Type 2 Diabetes: Demystifying the Global Epidemic

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Type 2 diabetes (T2D) has attained the status of a global pandemic, spreading from affluent industrialized nations to the emerging economies of Asia, Latin America, and Africa. There is significant global variation in susceptibility to T2D, with Pacific Islanders, Asian Indians, and Native Americans being considerably more prone to develop the disorder. Although genetic factors may play a part, the rapidity with which diabetes prevalence has risen among these populations reflects the far-ranging and rapid socioeconomic changes to which they have been exposed over the past few decades. Traditionally, obesity and its correlate, insulin resistance, have been considered the major mediators of T2D risk; however, recent evidence shows that early loss of β-cell function plays an important role in the pathogenesis of T2D, especially in nonobese individuals such as South Asians. Knowledge of the modifiable risk factors of T2D is important, as it forms the basis for designing cost-effective preventive and therapeutic strategies to slow the epidemic in populations at increased risk. Lessons learned from randomized prevention trials need to be implemented with appropriate cultural adaptations, accompanied by empowerment of the community, if the diabetes epidemic is to be slowed or halted.

The emergence of type 2 diabetes (T2D) as a global pandemic is one of the major challenges to human health in the 21st century. Long considered a disease of the affluent "Western" countries of Europe and North America, T2D has now spread to every corner of the world. Indeed, there are now more people with diabetes residing in the "emerging" economies than in the industrialized nations (1). In developing nations, the prevalence of diabetes is undoubtedly higher among urban versus rural populations (2), although it is also rapidly increasing in rural areas (3). A systematic review based on 109 population-based surveys involving 1,100,746 individuals reported that the global rural diabetes prevalence was 5.7% during 1985–1989, which increased to 8.7% during 2005–2011 (3). Diabetes is also more prevalent among the affluent in developing countries, in contrast to developed nations, where the prevalence of both T2D and obesity are higher among the poorer sections of society (4,5).

The reasons for the rapid spread of T2D to hitherto less affected parts of the world can be explained by a number of interrelated factors, some of which have not yet been fully characterized. Study of these factors will help in better understanding the pathophysiology of the disease and in planning efforts for its prevention. There are excellent reviews on diabetes in Asians (6,7); in this Perspective we look at some of the established and emerging factors that have led to the globalization of the diabetes epidemic over the past half century, with a major focus on developing nations.

EPIDEMIOLOGY OF DIABETES—TRULY A GLOBAL PANDEMIC

The latest figures from the International Diabetes Federation (IDF) indicate that as of 2015 more than 415 million people worldwide have diabetes (1). This number is expected to increase to 642 million by 2040. China and India have the largest numbers of people with diabetes (109.6 million and 69.2 million, respectively). However, the highest prevalence rates of diabetes are found in the Pacific Islands and the Middle East. A major concern today is the increasing numbers of people with T2D in low- and middle-income countries (8). Among the IDF regions, the Western Pacific has the highest number of people with diabetes (with China contributing the lion's

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share), followed by the Southeast Asian region. Currently, the lowest numbers are found in South and Central America and Africa (Fig. 1) (1,9). However, it has been estimated that by 2040 the number of people with diabetes will increase by 65% in South and Central America and double in sub-Saharan Africa (1). It should be remembered that these figures often hide large inter- and intracountry differences and that little or no data regarding diabetes prevalence are available from many countries (especially in Africa, where it is estimated that more than 65% of individuals with diabetes remain undiagnosed) (10). Nonetheless, it is abundantly clear that the

