Review

# New-Onset Diabetes Mellitus in Peritoneal Dialysis and Hemodialysis Patients: Frequency, Risk Factors, and Prognosis—A Review

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**Abstract:** New-onset diabetes mellitus (NODM) is observed in both hemodialysis (HD) and peritoneal dialysis (PD) patients. The prevalence of NODM in dialysis patients is slightly higher compared to subjects of the general population. Based on currently published data there is no convincing evidence that the risk of NODM is different between HD and PD patients. Data on the effect of glucose load on risk of NODM in dialysis patients remain controversial. PD modality (automated or continuous ambulatory PD) has no significant influence on NODM incidence. Chronic inflammation is associated with NODM in dialysis patients. Reported differences in NODM between PD and HD patients are possibly also influenced by differences in demographic factors between these patient groups. Mortality in NODM patients is lower than mortality in patients with preexisting DM. This may be partly explained by the younger age and lower number of comorbidities in patients with NODM. **Key Words:** Diabetes, Glucose Load, Hemodialysis, New-Onset Diabetes Mellitus, Peritoneal Dialysis.

Diabetes mellitus (DM) is one of the most frequent metabolic disorders worldwide. DM type 2 is associated with hyperglycemia due to defects of insulin secretion and response. The pathogenesis of age-related DM type 2 is linked with insulin resistance (IR) and decreased beta-cell function (1). The prevalence of this disease in all age groups increased in the last decades (2–4). Between 2011 and 2014 approximately 366–422 million people suffered from DM, corresponding to a prevalence of 8.3–8.5% (3,5–7). The number of diabetic patients is estimated to increase to 522 million in 2030 and to 592 million in 2035 (3,6,7).

DM is the most prevalent cause of ESRD (8). Nearly 40% of dialysis patients suffer from diabetic nephropathy (9). Incidence of ESRD in DM patients is 10-fold higher compared to nondiabetic subjects (10). Preexisting DM is associated with increased mortality in HD and peritoneal dialysis (PD) patients (10–12).

Some data suggest that new-onset DM (NODM) occurs more frequently in dialysis patients than in the normal population. PD is an alternative to extracorporeal renal replacement therapy. Due to the routine use of glucose-based fluids, glucose load is markedly higher in PD compared to HD patients. Therefore, it could be expected that PD is associated with an increased risk of NODM.

This review provides an overview of the present data on NODM rates in dialysis patients, possible pathogenic factors and differences between the HD and PD population regarding NODM risk.

### Diagnosis of NODM in PD patients

NODM and DM both are based on plasma glucose (PG) criteria and defined either as fasting PG (FPG) ≥ 7.0 mmol/L or 2-h PG > 11.1 mmol/L in the oral glucose tolerance test (OGTT). Recently,

the American Diabetes Association (ADA) defined an $Hb_{A1c}$ threshold of $\geq 6.5\%$ as the third criterion for diagnosis of DM and NODM (13). According to the ADA guidelines, the term "impaired glucose metabolism" includes both impaired fasting glucose (IFG) and impaired glucose tolerance (IGT) (13). Due to significant peritoneal glucose absorption into the systemic circulation, the term fasting glucose in PD patients is inappropriate, since the exact contribution of peritoneal glucose absorption at the time of blood sampling remains uncertain. Furthermore, additional peritoneal glucose absorption may also influence results of the OGTT, which requires application of a precise enteral dose of glucose. In order to measure FPG levels in PD patients, dialysis must be stopped temporarily, which cannot be performed easily during routine care. For that reason, no studies with peritoneal fasting and measurement of FPG levels in PD are available. Lambie et al. stated that enteral or oral fasting has no major influence on FPG levels in PD patients if there is no simultaneous peritoneal fasting (14). Szeto et al. defined that FPG (no food and fluid intake—except water for at least 8 h before the test) levels > 11.1 mmol/L implicate DM (11). Furthermore, patients with FPG levels of 7.0–11.1 mmol/L should be regarded as patients with IGT rather than diabetic patients. However, this definition does not correlate with the World Health Organization (WHO) and ADA criteria for DM. As the interpretation of fasting state in PD is complicated, the $Hb_{A1c}$ threshold $\geq 6.5\%$ is additionally used for diagnosis of NODM (15,16). Definitions of NODM used in the different clinical studies are summarized in Table 1.

