Additional cost of end-stage kidney disease in diabetic patients according to renal replacement therapy modality: a systematic review

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Abstract

The prevalence of end-stage kidney disease (ESKD) is growing worldwide; the survival of these patients requires renal replacement therapy (RRT, a complex and costly treatment). Over 20% of the patients that start RRT had diabetes. Limited evidence on the effect of comorbidities on the cost of RRT exists. This review summarizes the available evidence on the effect of diabetes mellitus (DM) on the cost of RRT. Electronic databases were searched using key words that combined RRT with DM and cost. References were identified with title, abstract, and full-text screening. The studies included were published in English and presented data on the cost of RRT in ESKD patients with comparison between DM status. Seventeen studies were included in this review. The crude and adjusted cost of care estimates for patients on dialysis was generally higher for DM patients. The cost of care of ESKD patients differed according to various treatment modalities and these differences, mainly driven by inpatient costs. Overall, we found an increased cost of RRT care in patients with DM regardless of the type of treatment. Future analysis of the effects of multiple comorbidities should be considered to better understand the effect of DM on the cost of RRT.

Keywords: Cost, Diabetes, Dialysis, Renal replacement therapy, Renal transplant

Background

The prevalence of end-stage kidney disease (ESKD) is continuing to increase worldwide. Long-term survival of these patients is dependent on renal replacement therapy (RRT) (hemodialysis [HD], peritoneal dialysis [PD], and/or kidney transplant). In Europe, over 20% of the RRT incident cases had diabetes, over 10% a cardiovascular disease, and over 50% are 65 years old or older [1].

ESKD has been recognized as a public health concern due to the financial and human burden, the complexity of care, and the growing prevalence of the disease [2]. In Europe, the number of prevalent patients increased from 641.6 per million population (pmp) in 1997 to 823 pmp in 2016 [3, 4]. This increase has been attributed to a surge of the prevalence of conditions that lead to chronic kidney disease (CKD), such as diabetes, cardiovascular disease, and older age [5].

In the USA, 47% of incident ESKD patients are attributed to diabetes [6]. Total spending for ESKD patients accounts for 7% of the Medicare budget and allocated to 1% of the population [7]. In France, 22.2% of the ESKD incident patients are attributed to diabetes [6]. The cost of RRT represented 3% of the total budget of the French national health insurance fund in 2013 and served less than 1% of the population [8]. Studies have found that the most clinically
effective and cost-effective treatment modality is kidney transplantation [9]. However, transplant availability is limited, and this modality is not suitable for all ESKD patients, particularly patients with one or several comorbidities [10], which limit the eligibility for kidney transplantation and self-care dialysis. Multiple comorbidities have been associated with an increased pattern of cost [11]; nonetheless, the available evidence remains limited.

Diabetes mellitus (DM) is recognized as the primary cause of ESKD in the USA, Europe, and other regions of the world, with a prevalence ranging between 23 and 39% in ESKD patients [1, 12, 13]. Diabetic patients on HD have a poorer quality of life, an increased risk of developing/worsening of cardiovascular disease, neurological diseases, and an increased mortality [14–16]. As the prevalence of diabetes is increasing worldwide [17], it is expected that a greater number of patients will develop diabetic chronic kidney disease and eventually ESKD [18]. In this narrative review, we will summarize the available evidence on the effect of DM on the cost of RRT according to the treatment modality.

Methods

Literature search

Seven electronic databases were searched from data inception to mid-February 2018 with no time or methodology restrictions through focused and highly sensitive search strategies: NHS Economic Evaluation Database, Health Technology Assessment (via EBM Reviews), Embase (via the Ovid platform), EconLit (via EBSCO), Cochrane library, APAlS Health (via Informit), and Medline (search from inception to July 2020). Databases were searched for medical subject headings (MeSH) and keywords, combining terms related to dialysis or kidney transplantation with terms related to DM and terms related to cost information (“cost”, “expenditure”, “costing”, “cost evaluation”). A manual search for grey literature was conducted to retrieve government documents or commission reports.

Inclusion criteria

This review included studies in English reporting data on costs in ESKD patients treated by RRT (HD and/or PD and/or kidney transplantation) and comparing patients with DM and patients without DM, regardless of the type of diabetes.

Exclusion criteria

Studies that did not report separate costs for DM patients, studies that reported costs for combined comorbidities, non-primary studies (review articles, commentaries, letters, editorials), and studies including only post-transplant DM were not included.

Study selection

Titles and abstracts were screened, removing irrelevant records (either not related to our topic or irrelevant study design (reviews or non-original data). Full texts were sourced for the remaining records, and their eligibility was assessed for inclusion. We extracted the following information: first author, year of publication, setting (i.e., country), study design, definition of DM, type of dialysis, data sources, perspective, currency, cost, cost categories, time period considered for calculation of costs. A narrative approach was used to synthesize the current findings.

