Review
Utility values in diabetic kidney disease: a literature review

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Abstract

Objective:
To summarize the published literature on utilities for health states associated with diabetic kidney disease (DKD), including end-stage renal disease (ESRD).

Research design and methods:
A literature review was conducted (MEDLINE, MEDLINE in process, EMBASE, NHS EED, HEED, CEA Registry, EconLit, RePEc, and HTA) to identify relevant articles published between January 2000 and July 2013. Results were assessed for relevance by two reviewers in line with the study protocol.

Main outcome measures:
For eligible studies, data extracted included patient population, health states, methods used to elicit utility values, and the source of the preference values.

Results:
Twelve studies satisfied the inclusion criteria. They reported various utility and/or disutility scores for different DKD health states using a range of patient populations, utility approaches, and sources of preference values. The most common study country was the USA. Most of the studies collected data at one time point, but two had a longitudinal design. Three different utility instruments – EuroQol (EQ-5D), Quality of Well-Being Scale (QWB), and 15-dimensional (15D) – were used to elicit utilities indirectly. The Time Trade-Off (TTO) approach was used in one study; another undertook a meta-analysis of published utility studies. Utilities were identified for different health states including DKD, ESRD–no dialysis, ESRD–dialysis, and transplant. One study reported utilities for patients by type of transplant. There was variation in values for the same health state between studies, and none of the studies reported utilities for the different stages of DKD. In the studies that undertook a comparison, utility values for those with DKD were generally found to be lower than those without DKD.

Conclusions:
This literature review highlights that at present utility scores (or disutility penalties) exist for relatively few health states in DKD. Further studies are needed to produce accurate and comprehensive utility scores that differentiate between different DKD health states.

Introduction

Diabetic kidney disease (DKD) is a chronic kidney disease (CKD) that can develop as a microvascular complication of diabetes mellitus (DM); it is traditionally termed diabetic nephropathy. In patients with DM, CKD is considered to be attributable to DM if the patient has severely increased albuminuria, or if moderately increased albuminuria is present with either diabetic retinopathy or in patients with type 1 diabetes mellitus (T1DM) of ≥10 years’ duration1. Diabetes mellitus is the leading cause of CKD3, with around 40% of DM patients...
having DKD. Almost all DM patients show histological signs of kidney damage, and individuals typically progress from a DM diagnosis to microalbuminuria, macroalbuminuria, and finally elevated plasma creatinine (≥175 mmol/L) or end-stage renal disease (ESRD). Importantly, DM is the primary diagnosis in 20–40% of individuals who start renal replacement therapy (RRT). As DM has a high and increasing worldwide prevalence (estimated at 382 million in 2013, and expected to be 471 million by 2035), it is predicted that the proportion of CKD attributable to DM will also continue to rise.

Health state utility values are used in economic analyses to predict the effect of technologies on patients’ health-related quality of life (HRQoL). They are useful because they represent an individual’s preference for a specific health state or outcome. The values are captured on a scale: 1.0 represents perfect health or the best possible health state; 0 corresponds with death; and negative values represent states worse than death. Economic analyses using utility values are becoming increasingly important because decision makers are being asked to optimize the allocation of health care resources across disease areas and patient groups. Indeed, cost–utility analyses (CUAs) are recommended as the reference case by some health technology assessment (HTA) bodies, including in the UK and Canada.

Utility values can be estimated using either direct or indirect methods. The standard gamble (SG) and the time trade-off (TTO) approaches are direct methods, in which utilities are elicited directly from patient responses to questions. With the indirect approach, preferences are mapped onto the utility scale indirectly using a multidimensional HRQoL questionnaire such as EuroQol (EQ-5D), 15-dimensional (15D), Short Form-6 dimension (SF-6D), and the Quality of Well-Being Scale (QWB). Responses from these questionnaires are converted to utility values using ‘tariffs’ or ‘weights’. These weights are derived from previous studies in which various possible health states have been calibrated by a trade-off method from a sample of the general population.

It is important to determine utility values associated with DKD to inform economic evaluations of novel therapies. Due to the progressive nature of DKD, drugs are required that slow or prevent its transition. The cost-effectiveness of potential DKD treatments will need to be modeled over time; thus, utility values are required that reflect the relevant disease stages (health states). One of the most prominent models in this area was developed on behalf of the Centers for Disease Control and Prevention CKD Initiative. This microsimulation model of the natural progression of CKD has seven mutually exclusive states representing no CKD, five stages of CKD, and death. Patients pass through the model based upon their glomerular filtration rate and albuminuria status. This model was adapted for use in a DM population, and it was shown that effective therapeutic intervention to slow progression to ESRD in high-risk DKD patients can result in medical benefits (i.e., ESRD cases avoided) and can be cost effective.