Due to the higher incidence of DM compared to the normal population and limited value of $Hb_{A1c}$ after start of dialysis, Freedman et al. suggested to measure $Hb_{A1c}$ and FPG levels in CKD patients before initiation of PD or HD (24). This may allow better differentiation between patients with preexisting DM and those who develop NODM after dialysis initiation.

### Glucose load and effect on NODM in PD patients

Glucose has a small molecular size of 180 Da. Therefore, it is quickly absorbed across the peritoneum and metabolized after entering the blood circulation. Glucose-free dialysate is rarely used in HD patients because of increased risk of hypoglycemia. While glucose is one of the components of hemodialysates, glucose load in HD is far less than in PD patients (25). Glucose is the most frequently used osmotic agent in PD fluids (11). In standard PD

**TABLE 1.** *Various new-onset DM (NODM) definitions used in studies on dialysis patients*

| Study group | NODM definition |
| --- | --- |
| Chou et al. (17) | Fasting PG $\geq 7.0$ mmol/L in at least two measurements |
| Szeto et al. (11) | Fasting PG $\geq 11.1$ mmol/L |
| Tien et al. (12) | DM type 2 diagnosed at least 3 months after dialysis initiation, $Hb_{A1c} > 6\%$ |
| Wang et al. (15) | ICD code for DM type 2, $Hb_{A1c} > 6.5\%$, Fasting PG $\geq 7.0$ mmol/L, random PG or 2-h PG > 11.1 mmol/L during OGTT |
| Woodward et al. (16) | ICD code for DM type 2, $Hb_{A1c} > 6.5\%$, Fasting PG $\geq 7.0$ mmol/L, random PG or 2-h PG > 11.1 mmol/L during OGTT |
| Salifu et al. (18) | $Hb_{A1c} > 6\%$ |
| Lindholm and Karlander (19) | DM type 2 definition not mentioned |
| Kurtz et al. (20) | DM type 2 definition not mentioned |
| Dong et al. (21) | Fasting PG $\geq 7.0$ mmol/L on two occasions or 2-h PG > 11.1 mmol/L during OGTT |
| Lambie et al. (14) | Random PG > 11 mmol/L |
| Chu et al. (10) | ICD code for DM type 2, $Hb_{A1c} > 6.5\%$, Fasting PG $\geq 7.0$ mmol/L, random PG or 2-h PG > 11.1 mmol/L during OGTT |
| Wu et al. (22) | ICD code for DM type 2, $Hb_{A1c} > 6.5\%$, Fasting PG $\geq 7.0$ mmol/L, random PG or 2-h PG > 11.1 mmol/L during OGTT |
| Liao et al. (23) | Fasting PG > 200 mg/dL or $Hb_{A1c} \geq 6.5\%$ |

ICD, international classification of disease; OGTT, oral glucose tolerance test; PG, plasma glucose.

fluids various glucose concentrations are available, ranging from 1.36 (1.5)% to 3.86 (4.25)% (26). In Table 2, unhydrated glucose content and caloric load (28) of available PD dialysate solutions are listed. Glucose absorption during a 6-h dwell ranges from 15–22 g when using 2 L of 1.5% dialysate to 46–60 g when using 2 L of 4.25% glucose solution (27). The usual glucose load in PD patients ranges between 50 g and 200 g per day.

Due to the rapid uptake of glucose, a decline or even discontinuation of ultrafiltration capacity can be observed especially during long dwells of dialysate in the peritoneal cavity. This phenomenon can be counteracted by the implementation of higher glucose concentrations in PD fluids, leading to steeper osmotic gradients, but also to higher systemic glucose absorption (29). However, data about the effect of glucose load on the risk of NODM

**TABLE 2.** *Available peritoneal dialysate solutions (14,27)*

| Dialysate concentration (%) | 1.36% | 2.27% | 3.86% | 1.5% | 2.3% | 4.25% |
|---|---|---|---|---|---|---|
| Daily dialysate glucose (unhydrated glucose) in g/L | 13.6 g/L | 22.7 g/L | 38.6 g/L | 15 g/L | 22.73 g/L | 42.5 g/L |
| Caloric load[†] 3.75 kcal/g conversion factor[‡] | 51 kcal/g | 85.13 kcal/g | 144.75 kcal/g | 56.25 kcal/g | 85.24 kcal/g | 159.38 kcal/g |
| Caloric load[†]16 kJ/g conversion factor[‡] | 217.6 kJ/g | 363.2 kJ/g | 617.6 kJ/g | 240 kJ/g | 363.68 kJ/g | 680 kJ/g |

