2-fold higher risk for renal events compared with patients who had neither risk factor. In a study on kidney plus pancreas transplantation in type 1 diabetic patients, Morath \textsuperscript{5} had shown that metabolic control improves long-term renal allograft and patient survival. A recent Austrian cohort study [6] of 798 first renal allograft recipients with a diagnosis of diabetes mellitus prior to transplantation also showed that glucose control was significantly associated with patient and graft survival after renal transplantation.

Blood glucose control is more problematic in kidney disease

Can one extrapolate that these very positive renoprotective effects of intensive glucose control are seen in all diabetic patients with CKD or end-stage renal disease (ESRD)? Unfortunately, results of prospective randomized controlled intervention studies are not yet available to answer this clinically relevant question, despite the fact that diabetes is present in 25–50\% of patients with ESRD.

The evidence in CKD

Information about the effect of strict glycaemic control on outcome in diabetic patients with CKD is very limited. In the PROactive study (Prospective Pioglitazone Clinical Trial in Macrovascular Events), patients with type 2 diabetes and CKD (\( n = 597; 11.6\% \) of the 5154 patients) had a particularly high CV risk and cardiovascular disease (CVD) [7]. The incidence of the combined end point (non-fatal myocardial infarction, stroke and death) was 18.3\% in patients with CKD compared with 11.5\% in patients without CKD (HR 1.65; \( P < 0.0001 \)). In addition, all-cause mortality was 10.9\% compared to 5.9\% (HR 1.86) in those without CKD. Remarkably, patients who had CKD and were treated with pioglitazone were less likely to reach the combined end point (HR 0.66; \( P < 0.001 \)) independently of the severity of renal impairment [7]. Since at study end the HbA1c difference between pioglitazone and placebo was only 0.5\% (6.9 vs 7.4\%), presumably a variety of well-documented anti-atherogenic effects of pioglitazone [8] were responsible for CV protection in diabetic patients presenting with CVD.

The evidence in ESRD

It is well known that the 5-year survival is much lower in diabetic vs non-diabetic patients on HD [9]. During the last decade, several observational studies [10–14] were published indicating that the survival of diabetic patients on haemodialysis (HD) is influenced by the glycaemic control. Morioka \textsuperscript{10} evaluated the impact of glycaemic control on survival in 150 diabetic subjects with ESRD starting HD treatment. During the short follow-up period of 2.8 years, 76\% of the patients died; however, in those with good control (HbA1c < 7.5\%), mortality was lower than in those with poor glycaemic control (HbA1c ≥ 7.5\%). Oomichi \textsuperscript{11} found in a 7-year observational study of 114 diabetic patients on HD that mortality was similar in patients with good HbA1c <6.5\% and fair glycaemic control (HbA1c > 6.5\% \(< 8.0\% \)), but mortality was significantly higher (HR 2.89; \( P = 0.01 \)) in those with poor glycaemic control (HbA1c > 8.0\%). Hayashino \textsuperscript{12} analysed mortality in the large Japanese Dialysis Out-
comes and Practice Pattern Study on 1569 HD patients with diabetes and 3342 patients without diabetes. Mortality was significantly higher in diabetic patients on HD whose HbA1c was in the fifth quintile (HbA1c ≥ 7.3%), but was not different in the four quintiles with HbA1c ranging from 5.0 to 7.2%.

In contrast to these studies in Asian dialysis populations, no correlation between HbA1c and survival was found at 12 months in 24,875 US diabetic dialysis patients [15]. The failure to see a beneficial effect of glycaemic control may be explained by the underlying differences in the tools used to measure glycaemia. Kalantar-Zadeh et al. [13] evaluated 23,618 US diabetic HD patients and evaluated survival as a function of HbA1c. He observed that higher HbA1c values were incrementally associated with higher mortality. Compared with patients with HbA1c in the range of 5–6%, patients with HbA1c >10% had higher HRs of adjusted all-cause and CV death: 1.41 and 1.73 (P < 0.001), respectively. Remarkably, this relationship was only seen in patients without anaemia (Hb > 11.0 g/day; n = 19,316) and not in patients with anaemia or malnutrition. Recently, Drechsler et al. [14] investigated the impact of glycaemic control on cardiac and vascular outcomes in 1255 diabetic HD patients in the German Diabetes and Dialysis Study (4D Study). During 4 years of follow-up, patients with HbA1c >8.0% or HbA1c from >6 to <8% had an increased risk of sudden death (HR 1.85 and 2.26, respectively; P < 0.003) compared with patients with HbA1c <6.0%. In contrast, the risk of myocardial infarction and all-cause mortality did not differ between the three groups.

The problems of evaluating glycaemic control in ESRD

Unfortunately, HbA1c is not an ideal control parameter to assess glycaemic control in patients with advanced kidney disease. As early as 1979, HbA1 levels were measured in patients on HD or with CKD using ion exchange chromatography; even then, the accuracy of this method in patients with advanced CKD had been questioned [16]. In chronic renal failure, the lifespan of erythrocytes is shortened, and low HbA1c values may therefore be artificially low because of shorter exposure of erythrocytes to glycaemia. Thus, HbA1 and HbA1c, as indicators of long-term glycaemic control, should be interpreted with caution in patients with serum creatinine concentrations >2.5 mg/dL [16]. Two recent studies [17,18] confirmed that in diabetic HD patients, HbA1c levels significantly underestimate glycaemic control, while glycated albumin reflects glycaemic control more accurately. Unfortunately, this method is not widely available. In ESRD patients, lower HbA1c values were associated with lower haemoglobin concentration and higher doses of erythropoietin, reflecting shorter erythrocyte half-lives.