Utility values associated with CKD health states that have been reported in existing systematic reviews may not be transferable to patients with DKD because HRQoL is likely to be poorer in patients with DKD. In meta-analyses, utility values (i.e., HRQoL estimates) were lower in patients with comorbid CKD and DM versus those with CKD only (0.81 vs. 0.91) and in patients with ESRD and DM versus those with ‘general DM’ (0.48 vs. 0.76). Consistent with this, data show that the presence of DM in patients with ESRD on hemodialysis is associated with a significantly lower HRQoL. For example, in a cross-sectional study of patients with ESRD on hemodialysis, those with DM (38% of patients) had a significantly lower World Health Organization QoL score (physical health component) than those without DM (physical health, P = 0.04). In another cross-sectional study, HRQoL was very poor in dialysis patients with DM, with Short Form-36 (SF-36) scores being lower than in other dialysis patients and in DM patients without dialysis. In a US study by Mujais et al., CKD patients with DM (29% of patients) had a significantly lower HRQoL than patients with CKD alone (SF-36 physical composite scores 37.3 vs. 41.6; P < 0.0001).

The aim of the present literature review was to identify published utility data for various DKD health states, discuss their suitability in economic evaluations and suggest areas for future research.

Methods

The aim of this review was to determine what literature exists on the topic and to identify gaps in the existing evidence base.

A combined protocol was developed to identify studies that estimated utilities in patients with both DM and CKD/ESRD (termed ‘DKD’ in this study), as well as CUAs of angiotensin-converting enzyme (ACE) inhibitor/angiotensin receptor blocker (ARB) treatment in DKD (for a separate review). The following electronic databases were searched: MEDLINE and MEDLINE in process (via PubMed), EMBASE, NHS Economic Evaluation Database (NHS EED), Health Economic Evaluations Database (HEED), Cost-Effectiveness Analysis (CEA Registry), EconLit, RePEc (Research Papers in Economics), and Health Technology Assessment database (HTA). Searches were carried out on July 2013 (MEDLINE), 26 July 2013 (NHS EED, HTA), 29 July 2013 (CEA Registry, RePEc), and 31 July 2013 (EMBASE, EconLit, HEED). All searches were limited to records with a publication date of 2000–2013.
An initial draft strategy was created in MEDLINE. This draft strategy was then developed through discussion in the research team. The search strategy was devised using a combination of subject indexing terms (MeSH) and free-text search terms in the title and abstract. The search terms were identified through discussion among the research team, viewing search strategies in selected published systematic reviews and systematic review protocols on the concepts of interest, examination of database records for known studies of interest, and browsing database thesauri. The final MEDLINE strategy was adapted appropriately for the other databases searched. The MEDLINE strategy is provided in the supplementary materials and the search strategies for the other databases are available on request from the authors. Eligible studies were English-language publications reporting estimated utilities as primary research (using indirect or direct methods) in DKD, as well as CUAs of ACE inhibitor/ARB treatment in DKD in adults. Studies solely reporting estimates from a visual analog scale (VAS), including the EQ-5D VAS, were excluded. Non-primary research studies including reviews, editorials, commentaries, and notes were excluded, as were single case reports and conference abstracts published in journals. Reference citations were downloaded into an Endnote database and all duplicate citations were removed. Two reviewers screened the titles and abstracts of identified studies to determine potential study eligibility. From this initial screening, references were selected for full text review, and eligible studies were identified that estimated utilities in DKD. The results were supplemented by manually checking the reference lists in eligible studies. For the final ‘included studies’, data were extracted (including health states with assigned utilities) and entered into data extraction tables. Data abstraction was completed by one reviewer and a subset of data collected was quality checked by a second reviewer.

Results

Results of search strategy

A total of 5236 database records remained from the combined search after removal of duplicates. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram (Figure 1) depicts the flow of information through the literature review by mapping out the number of records identified, included and excluded, and the reasons for exclusions. As shown in Figure 1, 17 studies remained after review of titles/abstracts, 11 after full text review, and one additional paper was identified by manually checking the reference lists in eligible studies (this paper was not picked up in the database searches as it made no reference to nephropathy, kidney disease or related synonyms in the title or abstract). Thus, there were a total of 12 included studies.

Description of included studies

The 12 included studies reported utility and/or disutility scores for different DKD health states using a range of (DM) patient populations, utility instruments, and sources of preference values (Table 1). All of the studies had a cross-sectional design. Ten studies collected data at one time point, and two involved a longitudinal analysis. In Grandy et al. (2012), individuals with self-reported DM, no DM, or at risk for DM completed the EQ-5D at baseline and 5 years later (2009) as part of the US Study to Help Improve Early evaluation and management of risk factors Leading to Diabetes (SHIELD). The analysis included patients with either type 2 diabetes mellitus (T2DM) or ‘no DM’ (data are presented here for patients with T2DM). In Sureshkumar et al. (2006), utilities were estimated in four groups of patients with T1DM and ESRD – simultaneous pancreas-kidney transplant (SPK), cadaver kidney transplant (CKT), living donor kidney transplant (LKT), and patients wait-listed for a kidney or kidney and pancreas transplant (WL). In a subgroup of patients in the SPK and CKT groups (who still had functioning allografts), utilities were evaluated at two time points, an average of 3 years apart.