[†]For 1 L dialysate.    [‡]Conversion factor for food energy according to according to Food and Agriculture Organization of the United Nations (28).

remain controversial. The results published by Szeto et al. suggested that new-onset hyperglycemia is observed in approximately 25% of incident PD patients even when treated with three exchanges with 1.5% glucose concentration per day, which resembles a low daily glucose exposure (11). Accordingly, Lambie et al. found that PG levels increased with peritoneal glucose load (14). In contrast, Armstrong et al. reported that dialysate exchanges using 1.5% glucose had only marginal effects on PG and insulin levels (30).

A close positive association between peritoneal transport rates and glucose absorption has also been reported, both when using 2.27% (2.5%) or 3.86% (4.5%) PD fluid (e.g. patients with fast peritoneal transport rates also have faster glucose absorption) (31–33). During a 4-h peritoneal equilibration test (using 2 L of 2.5% PD fluid) glucose absorption was 20.3 ± 0.4 g in patients with low peritoneal transport rates, 26.0 ± 0.1 g in the low-average transporter group, 31.1 ± 0.1 g in the high-average transporter group, and 35.4 ± 0.3 g in patients with high peritoneal transport rates (27). However, no data have been published describing any influence of peritoneal transport rates on the risk of NODM.

Automated PD (APD) is a heterogeneous treatment modality, including nocturnal intermittent PD (NIPD) and continuous cyclic PD (CCPD), high flow as well as low flow cycler regimens, and different number of daytime exchanges. All factors have significant influence on glucose absorption. Therefore, glucose absorption ranges between approximately 40 g and 60 g per treatment in patients on NIPD with low dialysate glucose concentration (34,35) and up to 200 g per treatment during CCPD with high night-time treatment volumes or day time exchanges with glucose-containing solution (36,37). Lambie et al. found no effect of PD modality per se, APD vs. continuous ambulatory PD (CAPD), on PG levels (14).

**Other possible risk factors for NODM in PD and HD patients**

According to a recent retrospective study, risk factors for NODM in dialysis patients include female sex, higher age, cardiovascular diseases (CVDs), hypertension, and chronic obstructive pulmonary disease (12). On the other side NODM triggers the risk of CVD, cerebrovascular disease, and progression of existing hypertension (38,39).

In the study by Dong et al. advanced age was associated with increased risk of NODM in PD patients (21). Furthermore, in other clinical studies NODM in dialysis patients was linked with higher age (4,10,22). Additionally, Szeto et al. confirmed that FPG-levels also significantly correlated with the age of PD patients (11). In two clinical studies (19,21) obesity appeared to be an essential risk factor for new-onset hyperglycemia in PD patients, which however, is in contrast to the study cohort of Szeto et al. (11). Chronic inflammation is associated with NODM in both PD and HD patients. In HD patients chronic inflammation plays a key role in DM manifestation (17,40–43). The elevation of CRP and proinflammatory cytokines, such as IL-6, due to the interaction between blood and dialyzer membrane is an important contributing factor in HD patients (44–46). Some recent studies report that in PD patients, endothelial dysfunction and oxidative stress cause subtle chronic inflammation (17,47). Interestingly, chronic inflammation leads to higher occurrence of NODM in PD patients (21). Furthermore, glucose per se and glucose degradation products (which are generated during heat sterilization of PD fluids) have local toxic effects, which can result in impairment of host defense in the peritoneal cavity, chronic inflammation, and thus raise NODM risk in PD patients. Further, protein energy wasting(48) is one of the contributing factors for NODM in ESRD patients (49).

Adjustment of metabolic acidosis in PD patients improves protein turnover and lowers protein degradation (50). Furthermore, treatment of metabolic acidosis reduces IR and hence decreases NODM risk in ESRD patients (51).

It cannot be excluded that improved appetite and increased food intake after dialysis initiation may contribute to occurrence of NODM, as hypothesized by Rivara and Mehrotra (49). However, only few data have been published on this issue in the

dialysis population. In a retrospective study, dietary intake and daily dialysate glucose (DDG) content had no influence on NODM risk in PD patients, but body fat mass was a predictor for NODM (21).

