vigil and support for use of skills by ASHA coupled with opportunities for refresher trainings will be imperative for witnessing positive results in terms of reductions in early neonatal mortality rate.

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Diabetes mellitus: A risk factor for cancer and non-vascular disease deaths too

Emerging Risk Factors Collaboration, Seshasai SR, Kaptoge S, Thompson A, Di Angelantonio E, Gao P, Sarwar N, Whincup PH, Mukamal KJ, Gillum RF, Holme I, Njølstad I, Fletcher A, Nilsson P, Lewington S, Collins R, Gudnason V, Thompson SG, Sattar N, Selvin E, Hu FB, Danesh J. (University of Cambridge, Cambridge, UK; St George's University of London, London, UK; Harvard University, Boston; Centers for Disease Control and Prevention, Atlanta, USA; Ullevål University Hospital, Oslo; University of Tromsø, Tromsø, Norway; London School of Hygiene and Tropical Medicine, London, UK; Lund University, Lund, Sweden; University of Oxford, Oxford, UK; Icelandic Heart Association and the University of Iceland, Reykjavik, Iceland; Medical Research Council Biostatistics Unit, Cambridge, UK; University of Glasgow, Glasgow, UK; Johns Hopkins University, Baltimore, USA; Harvard University, Boston, USA; ERFC Coordinating Centre at the Department of Public Health and Primary Care, University of Cambridge, Strangeways Research Laboratory, Cambridge, UK.) Diabetes mellitus, fasting glucose, and risk of cause-specific death. *N Engl J Med* 2011;**364:**829–41. Erratum in: *N Engl J Med* 2011;**364:**1281.

SUMMARY

The Emerging Risk Factors Collaboration (ERFC) is an international collaboration established for conducting detailed re-analyses of worldwide data for molecules with sufficient data for potential exploration. ERFC has established a central database of over 1.2 million participants by collating more than 110 prospective population-based studies. After an initial focus on several lipid and inflammatory markers, in 2009, ERFC extended its scope to the association of diabetes and other metabolic markers with the risk of vascular disease and cause-specific death. In this study it attempted to determine reliable estimates of any independent associations of diabetes mellitus and fasting blood glucose level with the risk of death from cancer or other non-vascular conditions from 97 prospective studies. These studies (i) had complete information about age, sex, smoking status, body mass index (BMI), diagnosis of diabetes or fasting blood glucose level at baseline, (ii) did not select participants with previous chronic disease, (iii) recorded cause-specific mortality using well-defined criteria and (iv) accrued more than 1 year of follow up. The contributing studies classified deaths according to the primary cause (or in its absence, the underlying cause) using codes from the International Classification of Diseases (ICD) to at least 3 digits (or using study-specific classification system) and ascertainment was based on death certificates supplemented by medical records and autopsy findings. Hazard ratios (HR) for cause-specific death according to baseline diabetes status and fasting glucose level were estimated using a 2-stage approach. In the first stage, HRs were calculated for each study using Cox proportional-hazard regression model stratified by study, sex and trial arm. In the second stage, estimates of adjusted exposure-risk relationships (study specific $\log_e$ HRs), and interactions derived from the first stage were combined using random-effects meta-analysis. Cumulative survival from 35 years of age and older were estimated by applying the HRs (specific to age at risk and sex) for cause-specific mortality associated with diabetes to the cause-specific mortality data for 35 years of age and older residents of European Union in 2000. Among the 820 900 participants included in the analyses of diabetes status or fasting glucose level, the mean (SD) age at baseline was 55 (9) years; 48% were women and the large majority were enrolled in Europe (58%) and North America (36%). A total of 715 061 participants were included in the analyses of diabetes status. Among them 40 116 (6%) had diabetes at the time of enrolment, 32.8% were smokers, 33.9% were alcohol users and 19.1% were physically inactive. During the 12.3 million person-years at risk, a total of 123 205 deaths were recorded: 41 320 from cancer, 44 407 from vascular disease, 27 661 from other causes and 9817 from ill-defined causes. After adjustment

