

Diabetes duration, HbA_{1c}, and cause-specific mortality in Mexico



Undoubtedly, the burden of morbidity and mortality attributable to diabetes represents one of the major challenges for health systems worldwide, particularly in low-income and middle-income countries.¹ In Mexico, national data² suggest that the prevalence of diagnosed diabetes has increased from 7·2% in 2006 to 9·4% in 2016, and it is likely that the burden is much higher when undiagnosed cases are taken into account. The same dataset suggests that diabetes-related mortality has similarly increased over the same period³.

On top of the challenges of increasing trends in diabetes prevalence and mortality in middle-income countries such as Mexico² comes the difficulty in understanding and managing premature mortality attributable to diabetes. There are gaps in the identification and measurement of variables and causal relations that determine cause-specific mortality in people with diabetes compared with general population. Prospective studies and meta-analyses^{4–6} have provided incomplete explanations and have mostly been done in high-income countries, where health systems might be better equipped to deal with diagnosis and treatment of diabetes and other conditions, and where other environmental factors might be different.

In *The Lancet Diabetes & Endocrinology*, the analysis of the Mexico City Prospective Study reported by William Herrington and colleagues⁷ responds to some of the gaps in knowledge to provide a more complete understanding of the causes of mortality in people with diabetes. The prospective cohort was established in 1998–2004 and includes about 100 000 women and 50 000 men aged 35 years and older from two areas in Mexico City. The investigators previously reported⁸ that diabetes was common in the cohort, that overall glycaemic control among those with diabetes was poor, and that—based on 12 years of follow-up—diabetes was associated with a worse prognosis than in wealthier countries, accounting for a third of all deaths between the ages of 35 and 74 years, particularly from renal, vascular, and infectious causes, as well as acute diabetic crises.

In the new analysis,⁷ based on 14 years of follow-up, the investigators dig deeper into the data to investigate

the role of diabetes duration and level of glycaemic control (HbA_{1c} at baseline) in determining cause-specific mortality in the cohort. Their results show that, compared with people without diabetes, the rates of deaths from causes strongly associated with diabetes (renal, vascular, and infectious) between the ages of 35 and 74 years increased with an increasing duration of diabetes, from a rate ratio of 3·0 for those with undiagnosed diabetes at baseline, 4·5 for those with a diabetes duration of less than 5 years, 6·6 for those with a duration of 5 years to less than 10 years, and 11·7 for those who had a diabetes duration of 10 years or more. Similarly, mortality increased with worsening glycaemic control, with a rate ratio of 5·2 for participants with HbA_{1c} less than 9%, 6·8 for those with an HbA_{1c} of 9% to less than 11%, and 10·5 for those with HbA_{1c} of 11% or higher. Notably, rate ratios for renal disease-related deaths increased at a greater rate with longer duration of diabetes than seen in other studies, with an increase of about 50% in rate ratio per 5 years additional duration.

Apart from vascular, renal, and infectious causes (and acute glycaemic crises), diabetes was not strongly associated with deaths from other causes—consistent with evidence from other countries.^{9–10} The novelty of the present analysis is in its analysis of these causes of death by duration of diabetes and level of glycaemic control, with important implications for public health in Mexico and other countries with similar burdens of diabetes. The epidemiological design of the study in Mexico City, the multi-causality model, and the variables included in the Cox models—as well as the magnitude and statistical significance of the associations identified—provide state-of-the-art of knowledge with respect to the issue of cause-specific mortality for people with diabetes in middle-income countries. In the context of current clinical practice and health policy, Herrington and colleagues' findings¹⁰ suggest that efforts to improve earlier diagnosis of diabetes and more efficient control of HbA_{1c} levels would lead to substantial improvements in the management of diabetes and large reductions in the premature mortality attributable to vascular, renal, and infectious causes.