## NODM FREQUENCY IN PD PATIENTS

A study conducted by Lameire et al. observed NODM in 15.5% of CAPD patients. However, the long observation period over 18 years explains the high frequency rate of DM compared to other studies. (26). In nondiabetic PD patients following PD initiation, 4.4% showed FPG levels >11.1 mmol/L and in 19% FPG levels from 7.0 to 11.1 mmol/L were found, respectively (11). The total NODM prevalence of 4.4% as observed in this latter study correlates with the results reported in earlier publications (1.2% in the study by Lindholm and Karlander and 4.75% in the study by Kurtz et al., respectively) (19,20). Similarly, Liao et al. found that 5% of the PD patients developed NODM (23). Further, the Global Fluid Study reported NODM (glucose levels >11.1 mmol/L) in 3.7% of incident PD patients and in 5.4% of prevalent PD patients (14). Accordingly, Dong et al. observed a 4.1% incidence of NODM in 621 PD patients (21).

## DIFFERENCES IN NODM FREQUENCY BETWEEN PD AND HD PATIENTS

In ESRD patients of the US Renal Data System report, NODM incidence was 12.7% vs. only 5% in the general population of the US Medicare System (9). Notably, another study detected a higher NODM risk in ESRD dialysis patients compared to healthy controls. Unfortunately, no distribution of HD and PD patient number was mentioned in this study (10). In a 3-year follow-up study, a NODM incidence of 20% per 1000 patient-years and a prevalence of 7.6%, after start of HD was observed (18). However, this study did not include PD patients. Only few investigations focused on incidence, risk factors, and impact of NODM in PD compared with HD patients and found controversial results. Some studies reported a lower incidence or prevalence of NODM in PD vs. HD patients. In the study by Woodward et al., the incidence of NODM in dialysis patients was 10.7% and 12.7% in PD patients and HD patients, respectively (16) (Table 3). Chou et al. showed a NODM incidence of 2.4 per 100 patient-years in PD patients and 3.7 per 100 patient-years in HD patients, respectively (17). In a Taiwanese study, the incidence of NODM was 6% and 8% in HD and PD patients, respectively

(12) (Table 3). No significant difference between HD and PD patients concerning the prevalence of NODM was reported (prevalence after adjustment 12.8% in HD patients vs. 12.2% in PD patients, respectively) (12). Despite the slightly higher incidence rate of NODM in PD patients, the authors concluded that dialysis modality was not a risk factor for development of NODM (12). However, 90.5% patients received HD, and only 9.4% patients received PD in this latter study (12). Wang et al. showed a NODM incidence of 9.10 per 1000 person-years in PD patients vs. 8.18 per 1000 person-years in HD patients (15). Similarly, a recent study found a NODM incidence of 4.89% in the total dialysis population (22). A NODM incidence rate of 15.98 per 1000 patient-years in PD patients and an incidence rate of 8.90 per 1000 patient-years in HD patients was seen, respectively (22).

In literature, the NODM incidence and prevalence rates differ among dialysis patients and between dialysis modalities. NODM incidence and prevalence rates of dialysis patients, patient number and information about study type of the above-mentioned studies are demonstrated in Table 3.

## POSSIBLE REASONS FOR DIFFERENCES IN STUDY RESULTS REPORTING RISK OF NODM IN PD AND HD PATIENTS

The varying NODM rates in PD and HD patients reported in previous studies can be explained by differences in demographic factors, patient selection, study design, patient number, PD prescription, or definition of NODM. The ethnic group is a valuable predictive factor for development of NODM in dialysis patients. Differences in the ethnicity of dialysis patients in study cohorts make interpretation of published results more difficult. For example, Caucasians have a lower NODM risk than Asians, Hispanics and African-Caribbeans (52). This fact is compatible with the finding that Asians have higher glucose levels than Caucasians and explains to some extent the finding of increased frequency of hyperglycemia in the studies conducted in the Asian population (11,12,15,17). However, the group of Caucasians has been used as the reference population for all DM criteria establishing institutions like WHO or ADA (5,13).