Should all diabetic patients be given the same antidiabetic treatment?

Currently, there is a worldwide debate whether all diabetic patients should be treated following the same algorithm as proposed in the American Diabetes Association–European
Association for the Study of Diabetes consensus [19] or whether alternatively a more individualized antidiabetic approach is appropriate, taking into account pathophysiological criteria (i.e., insulin resistance or insulin deficiency, comorbidity and risk of hypoglycaemia) [20].

Another point to consider is the cumulation of some oral antidiabetic agents or their metabolites. Furthermore, prolonged insulin half-life and low or absent renal gluconeogenesis put patients with CKD and ESRD at increased risk of severe hypoglycaemia. Therefore, aggressive glucose lowering with sulfonylureas or insulin should be avoided. Two reports from Japan [21] and Germany [22], respectively, documented that most emergency cases with severe hypoglycaemia had significantly impaired renal function and had been treated with either sulfonylurea agents or insulin. When the outcome was analysed in a UK observational study on 90 000 type 2 diabetic patients according to the type of oral antidiabetic drug, the use of sulfonylureas was associated with significantly increased mortality (HR 1.43) compared to metformin, whereas pioglitazone (HR 0.60) was associated with significantly lower mortality when compared with metformin [23].

Does antidiabetic treatment even increase mortality?

Two recent US observational studies [24,25] evaluated whether the type of antidiabetic treatment is relevant to the occurrence of death in haemodialysed diabetic patients. Brunelli et al. [24] assessed in a national cohort of 5290 incident US diabetic HD patients the effect of thiazolidinedione (TZD) use on survival. TZD use was associated with significantly lower all-cause mortality in insulin-free, but not in insulin-requiring, subjects; the adjusted HRs were 0.53 (0.31–0.89) and 0.82 (0.46–1.47), respectively. In contrast, in a much smaller study [25] of 2393 diabetic HD patients, treatment with rosiglitazone (n = 177), but not with pioglitazone (n = 1 18), was associated with a higher all-cause (HR 1.38) and CV mortality (HR 1.59; P < 0.02) compared with the use of non-TZD oral hypoglycaemic agents (n = 2050). For the selection of antidiabetic drugs (Figure 1), the degree of renal insufficiency is very important since many antidiabetic drugs are contraindicated in advanced chronic kidney disease (e.g., metformin, sitagliptin and miglitol) or require significant dose reduction (e.g., sulfonylureas, insulin, acarbose and exenatide).

Based on the available data, we recommend a HbA1c of 6.5–7.0% for the prevention of renal disease in diabetic patients, whereas in the advanced stages of diabetic kidney disease a higher HbA1c of about 7.5% is acceptable on the basis of available data especially for patients with established CVD [20]. Our suggestion is supported by a very large recent UK observational study [26] of 48 000 type 2 diabetic subjects in whom a median HbA1c of 7.5% was associated with the lowest mortality, whereas in those with a HbA1c of 6.4% mortality was higher in individuals on oral treatment (HR 1.52) and, in particular, those on insulin treatment (HR 1.79). These alarming observations are in line with the findings of the Action to Control Cardiovascular Risk in Diabetes (ACCORD) study [27], which showed that intensive glucose control (mean HbA1c: 6.5%) is associated with increased all-cause and CVD mortality in comparison to conventional therapy (mean HbA1c: 7.5%).

In conclusion, there is an urgent need for large prospective randomized studies in diabetic patients with CKD or on HD with the following goals: to compare different approaches of antidiabetic treatment and to study the efficacy and safety of different levels of glycaemic control.

Conflict of interest statement. None declared.

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The decades-long fight against HBV transmission to dialysis patients: slow but definite progress

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In the early days of haemodialysis (HD), hepatitis was frequent, both in patients and staff. The discovery in 1963 by Blumberg of the so-called Australia antigen in the serum of an aboriginal carrier, rewarded by the 1976 Nobel Prize, soon made it possible to demonstrate that the hepatitis B virus (HBV) was a major cause of hepatitis in HD. Screening blood donors with increasingly sensitive tests, understanding the routes of nosocomial HBV transmission, isolating HBV carriers in a separate HD room, and vaccinating HD patients and staff undoubtedly all contributed to the subsequent dramatic decrease of HBV incidence and prevalence in HD patients and virtually 0% incidence in staff [1]. Still, nosocomial HBV transmission remains a concern in HD patients, not only in emerging [2,3] but also in Western countries [4].

Many factors contribute to this persistent problem, the first being inadequate adherence to basic hygienic precautions. These are important for the prevention of transmission of all blood-borne pathogens (including HCV and HIV, in addition to HBV) and have recently been reviewed by the Kidney Disease Improving Global Outcomes (KDIGO) Hepatitis C Guidelines [5].

The second factor is the variability of actual vaccination rates. Indeed, in the USA in 2002 [6], only 56% of HD patients were given at least three doses of HBV vaccine. Similarly, in the UK [7], routine vaccination against HBV was even recently not offered to HD patients by most renal units. Interestingly, the reasons explaining this limited coverage include, a.o., a low perceived risk and impression of limited cost-effectiveness of vaccination [7]. Still, 15% of interviewed UK units experienced at least one recent seroconversion for HBV [7], a finding that contradicts the claim of low risk and suggests that vaccinating is indeed cost-effective as compared with the costly and disturbing management of seroconversions or even outbreaks. It should be stressed that suboptimal vaccination rates in HD are probably more common than seems apparent from the few available reports on this topic.