Cost assessment

To assess and categorize costs, we will use the terminology adopted by the French National Authority for Health to evaluate medico-economic strategies in the management of end-stage kidney disease. Costs related to consumption of hospital, ambulatory care, transportation, health program, and prescribed medications will be categorized as direct costs. Indirect costs refer to the impact of the disease on an individual’s ability or not to work as a result of reduced survival [19]. A top-down estimation refers to the estimation of costs using overall cost of a service of component; consequently, the estimation of unitary costs when using this method is the average cost; therefore, insensitive to between-patient variability. A bottom-up approach provides detailed information about the cost components per patient and identifies patient-specific unit costs. Person-based methods can more accurately assess and adjust for between-patient variability [20, 21].

Appraisal and quality assessment

Quality assessment used the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) checklist. This scale considers three major issues: selection (source of the population and its representativeness, sample size, missing values, exposure analysis), comparability (most important factor, other factors), and outcome (evaluation, statistical test).

Results

Literature search

The database searches performed in 2018 and 2020 identified 1416 records. After removing duplicate and irrelevant articles, 43 articles were submitted to full-text review. No studies of interest were identified in the grey literature. Twenty-five of these 43 references were excluded, as they did not report costs for diabetic patients or presented the costs of combined stages of CKD. At the end of the process, we identified 18 references (Fig. 1) [11, 22–38] (corresponding
to 17 studies, as one study was published in 2 parts [11, 22]).

Study characteristics
The 17 studies comprised no randomized controlled trials, 9 cohort studies [22, 24, 27, 29, 32–34, 36, 37], and 8 cross-sectional studies [11, 22, 25, 26, 28, 30, 31, 35, 38] (see Tables 1 and 2 for characteristics of the included studies). Four studies included incident patients [11, 22, 29, 32, 33], 2 studies included incident and prevalent patients [23, 34], and the rest of the studies included prevalent patients [24–28, 30, 31, 35–38]. Only 6 studies included transplanted patients [11, 29, 30, 35–37]. One article considered patients that were diagnosed with DM before and after kidney transplantation [37]. The proportion of diabetic patients ranged from 18 to 49% in the different groups and subgroups, except one article where DM patients were matched to non-DM [26].

Resource use and costs
All of the studies included in this review reported direct cost of care; none of the studies reported indirect cost of RRT. Three studies reported bottom-up cost estimates [24, 25, 28], 1 study reported a mix of bottom-up and top-down estimates [27], and the remaining studies used a top-down approach. Ten studies adopted an insurance perspective [11, 22, 24, 26, 28, 30, 31, 33, 34, 36], 4 studies adopted a provider perspective [25, 29, 32, 35], and 2 studies adopted a societal perspective [23, 27]. Five studies were based on national databases [11, 22, 24, 30, 37]. The types of costs reported in the studies in this review included inpatient in 7 studies [11, 22, 24, 26, 28, 30, 31, 35], outpatient in 6 studies [11, 22, 24, 26, 30, 31, 33], reimbursement in 4 studies [32, 33, 36, 37], transportation in 4 studies [27, 30, 31, 35], drugs in 3 studies [30, 35, 38], and dialysis procedure in 2 studies [31, 34]. The following were reported in individual studies: social services and patient out-of-pocket expenditure [23], amount paid by healthcare providers [25], caregiver costs [27], laboratory tests [35]. Six studies presented adjusted results [11, 22, 23, 27, 31, 32].

Quality appraisal of the studies
The overall study quality assessed by the CHEERS checklist was moderate to low, details in Table 2. Almost half of the studies included less than 400 patients, while the remaining studies comprised populations ranging between 1146 and 290,537 patients. Most of the studies are not representative of the general population, none of the studies addressed missing data, and only a few studies considered additional factors. Heterogeneous variables selected to adjust for confounders across studies (age, gender, comorbidities, income, and other variables) and the method of identification of DM varied (by medication consumption or previous medical records).