Daniel Sambraus/SPPL

Lancet Diabetes Endocrinol 2018

For future studies, some important considerations could strengthen this type of investigation. First, as in any study using Cox models, it is important to detail the potential for residual confounding or incomplete adjustment.¹¹ Although briefly mentioned by the investigators, a more thorough discussion of such limitations would be useful to inform the design of future studies. For example, some categories of controlled confounders can be so broad that they result in an imperfect adjustment, while other potentially relevant variables (eg, social security status) were not accounted for in the analysis. Furthermore, it would be useful in future research to include and deepen the analysis of qualitative variables, such as access to health services, lifestyle and physical activity, psychosocial support, socioeconomic disparities, habits and customs of patients with diabetes, etc. Might it be possible to develop and promote a mixed approach that can integrate quantitative and qualitative variables in analyses of cause-specific mortality in diabetes? Findings that can be generated from qualitative variables could fill the knowledge gap that quantitative variables have not solved by themselves. For example, poor glycaemic control and the delay in diagnosis of diabetes, as WHO has suggested,¹² surely have close links with qualitative variables related to social determinants of health in people with diabetes (income, occupation, cultural factors, obesogenic environments, etc).

It is important to highlight the potential implications of these findings in terms of public policy. In this sense, the premature mortality associated with diabetes, mainly due to renal and vascular causes, and its link to duration of diabetes and poor glycaemic control, suggest the need for greater allocation of resources for the detection of diabetes early in the disease course and to improve glycaemic control strategies. Health-service

resources should also be used to strengthen service delivery for patients with diabetes and comorbidities including kidney disease, vascular disease, and infections.

Armando Arredondo

National Institute of Public Health, CP 62100, Cuernavaca, Mexico
armando.arredondo@insp.mx

Copyright © The Author(s). Published by Elsevier Ltd. This is an Open Access article under the CC BY 4.0 license.

I declare no competing interests.

- 1 GBD 2016 Causes of Death Collaborators. Global, regional, and national age-sex specific mortality for 264 causes of death, 1980–2016: a systematic analysis for the Global Burden of Disease Study. *Lancet* 2017; **390**: 1151–210.
- 2 INSP. Encuesta Nacional de Salud y Nutrición de Medio Camino (ENSANUT 2016)—informe final de resultados. Cuernavaca: National Institute of Public Health, 2016. http://transparencia.insp.mx/2017/auditorias-insp/12701_Resultados_Encuesta_ENSANUT_MC2016.pdf (accessed Feb 6, 2018).
- 3 Arredondo A and Avilés R. Costs and Epidemiological Changes of Chronic Diseases: Implications and Challenges for Health Systems. *Rev. PLoS One*. 2015, Vol. 10, No. 3:1-13.
- 4 Roper NA, Bilous RW, Kelly WF, Unwin NC, Connolly VM. Cause-specific mortality in a population with diabetes: South Tees Diabetes Mortality Study. *Diabetes Care* 2002; **25**: 43–48.
- 5 Brun E, Nelson RG, Bennett PH, et al. Diabetes duration and cause-specific mortality in the Verona Diabetes Study. *Diabetes Care* 2000; **23**: 1119–23.
- 6 The Emerging Risk Factors Collaboration. Diabetes mellitus, fasting blood glucose concentration, and risk of vascular disease: a collaborative meta-analysis of 102 prospective studies. *Lancet* 2010; **375**: 2215–22.
- 7 Herrington WG, Alegre-Díaz J, Wade R, et al. Effect of diabetes duration and glycaemic control on 14-year cause-specific mortality in Mexican adults: a blood-based prospective cohort study. *Lancet Diabetes Endocrinology* 2018; [Ed: final details to be checked and OF publication details to be added].
- 8 Alegre-Díaz J, Herrington W, López-Cervantes M, et al. Diabetes and cause-specific mortality in Mexico City. *N Engl J Med* 2016; **375**: 1961–71.
- 9 Salles GF, Bloch KV, Cardoso CR. Mortality and predictors of mortality in a cohort of 575 Brazilian type 2 diabetic patients. *Diabetes Care* 2004; **27**: 1299–305.
- 10 Peters SA, Huxley RR, Woodward M, et al. Diabetes as a risk factor for stroke in women compared with men: a systematic review and meta-analysis of 64 cohorts, including 775 385 individuals and 12 539 strokes. *Lancet* 2014; **383**: 1973–80.
- 11 Greenland S. Modeling and variable selection in epidemiologic analysis. *Am J Public Health* 1989; **79**: 340–49.
- 12 WHO. Global monitoring of action on the social determinants of health: a proposed framework and basket of core indicators (consultation paper). Geneva: World Health Organization, 2016. http://www.who.int/social_determinants/consultation-paper-SDH-Action-Monitoring.pdf (accessed Jan 26, 2018).