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Editorial Comment

EDITORIAL COMMENT

European East–West divide in kidney disease: the need to understand the drivers of chronic kidney disease outcomes

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ABSTRACT

In this issue of *ckj*, Sever *et al.* (A roadmap for optimizing chronic kidney disease patient care and patient-oriented research in the Eastern European nephrology community. *Clin Kidney J*, this issue) present a roadmap for optimizing chronic kidney disease (CKD) patient care and patient-oriented research in Eastern Europe. The document clearly identifies current unmet needs and proposes corrective actions. Focusing on CKD epidemiology and outcomes, it collects evidence pointing to an East–West gradient for some key risk factors for CKD development. Thus, the prevalence of diabetes, raised blood pressure, obesity and tobacco use is higher in Eastern than in Western Europe. These risk factors may contribute to the higher CKD prevalence in Eastern Europe, which for the Eastern-most countries may be more than 2-fold higher than in Western Europe. The problem is compounded by the lower prevalence of dialysis and transplantation in Eastern Europe, especially in lower income countries. The combination of higher prevalence of CKD with lower prevalence of renal replacement therapy would be expected to result in higher CKD-associated mortality, but this is not the case. CKD-associated mortality may even be lower in the Eastern-most European countries than in Western Europe. The reasons for this discrepancy should be studied, since it may reveal serious additional healthcare issues, potentially related to high mortality from other non-communicable diseases (NCDs). If this is the case and the high mortality from other NCD is successfully addressed, pressure will further mount on renal replacement capacity needs in Eastern Europe.

Keywords: chronic kidney disease, dialysis, global burden of disease, mortality, renal replacement therapy, transplantation

WHAT IS CHRONIC KIDNEY DISEASE?

Chronic kidney disease (CKD) is among the three fastest growing causes of death worldwide and is expected to become the fifth global cause of death by 2040 and the second cause of death in some Western European countries before the end of the century [1, 2]. Indeed, the increased risk of death is intrinsic to the current definition of CKD. Thus, CKD is defined as abnormalities of kidney structure or function, present for longer than 3 months, with implications for health [3]. The abnormalities of kidney structure or function may be recognized clinically by different criteria: just one of these criteria is enough to diagnose CKD. The implications for health include an increased risk of CKD progression, all-cause death, cardiovascular death and acute kidney injury, among others. These risks have been demonstrated most clearly for pathological albuminuria or decreased glomerular filtration rate (GFR), which are the most widely used criteria to diagnose CKD and the parameters used

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to categorize CKD. In epidemiological studies, most information is derived from assessment of GFR. Thus, CKD categories G3–G5 (estimated GFR <60 mL/min/1.73 m^2) will be discussed in this manuscript when addressing CKD prevalence.

WHAT DID THE NEPHROLOGY AND PUBLIC POLICY COMMITTEE SAY?

The European Renal Association – European Dialysis and Transplant Association (ERA-EDTA) Nephrology and Public Policy Committee (NPPC) aims at developing proposals for raising awareness on the importance of kidney diseases for public health by producing a yearly research proposition [4]. In this issue of *ckj*, Sever *et al.*, on behalf of the NPCC, present a roadmap for optimizing CKD patient care and patient-oriented research in the Eastern European nephrology community [5]. To build the roadmap, they first identified key CKD-related medical issues that differ between Eastern and Western Europe, and they further stratified Eastern European countries according to gross national income (GNI) per capita. The key issues identified include a higher prevalence of CKD G3–G5 in Eastern than in Western Europe, as well as a faster increase in CKD prevalence overtime in Eastern Europe. They hypothesize that this higher prevalence of CKD G3–G5 may be driven by a higher prevalence of multiple risk factors for CKD in Eastern Europe (Figure 1A and B). However, a dissociation was found between the higher prevalence of CKD and the lower prevalence of renal replacement therapy (RRT) in Eastern than in Western Europe, be it by dialysis or transplantation (Figure 1C). Again, the reason for this discrepancy is unclear, but the NPPC hypothesizes that CKD G3–G5 patients may die prematurely before reaching kidney failure or that dialysis and transplantation cannot be provided to those who need it because of inadequate healthcare infrastructure and/or shortage of nephrologists in Eastern Europe. Once the health problem was diagnosed, research and intervention recommendations were made that cover raising public, medical personnel and healthcare authorities' awareness; early detection by screening high-risk populations; preventing progression and CKD-related complications by training health professionals and patients; promoting transplantation or home dialysis as the