Impact of DM on costs
In the group of studies that reported cost analysis using crude results, 2 studies did not find any statistical
| Author | Year | Country | Population | Period inclusion | Source | Outcome currency | Perspective | Costs included | Total | Subgroup 1 | Subgroup 2 | Subgroup 3 |
|--------|------|---------|------------|-----------------|--------|-----------------|-------------|----------------|-------|------------|------------|------------|
| Li et al. [11, 22] | 2015 | UK | Incident RRT adults, no cancer, no dialysis out of hospital | 2003–2006 | The UK Renal Registry (UKRR); Hospital Episode Statistics (HES) | Mean costs during the first year (€) | Insurance | Top-bottom cost estimation. Inpatient cost from Health Resource Group (HRG), 2012 tariff. Outpatient cost (appointments). | HD n= 12, 068 | Mean age = 68 DM= 34% | PD n= 4018 | Mean age = 68 DM= 29% | TX n= 4149 | Mean age = 27% |
| Grun et al. [23] | 2003 | UK | Incident and prevalent dialysis in patients 70 yrs. or older | 1995–1996 | North Thames dialysis Study medical records. | Societal | Top-bottom cost estimation. Medical and social services. Privately borne costs. | Dialysis n= 171 HD= 56% | Mean age= 77 DM= 20% |
| Kao et al. [24] | 2013 | Taiwan | Prevalent dialysis adults, no cancer, no dialysis out of hospital | 1997–2005 | National Health Insurance (NHI) | Total lifetime cost. Cost per patient per year (US$) | Insurance | Bottom up costs estimation. Out-patient medical expenses Inpatient medical expenses. | HD n= 36, 539 | Mean age = 61 DM= 49% | PD n= 3137 | Mean age = 53 DM= 26% |
| Su et al. [25] | 2010 | Taiwan | Prevalent dialysis patients | 2005–2006 | National Health Insurance Bureau's (NHI) medical records | Use of medical resources during dialysis. | Provider | Bottom-up cost estimation. Fixed and variable during dialysis | Dialysis n= 177 Mean age= 62 DM= 50% HD= 7% |
| Yang et al. [26] | 2001 | Taiwan | Prevalent dialysis patients > 1 yr. of dialysis | 1999 | 3 medical centers | Annualized cost per patient-year at risk (US$) | Insurance | Top-bottom cost estimation. Out-patient medical expenses Inpatient medical expenses. | Dialysis n= 212 1/1-paired DM |
| Hynes et al. [27] | 2012 | USA | Prevalent dialysis patients | 2001–2003 | Healthcare use Medicare claims databases Self-report | Adjusted 12-month total cost (US$) | Societal | Mix of bottom-up and top-bottom estimation. Direct cost (including travel and caregivers). | HD n= 334 Mean age= |
| Author          | Year | Country | Population                  | Period inclusion | Source                                                                 | Outcome currency                      | Perspective | Costs included                                                                 | Total   | Sub-group 1 | Sub-group 2 | Sub-group 3 |
|-----------------|------|---------|-----------------------------|------------------|------------------------------------------------------------------------|----------------------------------------|-------------|--------------------------------------------------------------------------------|---------|-------------|-------------|-------------|
| Bruns et al.    | 1997 | USA     | Prevalent dialysis patients  | 1994–1995        | Medical records University of Pittsburgh Hospital                      | Annualized costs per patient-year (US$) | Insurance   | Bottom-up cost estimation. All transaction - Inpatient - Outpatient             | Dialysis | DM=50%      | DM=39%      | DM=50%      |
| Salonen et al.  | 2003 | Finland | Incident adult patients     | 1991–1996        | Tempere University hospital                                            | Mean cost (US$)                        | Provider    | Bottom-up costs estimation. Direct health cost including overhead costs         | HD n=138 | Mean age =58.6 | Mean age =45 | Mean age =45 |
| Couillerot et al. | 2017 | France  | Prevalent adult RRT patients | 2009–2010        | French national health insurance information system (SNIIRAM). French national hospital computerized medical information system (PMSI). | Monthly cost (€)                        | Insurance   | Bottom-up cost estimation. Direct costs: - Inpatient - Outpatient - Drugs - Transport | RRT n=65,662 | Mean age =61 | DM=23%      | DM=23%      |
| Icks et al.     | 2010 | Germany | Prevalent dialysis patients  | 2006             | Medical records                                                         | Dialysis-related costs                  | Insurance   | Top-down cost estimation. Direct medical cost: dialysis treatment, related admissions, outpatient contacts related Drugs and patient transportation | HD n=344 | Mean age =60 |                       |             |
| Joyce et al.    | 2004 | USA     | Incident (new onset ESKD) patients | 1998–2002        | PharMetrics Patient-Centric Database                                   | First-year annual cost (US$)            | Provider    | Top-down cost estimation. Direct cost (health plan reimbursements)              | RRT n=4190 | >65 yrs. =26% | DM=48%      | DM=48%      |
| Mau et al.      | 2010 | USA     | Incident patients aged 67 or older | 1995–2005        | Medicare                                                               | First-year annual cost (US$)            | Insurance   | Top-down cost estimation. Medicare allowable cost                              | HD n=290,537 | Mean age =75.6 |                       |             |
| Author          | Year | Country     | Population            | Period inclusion | Source                                                                 | Outcome currency                                           | Perspective               | Costs included                                                                 | Total             |
|-----------------|------|-------------|-----------------------|------------------|------------------------------------------------------------------------|------------------------------------------------------------|---------------------------|----------------------------------------------------------------------------------|-------------------|
| Wong et al.     | 2012 | Australia   | Incidence and prevalence | 2004–2008         | Refined diagnosis-related group and Medicare benefits schedule Australia | Total cost of dialysis and receiving a deceased donor liver | Insurance                | Top-down cost estimation. Total cost of dialysis and receiving a deceased donor liver | 77.4              |
| Ghoddousi et al. | 2007 | Iran        | Prevalence            | 2000–2005         | Patient's hospital records                                             | Total cost of rehospitalizations after Tx (PPPS)            | Provider                  | Top-down cost estimation. Total hospital costs including hotel, medications, surgery, lab. test, imaging tests, health personnel, transportation. | Hx n=387 DM=18%  |
| Smith et al.    | 1989 | USA         | Prevalence            | 1981–1983         | Michigan Kidney Registry                                               | Annual Medicare allowable charges                          | Insurance                | Top-down cost estimation. Sum of the reimbursed amount paid by providers         | n=1146 DM=21%    |
| Woodward et al. | 2011 | USA         | Prevalence            | 1998–2002         | US Renal Data System                                                   | The lump sum of daily average Medicare payments per patient (8 yrs) | Insurance                | Top-down cost estimation. Institutional claims and physician's supplier claims       | n=24,816 DM=46.4% |
| Manley et al.   | 2005 | USA         | Prevalence            | 2003              | Dialysis Clinic Inc. DCI                                               | Average monthly cost of drugs taken at home by patients that receive dialysis | Provider                  | Top-down cost estimation. Medications used at home                               | n=10,230 DM=40%  |

