Low adherence to medication and risk of progression of chronic kidney disease: A linkage?

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SUMMARY

This is a prospective observational study of 3939 adults aged 21–74 years with mild–moderate chronic kidney disease (CKD) recruited at 7 clinical centres in the USA from 2003 to 2008. The study aimed to evaluate the association between self-reported medication adherence with progression of CKD and all-cause death among patients who had CKD. The researchers hypothesized that lower medication adherence would be associated with higher risk for progression of CKD.

The patients were followed up until death or withdrawal of consent. The chronic renal insufficiency cohort included patients with estimated glomerular filtration rate (eGFR) of 20 to 70 ml/ minute per 1.73 m². Patients who were unable to provide consent, institutionalized, pregnant, patients unable to participate in the required study procedures, at baseline had New York Heart Association Class III or IV heart failure, had cirrhosis, had known HIV infection and/or AIDS, previously received dialysis for at least 1 month, had a previous history of organ or bone marrow transplant and those who received immunosuppressive or other immunotherapy for primary renal disease or systemic vasculitis were excluded from the analysis.

During the study, 419 patients who did not complete the first visit, 101 patients who reported not taking prescription medication and 114 patients who had missing eGFR reports were excluded from the analysis. Hence, data of 3305 patients were analysed.

The independent variable (predictor) was adherence to medication assessed using a self-designed questionnaire, which consisted of 3 questions about their intake of medication in the past week. The first question assessed forgetfulness associated with intake of medication; the second question assessed unintentional non-adherence and the third question evaluated overuse of medication. Each question had 3 options: 0 day, 1 day and 2 days or more. Based on the responses to these questions, a scoring system was developed to classify patients into high-, medium- and low-medication adherence groups. The primary outcome variables were progression of CKD, which was defined as (i) 50% decline in eGFR from baseline or occurrence of end-stage renal disease, i.e. receipt of long-term dialysis therapy or kidney transplantation; and (ii) death from any cause.

At baseline, of the 3305 participants, 2258 (68%) had high adherence, 570 (17%) had medium adherence and 477 (15%) had low adherence. A total of 969 participants had progression of CKD, and there were 675 deaths over a median follow-up of 6 years. The CKD

progression event rate increased from high to medium to low adherence (5.82, 6.48 and 9.52 per 100 person-years, respectively) while the corresponding rates of all-cause death were 3.08, 2.97 and 3.99 per 100 person-years, respectively.

Compared to the high-adherence group, the low-adherence group had a signicantly increased risk for progression of CKD (adjusted hazard ratio 1.27; 95% condence interval [CI] 1.05–1.54). However, the risk for adverse outcomes was not signicantly increased for the medium-adherence group. The researchers concluded that low-medication adherence is an under-recognized but important risk factor for progression of CKD.

COMMENT

This study had several strengths including a large and ethnically diverse population, prospective study design with a long-term follow-up. However, the study has some methodological concerns. The assessment of medication adherence for chronic diseases is complex, and no gold standard exists for its measurement except perhaps direct observation.[1,2] The present study used a self-report questionnaire with an arbitrary-scoring criteria, which had not been validated previously. One of the 3 adherence questions assessed overuse non-adherence, i.e. the patient taking more than his prescribed medication—more likely in conditions such as chronic obstructive pulmonary disease (COPD),[3] which is unlikely to be causally related to progression of CKD.

Patients with CKD usually have comorbid conditions and are on medications for several of these such as hypertension (HTN), anaemia, diabetes and COPD.[4] An accurate estimation of adherence to medication in the comorbid CKD patient should assess and report medication adherence for each of these disease conditions independently and not jointly as was done in the present study. This is because the biological plausibility of progression to CKD is more likely to be present when the patient is non-adherent to antidiabetic or antihypertensive medication leading to poor glycaemic control and uncontrolled blood pressure, respectively compared to non-adherence to treatment for other disease conditions such as anaemia, osteoporosis or COPD. However, in the present study, a patient who was non-adherent to any medication irrespective of its relation to progression of CKD was classified as non-adherent. The assumption that medication adherence for different disease conditions such as diabetes and hypertension would be similarly correlated is inappropriate because the patient's perceived susceptibility to each of these disease conditions and the perceived side-effects from the medication intake that influences patient adherence if different.[5] Moreover, an increased number of comorbid conditions increase the total pill burden which can reduce adherence by causing pill fatigue and increasing complexity of the regimen.[6] Moreover, as this was a generic medication adherence questionnaire, it requires separate validation for specific disease conditions such as hypertension and diabetes.

The researchers found that patients with low medication adherence had a higher incidence of progression of CKD and deaths but the risk for adverse outcomes was not significantly increased in the medium-adherence group. This suggests that like most self-report measures of medication adherence, the questionnaire used had good specificity, so it could distinguish between patients with low and high adherence.

It is well established that low medication adherence in chronic diseases such as diabetes, hypertension and cardiovascular diseases increases the risk of adverse clinical outcomes.[7–9] Persistently increased blood sugar levels and high blood pressure secondary to poor medication adherence increases the risk of progression of

CKD. Therefore, it could be argued that the biological plausibility of non-adherence to medication being linked to poor health outcomes in patients with non-communicable diseases (NCDs) is strong, and the present study corroborates the existing evidence. Nevertheless, the prospective study design generates evidence with regard to the rate of progression of adverse outcomes in non-adherent CKD patients and indicates the gain in healthy life that can be achieved through improvement in medication adherence in them.

Finally, the non-pharmacological component in treating diabetes and hypertension includes adequate physical activity, healthy diet, cessation of smoking and avoiding harmful use of alcohol. The increased physical activity can independently protect against progression of CKD.[10] These factors were not assessed in this study, which could be a limitation due to their potential role as effect modifiers.

Relevance to India

CKD is a major public health problem in India due to a combination of the second highest global burden of diabetes mellitus, increasing burden of hypertension and improving longevity, all well-known risk factors for the disease.[11–13] CKD progressing to ESRD requires lifelong dialysis or a kidney transplant imposes enormous social and economic burden on patients, their families, and the country. Similar to the global pattern, diabetes and hypertension account for 40%–60% of cases of CKD in India.[14] Medication adherence in chronic diseases such as diabetes is also comparatively lower in India although it tends to be variable with community-based studies showing lower adherence compared to hospital-based studies.[15–17] The findings of this study are likely to be applicable in the Indian context and suggest that measures to improve medication adherence in those at risk or having early CKD should be undertaken aggressively. These efforts can delay the progression of CKD and related complications, improve patient quality of life and increase individual productivity while lowering long-term health costs. However, in contrast to the present study, in most developing countries including India, unintentional non-adherence is the primary challenge. This is because of inability to access or afford the cost of medication and particularly effects patients from the lower socioeconomic classes.[18,19] With the higher number of comorbid conditions and the presence of complications, there is a possibility of increased cost of care.[20] In low-resource settings with challenges in drug accessibility from the public health sector and a limited population having adequate health insurance coverage, refill adherence in chronic NCD patients can be compromised.

Conflicts of interest. None declared

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