for age, sex, smoking status and BMI, HRs among persons with diabetes as compared with persons without diabetes were: 1.80 (95% CI 1.71–1.90) for death from any cause, 1.25 (1.19–1.31) for death from cancer, 2.32 (2.11–2.56) for death from vascular causes and 1.73 (1.62–1.85) for death from other causes. Diabetes (*v.* no diabetes) was moderately associated with death from cancers of the liver, pancreas, ovary, colon-rectum, lung, bladder and breast. Aside from cancer and vascular disease, diabetes (*v.* no diabetes) was also associated with death from renal disease, liver disease, pneumonia and other infectious diseases, mental disorders, non-hepatic digestive diseases, external causes, intentional self-harm, nervous system disorders and chronic obstructive pulmonary disease. HRs were appreciably reduced after further adjustment for glycaemia measures, but not after adjustment for systolic blood pressure, lipid levels, inflammation or renal markers. Fasting glucose levels exceeding 100 mg/dl but not levels of 70–100 mg/dl were associated with death. Estimated survival curves showed that on an average, a 50-year-old person with diabetes died 6 years earlier than a person with no diabetes, with about 40% of the difference in survival attributable to excess non-vascular deaths.

COMMENT

Diabetes mellitus is well recognized to cause a significant burden of morbidity and disability. However, its contribution to mortality is not well recognized as only few deaths are attributable directly to complications or consequences of diabetes. While diabetes as a risk factor for vascular deaths is established, recently it has also been shown to be associated with non-vascular diseases especially cancer.[1,2] However, it is unclear whether such associations are direct (e.g. due to hyperglycaemia) or indirect (e.g. due to diabetes as a marker of underlying biological factors such as insulin resistance or hyperinsulinaemia that alter the risk of cancer) or due to shared risk factors (e.g. obesity) or a combination of these.[3–6] Thus, this study addresses a focused and relevant issue of assessing the independent association of diabetes with risk of death from both vascular and non-vascular conditions. From the findings, the authors concluded that in addition to vascular disease, diabetes was independently associated with substantial premature death from several non-vascular conditions such as cancers, infectious diseases, external causes, intentional self-harm and degenerative disorders.

Although causality has not been established for these, systemic and local factors have been proposed to explain them.[7,8] Besides cancers, the study reported strong positive associations of diabetes with deaths from renal and digestive diseases and infectious diseases. These results may reflect associated nephropathy, fatty liver disease and suppression of cellular immunity, respectively. Furthermore, diabetes was associated with death from injuries, which could be related to end-organ complications such as neuropathy and eye disease or to episodes of hypoglycaemia.

The strength of this study is the large sample size and standardized assessment of association after adjusting for several potential confounding factors. Measurement error in exposures and confounders were addressed through the analysis of repeat exposure measurements and sensitivity analyses was undertaken for time-dependent diabetic status to enhance the validity of the findings. The inclusion of heterogeneous studies is both a weakness and a strength of the study. The studies included had not adopted a similar protocol and resultant differences in study methodology and definitions could result in erroneous clubbing of data whereas the fact that the findings were similar across such a number of studies distributed over space and time adds robustness to the results. Imprecise measurement of potential confounding factors (dietary factors and physical activity), non-measurement of use of certain drugs which are associated with cancers such as aspirin and glucose-lowering drugs are weaknesses identified by the authors.