Indirect methods to elicit utilities

Ten studies used instruments to estimate utility values indirectly; three different questionnaires were used: the EQ-5D (n = 7), the QWB (n = 2), and the 15D (n = 1) (Table 2). In the majority of the studies, the source of the preference values used in the questionnaires was the general population. The study by Sureshkumar et al. (2006) did not provide specific details on the derivation of the QWB preferences, and the study by Lung et al. (2011) (a meta-analysis) did not provide the source of the preference values in the individual studies. The study by Sakthong et al. (2008) took an interesting approach as they used three different sets of preference weights (UK, USA, Japan) and applied these to the EQ-5D results from the Thai patient sample.

Direct methods to elicit utilities

Huang et al. (2007) elicited utilities using a direct approach (Table 2). The TTO method was applied in 1-hour face-to-face interviews with patients with DM and therefore the source of the preference values for the study by Huang et al. (2007) was patients with T2DM. Patients were given a description of a hypothetical health
state (e.g., DKD or kidney failure) and asked to consider what life would be like in that state. Patients gave their preference for 10 years in that health state versus a shorter period of time in perfect health. Using the 'ping-pong' method, they were asked a series of iterative questions where the time in perfect health was systematically altered by 1-year increments. This method is a widely used approach in which preference probabilities are traded back and forth between high and low values. The questioning was stopped when the patient was indifferent between a particular time choice. This point was used to calculate the utility score. For example, if 6 years of life in perfect health was equal to 10 years with a particular health state, the utility score would be 0.60.

Meta-analysis of studies using both indirect and direct methods to elicit utilities

The study by Lung et al. (2011)\textsuperscript{16} was a meta-analysis of studies using both indirect and direct methods to elicit utility values. For a total of 45 DM studies published up to 2009, mean utility scores were extracted for patients with selected health states (including ESRD as well as myocardial infarction, stroke, ulcer, amputation, diabetic retinopathy, blindness, and no complications). Meta-analyses (accounting for within-study correlation) were used to obtain average utility scores for each health state. For ESRD, utility scores were extracted from four studies (Table 2)\textsuperscript{23,30,31}. Three of these studies were captured in the present review, and used the indirect

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**Figure 1.** PRISMA flow diagram.
## Table 1. Studies included in the analysis.

| Reference (country) | Number of participants | Patient/DM characteristics | Utility instrument | Preference by | Relevant health states included |
|---------------------|------------------------|----------------------------|--------------------|---------------|---------------------------------|
| **Indirect methods** |                        |                            |                    |               |                                 |
| Ahola et al., 2010²⁹  | 900                    | T1DM, 100% (mean duration, 29 y) | 15D                | Population    | Microalbuminuria, macroalbuminuria, dialysis, renal transplant |
| (Finland)            |                        | Mean HbA1c, 8.0% Mean age, 46 y Males, 46% |                    |               |                                 |
| Coffey et al., 2002²⁸ | 2048                   | T1DM/T2DM, 100% (median duration, 20 y [T1DM]; 10 y [T2DM]) Mean HbA1c, NR Median age, 35 y (T1DM); 58 y (T2DM) Males, 45% (T1DM); 51% (T2DM) | QWB-SA             | US population sample | DKD, dialysis |
| (USA)                |                        |                            |                    |               |                                 |
| Grandy et al., 2012²⁰ | 6284                   | T2DM, 28%; (mean duration, 9 y) 'No DM', 72% Mean HbA1c, NR Mean age, 61 y (T2DM) Males, 40% (T2DM) | EQ-5D              | US population sample | DKD |
| (USA)                |                        |                            |                    |               |                                 |
| Javanbakht et al., 2012²⁷ | 3472       | T2DM, 100% (mean duration, 8 y) Mean HbA1c, NR Mean age, 59 y Males, 39% | EQ-5D              | UK population sample | DKD |
| (Iran)               |                        |                            |                    |               |                                 |
| Morgan et al., 2006²³  | 4502                   | T1DM/T2DM, 100% (mean duration, NR) Mean HbA1c, NR Mean age, 65 y (males), 64 y (females) Males, 58% | EQ-5D              | Patients with DM | ESRD |
| (Wales)              |                        |                            |                    |               |                                 |
| O’Reilly et al., 2011²⁹   | 1143                   | T2DM, 100% (median duration, 8 y) Mean HbA1c, 6.9% Mean age, 64 y Males, 47% | EQ-5D              | US population sample | ESRD |
| (Canada)             |                        |                            |                    |               |                                 |
| Sakamaki et al., 2006²⁰ | 220                    | T2DM, 100% (mean duration, 9 y) Mean HbA1c, 6.9% Mean age, 63 y Males, 50% | EQ-5D              | Japanese value set | DKD |
| (Japan)              |                        |                            |                    |               |                                 |
| Sakthong et al., 2008²⁶ | 303                    | T2DM, 100% (mean duration, 12 y) Mean HbA1c, 7.7% Mean age, 61 y Males, 29% | EQ-5D              | UK, USA, Japanese value sets | DKD |
| (Thailand)           |                        |                            |                    |               |                                 |
| Sureshkumar et al., 2006²⁵ | 120               | T1DM, 100% (mean duration, NR) Mean HbA1c, NR Mean age, 42–48 y across ESRD groups Males, 59% | QWB                | NR            | ESRD (SPK, CKT, LKT, WL) |
| (USA)                |                        |                            |                    |               |                                 |
| Zhang et al., 2012²⁷  | 7327                   | T2DM, 100% (mean duration, 11 y) Mean HbA1c, 8.0% Mean age, 62 y Males, 47% | EQ-5D              | US general population sample | Microalbuminuria, DKD, ESRD–transplant, ESRD–no dialysis, ESRD–dialysis |
| (USA)                |                        |                            |                    |               |                                 |
| **Direct methods**   |                        |                            |                    |               |                                 |
| Huang et al., 2007³⁰  | 701                    | T2DM, 100% (mean duration, 10 y) Mean HbA1c, 7.5% Mean age, 63 y Males, 42% | TTO                | Patients with T2DM | DKD, ESRD |
| (USA)                |                        |                            |                    |               |                                 |
| **Meta-analysis**    |                        |                            |                    |               |                                 |
| Lung et al., 2011¹⁸+  | Mean 184.6 (range, 9–701) | T1DM/T2DM, 100% (mean duration, NR) Mean HbA1c, NR Mean age, NR Males, NR | EQ-5D³²,³⁵,³⁶,³⁷,³⁸ | NA | ESRD |
| (N/A)                |                        |                            |                    |               |                                 |

