Epidemiology in diabetes mellitus and cardiovascular disease

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As one of the leading causes of death in the USA, diabetes mellitus (DM) has become an epidemic over the past few decades. Despite the high prevalence of diagnosed DM, close to half of all people with DM are unaware of their disease. The risk of type 2 DM is determined by interplay of genetic and metabolic factors. Patients with type 2 DM have a higher risk of death from cardiovascular causes compared with their nondiabetic counterparts, and the mortality rate of DM associated cardiovascular disease is different among ethnicity groups and sex groups. Because of its adverse effect on people's health, DM also imposes an economic burden on individuals and households affected, as well as on the healthcare system. Current guidelines for cardiovascular disease prevention have focused on lifestyle

management, blood pressure control, lipid control, blood glucose control, antiplatelet agent use, and tobacco use cessation. *Cardiovasc Endocrinol* 6:8–16 Copyright © 2017 Wolters Kluwer Health, Inc. All rights reserved.

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Introduction

Diabetes mellitus (DM) is one of the largest global health emergencies of the 21st century and the seventh leading cause of death in the USA in 2010 [1]. DM is also a major risk factor for cardiovascular disease (CVD), which is the most common cause of death among adults with DM [2]. Besides the well-recognized microvascular complications of DM, such as nephropathy and retinopathy, there is a growing epidemic of macrovascular complications, including diseases of coronary arteries, peripheral arteries, and carotid vessels, particularly in the burgeoning type 2 DM populations [3]. The purpose of this paper is to review current DM epidemiology and its major complication of CVD, in respect of prevalence, risk factors, morbidity and mortality, economic burden, and current prevention guidelines.

Prevalence of diabetes mellitus

DM is a group of metabolic diseases marked by high levels of blood glucose resulting from problems in insulin production, insulin use, or both. WHO has announced an increasing prevalence of DM over the past few decades in different parts of the world (Fig. 1). The most recent data from the International Diabetes Federation indicated that an estimated 415 million adults aged 20–79 years worldwide have DM in 2015 and the number will project to 642 million in 2040, with the prevalence increasing from 8.8 to 10.4%. Despite the high prevalence of diagnosed DM, as many as 193 million people representing close to half of all people with DM are unaware of their disease. Regionally, the age-adjusted prevalence of DM is 3.8% in Africa, 7.3% in Europe, 10.7% in Middle East and North Africa, 11.5% in North

America and Caribbean, 9.6% in South and Central America, 9.1% in Southeast Asia, and 8.8% in Western Pacific. China, India, and the USA remain the top three countries with the largest number of people with DM.

The three main types of DM are type 1 DM, type 2 DM, and gestational DM. Type 1 DM is one of the most common chronic autoimmune disorders that typically manifests in early childhood and adolescence [5]. The age-adjusted incidence of type 1 DM varies widely between populations from as low as 0.1 per 100 000 people per year in China to more than 40 in Finland [6]. According to Juvenile Diabetes Research Foundation, around 40 000 people are diagnosed with type 1 DM every year in the USA [7]. Although type 1 DM is less common, it still accounts for ~5% of all diagnosed cases of DM [1]. Gestational DM is a form of glucose intolerance diagnosed during the second or third trimester of pregnancy. Women with gestational DM have substantial future risk of developing type 2 DM, with a 7.4-fold increased risk and incidence estimates of 35–60% in the two decades following delivery [8–11]. Meanwhile, the intrauterine diabetic environment conveys a high risk for the development of DM and obesity in offspring, in addition to any effect that is transmitted genetically [12].

Type 2 DM is the most common type and accounts for about 90–95% of all diagnosed cases of DM [1]. The number of people with type 2 DM is growing rapidly worldwide. This rise is associated with aging population, economic development, increasing urbanization, less healthy diets, and reduced physical activity [13]. Many people remain undiagnosed because there are often few symptoms during the early years of type 2 DM or

Fig. 1

Trends in prevalence of diabetes, 1980–2014, by WHO region. Source: WHO [4].

symptoms that do occur may not be recognized as being related to DM. However, during this time the body is already being damaged by excess blood glucose, and as a result many people are affected by complications even before diagnosed with type 2 DM. Consistently high blood glucose levels can lead to serious diseases associated with heart and blood vessels, eyes, kidneys, and nerves. The CVDs that accompany DM include angina pectoris, myocardial infarction, stroke, peripheral artery disease (PAD), and congestive heart failure (CHD).

Risk factors for diabetes mellitus and cardiovascular disease

The risk of type 2 DM is determined by interplay of genetic and metabolic factors. Ethnicity, family history of DM, and previous gestational DM combine with older age, overweight and obesity, unhealthy diet, physical inactivity, and smoking to increase risk.