In the study by Woodward et al., the proportion of African-Americans as well as males was higher in HD patients listed for kidney transplantation compared to PD patients listed for kidney transplantation (16). This may be one explanation for the

**TABLE 3.** *Incidence and prevalence of new-onset DM (NODM) in dialysis patients after dialysis initiation and patient number in the studies*

| Study group and study type | PD NODM prevalence | HD NODM prevalence | Total dialysis NODM prevalence | PD NODM incidence | HD NODM incidence | Total dialysis NODM incidence | Total number of dialysis patients | PD patient number | HD patient number |
|---|---|---|---|---|---|---|---|---|---|
| Chou et al. (17) observational cohort study | Not mentioned | Not mentioned | Not mentioned | 2.4% | 3.7% | Not mentioned | 12 740 | 2548 | 10 192 |
| Szeto et al. (11) retrospective cohort study | 4.4% | Not mentioned | None | Not mentioned | Not mentioned | Not mentioned | 252 | 252 | None |
| Tien et al. (12) prospective cohort study | 12.2% | 12.8% | 12.7% | 8% | 6% | 4% | 26 166 | 2471 | 23 695 |
| Wang et al. (15) retrospective cohort study | Not mentioned | Not mentioned | Not mentioned | Not mentioned | Not mentioned | Not mentioned | 43 261 | 6382 | 36 879 |
| Woodward et al. (16) retrospective cohort study | Not mentioned | Not mentioned | Not mentioned | 10.7% | 12.7% | 6% | 7503 | Not mentioned | Not mentioned |
| Salifu et al. (18) retrospective cohort study | Not mentioned | 7.6% | Not mentioned | Not mentioned | 20% | Not mentioned | 59 340 | None | 59 340 |
| Lindholm and Karlander (19) observational study | 1.2% | Not mentioned | Not mentioned | Not mentioned | Not mentioned | Not mentioned | 13 | 13 | None |
| Kurtz et al. (20) retrospective cohort study | 4.75% | Not mentioned | Not mentioned | Not mentioned | Not mentioned | Not mentioned | 69 | 69 | None |
| US Renal Data System (9) retrospective cohort study | Not mentioned | Not mentioned | Not mentioned | Not mentioned | Not mentioned | 12.7% | Not mentioned | Not mentioned | Not mentioned |
| Dong et al. (21) prospective cohort study | Not mentioned | Not mentioned | Not mentioned | 4.1% | Not mentioned | Not mentioned | 612 | 612 | None |
| Lambie et al. (14) prospective cohort study | Not mentioned | None | Not mentioned | Not mentioned | None | Not mentioned | 569 | 569 | None |
| Chu et al. (10) retrospective cohort study | Not mentioned | Not mentioned | Not mentioned | Not mentioned | Not mentioned | Not mentioned | 18 489 | None | None |
| Wu et al. (22) retrospective cohort study | Not mentioned | Not mentioned | Not mentioned | Not mentioned | Not mentioned | 4.89% | 2228 | 136 | 2092 |
| Liao et al. (23) observational cohort study | Not mentioned | None | Not mentioned | 5% | None | None | 222 | 222 | None |

HD, hemodialysis; PD, peritoneal dialysis.

differences in the risk of NODM found between HD and PD patients (16).

Furthermore, differences in age, sex, and distribution of comorbidities between PD and HD patients, even after statistical adjustment for these conditions, may also have influenced the results. For example, in the study by Chou et al., PD patients were significantly younger than HD patients (17). Patients over 65 years have a threefold greater risk for NODM manifestation vs. patients aged below 45 years (12,26,29).

Wait-listed dialysis patients represent a positive selection of subjects with good general condition, probably explaining that the incidence of NODM is lower in this subgroup compared with predialysis ESRD patients or non-wait-listed dialysis patients (16).

A high drop-out of patients due to death, kidney transplantation, or switch of dialysis modality (in most cases transfer to HD like in the study by Szeto et al.) has to be considered as a significant limitation (11).

The different definitions of NODM used in each of the above-mentioned studies have to be regarded as another limiting factor (Table 1). Finally, in the above-mentioned studies, there was a wide variation in total sample sizes of dialysis patients. Moreover, the number of patients in the PD and HD subgroups was markedly different in most studies. In Table 3 the different sample sizes of each cohort of the above-cited studies, which focus on NODM after dialysis start, are illustrated. The number of PD patients ranged from 13 to 6382, whereas the number of HD patients ranged from 2092 to 59 340. In some clinical studies the percentage of PD patients was < 10%.

The lower NODM risk in PD patients reported in some studies may be linked with higher physical activity and more autonomy compared with HD patients, as most PD patients are engaged to practice the PD exchanges independently at home (17,53).

