Viewpoint

Intervening at prediabetes stage is critical to controlling the diabetes epidemic among Asian Indians

Two recent studies on Asian Indians reported one of the highest global rates of prediabetes progression to type-2 diabetes (T2DM)[1-3]. In an observational study, we reported prediabetes to T2DM progression rate of 71.52 per 1,000 person-years (95% CI 56.76-97.29) in a cohort of 144 individuals with prediabetes, followed for 32 (12- 48.96) months from eastern India[2]. In an epidemiologic study, Anjana *et al*[3] reported prediabetes to T2DM progression rate of 78.9 per 1,000 person-years; (68.0-90.9) in a cohort of 299 prediabetes individuals followed for 9.1 years, from southern India. These rates are second only to that observed in Pima Indians (87.3 per 1,000 person-years), and are much higher than that observed in Caucasians (35.0-40.0 per 1,000 person-years)[3,4]. In terms of annualized incidence rates, these translate to 15-19 per cent annual risk of progression to T2DM, which is much higher than 2.5 per cent observed in the Diabetes Prevention Program (DPP) study[5]. It must be highlighted that the incidence of T2DM among individuals with normal glucose tolerance among Asian Indian has been reported to be 22.2 per 1,000 person-years (19.4-25.4), which is much lower than the rates observed in individuals with prediabetes[3], suggesting occurrence of significant beta-cell loss and disease progression by the time prediabetes develops. This may be reflective perhaps of a more aggressive diabetes pathophysiology, where progression to T2DM from prediabetes is just a matter of time.

A large variety of agents (pioglitazone, acarbose, volgibose, valsartan, orlistat, colesevelam, glucagon like peptide-1 analogues, curcumin and vitamin-D) have been tried for prevention of T2DM[6-10]. However, their use in clinical practice has been limited by lack of concrete clinical evidence (positive outcomes only in small specific subset of individuals with prediabetes, significant adverse effects, evaluated in small ethnic groups or lack of adequate reproducibility of observations in different populations). Till date, lifestyle interventions followed by metformin are the two best-established options available for preventing T2DM. Moin *et al*[11] recently highlighted the extremely low use of metformin for T2DM prevention among individuals with prediabetes in USA. The authors observed that only 3.7 per cent of 17,352 adults with prediabetes between 2010 and 2012 received metformin for diabetes prevention[11]. This is in spite of the DPP study, published nearly 13 years back, which showed lifestyle intervention and metformin reduced T2DM incidence by 58 and 31 per cent, respectively[5], an observation which has subsequently been replicated across the globe including India[12]. The use of metformin among prediabetes in India is expected to be much lower. Just because metformin is inferior to lifestyle intervention, does not imply it should not be used for preventing T2DM, as an adjunctive to lifestyle intervention. Concerns have been raised regarding medicalization of "prediabetes", leading to increased health expenditure per person, and it has been feared that use of metformin in prediabetes, would lead to lesser emphasis on lifestyle interventions[13,14]. This may have some relevance in the western world where the dynamics of prediabetes (in Caucasians) is more benign, with lower disease burden, low annual rate of progression to T2DM (about 2%), and cost of health care in general believed to be high[13,14]. A recent study from Singapore revealed that metformin was in fact more cost-effective than therapeutic lifestyle modifications to prevent or delay the onset of T2DM among Southeast Asians[15].

It has also been suggested that metformin, being an anti-hyperglycaemic agent, lowers blood glucose and delays the development of T2DM, without any impact on disease pathophysiology[13,14]. However, this lowering of blood glucose in the prediabetes state should *per se* improve long term outcomes, considering dysglycaemia being a continuous spectrum, and evidence now showing increased occurrence of almost all end-

