The association between albuminuria and long-term renal risk
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CHAPTER 1

Introduction
Introduction

Diabetes mellitus is a chronic disease evoked by lifestyle risk factors and/or genetic predisposition\(^1,2\) which causes a systemic lack of insulin and insulin resistance. The condition of diabetes impacts all organs, which is why it is often called a systemic disease. The involvement of the kidney however, may be the most important comorbidity in the life of a patient with diabetes, since it is an omen for an increased risk of a number of cardiovascular and renal complications. Albuminuria is present in about two-thirds of the diabetic population\(^3\) and is one of the earliest signs of diabetic nephropathy. Accordingly, diabetes mellitus has a major impact on the progression to end-stage renal disease (ESRD).\(^4\) In type 1 diabetes, 50% of the patients with overt nephropathy develop ESRD within 10 years.\(^4\) In patients with type 2 diabetes and microalbuminuria, 20% – 40% progress to overt nephropathy and of those, 20% will developed ESRD within 20 years.\(^4\) Since the worldwide incidence of diabetes is increasing,\(^5\) the prevalence of diabetic nephropathy and ultimately ESRD increases as well.\(^6\) To reduce the long-term risk for ESRD in patients with diabetes mellitus, more effective treatment approaches are required especially at early stages of the disease. In order to find novel therapeutics optimal endpoints with regards to statistical power and early occurrence in the progression of diabetic kidney disease should be used. However, currently used endpoints in clinical trials of diabetic nephropathy are late events in the progression of diabetic kidney disease. Subsequently, new treatments are mainly studied in late stages of the disease progression, and their efficacy in early stages of diabetic kidney disease is not assessed. To overcome such obstacles alternative (surrogate) endpoints such as albuminuria change are required to study drug efficacy in early stages of diabetic kidney disease.

There is strong evidence that albuminuria qualifies as surrogate endpoint in clinical trials of diabetic nephropathy. Firstly, in many studies in different populations, a consistent association between baseline albuminuria and long-term renal risk is observed. It is steadily shown that higher levels of albuminuria are associated with poor renal outcomes (Table 1).\(^7-9\)

One could hypothesize that this relationship is explained by the fact that a damaged kidney leaks more albumin: the more damage the more leakage. However, there is also evidence indicating that albuminuria itself is a causal and accelerating factor in the
Table 1. Association between baseline albuminuria and long-term renal risk
The IDNT and RENAAL trial populations were stratified by tertiles of baseline albuminuria and subsequently the risk for ESRD was calculated.

<table>
<thead>
<tr>
<th>Trial</th>
<th>Albumin:creatinine ratio (mg/g)</th>
<th>HR</th>
<th>95% CI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>IDNT</td>
<td>583.6 Ref.</td>
<td></td>
<td>Ref. Ref.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1500.0 2.64</td>
<td>1.90 – 3.68</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3434.0 8.04</td>
<td>5.92 – 10.90</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td></td>
<td>431.8 Ref.</td>
<td></td>
<td>Ref. Ref.</td>
<td></td>
</tr>
<tr>
<td>RENAAL</td>
<td>1245.5 2.33</td>
<td>1.71 – 3.12</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3215.0 8.62</td>
<td>6.53 – 11.37</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
</tbody>
</table>

*Median

progression of renal function decline. It is hypothesized that an increased permeability of the glomerular endothelial layer leads to albumin leakage into the glomerulus and proximal tubule. Leaking albumin exposes glomerular cells to albumin and/or attached toxins. In addition, tubular cells are exposed to access levels of albuminuria/toxins which triggers an inflammatory response that by itself further decreases kidney function and increases permeability of the glomeruli (Figure 1).

Figure 1. Association between albuminuria and progressive renal dysfunction. Increased permeability of the glomerular endothelial layer leads to albumin leakage into the glomerulus and proximal tubule. Thereby, exposing cells to access levels of albumin/toxins, which triggers an inflammatory response that by itself further increases permeability of the glomeruli and damages the renal interstitium and decreases kidney function.

The Nephron
Secondly, short-term drug induced reductions in albuminuria are associated with improved long-term renal outcomes, adding evidence that albuminuria is involved in the cause of the disease, and that albuminuria could and should be used as a valid surrogate endpoint (Table 2).