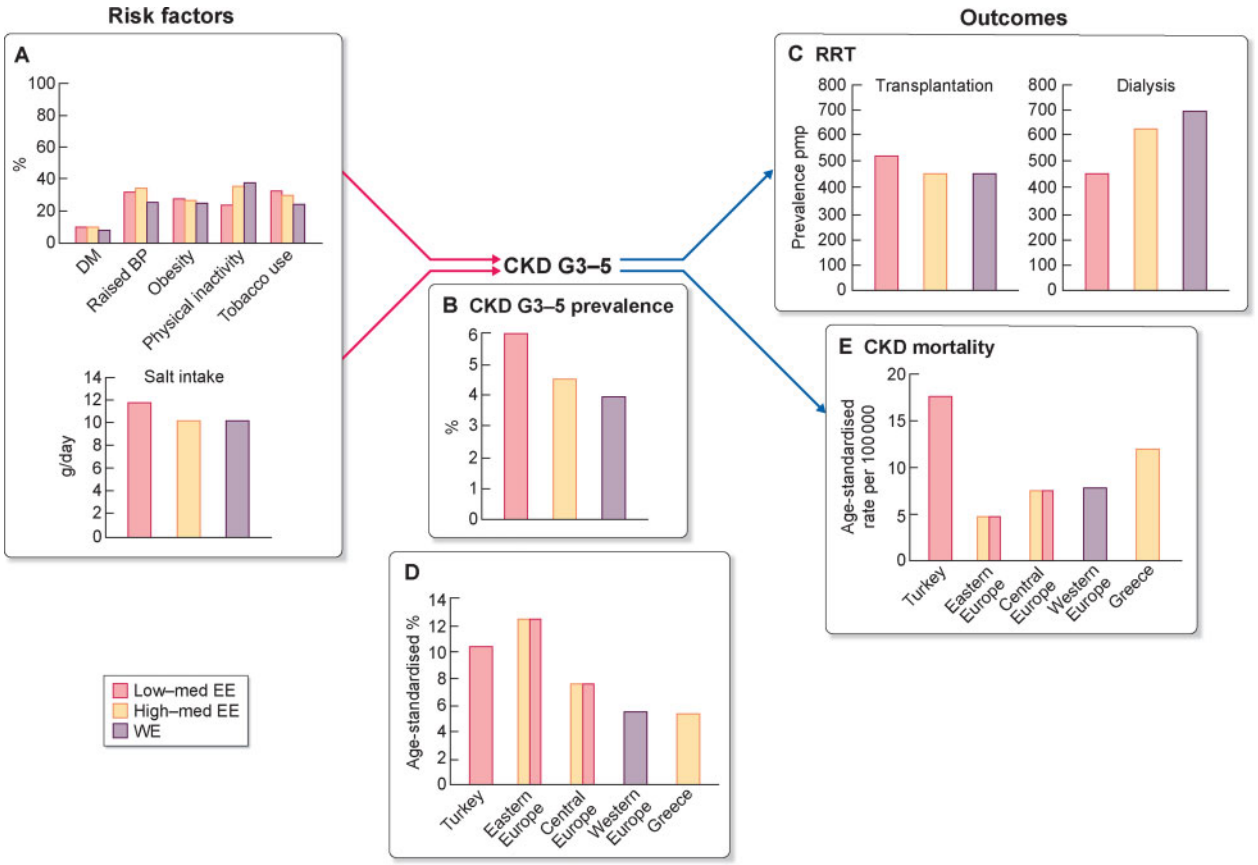

FIGURE 1: Risk factors for and outcomes of CKD in diverse European regions. For risk factors (**A**), CKD prevalence (**B**) and RRT (**C**), regions and data are as per Sever *et al.* [5]. Data are presented for Eastern European (EE) countries with low–medium (low–med) GNI per capita ≤12 000 USD (Ukraine, Moldova, Albania, North Macedonia, Belarus, Bosnia/Herzegovina, Serbia, Montenegro, Bulgaria, Russia, Turkey, Romania), EE with high–medium (high–med) GNI per capita >12 000 USD (Croatia, Poland, Hungary, Latvia, Lithuania, Slovak Republic, Greece, Czech Republic, Estonia, Slovenia, Cyprus) and Western Europe (WE) (Portugal, Spain, Italy, France, UK, Belgium, Germany, Finland, Austria, the Netherlands, Sweden, Denmark, Ireland, Iceland, Luxembourg, Norway, Switzerland). Additional CKD prevalence data, expressed as age-adjusted prevalence (**D**) and mortality data (**E**) are from the 2017 GBD study [6]. They correspond to a slightly different, geography-based distribution of countries, in which lower and higher income countries are mixed up. Turkey is not included among EE countries and Greece is listed as a WE country, as follows: EE (Belarus, Estonia, Latvia, Lithuania, Moldova, Russia, Ukraine), Central Europe (Albania Bosnia and Herzegovina Bulgaria, Croatia, Czech Republic, Hungary, Montenegro, North Macedonia, Poland, Romania, Serbia, Slovakia, Slovenia) and WE (Andorra, Austria, Belgium, Cyprus, Denmark, Finland, France, Germany, Greece, Iceland, Ireland, Israel, Italy, Luxembourg, Malta, the Netherlands, Norway, Portugal, Spain, Sweden, Switzerland, UK) [6]. Colour coding is as presented in the figure, except when indicated otherwise. Due to the different grouping of countries, Turkey and Greece are also shown as individual countries, each with the colour code