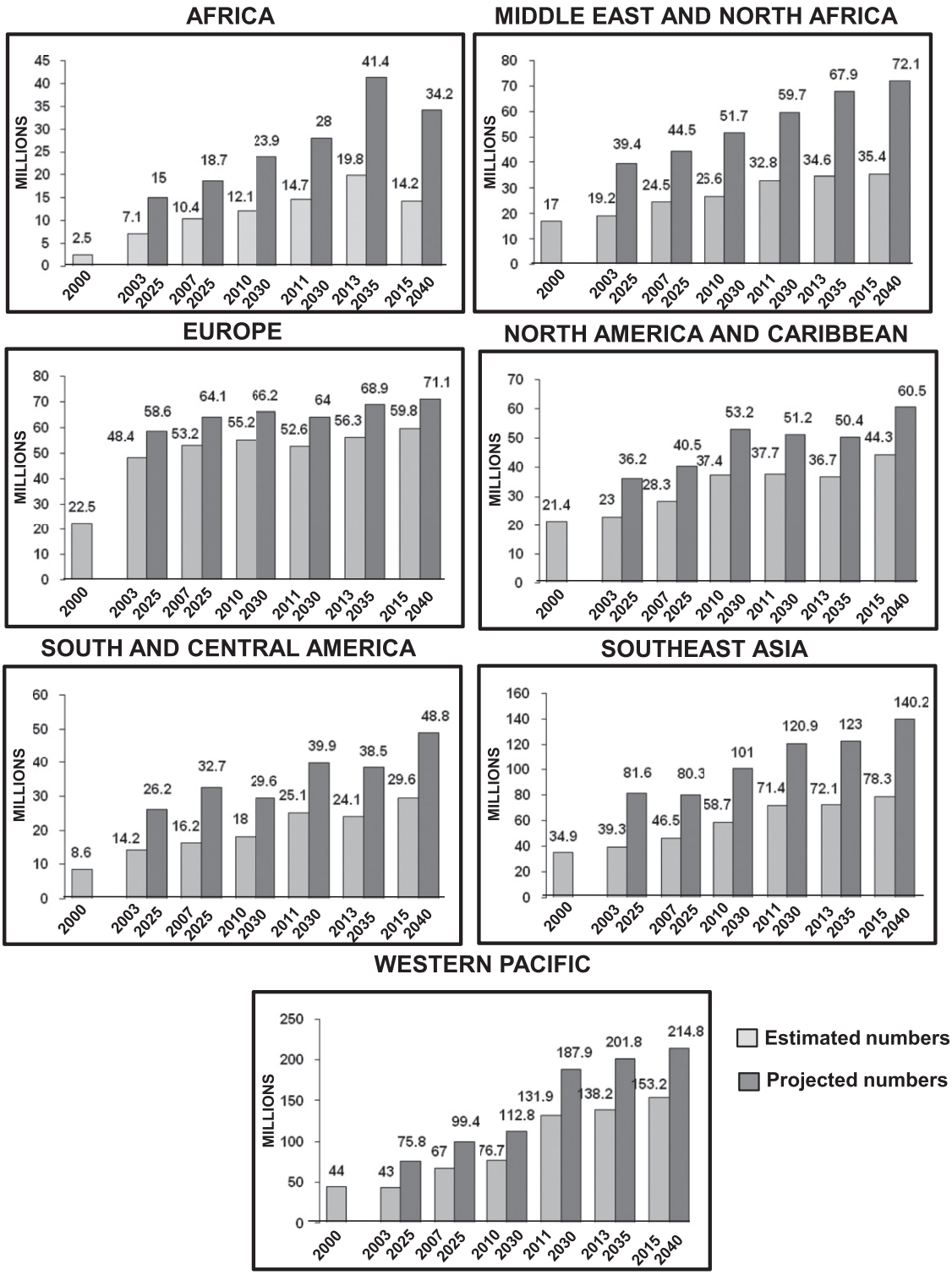

Figure 1—Rising prevalence of diabetes in IDF regions, 2000–2015 (1,9).

diabetes epidemic is no longer confined to the affluent nations of Europe and North America.

ETHNIC DIFFERENCES IN SUSCEPTIBILITY TO DIABETES

Studies conducted in multiethnic populations of different countries have shown that individuals of certain ethnicities are more prone to develop T2D. Furthermore, migration to developed countries has also been shown to be associated with a higher T2D risk. For example, Asian Indian immigrants have a higher prevalence of T2D than the white U.S. population and Europeans (11,12). A study conducted in Ontario, Canada, reported that, compared with immigrants from western Europe and North America, the risk for diabetes was higher among immigrants from South Asia, Latin America and the Caribbean, and sub-Saharan Africa, even after controlling for age, immigration category, level of education, level of income, and time since arrival. More worrisome was the fact that this increased risk for diabetes started at an early age (11). It is also well known that South Asians develop diabetes at younger ages and also tend to progress much faster from prediabetes to diabetes as compared with white Caucasians of comparable BMI (12,13).

Although few data are available on diabetes incidence, urban areas of low- and middle-income countries such as India and Mexico have been shown to have the highest incidence rates (14). While the incidence rates of T2D have stabilized in the U.S. over the past decade, this does not hold true for all ethnic groups. The Diabetes Study of Northern California (DISTANCE), a large prospective cohort study, assessed the incidence of T2D according to race/ethnicity in the U.S. among health plan members of Kaiser Permanente Northern California. This study reported that Koreans, Pacific Islanders, South Asians, and Filipinos had the highest incidence (20.3, 19.9, 17.2, and 14.7 cases per 1,000 person-years, respectively) of diabetes among all racial/ethnic groups (15). Even though these figures may reflect true ethnic differences in susceptibility, the possibility of environmental factors (such as high dietary carbohydrate loads and low levels of physical activity, among others) acting in concert with ethnicity should also be considered.

MECHANISTIC EXPLANATIONS FOR THE DEVELOPMENT OF DIABETES IN EMERGING NATIONS

T2D is characterized by varying degrees of pancreatic β-cell dysfunction in the presence of suboptimal insulin action (insulin resistance). The relative contribution of these two pathophysiological mechanisms to the development of diabetes varies from individual to individual and may also differ between ethnic groups. In addition, there may be perturbations in other hormonal systems (e.g., the incretin axis) that predispose individuals to the development of chronic hyperglycemia, but these alterations are, as yet, poorly characterized.

