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Critical review

Epidemiology

# Epidemiology of new-onset diabetes mellitus after dialysis

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## Abstract

### Introduction

Diabetic nephropathy is the leading cause of end-stage renal disease in patients undergoing dialysis. Most studies evaluate the association between pre-existing diabetes mellitus, but very few focus on new-onset diabetes mellitus after dialysis. Chronic dialysis patients are often older and have multiple comorbidities, including cardiovascular diseases and pancreatic disorder. In addition, these patients have been found to be in a state of chronic inflammation. These characteristics have been associated with the development of insulin resistance and diabetes. Herein, we critically review the epidemiology, risk factors and mortality of new-onset diabetes mellitus after dialysis.

### Conclusion

The dialysis population has a higher incidence of new-onset diabetes mellitus and a greater risk of mortality than the general population. In addition, the post-transplant incidence of diabetes mellitus, which always occurs the first year after transplant, is much higher than the pre-transplant incidence. However, dialysis modality does not appear to be associated with new-onset diabetes mellitus after dialysis and post-transplant. The independent predictors of new-onset diabetes mellitus are old age, cardiovascular comorbidity and dyslipidemia. Other possible contributing factors are inflammation and use of some commonly prescribed drugs for cardiovascular disease, such as statin. Physicians may need to pay more attention to the possibility of new-onset diabetes mellitus when treating high-risk patients undergoing dialysis.

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## Introduction

The number of end-stage renal disease (ESRD) patients undergoing dialysis has grown significantly in recent decades[1]. Diabetic nephropathy is the leading cause of ESRD[2], and many studies report an association between pre-existing diabetes mellitus (DM) at the initiation of dialysis and a poor outcome in ESRD patients undergoing dialysis[2,3].

ESRD patients on dialysis are always older and have multiple comorbidities, including cardiovascular disease (CVD), stroke and heart failure[2]. In addition, many of them have histological abnormalities and dysfunction of the pancreas[4–6]. They have also been found to be in a state of chronic inflammation associated with the development of insulin resistance and DM[7].

In recent years, new-onset diabetes mellitus (NODM) after the initiation of dialysis has been reported in several studies[7–10]. This critical review focuses on the epidemiology and risk factors of NODM after dialysis. We also evaluate the association between different modes of dialysis and NODM and discuss its impact on mortality in this patient population.

## Discussion

The authors have referenced some of their own studies in this review. These referenced studies have been conducted in accordance with the Declaration of Helsinki (1964) and the protocols of these studies have been approved by the relevant ethics committees related to the institution in which they were performed. All human subjects, in these referenced studies, gave informed consent to participate in these studies.

### Epidemiology of new-onset diabetes mellitus after dialysis

Several studies have reported that NODM occurs among patients receiving dialysis at rates greater than in the general population[7–9]. According to the Centre for Disease Control's web page[11], the incidence rate for DM in the general population in the US fluctuated around 0.5%–0.9% per year from 2000 to 2009. Using data from the United States Renal Data System from January 2000 to December 2001 to study patients aged 18–80 years old in a three-year follow up study, Salifu et al.[7] found the incidence of NODM after dialysis to be 20 per 1,000 patient-years and its prevalence to be 4.6% in the first year after initiation of dialysis.

In Taiwan, the incidence of DM in the general population from 2000 to 2009 was 0.7%–0.9% per year[12]. In our study, we used Taiwan's national health insurance claims for ESRD patients who initiating dialysis between 1999 and 2005 to follow

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26 166 dialysis patients without underline DM patients until death, transplant, dialysis withdrawal, or end of 2008[8], and found the cumulative incidence rate of NODM to be 4% at one year, 9% at three years and 14% at five years.

With regard to the incidence of NODM in renal transplantation patients, one study examining the United States Renal Data System's 1994–1998 clinical and financial records of all adults, first, single-organ, renal transplantations in either 1996 or 1997[9] observed the incidence of NODM to be approximately 6% per year among dialysis patients wait-listed for a transplant. The post-transplant incidence of DM was noticeably higher than the pre-transplant values and occurred during the first year after renal transplant, with post-transplant incidence being 8.1% and 9.1% for peritoneal dialysis (PD) and haemodialysis (HD), respectively.

**Dialysis mode and new-onset of diabetes mellitus**

Glucose makes up one of the contents found in haemodialysates[13] and peritoneal dialysates[14]. Although patients on PD receiving continued high-glucose-concentration peritoneal dialysates can develop hyperglycaemia and transient hyperinsulinism[15], it is unclear whether there is an association between dialysis modality and NODM. Szeto et al.[10], studying the fasting plasma glucose levels in 252 Chinese PD patients without underline DM one month after being stable on PD therapy, found those levels to be higher than 200 mg/dL in 21 patients (8.3%) and found them to range between 126 and 200 mg/dL in 48 patients (19.0%) after PD was initiated. In that study, seven patients required insulin therapy, three required low-dose sulfonylurea therapy and all other patients had glucose levels controlled by means of dietary restriction only.