UKRR The UK Renal Registry, HES Hospital Episode Statistics, HD hemodialysis, PD peritoneal dialysis, CAPD continuous ambulatory peritoneal dialysis, RRT renal replacement therapy, ESKD end-stage kidney disease, NODAT new onset DM after transplant.
| Author       | Year | Design       | Prospective | Data source | Comorbidities definition | Confounder | Adjustment | Selection | Sample size | Missing data | Exposure Analysis | Comparability | Outcome | Evaluation | Total |
|--------------|------|--------------|-------------|-------------|--------------------------|------------|------------|-----------|-------------|--------------|------------------|---------------|----------|------------|-------|
| Li et al. [11, 22] | 2015 | Cross-sectional | Retrospective | National | Discharge codes from hospitalizations prior to starting RRT-ICD 10 | None | None | *         | *           | *             | *               | *             | *       | *         | 5     |
|              | 2016 | *            | MRM         | Age, sex, years since starting RRT, treatment modality, events, comorbidities | ** | *          | **         | *           | *             | *               | *             | *         | *         | 6     |
| Grun et al. [23] | 2003 | Cohort       | Prospective | 4 dialysis units | At baseline | None | Sex, age, treatment modality, comorbid conditions, cohort, length of time since initiation | *         | *           | *             | *               | *             | *         | *         | 4     |
| Kao et al. [24] | 2013 | Cohort       | Retrospective | National | Stratification | Stratification by matched HD-PD on age, sex, DM status | *         | *           | *             | *               | *             | *         | *         | 3     |
| Su et al. [25] | 2010 | Cross-sectional | Prospective | One district | MRM | Comorbidities, age | *         | *           | *             | *               | *             | *         | *         | 3     |
| Yang et al. [26] | 2001 | Cross-sectional | Prospective | 3 medical centers | Matching | Matched DM—no DM on age, sex, duration of dialysis | *         | *           | *             | *               | *             | *         | *         | 2     |
| Hynes et al. [27] | 2012 | Cohort       | Prospective | Veterans Affairs facilities | Year prior the index date-ICD 9 | MRM | Age, gender, race, income, insurance, comorbidities, quality of well-being | *         | *           | *             | *               | *             | *         | *         | 5     |
| Bruns et al. [28] | 1997 | Cross-sectional | Retrospective | 1 medical center | Stratification | Stratification by age | *         | *           | *             | *               | *             | *         | *         | 1     |
| Salonen et al. [29] | 2003 | Cohort       | Prospective | 1 medical center | MRM | Stratification by treatment modality | *         | *           | *             | *               | *             | *         | *         | 2     |
| Couillerot et al. [30] | 2017 | Cross-sectional | Retrospective | National | Use of drugs for DM | Stratification on age and | *         | *           | *             | *               | *             | *         | *         | 4     |
Table 2 Quality assessment of included articles (Continued)