Studies on differential susceptibility of non-Caucasian ethnic groups to T2D have traditionally focused on the role of obesity and insulin resistance. A classic example is the Pima Indians in the U.S., in whom high levels of obesity and insulin resistance have been associated with some of the highest prevalence rates of T2D in the world (16). Similarly, obesity-driven reductions in insulin sensitivity appear to underlie the dramatic increase in diabetes prevalence seen in Pacific Island populations (17). However, the relationship between excess adiposity, insulin resistance, and T2D among other ethnic groups is not as straightforward. For any level of BMI, Asian Indians have higher waist circumference, more visceral fat, and lower insulin sensitivity compared with white Caucasians (the "thin-fat" Indian) (18).

Whereas the focus of earlier studies was on insulin resistance, there is an increasing focus on the β-cell. In his brilliant Kelly West Award Lecture, Venkat Narayan eloquently argues that rapid pancreatic β-cell loss may be equally if not more important in some populations, such as Asian Indians (19). He makes a compelling argument comparing two "Indians" with contrasting phenotypes: the Pima Indians in Arizona, who are obese, markedly insulin resistant, and hyperinsulinemic, in contrast to Asian Indians, who are relatively thin and most severely insulinopenic. Narayan hypothesizes that there could be two distinct subtypes of T2D: the Pima Indian–like phenotype that he calls "type 2A," characterized by marked obesity, insulin resistance, and relatively better preserved β-cell function, and the Asian Indian–type phenotype called "type 2B," characterized by a leaner body mass and more severe β-cell dysfunction. It is thus entirely plausible that treatment approaches may differ in the two subtypes, with insulin sensitizers being the prominent drugs in the former and insulin secretagogues being the main drug in the latter. However, further research is needed before this hypothesis can be evaluated with treatment approaches and/or used in clinical practice. Specifically, β-cell function studies comparing lean versus obese individuals with T2D are needed, as are randomized clinical trials comparing the effects of secretagogues with those of sensitizers in lean versus obese patients with T2D.

Unfortunately, pancreatic β-cell dysfunction has not been as extensively studied as insulin resistance in the pathophysiology of T2D. Although it is evident that some degree of β-cell secretory deficiency is essential for the development of T2D, the fact that the insulin secretory defect occurs earlier, and is more severe, in T2D is getting increasing attention. It has been shown, for example, that by the time an individual's blood glucose levels cross the thresholds diagnostic of diabetes, nearly 80% of the β-cell reserve has been lost (20). In that study, β-cell function was measured using the gold standard,

i.e., the insulin secretion/insulin resistance index, or the so-called disposition index (DI_o) [$DI_o = (\Delta insulin_{0-30}/\Delta glucose_{0-30}) \times (1/fasting\ insulin)$].

It is likely that β-cell dysfunction may play a more important role in the pathogenesis of T2D in populations or subgroups where the prevalence of T2D is high but the BMI is low (19). Indeed, studies have shown that β-cell function may decline very early in the natural history of T2D among South Asians. In a cross-sectional study of South Asian Indians with different glycemic statuses, β-cell function measured using DI_o was shown to be impaired even among those with mild dysglycemia (e.g., fasting glucose 100–126 mg/dL and/or 2-h glucose 140–199 mg/dL), independent of age, adiposity, insulin sensitivity, and family history of diabetes (21). The Whitehall II cohort study conducted by Ikehara et al. (22) in the U.K. among South Asian and white participants aged 39–79 years reported that South Asians may have inadequate pancreatic β-cell reserve, as a significantly steeper age-related increase in fasting glucose was observed compared with Europeans. In this study, HOMA β-cell function (HOMA2 %B, a marker of insulin secretion) was calculated with the HOMA2 calculator using fasting glucose and fasting insulin values. It was concluded that although Asian Indians had significantly higher levels of plasma insulin at younger ages, their β-cells were unable to further increase insulin output in response to age-related decreases in insulin sensitivity.

Another study conducted in the Netherlands investigated β-cell function (calculated using area under the curve for incremental insulin secretion rates and DI_o) and insulin sensitivity simultaneously in South Asian and Caucasian patients with T2D and their first-degree relatives. This study suggested that in South Asian individuals, rapid β-cell deterioration might occur under insulin-resistant conditions, and the alterations in β-cell dynamics may explain their earlier onset of T2D compared with Caucasians (23).

Schwartz et al. (24) have recently called for a reclassification of diabetes with a greater β-cell–centric approach. The β-cell–centric model presupposes that all diabetes originates from a final common denominator—the abnormal pancreatic β-cell. This model recognizes the interactions between genetically predisposed β-cells and a number of factors, which include insulin resistance, susceptibility to environmental influences, and immune dysregulation/inflammation, leading to the range of hyperglycemic phenotypes within the spectrum of T2D.

T2D: AN INEVITABLE CONSEQUENCE OF PROSPERITY?