15D, 15-dimensional, self-administered questionnaire; CKT, cadaver kidney transplant; DKD, diabetic kidney disease; EQ-5D, EuroQol-5 Dimensions questionnaire; ESRD, end-stage renal disease; HbA1c, glycosylated hemoglobin; LKT, living donor kidney transplant; NA, not applicable; NR, not reported; QWB-SA, Self-Administered Quality of Well-Being Scale; SG, standard gamble; SPK, simultaneous pancreas–kidney transplant; T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus; TTO, time trade-off; WL, wait-listed for a kidney or kidney and pancreas transplant.

*Data for four ESRD studies²³,²⁵,³⁰,³¹.
EQ-5D method\textsuperscript{23,25} or the direct TTO method\textsuperscript{30}. The fourth study\textsuperscript{31}, which used the direct SG method, was published outside of the dates specified for the present review.

Participants

In 11 of the 12 included studies, all participants recruited had DM – T1DM and/or T2DM (Table 1)\textsuperscript{16,21–30}. In Grandy et al. (2012)\textsuperscript{22}, 1741 (28%) patients had T2DM and 4543 (72%) had ‘no DM’; utility values are presented here for the patients with T2DM and nephropathy (i.e., DKD).

All study populations were adult (aged \( \geq \)18 years), except for the study by Javanbakht et al. (2012)\textsuperscript{22}, which enrolled patients aged \( \geq \)16 years.

Utility and disutility scores for DKD health states in T1DM and T2DM

Table 3 summarizes the patient populations and utility/disutility scores reported in the 12 included studies. Scores were reported for T1DM only (\( n = 2 \)), T2DM only (\( n = 7 \)), or both T1DM and T2DM (\( n = 3 \)). They were reported separately in Coffey et al. (2002)\textsuperscript{28} and combined in Morgan et al. (2006)\textsuperscript{23} and Lung et al. (2011)\textsuperscript{16}.

Type 1 diabetes mellitus

Two studies reported utility scores for T1DM for a total of three health states: DKD, ESRD-dialysis, and ESRD-transplant (Table 4A)\textsuperscript{21,28}. For DKD (\( n = 1 \)), the QWB-self-administered (QWB-SA) score was 0.525, and for ESRD-dialysis (\( n = 1 \)), the QWB-SA score was 0.453\textsuperscript{28}.

In Sureshkumar et al. (2006), ESRD-transplant was divided into SPK, CKT, LKT, and WL (Table 4A). In the cross-sectional component of the study, QWB scores ranged from 0.54 to 0.62, and were significantly better in the SPK group than the WL group (0.62 vs. 0.55; \( P < 0.05 \)). In the longitudinal component of the study, QWB scores declined in the 3 years following transplant, both in the CKT group (0.67 vs. 0.61; \( P = 0.010 \)) and in the SPK group (0.69 vs. 0.63; \( P = \text{not significant [NS]} \))\textsuperscript{21}.