## EVALUATION OF NUTRITIONAL STATUS IN DIALYSIS PATIENTS WITH NODM

Malnutrition already has been observed in diabetic and nondiabetic dialysis patients (54). Around 27% of HD and 20% of PD patients suffered from malnutrition (55). Regarding evaluation of nutritional status, no guidelines have been published which specially focus on NODM patients on dialysis. Serum albumin concentrations are associated with nutritional status. However, assessment of albumin is limited due to the large influence of inflammation, albuminuria, hydration status, and peritoneal albumin loss in PD (56). Other methods and tools for nutrition evaluation include the Subjective Global Assessment (SGA) (57–59), Malnutrition and Inflammation Score (60), Objective Score of Nutrition on Dialysis (61,62), and Inflammatory Score (63).In PD patients, protein equivalent of total nitrogen appearance can be analyzed for nutrition evaluation (64,65). Some clinical studies implemented dual-energy X-ray absorptiometry (66–68), bioelectric impedance analysis (58,68,69), and CT (58,69) to assess fat mass. Finally, anthropometric parameters, including hand grip strength (70,71), can be obtained for nourishment estimation.

## DIAGNOSTIC AND THERAPEUTIC APPROACHES IN PD AND HD PATIENTS WITH NODM

The question how antidiabetic therapy should be monitored in dialysis patients has been discussed controversially. Some authors and the recent International Society for Peritoneal Dialysis (ISPD) guidelines recommend measuring $Hb_{A1c}$ in diabetic PD patients (72,73). This is supported by the fact that the correlation of $Hb_{A1c}$ with blood glucose levels is better in PD compared with HD patients. $Hb_{A1c}$ is also an useful tool in predicting mortality risk in diabetic PD and HD patients (74). However, due to increased erythropoiesis especially during treatment with erythropoiesis stimulating agents, the $Hb_{A1c}$ in both HD and PD patients is often lowered (24,75,76). Therefore, more recent studies favor glycated albumin for NODM diagnosis and monitoring of antidiabetic treatment in HD and PD patients (24,75–77). Peritoneal protein loss may influence the period of interaction between PG and albumin (72). However, Kobayashi et al. compared $Hb_{A1c}$ and glycated albumin in diabetic dialysis patients and concluded that glycated albumin was not significantly influenced by protein loss, hemoglobin, serum albumin, and erythropoietin dose (76). Furthermore, Hoshino et al. reported that in HD patients glycated albumin was a better predictor of mortality compared to $Hb_{A1c}$ (78).

Alternatively, Mehrotra et al. and Coelho et al. proposed to establish a new threshold for $Hb_{A1c}$ in ESRD and predialysis CKD patients (e.g. adjusted for anemia or individualized) instead of replacing $Hb_{A1c}$ with glycated albumin as a diagnostic marker (72,79). Possibly, daily repeated PG profiles in addition to glycated albumin (if available) or $Hb_{A1c}$

measurements may allow a more accurate assessment of glycemic status in dialysis patients. Considering the increased mortality in NODM patients, antidiabetic treatment should follow a strict prescription, similar to patients with preexisting DM. However, for the medical treatment of NODM in dialysis patients, no particularly different guidelines compared to the recommendations for therapy of preexisting DM in dialysis patients have been published. Intensity of antidiabetic treatment should be based on age and comorbidity, rather than on type of DM (preexisting DM vs. NODM). According to KDOQI Guidelines for Diabetes and CKD and ADA criteria, a recent ISPD guideline recommended that in PD patients $Hb_{A1c}$ should be targeted at approximately 7%. However, a higher $Hb_{A1c}$ target of up to 8.5% is acceptable for older PD patients or those with high comorbidity, in order to avoid hypoglycemia (73,80,81). Rivara and Mehrotra also concluded that reduction of the DDG content did not lead to clinically meaningful outcomes (49).

Icodextrin containing PD fluid is usually prescribed for long dwell times, for example during the night in patients on CAPD or during daytime in patients on APD.

