Nephropathy and chronic renal insufficiency

Nicola Napoli, Flavia Tramontana

Department of Endocrinology and Diabetology, Campus Bio-Medico University, Rome, Italy; Italian Society of Gerontology and Geriatrics, Florence, Italy; Italian Society of Diabetology, Rome, Italy

1. RECOMMENDATIONS

- A. All patients with diabetic nephropathy should be considered as having high cardiovascular risk and should undergo treatment to modify all related risk factors (grade 4A) ¹.
- B. Blood pressure targets for patients with micro- and macro-albuminuria should be < 130/80 mmHg (grade 4A) ².
- C. Older DM patients should be screened for kidney disease using yearly albuminuria measurement (grade 4A) ³.
- D. The recommended method to evaluate albuminuria is to measure the albumin-to-creatinine ratio in a spot urine sample ³. Serum creatinine should be measured annually independent of urinary albumin levels ¹.
- E. Estimated glomerular filtration rate (eGFR) should be calculated according to the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation, in line with international recommendations and should be assessed at least once a year ³.
- F. Drugs associated with lower risk of hypoglycemic events should be preferred, such as: metformin (if not contraindicated due to reduced eGFR), DPP-IV inhibitors, SGLT2-i, pioglitazone, GLP-1RA, or their combinations (grade 2A) ¹. If sulfonylureas are to be used, gliclazide should be preferred because it is associated with a lower risk of hypoglycemia compared to other drugs in this class (grade 2A) ¹. Although repaglinide is not excreted by kidney, its use in the elderly should be avoided because of the lack of studies in geriatric patients and the risk of hypoglycemia. In addition, the dose of repaglinide should be halved in patients with CrCl < 30 ml/min. Repaglinide is not indicated in patients with end-stage kidney disease. Metformin use can be considered with caution in patients with an eGFR up to 30 ml/min/1.73m², taking also into account risk factors for kidney function decline (grade 1A). In elderly patients treated with metformin, eGFR should be monitored at least once a year as well as at every dose increase (grade 1A).

Received: July 30, 2021
Accepted: September 16, 2021

Correspondence

Nicola Napoli

Department of Endocrinology and Diabetology,
Campus Bio-Medico University, via Alvaro del
Portillo 21, 00128 Rome, Italy
E-mail: n.napoli@unicampus.it

How to cite this article: Napoli N, Tramontana F. Nephropathy and chronic renal insufficiency. *Journal of Gerontology and Geriatrics* 2021;69:262-264. <https://doi.org/10.36150/2499-6564-N455>

© Copyright by Società Italiana
di Gerontologia e Geriatria (SIGG)

OPEN ACCESS

This is an open access article distributed in accordance with the CC-BY-NC-ND (Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International) license. The article can be used by giving appropriate credit and mentioning the license, but only for non-commercial purposes and only in the original version. For further information: <https://creativecommons.org/licenses/by-nc-nd/4.0/deed.en>

2. STRENGTH OF THE RECOMMENDATIONS

The quality of the evidence is high. Recommendations are supported by published evidence.

3. SUPPORTING EVIDENCE

See appendix.

4. AREAS OF UNCERTAINTY AND FUTURE PERSPECTIVES

Recent clinical trials on GLP-1RA and SGLT2 inhibitors have shown a significant protective effect of these drugs on kidney function, delaying the onset of nephropathy. However, evidence in elderly patients is limited and further studies are needed. SGLT2 inhibitors should be used with caution in the elderly given the risk of urinary and genital infections.

APPENDIX

Diabetic nephropathy occurs in 20-40% of T2DM patients³, especially in adults aged > 70 years. Older people are generally more affected by renal disorders, which are diagnosed in about 25% of people aged 65-74 years and over 50% of those aged ≥ 70 years^{4,5}. The term “diabetic kidney disease” (DKD) is used to describe heterogeneous types of kidney damage that can arise during the natural history of DM⁶. A reduction in GFR and/or the presence of increased urinary albumin excretion for at least three months are the main clinical characteristics of renal damage in DM patients. These conditions often occur together but there may also be situations where an increase in albuminuria is seen without a drop in GFR or where GFR decreases without a change in urinary albumin excretion⁷.

DKD can begin with micro-albuminuria, which can then progress to macro-albuminuria. Therefore, diabetic nephropathy screening is generally carried out using an assessment of micro-albuminuria and eGFR with validated tools such as the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI)³ equation. In Italy, the prevalence of micro- and macro-albuminuria in patients with DM is between 27 and 34%¹. Patients with macro-albuminuria (≥ 300 mg/24 hours) are highly likely to develop end-stage kidney disease within a few years. A recent meta-analysis on approximately 30,000 individuals showed that variations in albuminuria can be used as a proxy for DKD progression⁸. Although progression to end-stage kidney disease is a major concern, cardiovascular disease (CVD) is another important issue. Indeed, it has long been known that kidney failure due to any cause is associated with a 2-4 fold increase in the risk of CVD morbidity and mortality, independent of the presence of well-established CVD risk factors⁹. Patients with chronic kidney disease are more likely to die from cardiovascular events than for end-stage kidney disease. In patients with an eGFR ≤ 60 mL/min/1.73m², the risk of experiencing a cardiovascular event may be up to ten times higher than the risk of developing end-stage kidney disease^{10,11}. The risk of cardiovascular events increases so much that both reduced eGFR and increased albuminuria have been recognized