| Author            | Year | Design | Prospective Retrospective | Data source                                      | Comorbidities definition | Confounder | Adjustment | Selection | Sample size | Missing data | Exposure Analysis | Comparability | Outcome | Total |
|-------------------|------|--------|----------------------------|-------------------------------------------------|---------------------------|------------|------------|-----------|-------------|--------------|-----------------|-----------------|----------|-------|
| Icks et al. [31]  | 2010 | Cross-sectional | Prospective 1 medical center | MRM | RRT modality, events | Gender, age, ESKD duration, time of dialysis | * | * | * | * | * | * | * | * | 3 |
| Joyce et al. [32] | 2004 | Cohort | Retrospective  | Commercially insured patients in 61 Health Plans | Year prior the index date-ICD 9 | MRM | Age, gender, insurance, comorbidities, region, medication use. No adjustment on RRT modality. | * | * | * | * | * | * | * | * | 4 |
| Mau et al. [33]   | 2010 | Cohort | Retrospective National  | 2 years prior the index date-ICD 9 | MRM | Age, gender, race, comorbidities, Hb, eGFR, albumin, BMI, hospital days pre-onset | * | * | * | * | * | * | * | * | 6 |
| Ghoddousi et al. [35] | 2007 | Cross-sectional | Retrospective 1 medical center | Reported in the EMR | None | None | * | * | * | * | * | * | * | * | 3 |
| Smith et al. [36] | 1989 | Cohort | Retrospective Michigan database | None | None | None | * | * | * | * | * | * | * | * | 3 |
| Woodward et al. [37] | 2011 | Cohort | Retrospective US Renal Data System | ICD 9 | None | None | * | * | * | * | * | * | * | * | 6 |
| Wong et al. [34]  | 2012 | Cohort | Retrospective National | Australian Refined Diagnosis Related Groups | Stratification | None | * | * | * | * | * | * | * | * | 5 |
| Manley et al. [38] | 2005 | Cross-sectional | National | None | None | None | * | * | * | * | * | * | * | * | 4 |

* used to mark the characteristic as present in the study.

MRM multiple regression model, RRT renal replacement therapy, ESKD end-stage kidney disease
differences in terms of crude mean cost between patients with or without DM receiving dialysis (HD and PD grouped together) (Table 3) [23, 25]. One study found a 23% difference for the cost per patient-year, varying according to age from 61% in the 65–74 years age-group vs −22% in DM patients ≥ 75 years [28]. One study found a 12% difference in total cost per patient-year, mainly explained by the difference in terms of utilization of resources during hospitalization between non-DM and DM patients [26]. The last study to report differences within the HD+PD group showed increased annual costs among DM patients for all comparator groups ranging from 17 to 44%, except for the annual costs related to at-home continuous ambulatory peritoneal dialysis training (CAPDTR) that were 3% lower among DM patients [36].

Table 4 contains details of the studies that reported HD and PD cost estimates separately. In the HD group, four studies found a higher cost for DM patients between 4 and 32%, regardless of the comparator used or the age group or the treatment modality [11, 29, 30, 38]. Among PD patients, three studies found a higher cost in DM patients, between 4 and 52%, regardless of the comparator used or the age group or the type of PD [11, 29, 30]. One study found a lower total lifetime cost in DM patients with −48 and −42% for HD and PD. The differences expressed in terms of life years were 23 and 32%, respectively [24].

In transplanted patients (Table 5), four studies found a higher cost in DM patients regardless of the comparator ranging between 14 and 100% [11, 30, 35, 37]. Salonen et al. reported a lower cost for DM in the comparator group for the first 6 months (−4%) and during the second year after transplant (−10%) [29]. Two studies presented cost estimates for all RRT patients, and both reported higher costs for DM patients, ranging between 5 and 50% [32, 34].

Six studies presented adjusted cost analyses (Table 6), and 3 of these studies reported significant results suggesting a positive relationship between DM and increased cost [22, 32]. Three studies, based on relatively small sample sizes, did not find any statistical association between DM and costs [23, 27, 31].

**Discussion**

Our narrative review shows for the first time to our knowledge the different costs of care between DM and non-DM patients by type of RRT. This review found that higher costs are generally reported for patients with DM in RRT. The costs most commonly reported were inpatient costs and outpatient costs. The difference between DM and non-DM patients was observed