of the original NPPC grouping, and columns representing GBD Eastern and Central Europe countries are mixed colour, representing the presence of both lower and higher income Eastern Europe countries from the NPCC categorization both in GBD Eastern Europe and in GBD Central Europe (D and E). DM, diabetes mellitus; BP, blood pressure.

preferred modality of RRT; and encouraging/supporting country-specific research as well as international projects.

However, a key issue is non-addressed in the NPPC hypothesis that CKD G3–G5 patients may die prematurely is identifying the cause of this premature death. According to data from the largest global epidemiological study, the Global Burden of Disease (GBD) study, the cause of death may not be CKD in at least some countries, and this may have several potential consequences for nephrology [6].

WHAT ARE THE DRIVERS OF CKD PATIENT MORTALITY IN EASTERN EUROPE?

The GBD study recently provided the global, regional and country-specific estimates for CKD G3–G5 prevalence and CKD-related mortality for 2017 [6]. The study provided Eastern, Central and Western European data (Figure 1D and E). However, the criteria used by GBD to separate Eastern and Central European countries were merely geographical not based on income. As a result, Eastern lower and higher income countries that were clearly separated by the NPCC, are found mixed up within the Eastern Europe and Central Europe categories. Furthermore, GBD does not include Turkey nor Greece in their Eastern Europe category: Greece is considered Western Europe. With these caveats in mind, GBD confirmed the West to East gradient of increasing CKD G3–G5 prevalence and indeed the prevalence of CKD G3–G5 in Turkey was close to that of Eastern Europe (Figure 1D). However, the CKD G3–G5 prevalence in Greece was closer to Western Europe.