The most marked increases in the prevalence of diabetes have been noted in those countries that have experienced rapid economic growth, transitioning from low-income to high-income economies over a short period of time. Perhaps the most extreme example of this can be found in the tiny Pacific Island nation of Nauru. In the 1960s, exploitation of the island's vast phosphate resources led to an economic boom and widespread prosperity for the islanders. This change was accompanied by an increase in the prevalence of T2D from near zero in the early 1960s to nearly 35% by the 1970s (25). Subsequently, as the phosphate deposits ran out, national income fell, and latest figures indicate that the prevalence rates of obesity and T2D are also declining (26).

Similar (albeit less marked) transitions also underlie the epidemic of diabetes in China, India, Mauritius, Fiji, and the Middle East. In all these countries, rapid economic development has been accompanied by lower mortality from communicable diseases and improvements in life expectancy. The populations of these countries are older than they were a couple of decades ago, which makes them prone to develop age-related noncommunicable diseases such as T2D. Indeed, a recent study by Gujral et al. (27) showed that in contrast to the situation a couple of decades ago, when migrant Asian Indians had two- to threefold higher rates of diabetes compared with Indians living in India, Indians living in urban India today have prevalence rates of diabetes higher than migrant Indians in the U.S. (27). The epidemic of diabetes in these countries can therefore be partly explained as an inevitable upshot of economic development. India, for example, underwent a dramatic change in its economic policies in 1991 leading to an opening up of its economy and a sharp increase in its gross domestic product.

DO GENETIC FACTORS UNDERLIE THE EPIDEMIC?

T2D has a strong familial component. Also, the marked predilection of certain ethnic groups (e.g., Pima Indians, Pacific Islanders) to T2D raises the possibility of heightened genetic susceptibility to the disease among them. However, efforts to pinpoint the genetic etiology of T2D have proved frustratingly inconclusive. The current consensus is that T2D is a polygenic disorder, with multiple susceptibility genes, each with a small effect size on the overall risk of developing the disease. Studies have failed to substantiate a greater genetic risk of T2D in Asians compared with white Caucasians (28), with the majority of single-nucleotide polymorphisms identified having similar risk estimates and population burden in white Caucasians and Asians. Fuchsberger et al. (29) reported that although genome-wide association studies (GWAS) have identified scores of common variants associated with T2D, in aggregate those variants explain only a fraction of the heritability of the disorder. The Genetics of Type 2 Diabetes (GoT2D) and the Type 2 Diabetes Genetic Exploration by Next-generation sequencing in multi-Ethnic Samples (T2D-GENES) consortia performed whole-genome sequencing in 2,657 European individuals with and without diabetes and exome sequencing in 12,940 individuals from five ancestry groups. The group concluded that variants associated with T2D were overwhelmingly common and most fell within regions previously identified by GWAS. Thus, large-scale sequencing does

not support the idea that lower-frequency variants have a major role in predisposition to T2D. Although some unique genes have been identified in South Asians by GWAS (30,31), their effect sizes were low. Hence, it is highly unlikely that genetic factors are responsible for the current epidemic of diabetes. Moreover, the genetic makeup of a population cannot change in the course of two or three generations, which is the time frame in which the prevalence rates of diabetes have increased multifold in these populations.

The elegant studies of Yajnik and colleagues from Pune, India (32,33), with painstaking follow-up of cohorts from the prepregnancy stage through the pregnancy and subsequent follow-up of offspring until adulthood, provide strong evidence for the link between intrauterine programming, lower birth weight, and subsequent catch-up growth and insulin resistance and T2D in Asian Indians.

In recent years, many studies have indicated that epigenetic modifications play a critical role in the development and pathogenesis of chronic disorders such as T2D (Fig. 2). Epigenetics is the study of heritable changes in gene function without any changes in the nucleotide sequence. The important epigenetic mechanisms are DNA methylation, histone modification, and noncoding RNA–mediated pathways. DNA methylation results in gene silencing, while histone modification results in promotion or repression of gene transcription. Noncoding RNA (microRNA, miRNA) is believed to have a role in gene expression. Many environmental factors are known to cause changes in gene expression through epigenetic modifications such as altered DNA methylation or histone modification.

A recent nested case-control study (London Life Sciences Prospective Population [LOLIPOP] Study) assessed DNA methylation in Asian Indians and Europeans with incident T2D among 25,372 participants who were followed up for 8 years (34). The study reported that methylation markers at five loci (ABCG1, PHOSPHO1, SOCS3, SREBF1, and TXNIP) were associated with future incident T2D. The association of DNA methylation score with risk of T2D was also observed in normoglycemic Indian Asians, among whom high levels of methylation in metabolically unhealthy obese individuals were associated with a high risk of future T2D. This supports the views of Narayan (19) and others that Asian Indians may have an inherent susceptibility to diabetes that is probably linked to heightened β-cell dysfunction. Chambers et al. (34) suggest that DNA methylation might provide new insights into the pathways underlying T2D and offer new opportunities for risk stratification and prevention of T2D.