| Table 3 Crude cost estimate reported in dialysis patients (HD + PD) |
|-----------------|-----------------|-----------------|-----------------|
| Author          | Year            | comparator      | Stratification  | Value of non-DM (SD) | Value of DM (SD) | Diff | p     |
| Grun et al. [23]| 2003            | Mean cost per day (£) | None          | 68.5 (30.5)        | 68.1 (28.1)       | −1%  | 0.94  |
| Su et al. [25]  | 2010            | Dialysis cost (NT)| None          | 1467.53 (220.9)    | 1481.6 (209.13)   | 1%   | 0.664 |
| Yang et al. [26]| 2001            | Total cost (US$/patient-year) | None          | 24,146            | 26,988           | 12%  |       |
|                |                 | Outpatient (US$/patient-year) | None        | 22,820            | 22,311           | −2%  |       |
|                |                 | Dialysis and EPO | None          | 21,209            | 19,841           | −6%  |       |
|                |                 | Other clinic     | None          | 1611              | 2470             | 53%  |       |
|                |                 | Hospitalization (US$/patient-year) | None        | 1325              | 4677             | 253% |       |
|                |                 | Dialysis and EPO | None          | 409               | 1093             | 167% |       |
|                |                 | Others           | None          | 916               | 3584             | 291% |       |
| Bruns et al. [28]| 1997            | Costs per patient-year ($) | All          | 55,581            | 68,228           | 23%  |       |
|                |                 | 20–44            | None          | 48,927            | 51,884           | 6%   |       |
|                |                 | 45–64            | None          | 65,707            | 72,643           | 11%  |       |
|                |                 | 65–74            | None          | 48,062            | 77,418           | 61%  |       |
|                |                 | ≥75              | None          | 59,594            | 46,746           | −22% |       |
| Smith et al. [36]| 1989            | Annual charges HD in centers | None          | 23,470            | 27,463           | 17%  |       |
|                |                 | Annual charges PERI in centers | None        | 22,529            | 26,486           | 18%  |       |
|                |                 | Annual charges CAPDTR | None        | 18,408            | 17,879           | −3%  |       |
|                |                 | Annual charges CAPDH | None        | 22,753            | 29,435           | 29%  |       |
|                |                 | Annual charges Other | None        | 28,342            | 40,779           | 44%  |       |
|                |                 | Weighted average | None          | 24,976            | 29,671           | 19%  |       |

Note: NT New Taiwan, EPO erythropoietin, PERI in center peritoneal dialysis, CAPDTR continuous ambulatory peritoneal dialysis training, CAPDH combinations of dialysis treatments
## Table 4: Crude cost estimate reported in HD and PD separate groups.

| Author              | Year | Comparator | HD patients                          | PD patients                          |
|---------------------|------|------------|--------------------------------------|--------------------------------------|
|                      |      |            | Stratification Value of non-DM (SD)  | Value of DM (SD)                      | Diff | p     | Strata     | Value of non-DM (SD) | Value of DM (SD) | Diff | p     |
| Li et al. [11, 22]  | 2015 | Mean inpatient cost (£) | None | 6685 (6415, 6956)* | 8454 (8049, 8858)* | 26% | < 0.0005 | None | 4492 (4215, 4770)* | 6814 (6321, 7307)* | 52% | < 0.0005 |
|                     |      | Mean outpatient cost (£) | None | 1081 (1051, 1110)* | 1346 (1303, 1389)* | 25% | < 0.0005 | None | 1789 (1453, 1543)* | 2064 (1976, 2152)* | 15% | < 0.0005 |
| Kao et al. [24]     | 2013 | Total lifetime (US$) | None | 216,457 (12,853) | 112,516 (5318) | −48% | 157,374 (10,531) | 90,945 (10,935) | −42% |
| Salonen et al. [29] | 2003 | Mean cost 0–6 months (US$) | None | 32,741 | 34,006 | 4% | 42,323 | 29,882 | 28% |
|                     |      | Mean 7–12 months (US$) | None | 26,155 | 28,908 | 11% | 29,892 | 22,732 | 42% |
|                     |      | Mean year 2 (US$) | None | 52,287 (12,853) | 63,781 (5318) | −22% | 43,386 | 51,027 | 20% |
| Couillerot et al. [30] | 2017 | Mean monthly health care costs (euros) for a stable prevalent patient | 18–44 yrs. | 6915 (2455) | 8298 (2420) | 20% | 3214 (1269) | 4382 | 36% |
|                     |      | In-center Home Self-care Home | 6915 (2455) | 8298 (2420) | 20% | 3214 (1269) | 4382 | 36% |
|                     |      | 45–69 yrs. | Home Self-care Home | 6964 (2391) | 7992 (2306) | 15% | 3856 (1344) | 4093 (1253) | 6% |
|                     |      | In-center | 4739 (1791) | 5886 (1811) | 24% | 4208 (1370) | 5376 (2071) | 28% |
|                     |      | Home Self-care Home | 4083 (1567) | 5360 (2021) | 31% | 4850 | 6018 | 24% |
|                     |      | 70+ yrs. | In-center Home Self-care Home | 6016 (1867) | 7736 (2014) | 12% | 3462 (1348) | 4295 (1287) | 24% |
|                     |      | Home | 5136 (1672) | 5810 (1641) | 13% | 4324 (1410) | 4984 (1446) | 15% |
|                     |      | Self-care Home | 4304 (1461) | 4940 (1698) | 15% | 4899 (1885) | 6497 (2406) | 33% |
|                     |      | 70+ yrs. | In-center Home Self-care Home | 7716 (13683) | 9467 (6999) | 23% | 10,882 (11,691) | 13,345 (9978) | 23% |
|                     |      | Home | 5003 (1632) | 5425 (1756) | 8% | 4085 (1390) | 5118 (1691) | 25% |
|                     |      | Self-care Home | 4340 (1282) | 4696 (1349) | 8% | 4932 (1565) | 5923 (1848) | 20% |
|                     |      | 70+ yrs. | In-center Home Self-care Home | 7797 (10717) | 8632 (6809) | 11% | 9647 (9441) | 9654 (7981) | 0% |
|                     |      | Home | 3484 (1251) | 4374 (1756) | 26% | 5265 (1653) | 5796 (2069) | 10% |
|                     |      | 18–44 yrs. | Cost of the first month of treatment for incident patients. | 7716 (13683) | 9467 (6999) | 23% | 10,882 (11,691) | 13,345 (9978) | 23% |
|                     |      | 45–69 yrs. | | 7797 (10717) | 8632 (6809) | 11% | 9647 (9441) | 9654 (7981) | 0% |
|                     |      | 70+ yrs. | | 7851 (6767) | 8667 (7434) | 10% | 8810 (8276) | 11,244 (8860) | 28% |
regardless of the treatment modality (dialysis or transplantation) and was mainly driven by the higher costs of hospitalization.