Disutility scores for T1DM were reported in the same two studies for a total of five health states (Table 5A)\textsuperscript{28,29}. In Ahola et al. (2010)\textsuperscript{29}, the mean 15D score for patients with normal albumin excretion rate (AER) was 0.928. There was no difference versus patients with microalbuminuria \((-0.003; P = \text{NS})\). However, mean 15D scores were significantly lower for patients with macroalbuminuria \((-0.036, \text{ESRD–transplant} \(-0.053), \text{and ESRD–dialysis} \(-0.082)\) (all \( P < 0.001 \) vs. normal AER). Importantly, the authors state that a difference of \( \pm 0.03 \) in the 15D score is clinically important. Also of note is that scores were worse in patients on dialysis than in those with a transplant. In Coffey et al. (2002)\textsuperscript{28}, the mean QWB-SA score for diet-controlled, nonobese men with T1DM without microvascular, neuropathic, or cardiovascular complications was 0.672. This decreased in patients with DKD (0.017) and ESRD–dialysis (0.023) (P-values not reported).

Type 2 diabetes mellitus

Six studies reported utility scores for T2DM for a total of six health states: microalbuminuria, DKD, ESRD,
Table 4. Estimated utility values by health state in patients with (A) T1DM, (B) T2DM, and (C) general DM.

| Health State | Utility Value | p Value, if reported | Definition of Health State, if reported | Utility Instrument | Reference |
|--------------|---------------|-----------------------|------------------------------------------|--------------------|-----------|
| **(A) Patients with T1DM** | | | | | |
| DKD | 0.525 | – | – | QWB-SA | Coffey et al., 2002 |
| ESRD–transplant | | | | | |
| Cross-sectional component | P < 0.05 for SPK vs. WL | – | QWB | Sureshkumar et al., 2006 |
| 0.62 (SPK) | | | | |
| 0.61 (CKT) | | | | |
| 0.55 (WL) | | | | |
| Longitudinal component | | | | |
| 0.69 (SPK) study start | P = NS for SPK start vs. 3 years | QWB | Sureshkumar et al., 2006 |
| 0.63 (SPK) 3 years | | | | |
| 0.67 (CKT) study start | | | | |
| 0.61 (CKT) 3 years | | | | |
| ESRD–dialysis | 0.453 | – | – | QWB-SA | Coffey et al., 2002 |
| **(B) Patients with T2DM** | | | | | |
| Microalbuminuria | | | | | |
| DKD | 0.80 | – | – | EQ-5D | Zhang et al., 2012 |
| 0.509 | | | | |
| 0.80 (median) | | | | |
| 0.95 (mode) | | | | |
| 0.71 | | P < 0.001 vs. without DKD (0.66) | EQ-5D 3L | Javanbakht et al., 2012 |
| 0.81 | | NS vs. without DKD (0.87) | EQ-5D (Japanese) | Sakamaki et al., 2006 |
| 0.67 (UK preference weights) | | | | |
| 0.75 (US preference weights) | | | | |
| 0.68 (Japanese preference weights) | | | | |
| 0.79 | | | | |
| ESRD–general | 0.35 | – | Based on previous descriptions | TTO | Huang et al., 2007 |
| 0.25 (median) | | | | |
| 0.05 (mode) | | | | |
| ESRD–transplant | 0.83 | – | – | EQ-5D | Zhang et al., 2012 |
| ESRD–no dialysis | 0.76 | – | – | EQ-5D | Zhang et al., 2012 |
| ESRD–dialysis | 0.404 | – | – | EQ-5D-SA | Coffey et al., 2002 |
| 0.68 | | – | – | EQ-5D | Zhang et al., 2012 |
| **(C) Patients with general DM** | | | | | |
| ESRD–general | 0.402 | – | – | EQ-5D | Morgan et al., 2006 |
| 0.328 | | | | |
| 0.415 | | | | |
| 0.404 | | | | |
| 0.515 | | | | |
| 0.48 (range, 0.33–0.81) | | | | |

CKT, cadaver kidney transplant; DKD, diabetic kidney disease; EQ-5D, EuroQol-5 Dimensions questionnaire; ESRD, end-stage renal disease; LKT, living donor kidney transplant; NS, not significant; SPK, simultaneous pancreas–kidney transplant; T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus; TTO, time trade-off; WL, wait-listed for a kidney or kidney and pancreas transplant.

Mean utility values are presented unless otherwise stated. In the following studies, utility scores were adjusted: Javanbakht et al. (2012) adjusted for age, sex, education level, employment status, DM duration, and comorbidity; Morgan et al. (2006) adjusted for gender, age, and body mass index; Sakamaki et al. (2006) adjusted for sex and age; and Zhang et al. (2012) adjusted for demographic and clinical characteristics and for disease states.

In Morgan et al. (2006), vascular complications studies were ESRD, coronary heart disease, cerebrovascular disease, ‘diabetic foot’, and retinopathy.

*All patients with ESRD.

*Patients with ESRD and no other vascular complication.