organ damage (including neuropathy, nephropathy and retinopathy) in prediabetes, along with the current understanding of the concepts of "glycaemic memory" and "legacy effect"[16,17]. Metformin is the oldest among all the currently available oral antidiabetic medications for clinical use, being available in the British National Formulary since 1958, and its clinical use has stood the test of time[18]. Apart from T2DM and prediabetes, metformin has been found to be beneficial in gestational diabetes, polycystic ovarian syndrome and fatty liver disease. Adverse effects commonly associated with metformin are usually mild and primarily gastrointestinal (diarrhoea, cramps, nausea, vomiting, and flatulence). Several large studies and meta-analysis have now shown that metformin use is not associated with increased risk of lactic acidosis[19,20]. Long term metformin use, especially at high doses of >2,000 mg per day for more than 10 years has been linked with vitamin-B12 deficiency, warranting monitoring of serum vitamin-B12 levels in these patients[21,22]. For T2DM prevention, metformin is usually recommended at low dose of 0.5 g/day. It must be highlighted that metformin should not be used in type-1 diabetes and other rare forms of diabetes. As per National Institute for Health and Clinical Excellence (NICE)[23], Canadian Diabetes Society (CDS)[24] and the Australian Diabetes Society (AuDS)[25], metformin should be used with caution in patients with estimated glomerular filteration rate (eGFR) <45 ml/min per 1.73 m², and is contraindicated[26] in patients with eGFR<30 ml/min per 1.73 m².

Implementing lifestyle intervention has been challenge across the globe, has poor long term compliance, and involves extensive use of human resources. These challenges are perhaps far greater in countries with limited population awareness like India. India with a population of more than 1.25 billion, 9 per cent diabetes prevalence, 10-14 per cent prediabetes prevalence, highest global rates of progression to T2DM[27], compounded by scarcity of doctors (0.7/1,000 population), poor health infrastructure, and out-of-pocket health expenditure[28], is ill equipped to manage this grave socio-economic crisis[1]. In fact, a study published recently involving urban individuals in South Asia has suggested that the magnitude of the problem may be graver than the current estimates[29]. An evaluation of 16,288 subjects aged ≥20 yr (Chennai: 6906, Delhi: 5365 and Karachi: 4017) revealed a very high prevalence of prediabetes (31.1% in Karachi, 37.9% in Chennai, 47.6% in Delhi). Overall, 47.3-73.1 per cent of the population had either diabetes or prediabetes[26].

Government initiated health programmes for diabetes screening, and spreading awareness regarding lifestyle interventions among those with prediabetes, can go a long way in controlling this diabetes epidemic and the associated morbidity. Therapeutic lifestyle intervention remains the first step and the involvement of nurses, paramedics, social workers, teachers and school children is critical to mobilization of citizens, and generation of subsequent political will, and policy of the state, necessary for success of such programmes[1]. Metformin is a generic drug, cheap and widely available both in government and private health care services in India. Hence additional use of metformin may be encouraged in the subset of prediabetics with multiple risk factors, which are associated with highest risk of progression to T2DM. These risk factors include presence of strong family history of T2DM, obesity especially central obesity, history of gestational diabetes; occurrence of both impaired fasting glucose and impaired glucose tolerance.

Hence in contrast to concerns raised regarding medicalization of prediabetes, it is perhaps high time that prediabetes is treated with due seriousness. Lifestyle intervention is the first line intervention and should be aggressively implemented in individuals with prediabetes and awareness should be spread regarding the use of metformin in prediabetics for T2DM prevention (especially in high-risk ethnic groups like Asian Indians with multiple risk factors), till better alternatives are made available in future. Urgent large multi-centric trial is warranted from India to further substantiate the beneficial effects of metformin in diabetes prevention among individuals with prediabetes.

Conflicts of Interest: None.

Deep Dutta[1] & Satinath Mukhopadhyay[2]
[1]Department of Endocrinology,
Post Graduate Institute of Medical Education &
Research (PGIMER) &
Dr Ram Manohar Lohia (RML) Hospital,
1 Baba Kharak Singh Marg,
New Delhi 110 001 &
[2]Department of Endocrinology & Metabolism,
Institute of Post-Graduate Medical Education &
Research (IPGMER) & Seth Sukhlal Karnani
Memorial (SSKM) Hospital, 244 AJC Bose Road,
Kolkata 700 020, West Bengal, India
[1]*For correspondence*:
deepdutta2000@yahoo.com

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