IS THERE A MODIFIABLE (ENVIRONMENTAL) COMPONENT?

In many countries, economic development has drastically modified lifestyles over the course of a single generation. The two aspects of this transition that are of most interest to students of diabetes epidemiology are the changes in physical activity levels and food habits. In addition to these changes, novel risk factors, including exposure to environmental pollutants, smoking, depression, short sleep duration, and the built environment (BE), have also been shown to be associated with increased diabetes risk (14). Knowledge of these factors is important, as they are eminently modifiable.

Physical Inactivity

It is well established that physical inactivity increases the risk of T2D in all ethnic groups (35). Traditionally, occupational physical activity levels are high in developing nations, where most individuals are engaged in unmechanized agricultural

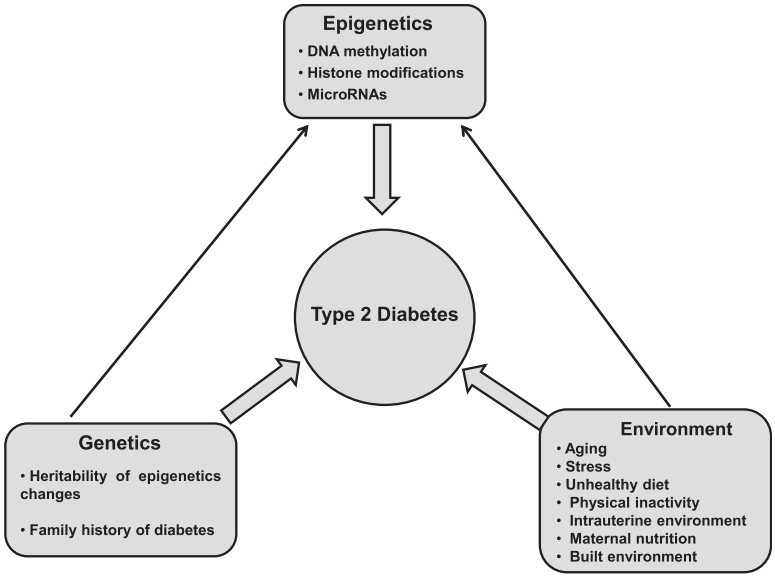

Figure 2—Schematic presentation of the interplay of mechanisms involved in development of T2D.

activities. Therefore, absence of recreational physical activity did not adversely affect overall physical activity levels in these societies. In recent years, however, industrialization and mechanization have shifted the workforce away from agriculture and into less physically demanding occupations, causing drastic declines in overall physical activity levels. Unfortunately, levels of recreational physical activity are abysmally low in most parts of the developing world and are insufficient to compensate for the decline in occupational physical activity. In India, for example, less than 10% of individuals report doing any recreational physical activity (36).

A number of studies worldwide have shown that individuals who are active have a lower risk of developing T2D compared with those who are sedentary (37,38). A recent systematic review conducted on three studies pertaining to T2D reported that an increase from being inactive to achieving recommended physical activity levels (150 min of moderate-intensity aerobic activity per week) was associated with a 26% lower risk of T2D incidence after adjustment for body weight (38).

Dietary Factors

In most parts of the world, economic development has been accompanied by a rapid nutrition transition. The most apparent aspect of this transition has been the wide adoption of Western-style fast foods and sweetened beverages, particularly by the younger generation in urban areas. However, the ramifications of the nutrition transition are far more widespread. Traditionally, diets in most parts of the developed world consisted chiefly of unpolished whole grains as the staple. These diets were rich in fiber and low in refined carbohydrates and hence had a low glycemic index and glycemic load. With increasing affluence and availability of modern food processing technologies, there has been a wholesale shift away from unpolished whole grains to refined polished cereals. Intake of *trans* fats and sweetened beverages has increased, but that of fiber, fruits, and vegetables has come down (39).

Dietary patterns characterized by increased intake of fruits and vegetables, whole grains, low-fat dairy products, low glycemic load, and plant-based diets have been associated with substantially lower risk of developing T2D. In contrast, dietary patterns that include high intakes of refined grains, processed meats, and added sugars and a low-fiber diet have been associated with increased T2D risk. Several studies have assessed the link between cereal intake and risk of developing T2D. Table 1 summarizes the observational studies that have looked at this relationship (40–45). The majority of studies have used a food frequency questionnaire (FFQ), which is the most common method used to estimate the usual dietary intake of the population and to rank an individual based on his or her dietary intake in order to relate it to chronic disease risk over time. FFQ-based dietary intake pertains to a longer period (usually a year) and is more representative of usual intake than a few days of diet records. However, measurement error with FFQ is inevitable (e.g., recall bias). Another limitation of the FFQ can be its length and the number of food items it includes—it may be limited to 100 or 200 of the most commonly consumed foods. To include all the foods available would further increase the length of the questionnaire, making it take more time, which could cause interviewer and respondent fatigue. Despite these limitations, if an appropriate culturally specific and validated FFQ is used, it can still provide a more realistic picture of dietary intake than the 24-h recall method.