<table>
<thead>
<tr>
<th>Trial</th>
<th>Albumin:creatinine reduction</th>
<th>HR</th>
<th>95% CI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>IDNT</td>
<td>≤ -11.3%</td>
<td>Ref.</td>
<td>Ref.</td>
<td>Ref.</td>
</tr>
<tr>
<td></td>
<td>&gt; -11.3%</td>
<td>1.48</td>
<td>1.20 – 1.82</td>
<td>0.0002</td>
</tr>
<tr>
<td>RENAAL</td>
<td>≤ -9.4%</td>
<td>Ref.</td>
<td>Ref.</td>
<td>Ref.</td>
</tr>
<tr>
<td></td>
<td>&gt; -9.4%</td>
<td>1.37</td>
<td>1.14 – 1.64</td>
<td>0.0009</td>
</tr>
</tbody>
</table>

However, there is still uncertainty regarding the association between albuminuria changes and long-term renal risk. This uncertainty arises because first, the association between albuminuria and renal risk is not always present, second, because albuminuria reduction (with drug intervention) does not always lead to better renal protection, and third, the renal protective effects of drugs are not always associated with albuminuria reduction. In this thesis, we postulate that some of these non-supportive findings can be explained by the techniques and methods that were used to assess the association between albuminuria changes and risk for ESRD.

In previous studies the association between changes in albuminuria and renal risk reduction were analyzed within one trial without taking into account the placebo effect, leaving the results prone to bias and confounding. To reduce such bias, Inker et al. approached this problem by conducting a meta-analysis of clinical trials, which found no clear association between a reduction in albuminuria and risk for ESRD in the pooled analysis. One possible explanation for this lack of association may be due to the inclusion of many small trials with low event rates leading to low statistical power. Further, in that study, only trials conducted before 2007 were included, thereby missing results of recent, large clinical trials. Building on the work of Inker et al., in this thesis, we conduct a meta-analysis of clinical trials to assess this association. However, we include recent large clinical trials and restrict the included trials to a minimum event rate and patient follow-up time. This approach increases the statistical power of our analysis, allowing
for a more precise estimation of the association between albuminuria changes and renal risk.

Following the results of this meta-analysis, the question arises whether the initial change in albuminuria fully captures the long term renal risk. This is only a valid assumption if the initial drug response is stable during prolonged follow-up. Hence, we hypothesize that individual albuminuria fluctuations during prolonged follow-up dilute the association between the initial change in albuminuria and ESRD. If that is true, incorporating albuminuria changes, following the initial drug response in prediction models and treatment monitoring should improve renal risk prediction. Using these two approaches, a more complete understanding regarding the association between albuminuria changes and long-term renal risk can be achieved.

Apart from the above mentioned methodological issues, it is unknown how often albuminuria should be measured to assess albuminuria changes and to be used as a surrogate endpoint to assess drug efficacy in clinical trials of diabetic nephropathy. Often albuminuria change is determined between two predefined time-points, thereby neglecting variability over time. Therefore, in this thesis we study the impact of the number and frequency of urine collections for albuminuria assessment during follow-up on the precision of renoprotective drug effects.

The same holds true for the use of albuminuria transitions as endpoint in clinical trials of diabetic nephropathy. There is no optimal definition for an albuminuria transition (from normo- to microalbuminuria or from micro- to macroalbuminuria) used as an endpoint in clinical drug trials. Hence, different endpoint definitions based on a variable number of albuminuria measurements with or without requirement for confirmation or minimal required increase from baseline have been used. In this thesis, we explore whether improving the precision of drug effect estimates derived from albuminuria transitions would lead to a gain in statistical power to assess drug efficacy.