*Patients with ESRD plus other vascular complication(s).

*Patients specifically admitted for ESRD, but no other vascular complication.

*Patients specifically admitted for ESRD and other complication(s).
Table 5. Estimated disutility values by health state in patient with (A) T1DM, (B) T2DM and (C) general DM.

| Disutility value by health state | Definition of health state, if reported | Reference group (utility value) | p Value, if reported | Utility instrument | Reference |
|----------------------------------|----------------------------------------|---------------------------------|----------------------|-------------------|-----------|
| **(A) Patients with T1DM**      |                                        |                                 |                      |                   |           |
| Microalbuminuria                 | AER $\geq$ 20 and $<200 \mu$g/min or $\geq$ 30 and $<300 \mu$g/24 h | Normal AER (0.928)             | NS                   | 15D               | Ahola et al., 2010$^{29}$ |
| Macroalbuminuria                 | AER $\geq$ 200 $\mu$g/min or $\geq$ 300 $\mu$g/24 h | Normal AER (0.928)             | P $<$ 0.001          | 15D               | Ahola et al., 2010$^{29}$ |
| DKD                              | Diet-controlled nonobese men with T1DM and no microvascular, neuropathic, or cardiovascular complications (0.672) | –                              | –                    | QWB-SA           | Coffey et al., 2002$^{28}$ |
| **(B) Patients with T2DM**      |                                        |                                 |                      |                   |           |
| DKD                              | Diet-controlled nonobese men with T2DM and no microvascular, neuropathic, or cardiovascular complications (0.689) | –                              | –                    | QWB-SA           | Coffey et al., 2002$^{28}$ |
| ESRD–transplant                  | Broad definition of a reported diagnosis of CKD, dialysis, ESRD, kidney transplant, or urinary protein | Disutility is from baseline to 5 y | 0.43                | EQ-5D             | Grandy et al., 2012$^{20}$ |
| ESRD–dialysis                    | –                                      | –                              | –                    | –                 | –         |
| ESRD–general                     | All patients with DM (0.75)             | P $<$ 0.05                      | EQ-5D               | O’Reilly et al., 2011$^{24}$ |
| ESRD–dialysis                    | Diet-controlled nonobese men with T2DM and no microvascular, neuropathic, or cardiovascular complications (0.689) | –                              | –                    | QWB-SA           | Coffey et al., 2002$^{28}$ |
| ESRD–general                     | Healthy individuals (0.920)             | P $\leq$ 0.05                   | EQ-5D               | Zhang et al., 2012$^{27}$ |
| **(C) Patients with general DM** |                                        |                                 |                      |                   |           |
| ESRD–general                     | Patients with DM and no vascular complications (0.735) | P = 0.063 (GLM)                | EQ-5D               | Morgan et al., 2006$^{23}$ |
| Penalties:                       |                                        |                                 |                      |                   |           |
| $-0.333$ (penalty)               |                                        |                                 |                      |                   |           |
| $-0.407$ (penalty)               |                                        |                                 |                      |                   |           |
| $-0.320$ (penalty)               |                                        |                                 |                      |                   |           |
| GLM:                             | –                                      | 0.082                           |                      |                   |           |

15D, 15-dimensional, self-administered questionnaire; AER, urinary albumin excretion rate; CKD, chronic kidney disease; DKD, diabetic kidney disease; DM, diabetes mellitus; EQ-5D, EuroQol-5 Dimensions questionnaire; ESRD, end-stage renal disease; GLM, general linear model; NS, not significant; QWB-SA, Self-Administered Quality of Well-Being Scale; T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus.

Mean disutility values are presented. In the following studies, disutility scores were adjusted: Grandy et al. (2012)$^{20}$ adjusted for age, gender, race, education, household income, and body mass index; Morgan et al. (2006)$^{23}$ adjusted for gender, age, and body mass index; O’Reilly et al. (2011)$^{24}$ adjusted for age, gender, and duration of DM; and Zhang et al. (2012)$^{27}$ adjusted for demographic and clinical characteristics and for disease states. In Morgan et al. (2006)$^{23}$, vascular complications studies were ESRD, coronary heart disease, cerebrovascular disease, ‘diabetic foot’, and retinopathy.

$^a$All patients with ESRD.

$^b$All patients with ESRD and no other vascular complication.

$^c$Patients with ESRD plus other vascular complication(s).
ESRD–no dialysis, ESRD–dialysis, and ESRD–transplant (Table 4B)\(^22,25–28,30\). For microalbuminuria (n = 1), the EQ-5D value was 0.80\(^27\). For DKD (n = 6), utilities, estimated using a range of methods, ranged from 0.509 to 0.81\(^22,25–28,30\). In Sakthong et al. (2008)\(^26\), EQ-5D scores for DKD varied according to which preference weights were used: using UK, Japanese, and US values, the EQ-5D scores were 0.67, 0.68, and 0.75, respectively.