Studies have suggested that consuming dairy products lowers the risk of developing T2D. The Health Professionals Follow-up Study (HPFS) assessed the relation between dairy intake and incident cases of T2D in 41,254 male participants and concluded that dietary patterns characterized by higher dairy intake, especially low-fat dairy intake, may lower the risk of T2D (46).

Several studies have assessed the association between coffee/tea intake and risk of T2D. A recent study reported that substituting unsweetened tea or coffee for soft drinks and sweetened-milk beverages reduced T2D incidence (47). Table 2 summarizes the current dietary habits and strategies to reduce the global epidemic of diabetes.

Role of the BE

Recent studies have shown that development of T2D is also influenced by the BE, which is defined as "the environments that are modified by humans, including homes, schools, workplaces, highways, urban sprawls, accessibility to amenities, leisure, and pollution" (48). The BE is one of the environmental factors that influences lifestyle and habits of its inhabitants, including opportunities for physical activity, food, rest, relaxation, and sleep. Recently, a retrospective cohort study was conducted to assess the impact of neighborhood walkability on diabetes incidence among 214,882 immigrants relative to 1,024,380 long-term residents who were free of diabetes and living in Toronto, Canada. The study concluded that neighborhood walkability was a strong predictor of diabetes incidence independent of age and income, particularly among recent immigrants. Diabetes incidence varied threefold between recent immigrants living in low-income/low-walkability areas (16.2 per 1,000) and those living in high-income/high-walkability areas (5.1 per 1,000) (49).

In a community-based study conducted in Chennai in southern India, standard lifestyle advice (e.g., increasing physical activity and improving diet) was provided to the participants at baseline. After a 10-year follow-up, a 277% increase was reported in the exercise levels of residents of a middle-income colony (the Asiad Colony) following the construction of a park by the residents themselves (50). In this colony, the prevalence of diabetes only increased modestly, from 12.4% to 15.4% (i.e., a 24% increase), over a 10-year follow-up period (51). In contrast, during the same period in another colony where no such improvement in BE was made, the prevalence of diabetes increased from 6.5% to 15.3% (a 135% increase). This indicates that a moderate investment of time and effort

Table 1—Studies on refined cereal intake and risk of diabetes

Study, location	Study participants (*n*)/age range (years)/cases	Follow-up period	Exposure and assessment methods	Adjusted RR/OR (95% CI) for diabetes
Health Professionals Follow-up Study, U.S. (40)	39,765 males 32–87 2,648	20 years/702,920 person-years	FFQ of 116–131 food items (cooked white rice); self-reported diabetes	1.02 (0.77–1.34) for highest quintile of white rice consumption (≥112.9 g/day) compared with <5.3 g/day
Nurses' Health Study, U.S. (40)	69,120 females 37–65 5,500	22 years/1,404,373 person-years	FFQ of 116–131 food items (cooked white rice); self-reported diabetes	1.11 (0.87–1.43) for highest quintile of white rice consumption (≥112.9 g/day) compared with <5.3 g/day
Nurses' Health Study II, U.S. (40)	88,343 females 26–45 2,359	14 years/1,210,903 person-years	FFQ of 116–131 food items (cooked white rice); self-reported diabetes	1.40 (1.09–1.80) for highest quintile of white rice consumption (≥112.9 g/day) compared with <5.3 g/day
Melbourne Collaborative Cohort Study, Australia (41)	36,787 males and females 40–69 365	5 years/129,190 person-years	FFQ of 121 food items (cooked white rice); self-reported diabetes	0.93 (0.68–1.27)* for highest quartile of white rice consumption (≥56 g/day) compared with <23 g/day
Shanghai Women's Health Study, China (42)	64,191 females 40–70 1,608	5 years/297,755 person-years	FFQ of 77 food items (raw white rice); self-reported diabetes	1.78 (1.48–2.15) for highest quartile of white rice consumption (≥750 g/day) compared with <500 g/day
Japan Public Health Center-based Prospective Study, Japan (43)	33,622 females 45–75 478	5 years/168,110 person-years	FFQ of 147 items (cooked white rice); self-reported diabetes	1.65 (1.06–2.57) for highest quartile (≥437 g/day) compared with <278 g/day
Japan Public Health Center-based Prospective Study, Japan (43)	25,666 males 45–75 625	5 years/128,330 person-years	FFQ of 147 items (cooked white rice); self-reported diabetes	1.19 (0.85–1.68) for highest quartile (>560 g/day) compared with <315 g/day
Pizarra study, Spain (44)	605 males and females 18–65 54	6 years/4,253 person-years	FFQ (cooked white rice); OGTT	0.43 (0.19–0.95)* for 2–3 times per week intake of rice compared with once or less per week
Chennai Urban Rural Epidemiology Study, India (45)	1,376 males and females ≥20 385	10 years/11,629 person-years	Semiquantitative FFQ of 222 items (refined cereals included white rice, rice grits–based products, rice flour, refined wheat flour, semolina, and refined millet flour); OGTT	1.85 (1.20–2.87) for highest quartile (>470 g/day) compared with <254 g/day#

OGTT, oral glucose tolerance test; RR, relative risk; OR, odds ratio. *Odds ratio. #Data acquired from study group on request.