Indian perspective

India has the largest number of people with diabetes in the world (50.8 million) and this is projected to increase to 87 million by the year 2030.[9] Misra *et al.*[10] have reported that the prevalence of diabetes is rising in rural India at a rate of 2.02 per 1000 population per year and the rate of increase was high in men (3.33 per 1000 per year) as compared to women (0.88 per 1000 per year). Besides urban–rural and gender differences, there is a wide disparity in the prevalence of diabetes among regions, especially the North and the South. The prevalence ranges from 2.1% to 13.2% in southern India[11,12] while it varies from 2.4% to 7.5% in northern India.[13,14] The average Indian with diabetes spends about US$ 575 annually for diabetic care. Indirectly, it is estimated to cost another US$ 102 or more annually in lost work-time while seeking and undergoing treatment. On extrapolating the direct and indirect estimates to the Indian population, the annual costs for diabetes could be US$ 31.9 billion in 2010.[15]

India recently launched the National Programme for Prevention and Control of Cancer, Diabetes, Cardiovascular Disease and Stroke.[16] The linking of cancer with diabetes as a part of an integrated programme is strengthened by the results of this study. In addition to the health promotion efforts and strengthening of health system, it is proposed to screen over 70 million (7 crore) adults (>30 years) for diabetes and hypertension for early diagnosis and provision of treatment of non-communicable diseases.

This study was based almost entirely on European and American population (except a small Japanese population; Asians were conspicuous by their absence) and its extrapolation to India must be guarded. There are many differences in the epidemiology and natural history of diabetes in India as compared to the West. Indians with diabetes are less likely to develop blindness and kidney disease, but much more likely to suffer coronary artery disease at a relatively young age.[17] It occurs much earlier with CURES[18] reporting a rising prevalence of diabetes in children and young adults with a prevalence of 6.6% of type 2 diabetes among those between 20 and 30 years of age resulting in a longer duration of exposure. Poor people who have diabetes are more prone to complications as they have less access to quality healthcare.[19]

Along with these, large treatment gap, low adherence to drugs and non-pharmacological interventions and lower use of insulin means that complications are likely to be more in the Indian population. This study reported a continuous relationship between fasting glucose levels till 100 mg/dl and risk of death. In India, there is a large pool of pre-diabetics who have high risk of conversion to overt diabetes. NUDS[20] have reported impaired glucose tolerance (IGT) in 14% while a study in Kerala reported[21] IGT in 11.2% and CURES[18] have reported IGT in 10.6%. Thus, one would intuitively pitch for higher rates of consequences and complications including deaths in the Indian setting.

Similar estimates for increased risk of death due to different causes among people with diabetes are not available from India even through small studies. This is because (i) there are very few cohort populations in India which have adequate information on diabetes status, (ii) over three-quarters of deaths in India occur at home and more than half of these do not have a certified cause,[22] and (iii) diabetes is rarely recorded as a direct cause of death in death certificates[23] and in verbal autopsy. In India, majority of the hospital-based studies have reported coronary artery disease (CAD) as the leading cause of death in people with diabetes,[24–26] while Bhansali *et al*.[27] and Zargar *et al*.[28] have reported infections as the leading cause of death in people with diabetes. The Chennai Urban Population Study (CUPS)[29] was the first population-based study to report mortality rates in people with diabetes from India. The overall mortality rates were nearly three-fold higher in those with diabetes compared with those who did not have diabetes (18.9 *v.* 5.3 per 1000 person-years). The HR for all-cause mortality for diabetes was found to be 3.6 (95% CI 2.02–6.53) compared to those who did not have diabetes which is very high in contrast to 1.80 (95% CI 1.71–1.90) in the present study. This is not surprising given the facts enumerated above. This study also highlights the need for establishment of diabetes registries and cohort studies for studying clinical and epidemiological aspects of diabetes in different parts of India. The Indian Council of Medical Research has launched Registry of People with Diabetes with Young Age at Onset at 8 centres with the aim to understand the magnitude of the problem, disease pattern or types including the geographic variation and incidence and prevalence rate of complications.[30]

Conclusion

In addition to vascular disease, diabetes is associated with substantial premature death from several cancers, infectious diseases, external causes, intentional self-harm and degenerative disorders, independent of several major risk factors. The information generated by this study helps in improving our estimation of the burden due to diabetes. This is useful for advocacy efforts aimed at policy-makers, programme managers as well as international agencies and donors.

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