The results should be interpreted cautiously, 8 of the studies were published over 10 years ago, and there are numerous methodological pitfalls the observational studies included. A quality score higher than 5 was observed for only 3 studies. Thirteen studies were based on local databases and were less representative of the general population. Six studies adjusted for patient

Table 4 Crude cost estimate reported in HD and PD separate groups. (Continued)

| Author     | Year | Comparator | HD patients | PD patients |
|------------|------|------------|-------------|-------------|
|            |      |            | Value of non-DM (SD) | Value of DM (SD) | Diff | p  | Strata | Value of non-DM (SD) | Value of DM (SD) | Diff | p |
| Manley     | 2005 | Monthly cost of ambulatory medications. | 571.04 (287.36) | 691.04 (271.59) | 21% |   |       |                 |                 |      |

*95% CI limits
CAPD continuous ambulatory peritoneal dialysis; Non-ass CAPD non-assisted CAPD, Ass CAPD assisted CAPD

Table 5 Crude cost estimate reported in transplanted and unspecified RRT patients:

| Author     | Year | Comparator | Stratification | Value of non-DM (SD) | Value of DM (SD) | Diff | p       |
|------------|------|------------|----------------|----------------------|-----------------|------|---------|
| Transplanted patients | 2015 | Mean inpatient cost (£) | None | 3626 (3439, 3813)* | 5921 (5499, 6343)* | 63% | <0.0005 |
| Li et al. [11, 22] | 2003 | Mean cost 0–6 months (US$) | None | 38,946 | 37,299 | −4% |         |
|              | 2017 | Mean monthly health care costs (euros) for a stable prevalent patient | 18–44 years | 1043 (1188) | 2091 (1998) | 100% |       |
|              |      |            | 45–69 years | 1075 (1065) | 1640 (1337) | 53% |         |
|              |      |            | 70+ years | 1038 (888) | 1475 (1129) | 42% |         |
| Ghoddousi et al. [35] | 2007 | Total cost (PPP $ rehospitalization) | None | 863.93 (1165.2) | 1261.98 (1930.5) | 46% |       |
| Smith et al. [36] | 1989 | Year of transplant annual charges LTRAN | None | 41,553 | 46,797 | 13% |         |
|              |      | Year of transplant annual charges CTRAN | None | 42,074 | 61,493 | 46% |         |
|              |      | Year of transplant annual charges FTRAN | None | 58,672 | 63,670 | 9% |         |
|              |      | Year after transplant annual charges LTRAN | None | 3836 | 4320 | 13% |         |
|              |      | Year after transplant annual charges CTRAN | None | 5696 | 8325 | 46% |         |
|              |      | Year after transplant annual charges FTRAN | None | 47,057 | 50,584 | 7% |         |
| Woodward et al. [37] | 2011 | DM before transplant. Cumulative cost per patient from 3 years before transplant to 5 years after transplant | None | 114,686 | 162,048 | 29% |       |
|            |      | NODAT before transplant. Cumulative cost per patient from 3 years before transplant to 5 years after transplant | None | 114,686 | 146,915 | 22% |       |
| RRT        | 2004 | Annual cost for the 12 months post onset of ESKD ($) | None | 57,249 | 86,081 | 50% |       |
| Joyce et al. [32] | 2012 | Total costs ($) | 45 years old | 119,329 | 136,677 | 13% |         |
|            |      | Total costs ($) | 60 years old | 143,004.98 | 151,168.29 | 5% |         |

ESKD end-stage kidney disease, DM diabetes mellitus, PPP power parity dollar, LTRAN living related donor, CTRAN cadaver donor, FTRAN failed, NODAT new onset DM after transplant
characteristics for cost modelling. Most studies did not consider comorbidities. Social, transport, and out-of-pocket expenses were not considered in the majority of studies. The diversity of comparators, populations, sources of costs, and the perspectives used in the various studies prevented us from performing a dollar-to-dollar comparison between the various studies or a meta-analysis.