In clinical studies icodextrin in combination with or without amino acid-containing PD fluids as part of the daily prescription proved to ameliorate glycemic status especially in diabetic PD patients (82,83). Furthermore, De Moraes et al. showed that use of icodextrin reduced IR in nondiabetic PD patients (84). However, only few data indicate that application of icodextrin reduces the risk of NODM in PD patients. Importantly, the recent publication by Wang et al. showed a lower incidence of NODM in PD patients using icodextrin compared to nonicodextrin users. However, only one third of PD patients used icodextrin containing PD fluids. When looking at propensity score matched groups, patients who utilized icodextrin had a 40% decrease of the hazard ratio of NODM compared with icodextrin nonusers (NODM incidence 6.6 vs. per 1000 person-years compared to 12.1 per 1000 person-years) (15).

## PROGNOSTIC IMPORTANCE OF NODM IN DIALYSIS PATIENTS

In PD patients, not only manifest DM and IFG but also increased FPG levels in nondiabetic patients predict mortality (11). Similarly, Tien et al. showed that NODM was associated with higher mortality risk of 10% in dialysis patients (12). Accordingly, Salifu et al. found a significantly higher mortality rate in patients with NODM undergoing HD (49.2% NODM compared to 41.0% without NODM) (18).

While NODM increases mortality, a higher survival rate of dialysis patients with NODM compared to those with preexisting DM has been reported by Tien et al. and Szeto et al. (11,12). This could at least partly be explained by the fact that patients with NODM were younger and had a lower number of comorbidities compared to patients with preexisting diabetes, even though the difference in risk of death remained in a multivariate analysis (12).

Bergrem et al. concluded that pretransplant glycemia leads to a higher risk of posttransplantation DM (PTDM) (85). However, results about a possible influence of PD on the risk of PTDM remain conflicting (85). Madziarska et al. described that besides older age and positive family history of DM, PD was significantly associated with PTDM (86,87). In contrast, Courivaud et al. and Woodward et al. reported no effect of dialysis modality prior to transplantation on consecutive occurrence of PTDM (16,88).

## ASPECTS FOR FUTURE RESEARCH

Screening of the CKD population for metabolic changes prior to PD initiation may be an interesting but expensive strategy in order to prevent NODM. Further studies in the general population vs. CKD and dialysis patients are required in order to identify new thresholds for $Hb_{A1c}$ and for glycated albumin in dialysis patients. CKD patients show signs of genetic instability and even genetic damage, for example due to impaired DNA repair. As a result of aggregation of uremic toxins and oxidative stress mediators DNA strands might break up; point mutations and abnormal DNA cross-linkings can be created (89). There is a considerable lack of knowledge about toxic effects of cytokines or other uremic toxins on beta-cells, possibly contributing to NODM in PD and HD patients. Furthermore, there is no data about cytotoxic effects of PD solutions on beta-cells. Future research should also focus on the question if glucose-sparing PD regimens (including icodextrin and/or amino acid containing dialysates) can significantly reduce the risk of NODM in PD patients. Endothelin-1 gene polymorphisms and micro-RNA are closely linked with diabetic kidney disease (90,91). However, the importance of Endothelin-1 gene polymorphisms and micro-RNAs in the pathogenesis of NODM in dialysis patients is unknown. Furthermore, no data are available on the role of various adipokines, namely monocyte

chemotactic protein-1, retinol binding protein-4, omentin, vaspin, progranulin, osteopontin, C1q/tumor necrosis factor related protein, family adipokines, adipsin, glypican family adipokines, and proneurotensin in the pathogenesis of NODM in PD patients.

The influence of visceral fat areas on $Hb_{A1c}$ levels in PD patients, is well known (92). Finding a cut-off level for visceral fat area, which could predict an increased NODM risk in PD patients, could be an interesting scientific approach. Future studies regarding the importance of nutritional aspects on NODM risk in dialysis patients are required. Furthermore, development of risk scores for occurrence of NODM in PD and HD patients are required in clinical practice. More data are required in order to study the influence of APD vs. CAPD, the effect of different APD modalities (i.e. NIPD, CCPD), and the influence of peritoneal transport types on the risk of NODM.

## CONCLUSIONS

In summary, currently published data suggest that the risk of new-onset diabetes mellitus in dialysis patients is higher compared to healthy subjects. However, there is no clear evidence that NODM risk is higher in PD patients compared to HD patients. Several established risk factors of the general population may not be as important in dialysis patients. Further studies with more adequate study design, larger sample size, and longer observation periods are required in order to find definite and clear answers to open questions regarding this important topic.

**Conflict of Interest:** None.

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