For ESRD, utility scores varied for general ESRD (n = 1; TTO, 0.35)\(^30\), ESRD–no dialysis (n = 1; EQ-5D, 0.76)\(^27\), ESRD–dialysis (n = 2; QWB-SA, 0.404 and EQ-5D, 0.68)\(^27,28\), and ESRD–transplant (n = 1; EQ-5D, 0.83)\(^27\).

In general, the studies that reported P-values showed that the utility values in patients with T2DM were statistically significant between those with and those without DKD (Table 4B). In Zhang et al. (2012)\(^27\), mean EQ-5D scores were among patients with no nephropathy (0.80), microalbuminuria (0.80), DKD (0.79), and the ESRD health states no dialysis (0.76), dialysis (0.68), and transplant (0.83). Patients with DKD had significantly lower utilities than DM patients without nephropathy in the studies by Javanbakht et al. (2012)\(^22\) (P < 0.001) and Sakthong et al. (2008)\(^26\), but not in Sakamaki et al. (2006)\(^25\) (P = NS).

Disutility scores for T2DM were reported in four studies for a total of three health states: DKD, general ESRD, and ESRD on dialysis (Table 5B)\(^20,24,27,28\). In Grandy et al. (2012)\(^20\), in patients with DKD (which had a broad definition of a reported diagnosis of CKD, dialysis, ESRD, kidney transplant, or presence of urinary protein), the EQ-5D score decreased by 0.047 over 5 years. Of note is that this decline in EQ-5D over 5 years was not significantly different from the decline among T2DM respondents without nephropathy (–0.030; P = 0.43). In Coffey et al. (2002)\(^28\), the mean QWB-SA score for diet-controlled, nonobese men with T2DM without microvascular, neuropathic or cardiovascular complications was 0.689, and this decreased in patients with DKD (–0.011) and ESRD on dialysis (–0.078). In the study by O’Reilly et al. (2011)\(^24\), the mean EQ-5D score for all patients with T2DM was 0.75, and this significantly decreased in patients with ESRD (–0.1018; P < 0.05). In Zhang et al. (2012)\(^27\), the mean EQ-5D for healthy individuals was 0.920, and this decreased significantly in patients with ESRD on dialysis (–0.060; P ≤ 0.05).

**Discussion**

This literature review highlights that there is a limited utilities evidence base for health states associated with DKD. Utilities are used to inform CUAs of new treatments; they must be valid and accurate, and available for the full range of possible health and treatment states included in economic evaluations. Previous models of the cost-effectiveness of treatments for CKD have employed utility values for different levels of estimated glomerular filtration rate (a measure of the level of renal function). It is likely that future models assessing the cost-effectiveness of DKD treatments (designed to slow DKD progression in patients with DM) will employ a similar methodology. However, this is currently not possible in the absence of available standardized utilities in DM. Disutility scores, which represent the decrement in utility associated with a particular health state, are also underreported. This limits the ability of researchers to take into account the effect of multiple complications experienced by patients.

In this review, utility values were found to vary widely between studies. Consistent with these findings, the meta-analysis by Lung et al. (2011)\(^16\) reported that utility scores for ESRD range from 0.33 to 0.81. Previous systematic reviews of CKD utility health states also reported widely ranging utility values\(^14,15\). According to Lung et al. (2011)\(^16\), a high degree of heterogeneity in reported utilities between studies may be explained in part by variations in average patient characteristics such as age, proportion of males/females, and methods used to elicit utilities. In addition, the different definitions of health states used by study authors may have contributed to the widely differing utility scores estimated. For example,
in Grandy et al. (2012)²⁰ DKD had a broad definition of a reported diagnosis of CKD, dialysis, ESRD, kidney transplant, or presence of urinary protein, whereas in other studies the definition of DKD was not reported.

Studies have shown that utility values are lower for ESRD than for other health states. For example, O’Reilly et al. (2011)²⁴ reported that kidney failure was associated with a lower EQ-5D disutility (−0.102) than amputation (−0.063), myocardial infarction (−0.059), or stroke (−0.046). Similarly, in Morgan et al. (2006)²³, patients with ESRD had a larger decrement in EQ-5D (−0.407) than those with other vascular complications, including coronary heart disease (−0.185), stroke (−0.306), diabetic foot (−0.223), and retinopathy (−0.129). In the present review, studies comparing different ESRD treatment modalities showed that dialysis was associated with lower utility scores than kidney transplant (EQ-5D: 0.68 vs. 0.83²⁷) as well as lower disutility scores (15D: −0.082 vs. −0.053²⁷). A study by Liem et al. (2008)¹² showed that CKD patients on dialysis had lower utility scores than patients with a kidney transplant; TTO scores for hemodialysis, peritoneal dialysis, and transplant were 0.61, 0.73, and 0.78, respectively, and corresponding EQ-5D scores were 0.56, 0.58, and 0.81, respectively. Consistent with this, in the meta-analysis by Wyld et al. (2012)¹⁵, utilities were highest for kidney transplant (0.82; 95% confidence interval [CI]: 0.74, 0.90), followed by pre-treatment CKD (0.79; 95% CI: 0.70, 0.89), dialysis (0.70; 95% CI: 0.62, 0.78), and conservative care (0.62; 95% CI: 0.43, 0.82) (interaction P<0.001).