There is evidence in the literature for a higher healthcare cost in the DM population regardless of their kidney disease status that is mainly driven by inpatient costs due to long hospital stays [39]. Yang et al. showed that the number of hospitalizations, and the mean length of hospital stay were the main drivers of the increased costs among DM patients [40]. Other studies in our review do not provide any insight into the drivers for higher costs for DM patients.

Higher costs for DM patients can also be explained by the number and total cost of medications, as patients with DM were more frequently prescribed cardiovascular, gastrointestinal, and endocrine drugs than non-DM patients treated by RRT [38], which is consistent with the metabolic complications intrinsic to DM and the high rate of vascular and neurological comorbidities in the DM population [41].

Wong et al. and Kao et al. [24, 34] reported lifetime costs of DM. In their study, the overall cost of RRT was higher for non-DM patients. However, when corrected by the expected years of life, the cost of RRT was higher in DM patients, as DM patients with ESKD are known to have a shorter life expectancy than non-DM patients [15, 42, 43].

A more marked difference in costs between non-DM and DM patients was generally observed in the younger population, which could likely be explained by the lower rate of comorbidities in young non-DM patients. Younger patients are more likely to have type 1 DM; insulin therapy represents a high proportion of the cost of treatment for these patients. Younger patients have also been reported to have a higher first month cost when starting treatment as a result of training to perform PD independently and clinical evaluations for inclusion on transplant waiting lists [30]. This interesting point should be taken into account when performing future analyses of the costs associated with comorbidities and differences according to age groups and the reference time-points to be used. In the study by Bruns et al., the greatest difference was observed in an older age group (between the ages of 65 and 74). The distribution of the population in this study was slightly different from that of the general population, as outliers were likely to have an impact in the 65- to 74-year age group.

Table 6 Adjusted cost estimations of patients receiving RRT (DM and non-DM patients)

| Author          | Year | Stratification | Comparator | Estimation                                                                 | Adjusted results ($, £, € (95% CI)) | p-value |
|-----------------|------|----------------|------------|---------------------------------------------------------------------------|-------------------------------------|---------|
| Li et al. [22]  | 2016 | None           | Increase in mean annual costs ($) GLM coefficient for inpatient GLM | 1046 (734, 1359)                  | <0.05                             |
|                 |      |                | Increase in mean annual costs ($) GLM coefficient for outpatient GLM | 593 (515, 671)                    | <0.05                             |
| Li et al. [22]  | 2016 | None           | Increase in mean annual costs ($) GLM coefficient for inpatient GLM | 1191 (929, 1453)                  | <0.05                             |
|                 |      |                | Increase in mean annual costs ($) GLM coefficient for outpatient GLM | 248 (211, 284)                    | <0.05                             |
| Grun et al. [23]| 2003 |                | Adjusted difference of means cost per day ($) linear regression | −0.8 (−11.8, 10.1)               | 0.88                              |
| Hynes et al. [27]| 2012 | DM             | Adjusted annual cost difference ($) GLM marginal effect | −1623 (−14,973; 11,727)           | 0.81                              |
|                 |      | Complicated DM | Relative cost differences (euros, GLM) | 1.04 (0.98, 1.10)                | 0.37                              |
| Icks et al. [31]| 2010 | None           | Case-mix-adjusted estimate | 0.0275 (0.0014)                  | <0.001                            |
|                 |      |                | Relative cost | 1.03                        |                                    |
| Joyce et al. [32]| 2004 | None           | Adjusted annual cost difference ($) GLM marginal effect | 42,361                             | <0.001                            |

DM diabetes mellitus, TX transplant patients, GLM generalized linear model
both groups [29], supporting evidence that kidney transplantation is the RRT modality associated with the greatest economic benefits after the first year regardless of DM status [43].

Conclusions
We found an increased cost of RRT in patients with DM regardless of the treatment modality when compared to patients without DM. Given the increased prevalence of DM in the population, we can anticipate higher healthcare cost for this group of patients. The effects of presence of multiple comorbidities (in non-DM and DM patients), life expectancy, and specificity of type of dialysis treatment should be taken into account in future studies to obtain a better understanding of the effect of DM in RRT care. Additional information is also needed on indirect costs.

Abbreviations
CAPDTR: Continuous ambulatory peritoneal dialysis training; CHEE RS: Consolidated Health Economic Evaluation Reporting Standards; CKD: Chronic kidney disease; DM: Diabetes mellitus; ESKD: End-stage kidney disease; HD: Hemodialysis; PD: Peritoneal dialysis; RRT: Renal replacement therapy

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Authors’ contributions
CC developed the idea and performed the preliminary search and screening. IV performed screening of abstracts and titles as well as full-text screening, and data extraction and wrote the manuscript. CP and PT reviewed and edited the manuscript. All authors discussed and approved the manuscript.

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