as independent risk factors for cardiovascular mortality¹². In particular, a 0.4 mg/mmol increase in urine albumin/creatinine ratio (ACR) corresponds to a 5.9% increase in the risk of developing a cardiovascular event¹³. Patients with chronic kidney disease are also at increased risk of hypoglycemia^{14,15}, which further contributes to increased cardiovascular mortality and morbidity¹⁶. There are several reasons why chronic kidney disease is associated with an increase in hypoglycemic events: i) the counterregulatory response to hypoglycemia is blunted, and renal gluconeogenesis is impaired mainly due to a reduced kidney mass that results in a reduced ability to release glucose; ii) there is a reduction in the kidney's insulin clearance capacity. Reducing the risk of hypoglycemia is one of the main therapeutic targets in elderly, frail DM patients, who are already at risk of falls. For this reason, particular care should be taken when choosing the antidiabetic drugs to be used in elderly DM patients with kidney damage. Glucose-lowering drugs such as sulfonylureas should be avoided, as exacerbating the risk of hypoglycemia may increase the occurrence of adverse clinical events (angina, arrhythmias, falls). The use of pioglitazone also requires careful clinical evaluation, as adverse events, including a reduction in bone mass and increased risk of heart failure make it a potentially unsuitable pharmacological therapy for older persons, especially those over 75 years of age. Among the available DPP-4 inhibitors, linagliptin does not need dose adjustment because its renal clearance is minimal renal, while dosage of others drugs in this class that needs to be adjusted according to eGFR.

Some drugs such as SGLT2-i have a significantly positive effect on kidney function. For example, two randomized-controlled studies (CANVAS and CRE-DENCE) have shown that treatment with canagliflozin in patients with T2DM leads to a greater reduction in annual albuminuria progression and less loss of kidney function than placebo^{16,17}. In addition, the LEADER and SUSTAIN-6 studies have shown a potential positive effect of Glucagon-Like Peptide-1 Receptor Agonists (GLP-1RAs), such as liraglutide and semaglutide, which are associated with a 22% reduction in the incidence of nephropathy and a 26% decrease in kidney disease progression^{18,19}. The REWIND study reported a 40-50% reduction in eGFR decline in patients administered dulaglutide²⁰.

The UKPDS study showed that improved blood pressure control is associated with a reduction in diabetic nephropathy²¹. The use of ACE-inhibitors in patients with macro-albuminuria leads to a reduction in the progression of albuminuria levels and to slower GFR decline²². Angiotensin receptor blockers (ARBs) have also proved to be an effective treatment for diabetic nephropathy as their use is associated a lower progression from micro- to macro-albuminuria²³.

Ethical consideration

None.

Acknowledgement

None.

Funding

None.