The surprise comes from the CKD mortality data (Figure 1E). The expectation of higher CKD deaths in Eastern Europe that may explain the gap between CKD G3–G5 prevalence and RRT prevalence was not confirmed. Thus, the gap between higher CKD prevalence of non-dialysis CKD G3–G5 and lower prevalence of RRT in Eastern Europe remains unexplained as patients are not apparently dying prematurely from CKD-related issues or from lack of access to RRT. In fact, CKD mortality was clearly lower in GBD Eastern Europe than in GBD Western Europe, and was similar in Central to in Western Europe. If CKD patients are not dying from CKD and they are not being treated with RRT, what is the fate of the excess CKD G3–G5 patients from Eastern Europe? The explanation is likely complex and country-specific issues may be at play, as Eastern Europe is not a homogeneous bloc. In addition to the income differences highlighted by the NPPC [5], there is also a North–South gradient in terms of environment and diet that may also impact outcomes. Thus, Eastern Europe, as defined by the NPPC, includes Mediterranean countries with some of the highest life expectancy in the world (e.g. Greece), together with countries with the lowest life expectancy in Europe.

The issues at play may be different for different countries. For example, Turkey, which is a Mediterranean country, has a high prevalence of CKD G3–G5 according to GBD and also a high CKD mortality, which would be aligned with the high CKD prevalence (Figure 1D and E). Thus, the largest discrepancy between CKD prevalence and CKD mortality can be pinpointed to a small Eastern European bloc of countries: Belarus, Estonia, Latvia, Lithuania, Moldova, Russia and Ukraine, and to a lower extent, to Central European countries. Moreover, individual differences might be present between countries within these blocs. These are not Mediterranean countries and they had some of the highest values for age-standardized years of life lost due to premature avertable mortality from non-communicable diseases (NCD) in the world for 2017, in the range found in African countries such as Libya, Egypt and Sudan [7]. By contrast, premature avertable mortality from NCD in Turkey is much lower, in the range found in Poland or the USA. Given the low CKD-related mortality, we also know that the excess NCD mortality is not dependent on CKD. In this regard, the concept of CKD-related mortality in GBD is ample and includes the contribution of CKD to premature death beyond the mortality observed in ESRD patients. Thus, we basically are faced with two alternative possibilities: (i) either GBD is underestimating CKD-related deaths in GBD Eastern European countries or (ii) the reason for the high CKD/low RRT prevalence is that patients are dying prematurely from premature avertable NCD beyond CKD. In the latter scenario, interventions that decrease non-CKD NCD mortality may result in an avalanche of CKD G3–G5 patients surviving long enough to require RRT. Thus a key research need is to clarify the reasons for the gap between CKD and RRT prevalence in countries belonging to the GBD Eastern Europe region and, eventually, to plan for a surge in the number of patients requiring RRT if needed. While there is the distinct possibility that addressing the risk factors for CKD (e.g. raised blood pressure, salt intake and others) decreases both CKD prevalence and non-CKD NCD mortality, it is also possible the lag time between addressing these risk factors and impact on disease outcomes is seen earlier for non-CKD NCD than for CKD, a chronic condition, again potentially resulting in a surge of patients needing RRT.

THE NEED TO CLARIFY THE REASONS FOR THE DISCREPANCY IN CKD/RRT PREVALENCE IN EASTERN EUROPE

In conclusion, research is needed to address the cause of the discrepancy between CKD and RRT prevalence, especially in countries where this discrepancy does not appear to result from or cause an excess of CKD deaths. Some of the potential explanations for the discrepancy, like CKD patients dying from other avoidable causes, may eventually result in a surge of patients needing RRT once these alternative causes of death decrease. Thus, a correct understanding of the drivers of these trends is needed for optimal planning of future healthcare needs, which may include a further emphasis on training of specific healthcare personnel and deployment of dialysis facilities.

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CONFLICT OF INTEREST STATEMENT

None declared.

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