Still there are conflicting data regarding the relation between glycaemic load and the development of NODM. For example, although high intake of foods with high glycaemic loads has been found to increase the risk of type 2 DM in Chinese[16], Mosdol et al.[17] did not find such an association in the Whitehall II study. Pure glucose has the highest glycaemic index, but few long-term follow-up studies have investigated the glucose load and the risk of DM, especially in patients with ESRD.

Both patients on HD and those on PD are associated with similar high incidence of NODM. One of our studies[8] found no significant difference in percentage of those developing NODM after the initiation of dialysis between patients receiving HD (12.80%) and patients receiving PD (12.20%) (PD to HD hazard ratio of NODM: 0.94, 95% CI 0.83–1.06). This finding was similar to that reported by Woodward et al.[9] in a study following wait-listed transplanted renal allograft recipients. They observed the different type of dialysis modality made a noticeable difference in the incidence of NODM two years pre-transplant. During the two-year pre-transplant period, 10.7% of PD patients and 12.7% of HD patients, who were previously non-diabetic, developed NODM. The post-transplant incidence of DM was noticeably higher than the pre-transplant values. During the first year post-transplant, 13.2% and 14.9% of the PD and HD patients, respectively, developed NODM. After multivariate adjustment, there was no significant difference between PD and HD patients who developed NODM during post-transplant period in their study.

**Risk factors and possible mechanisms**

Although the underlying mechanism for the relationship between ESRD dialysis and NODM are not fully understood, the factors associated with ESRD dialysis, including being older[2], having histological abnormalities and dysfunction in the pancreas[4–6], having CVD[2], including stroke and heart failure, and in a state of chronic inflammation[7], can induce insulin resistance and the development of type 2 DM.

Szeto et al.[10] reported significant correlations between plasma glucose levels and age, Charlson comorbidity score, and serum C-reactive protein level in patients receiving PD. In our analysis using Taiwan's National Health Insurance Research Database, being older, having hypertension, congestive heart failure, coronary artery disease and a cerebrovascular accident and dyslipidaemia were found to be independent risk factors for NODM in dialysis patients[8].

The relationship between CVD and NODM might explain the presence of underlying inflammation. Dyslipidaemia and vascular inflammation result in endothelial dysfunction and atherosclerosis[18]. Elevated values of circulatory makers such as interleukin-6 and high sensitivity C-reactive protein commonly accompany CVD. Vascular inflammation and endothelial dysfunction may also be associated with an increased risk of developing DM[19,20]. In addition, use of some commonly prescribed drugs for CVD, such as statin, might also lead to the development of dysglycaemia, as many meta-analyses report an association between statin use and increased risk for incident DM[21–23].

**Impact on mortality**

NODM has been associated with higher mortality in patients on maintenance dialysis. Increased plasma glucose levels have been found to be an independent risk factor for mortality in PD patients, even in those with a minor degree of hyperglycaemia[10]. Szeto et al.[10] found actuarial survival rates at 36 months for patients with fasting plasma



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glucose levels less than 100, 100 to less than 126, 126 to less than 200 and 200 mg/dL or greater are 93.7%, 85.3%, 81.6% and 66.7%, respectively.

In our study[8], cumulative survival rates in dialysis patients who developed NODM was 96% at one year, 68% at five years and 42% at nine years; and for those who did not have DM, the rates were 95% at one year, 74% at five years and 58% at nine years. After multivariate adjustment for sex, age and comorbidities, NODM patients had 10% increased death risk compared with non-DM patients (hazard ratio: 1.10, 95% CI: 1.03–1.17), suggesting that NODM was an independent risk factor for mortality.

The explanation for the increased mortality in dialysis patients with NODM remains speculative. A high fasting plasma glucose level is reported to be a probable surrogate indicator of elderly patients with multiple comorbid conditions and systemic inflammation[10]. Hyperglycaemia has been associated with increased morbidity and mortality in critically ill patients and acute myocardial infarction, even in the absence of diabetes[24–26]. In addition, there is evidence indicating that hyperglycaemia per se is a proinflammatory agent[27], which may be related to acceleration of cellular and metabolic processes known to affect cardiovascular morbidity[28,29].

## Conclusion

In summary, there is a higher incidence of NODM in a dialysis population than in a general population. The incidence of DM is noticeably higher in post-transplant patients, in whom it occurs within the first year, than in pre-transplant patients. Although there is a reported association between high-glucose-concentration peritoneal dialysates and hyperglycaemia and transient hyperinsulinism, dialysis modality does not appear to be associated with NODM after dialysis and post-transplant. The risk factors of NODM after dialysis are age, cardiovascular comorbidity, dyslipidaemia and serum C-reactive protein level. NODM has been associated with higher mortality in dialysis patients. Increased plasma glucose levels have been found to be an independent risk factor for mortality, even in those with a minor degree of hyperglycaemia. Physicians may need to pay more attention to the possibility of NODM when treating high-risk patients undergoing dialysis.

## Abbreviations list

CVD, cardiovascular diseases; DM, diabetes mellitus; ESRD, end-stage renal disease; HD, haemodialysis; NODM, new-onset diabetes mellitus; PD, peritoneal dialysis.

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