Conflict of interest

Abiogen, Eli-Lilly, UCB

References

- ¹ Associazione Medici Diabetologi (AMD), Società Italiana di Diabetologia (SID). Standard italiani per la cura del diabete mellito, 2018 (https://www.siditalia.it/pdf/Standard%20di%20Cura%20AMD%20-%20SID%202018_protetto2.pdf).
- ² Khwaja A. KDIGO clinical practice guidelines for acute kidney injury. *Nephron Clin Pract* 2012;120:c179-184. <https://doi.org/10.1159/000339789>
- ³ American Diabetes Association (ADA). Standards of medical care in diabetes, 2020. *Diabetes Care* 2020;43(Suppl 1):S37-S47. <https://doi.org/10.2337/dc20-S004>
- ⁴ Couser WG, Remuzzi G, Mendis S, et al. The contribution of chronic kidney disease to the global burden of major noncommunicable diseases. *Kidney Int* 2011;80:1258-1270. <https://doi.org/10.1038/ki.2011.368>
- ⁵ Hemmelgarn BR, Zhang J, Manns BJ, et al. Progression of kidney dysfunction in the community-dwelling elderly. *Kidney Int* 2006;69:2155-2161. <https://doi.org/10.1038/sj.ki.5000270>
- ⁶ Doshi SM, Friedman AN. Diagnosis and management of type 2 diabetic kidney disease. *Clin J Am Soc Nephrol* 2017;12:1366-1373. <https://doi.org/10.2215/cjn.11111016>
- ⁷ de Boer IH, Steffes MW. Glomerular filtration rate and albuminuria: twin manifestations of nephropathy in diabetes. *J Am Soc Nephrol* 2007;18:1036-1037. <https://doi.org/10.1681/asn.2007020189>
- ⁸ Heerspink HJL, Greene T, Tighiouart H, et al. Change in albuminuria as a surrogate endpoint for progression of kidney disease: a meta-analysis of treatment effects in randomised clinical trials. *Lancet Diabetes Endocrinol* 2019;7:128-139. [https://doi.org/10.1016/s2213-8587\(18\)30314-0](https://doi.org/10.1016/s2213-8587(18)30314-0)
- ⁹ Gansevoort RT, Correa-Rotter R, Hemmelgarn BR, et al. Chronic kidney disease and cardiovascular risk: epidemiology, mechanisms, and prevention. *Lancet* 2013;382:339-352. [https://doi.org/10.1016/s0140-6736\(13\)60595-4](https://doi.org/10.1016/s0140-6736(13)60595-4)
- ¹⁰ Eriksen BO, Ingebrechtsen OC. The progression of chronic kidney disease: a 10-year population-based study of the effects of gender and age. *Kidney Int* 2006;69:375-382. <https://doi.org/10.1038/sj.ki.5000058>
- ¹¹ Bansal N, Katz R, Robinson-Cohen C, et al. Absolute rates of heart failure, coronary heart disease, and stroke in chronic kidney disease: an analysis of 3 community-based cohort studies. *JAMA Cardiol* 2017;2:314-318. <https://doi.org/10.1001/jamacardio.2016.4652>
- ¹² Hemmelgarn BR, Manns BJ, Lloyd A, et al. Relation between kidney function, proteinuria, and adverse outcomes. *JAMA* 2010;303:423-429. <https://doi.org/10.1001/jama.2010.39>
- ¹³ Gerstein HC, Mann JF, Yi Q, et al. Albuminuria and risk of cardiovascular events, death, and heart failure in diabetic and nondiabetic individuals. *JAMA* 2001;286:421-426. <https://doi.org/10.1001/jama.286.4.421>
- ¹⁴ Moen MF, Zhan M, Hsu VD, et al. Frequency of hypoglycemia and its significance in chronic kidney disease. *Clin J Am Soc Nephrol* 2009;4:1121-1127. <https://doi.org/10.2215/cjn.00800209>
- ¹⁵ Alsahli M, Gerich JE. Hypoglycemia, chronic kidney disease, and diabetes mellitus. *Mayo Clin Proc* 2014;89:1564-1571. <https://doi.org/10.1016/j.mayocp.2014.07.013>
- ¹⁶ Neal B, Perkovic V, Mahaffey KW, et al. Canagliflozin and cardiovascular and renal events in type 2 diabetes. *N Engl J Med* 2017;377:644-657. <https://doi.org/10.1056/nejmoa1611925>
- ¹⁷ Perkovic V, Jardine MJ, Neal B, et al. Canagliflozin and renal outcomes in type 2 diabetes and nephropathy. *N Engl J Med* 2019;380:2295-2306. <https://doi.org/10.1056/nejmoa1811744>
- ¹⁸ Mann JFE, Ørsted DD, Brown-Frandsen K, et al. Liraglutide and renal outcomes in type 2 diabetes. *N Engl J Med* 2017;377:839-848. <https://doi.org/10.1056/nejmoa1616011>
- ¹⁹ Verma S, Bain SC, Monk Fries T, et al. Duration of diabetes and cardiorenal efficacy of liraglutide and semaglutide: a post hoc analysis of the LEADER and SUSTAIN 6 clinical trials. *Diabetes Obes Metab* 2019;21:1745-1751. <https://doi.org/10.1111/dom.13698>
- ²⁰ Gerstein HC, Colhoun HM, Dagenais GR, et al. Dulaglutide and cardiovascular outcomes in type 2 diabetes (REWIND): a double-blind, randomised placebo-controlled trial. *Lancet* 2019;394:121-130. [https://doi.org/10.1016/s0140-6736\(19\)31149-3](https://doi.org/10.1016/s0140-6736(19)31149-3)
- ²¹ UK Prospective Diabetes Study Group. Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 38. UK Prospective Diabetes Study Group. *BMJ* 1998;317:703-713.
- ²² Lewis EJ, Hunsicker LG, Bain RP, et al. The effect of angiotensin-converting-enzyme inhibition on diabetic nephropathy. The Collaborative Study Group. *N Engl J Med* 1993;329:1456-1462. <https://doi.org/10.1056/nejm19931113292004>
- ²³ Lewis EJ, Hunsicker LG, Clarke WR, et al. Renoprotective effect of the angiotensin-receptor antagonist irbesartan in patients with nephropathy due to type 2 diabetes. *N Engl J Med* 2001;345:851-860. <https://doi.org/10.1056/nejmoa011303>

This statement is:

- ☒ **Recommendation** (supported by published evidence)
- ☒ **Best practice** (supported by expert opinion)

Quality of the evidence (in the case of recommendation):

- ☐ Low
- ☐ Moderate
- ☒ **High**