Table 2—Current dietary habits and suggested strategies to reduce the global diabetes epidemic

Food habits increasing diabetes risk	Beneficial replacements
Refined grains and sugars	Whole grains and millets
Simple and easily digestible carbohydrates (high GI foods)	Complex carbohydrates with high dietary fiber (low GI foods)
Red meat	Fatty fish (n-3 PUFA) and legumes and pulses
Saturated fats and industrial *trans* fats	Combination of vegetable oils, nuts, and oilseed (rich in MUFA)
Ready-to-eat processed foods	Fruits and vegetables
Sugar and sugar-sweetened beverages	Whole fruits

GI, glycemic index; PUFA, polyunsaturated fatty acid; MUFA, monounsaturated fatty acid.

in improving the BE might help slow the epidemic of diabetes.

Environmental Pollutants

Emerging scientific evidence suggests that T2D is associated with environmental pollutants, exposure to which is also abundant in most developing countries. The various environmental exposures that have been shown to be associated with diabetes include persistent organic pollutants (POPs), arsenic, bisphenol A, phthalates, organotins, nonpersistent pesticides, and air pollution. POPs have been shown to be associated with insulin resistance and T2D in several studies (52). A recent meta-analysis on association of some organochlorine POPs concluded that hexachlorobenzene and total polychlorinated biphenyls, but not dichlorodiphenyldichloroethylene or dichlorodiphenyltrichloroethane, are significantly associated with T2D (53).

Many studies have assessed the relationship between traffic-related air pollutants, including nitrogen oxides, nitrogen dioxide, and particulate matter (diameter $\leq$10 μm and diameter $\leq$2.5 μm) and T2D. The majority of the studies have demonstrated an association between air pollution and diabetes (54,55). However, Dijkema et al. (56), in a cross-sectional study that evaluated exposure to traffic air pollution and T2D, concluded that there was no relationship between the two.

Role of Lifestyle Modification in the Prevention of Diabetes

Randomized controlled trials from populations in developed and developing countries have demonstrated that supervised exercise programs, with or without dietary modifications, significantly reduced the incidence of diabetes in high-risk groups by up to 67%. In the Malmö trial (57), a nonrandomized trial conducted in 260 men with impaired glucose tolerance (IGT), the cumulative incidence of diabetes in the intervention group was found to be 11%, compared with 21% in the control group (after 6 years of follow-up). The first of the randomized trials of lifestyle intervention for prevention of diabetes was the Da Qing IGT and Diabetes Study (58). In this study, conducted in China, the risk for diabetes in the exercise group was reduced by 46% compared with a control group after 6 years of active intervention. In both the Finnish Diabetes Prevention Study (DPS) (59) and the Diabetes Prevention Program (DPP) conducted in the U.S. (60), diet and exercise intervention reduced the incidence of diabetes by 58%. In a Japanese trial conducted in 458 men with prediabetes, intensive lifestyle modification reduced the risk of diabetes by 67% (61).

The Indian Diabetes Prevention Program (IDPP) reported that after 3 years of follow-up the relative risk reduction for diabetes was 28.5% with lifestyle management, 26.4% with metformin, and 28.2% with combined interventions (62). In IDPP-3, a total of 537 participants were randomly assigned to a mobile phone messaging intervention with frequent SMS text messages or to standard care. The cumulative incidence of diabetes was lower in those who received mobile phone messages (18%) than in control subjects (27%) (63).

The Zensharen Study for Prevention of Lifestyle Diseases (64), conducted in overweight Japanese individuals with impaired fasting glucose (IFG), reported that lifestyle modifications reduced risk for diabetes by 44.1% among individuals with IFG and by 59% among those with combined IFG and IGT. The 20-year follow-up of participants in the Da Qing Diabetes Prevention Study (DQDPS) (65) reported a risk reduction of diabetes by 43% in the intervention group compared with the control group. The Diabetes Community Lifestyle Improvement Program (D-CLIP) was a randomized controlled translational trial that studied 578 overweight/obese Asian Indian adults with prediabetes (IGT or IFG or both). This study used a culturally tailored lifestyle education curriculum based on the U.S. DPP, plus stepwise addition of metformin (500 mg twice daily) (66). During 3 years of follow-up, 34.9% of subjects in the control group and 25.7% in the intervention group developed diabetes; the relative reduction in diabetes incidence was 32%. Figure 3 summarizes the results of various prevention trials.