Studies included in the present review highlight that other factors might affect utility values. Ahola et al. (2010)²⁹ state that utility values elicited from patients with T2DM may not apply to patients with T1DM. This underlines the importance of producing separate utilities for these different patient populations. The study by Sakthong et al. (2008)³⁰ highlighted that utility values can vary from one country to another, depending on the preference weights used. The authors applied preference rates from three countries (UK, US, and Japan) to Thai patients with DM. This produced different utilities, with values being higher with US than UK preference weights. This highlights the importance of using local preference values.

The present utility values for DKD health states appear to be lower than those reported in published meta-analyses of CKD health states¹⁵,¹⁷-¹⁹. This was highlighted in the meta-analysis by Wyld et al. (2012)¹⁵, who reported that a group of patients with DM had utilities 0.10 lower than a group of patients without DM, 0.81 (95% CI: 0.70, 0.91) versus 0.91 (95% CI: 0.82, 1.00). Although further research is needed, this finding suggests that DKD may be associated with a lower HRQoL than CKD, and highlights the need for accurate and specific utility scores.

In addition to the present review, the limited utility data available in patients with DM have been highlighted in Lung et al. (2011)¹⁶. Future studies are clearly needed to produce comprehensive and accurate utility scores in DKD health states in patients with DM. Importantly, the scores should differentiate between different DKD health states. Each of the included studies in the present review elicited values for few health states. There was a lack of distinction between different ESRD treatment modalities. Indeed, Morgan et al. (2006)²³ stated that the parameters used in their model did not distinguish between transplant and dialysis patients who may well have different utility scores. There was also a lack of utility values for pre-ESRD health states in the present review. Consistent with this finding, the systematic review of CKD health state utilities by Dale et al. (2008)¹⁴ included 33 studies with utilities for ESRD, but only two studies with utilities for pre-ESRD health states. According to Huang et al. (2007)³⁵, accounting for the effects of different health states in CUAAs may influence the findings because the incidence of intermediate complications is high compared with ESRD.

Conclusion

This review has highlighted a number of areas that require further investigation. Disutility data are often applied to capture the deficit associated with individual health states or complications and enable researchers to customize the utility according to a person’s demographic profile and/or their disease state (including complications). Morgan et al. (2006)²³ concluded that while previous studies have assumed that the mean disutilities for individual complications can be multiplied, their study shows that this method may be invalid and further research is warranted. The study by Grandy et al. (2012)²⁰ highlights the need for further investigations to improve our ability to interpret disutility data. The authors state that a minimally important difference for the EQ-5D has not been defined for patients with T2DM in clinical practice. Although a value of 0.07 has been suggested, it was not derived from patients with T2DM.

In addition, further research may be needed to determine which utility instrument(s) should be used to elicit utilities for DKD health states. The studies identified in the present review used a range of instruments. The EQ-5D measures only three levels of function in five domains. In contrast, the QWB-SA measures multiple levels of function on three domains and 58 symptoms and health problems, and may be more sensitive to small differences in health²⁸. Particular elicitation methods may be more or less appropriate for different CUA studies. Furthermore, different HTA bodies may require that utility scores are elicited by a particular method; for example, the National
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Institute for Health and Care Excellence (NICE) in the UK states that the EQ-5D is the preferred method\textsuperscript{13}.

As more comprehensive utility data become available for DKD health states, it will be important for investigators to identify the most appropriate scores to use in their CUAs. An increased use of meta-analyses may be useful in this regard\textsuperscript{16}. Lung et al. (2011)\textsuperscript{16} stated that an advantage of meta-analyses is that they provide both an average utility value and a range of scores across different studies, and this is useful if the utility values reported are heterogeneous.

A limitation of the present literature review is that the search strategies made use of indexes, as well as title and abstract searches, to identify studies that elicited utilities in DKD health states. This approach may not have captured potentially relevant studies that mentioned DKD or nephropathy only in the full text of the paper. In addition, we limited our search to English-language publications.

In conclusion, this literature review highlights that at present utility scores (or disutility penalties) exist for relatively few health states in DKD. This limits researchers’ ability to conduct CUAs of new treatments designed to slow disease progression in patients with DKD. Future studies are needed to produce accurate and comprehensive utility scores that differentiate between different DKD health states.

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R.P. has disclosed that she is an employee of Eli Lilly and Company. T.K.-M. has disclosed that she is an owner and employee of Kennedy-Martin Health Outcomes Limited. S.R. has disclosed that she worked for Kennedy-Martin Health Outcomes Limited on this project.

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