**Goal of this thesis**

To add evidence to the causal association between albuminuria changes and risk for end stage renal disease (ESRD) and subsequently improve the use of albuminuria changes between predetermined time-points as well as the use of albuminuria class transitions as endpoints in clinical trials of diabetic nephropathy.
Chapter 1

Part 1: Association between the initial albuminuria reduction and the risk for end stage renal disease

Chapter 2: Drug-induced reduction in albuminuria is associated with subsequent renoprotection - a meta-analysis

The progression of diabetic nephropathy to ESRD takes decades to manifest and is characterized by increasing albuminuria levels. Therefore, clinical trials that aim to study drug effects on ESRD would either only be conducted in high risk populations or would require an impractical long follow-up time in order to find a sufficient number of events for a precise drug effect assessment. Therefore, albuminuria has been proposed as a surrogate endpoint for clinical trials in diabetic nephropathy. Unfortunately, most evidence supporting the use of albuminuria as an endpoint in clinical trials is derived from observational studies which are prone to selection bias and residual confounding. Therefore, conducting a meta-analysis of clinical trials in order to correlate the placebo controlled drug effect on albuminuria and ESRD might reduce such bias. The second chapter of this thesis describes the methodology and results of this analysis.

Chapter 3: Individual long term albuminuria exposure during ARB therapy is the optimal predictor for renal outcome

Albuminuria is a good predictor and risk marker for renal morbidity and mortality. Therefore, the individual long-term renal risk can be estimated using the initial treatment effect on albuminuria. Connecting the initial lowering of albuminuria levels to subsequent renoprotection assumes that the initial albuminuria reduction remains stable during follow-up. However, despite stable treatment regimen, many patients show a subsequent further fall or rise of albuminuria either due to an enhanced treatment response, drug effect escape, or progression of the underlying disease. Therefore, assessment of the individual albuminuria variability after the initial treatment response is established, and considering this variability in risk algorithms, should improve renal risk stratification and prediction of outcome. The third chapter of this thesis describes the methodology and results of this analysis.
Part 2: Optimizing the use of albuminuria in clinical trials in nephrology

Chapter 4: Number and frequency of albuminuria measurements in clinical trials in diabetic nephropathy.
In early stages of drug discovery albuminuria is often used as an endpoint in clinical trials. In these trials drug effects are often ascertained between baseline and the end of treatment. However, many more urine samples for albuminuria measurement are usually collected during follow-up but not used to assess the drug efficacy. Taking the large day to day variability of albuminuria into account it is questionable whether considering the albuminuria change between baseline and the end of the treatment is the optimal approach for precise drug effect assessment. Variability in albuminuria during prolonged follow-up may hamper the precision of drug effect estimates if not taken into account. Based on these assumptions, increasing the number of urine collections at a single study visit as well as increasing the number of urine collections during follow-up might improve the precision of drug effect estimates. The fourth chapter of this thesis describes the methodology and results of this analysis.

Chapter 5: The optimal protocol for measuring an albuminuria class transition in clinical trials in diabetic kidney disease
Albuminuria transition from normo- to microalbuminuria or from micro- to macroalbuminuria is a hallmark of progression of diabetic kidney disease and is therefore used in clinical trials to assess renoprotective drug effects. In past trials different definitions for albuminuria transitions were applied based on variable numbers of urine collections at a single study visit or a variable number of study visits during follow-up. Additionally some trials require confirmation of elevated albuminuria levels at a subsequent visit scheduled within varying time intervals in different clinical trials. Some trials also add a requirement for a minimal percentage increase compared to baseline to the endpoint definition. Since there are no guidelines stating the optimal definition for an albuminuria transition endpoint used to study drug efficacy we assess the impact of these endpoint definitions. The fifth chapter of this thesis describes the methodology and results of this analysis.

Chapter 6: Summary and future perspectives
Finally the results of conducted studies are summarized and an overview of future perspectives is given.
Supplement: Using albuminuria and eGFR to predict long term renal outcomes

Supplement: Early renin-angiotensin-system intervention is more beneficial than late intervention in delaying end-stage renal disease in patients with type 2 diabetes

It has been suggested that treatment in the early stages of diabetic kidney disease (DKD) might be more effective in delaying ESRD compared to late interventions. However, this hypothesis is not tested in prospective, clinical trials because such trials would require an unfeasibly long follow-up time. In this study, we were able to build a simulation model that gives us the ability to study drug effects over the whole course of DKD from early onset to ESRD, using discrete disease stages defined by eGFR and albuminuria. Hence, the content of the sixth chapter describes the development and validation of this simulation model adding evidence to the use of albuminuria as outcome in clinical trials.
Introduction

References


Chapter 1


PART 1

Association between the initial albuminuria reduction and the risk for end stage renal disease