THE WAY FORWARD

The spread of the diabetes epidemic to the developing world represents a major challenge to public health and health care delivery systems. The sheer number of people with diabetes is likely to put an enormous strain on the health care systems of these countries, many of which are still grappling with communicable diseases. Delayed diagnosis, inadequate follow-up, and suboptimal care of people with diabetes predisposes them to the development of acute and chronic complications, which further increases the treatment cost and places a heavy burden on the individual, society, and the nation. This is all the more

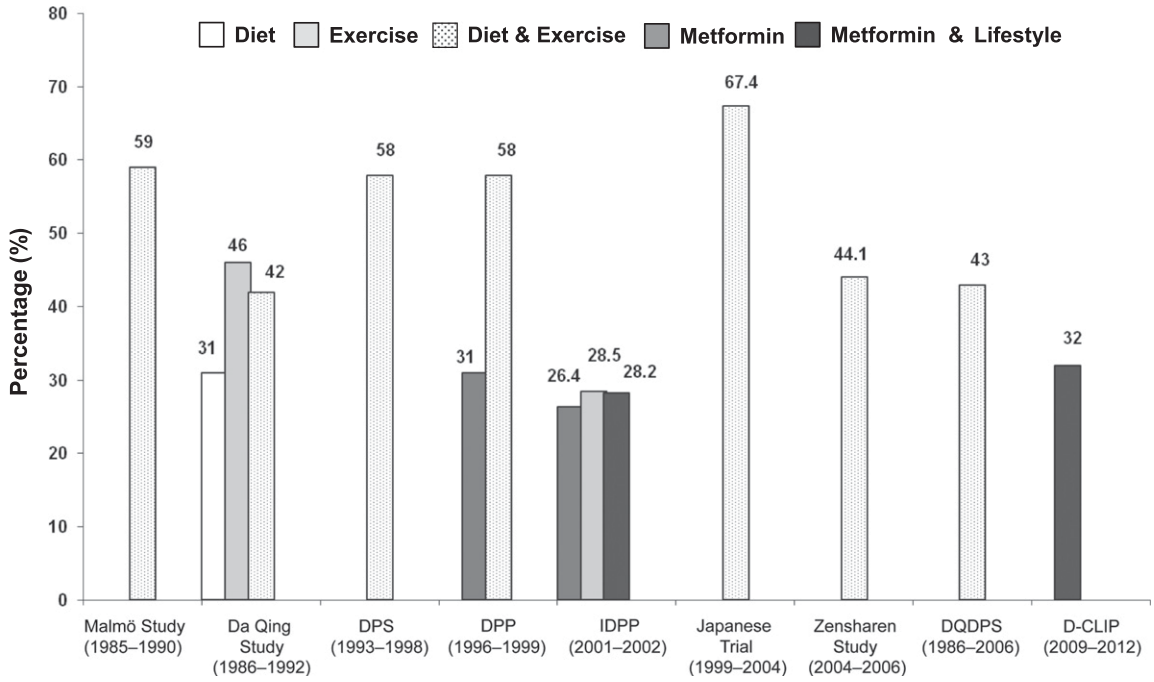

Figure 3—Evidence for lifestyle intervention and prevention of T2D (57–62,64–66).

true in countries that do not have a robust publicly funded health care system or widespread availability of health insurance. It is all the more worrying that, even in developing countries, the diabetes epidemic is now spreading to the poorer sections of society, who can least afford to pay for its treatment.

The need of the hour, therefore, is to use our knowledge of the etiopathogenesis of diabetes to design cost-effective strategies to prevent susceptible individuals from developing diabetes. While economic development and the consequent prosperity are unquestionably to be welcomed, the accompanying deleterious changes in lifestyle need to be identified and addressed. Multisectoral efforts are needed to improve physical activity levels and dietary quality in newly developed nations. Improvement of antenatal care and maternal nutrition can be expected to reduce risk of diabetes in the offspring. Cost-effective and validated tools such as Diabetes Risk Scores can be used to identify individuals who are candidates for diabetes screening, ensuring early diagnosis of diabetes in those at the highest risk (67).

CONCLUSIONS

T2D can no longer be considered a disease of affluence or of developed nations, with more than 60% of all individuals with the disorder residing outside the developed countries. China and India are the two major epicenters of the diabetes epidemic, but sub-Saharan Africa, Oceania, and Latin America also have large (and rapidly increasing) numbers of people with diabetes. The increase in prevalence of diabetes is intimately linked to economic development and the subsequent changes in lifestyle that promote an obesogenic environment. Although the link between obesity and T2D is linear, certain ethnic groups (such as Asian Indians) develop T2D at relatively low levels of BMI. Defects in β-cell function, mediated by genetic or early-life influences, may underlie many of these cases of "lean" T2D. A thorough understanding of the etiopathogenesis of diabetes in various ethnic groups is essential to plan the most cost-effective therapeutic and preventive strategies. It is unlikely that "one size" would fit all. When translating the results of international trials to middle- and low-income countries, low-cost, culturally adaptable solutions will have to be used along with community empowerment if the increasing diabetes epidemic is to be halted in its tracks, or at least slowed down. The time to act is now!

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