Excess body fat is commonly associated with insulin resistance [14] and is a major risk factor for the development of type 2 DM and CVD [15]. Compared with adults with normal weight, adults with a BMI of 40 or higher had an odds ratio of 7.37 [95% confidence interval (CI): 6.39–8.50] for diagnosed DM, 6.38 (95% CI: 5.67–7.17) for high blood pressure (BP), and 1.88 (95% CI: 1.67–2.13) for high cholesterol levels [16]. However, evidence from some prospective studies in Asia suggests that type 2 DM occurs in individuals with lower BMI (≥ 25 kg/m²) than people with the same disease in

developed countries [17–19]. Thus, although Asians have lower BMI levels than people of European decent, they have a higher prevalence of type 2 DM [20]. The Behavioral Risk Factor Surveillance System shows that similar proportions of Asian and non-Hispanic white Americans report having DM, but after accounting for the lower BMI of Asians the adjusted prevalence of DM is 60% higher in Asian Americans [21]. India has the lowest rate of obesity in the world [22], but the prevalence of type 2 DM increased 10-fold over the past 40 years [23], with 67 million people having DM in 2014 and the number will project to double by 2030 [24].

A sedentary lifestyle should be considered another important modifiable risk factor for type 2 DM and CVD in the general population. In the Women's Health Study, a 6.9-year follow-up of nearly 38 000 US female health professionals aged 45 years and older showed that participants who reported walking 2–3 h/week were 34% less likely to develop DM than women who reported not walking [25], and walking at least 1 h/week was associated with a 50% reduction in CHD risk over 7 years in individuals reporting no vigorous physical activities such as running or bicycling [26]. In the Kuipio Ischemic Heart Disease Risk Factor Study, which followed 897 Finnish men aged 42–60 years old for 4.2 years, respondents who performed at least 40 min/week of leisure-time physical activity with an intensity of at least 5.5 metabolic equivalents (exercise intensity measurement) were 56% less likely to develop DM than men who did not achieve

this level of physical activity, after factoring out the effects of BMI and other covariates [27]. In an 8-year follow-up of 2449 adults with DM in the National Health Interview Survey, walking at least 2 h/week was associated with a 41% reduction in CVD mortality compared with not walking [28].

Dyslipidemia and hypertension are recognized as prominent risk factors for CVD as well [29,30]. Blood lipids are fundamentally involved in the atherosclerotic process in both diabetic and nondiabetic individuals. Lipid abnormalities including high levels of low-density lipoprotein cholesterol (LDL-C), elevated triglycerides, and low levels of high-density lipoprotein cholesterol (HDL-C) are associated with an increased risk of cardiovascular events. One study among 371 221 veterans showed that almost two-thirds (66.3%) of diabetic patients also have dyslipidemia and hypertension, which is more than twice the rate (23.8%) of concomitant hypertension and dyslipidemia observed in the nondiabetic veterans [31]. Lowering the level of LDL and increasing the level of HDL is an attractive target for the reduction of CHD in DM [32]. The Strong Heart Study investigating American Indians population concluded that a 0.26 mmol/L increase in LDL-C was associated with a 12% increase in cardiovascular risk, and a 0.26 mmol/L decrease in HDL-C was associated with a 22% increase in risk. [33]. The largest analysis to date, the Emerging Risk Factor Collaboration [34] in more than 300 000 individuals without CVD at baseline, provided a strong evidence in the association between lipids and CVD event. As for hypertension, a prospective cohort study examining 12 550 adults [35] indicates that the development of type 2 DM was almost 2.5 times as likely in persons with hypertension than in their normotensive counterparts, which suggested that these two common chronic diseases frequently coexist. In the UK Prospective Diabetes Study, the relative benefit on CVD risk reduction was conferred in a far more powerful manner by intensive BP reduction rather than by tight glucose control [36,37], and significantly fewer diabetic microvascular and macrovascular complications and diabetic-related deaths occurred in the group with a mean BP of 144/82 mmHg compared with the group with a mean BP of 154/87 mmHg [38].

Indeed, DM has long been recognized to be an independent risk factor for CVD, and prospective studies such as Framingham, Honolulu, and San Antonio Heart Studies, as well as numerous more recent population studies in the USA and other countries, have documented the excess CVD risk in patients with DM from multiple racial and ethnic groups. Prospective studies indicate that all of the major cardiovascular risk factors, including cigarette smoking, hypertension, and high serum cholesterol, continue to act as independent contributors to CVD in patients with DM.

Morbidity and mortality of cardiovascular disease in diabetes mellitus patients

Patients with type 2 DM have a risk of death from cardiovascular causes that is two to six times that among persons without DM, and among white Americans the age-adjusted prevalence of coronary heart disease is twice as high among those with type 2 DM as among those without DM [39–42]. Main attributable causes of death in those with DM include ischemic heart disease, other heart disease, DM, malignant neoplasms, cerebrovascular disease, and pneumonia/influenza [43].

Cardiovascular death accounts for 44% of death in type 1 DM and 52% of deaths in type 2 DM [44]. In San Antonio Heart Study [45], 4875 patients were followed up for 7–8 years, and DM was significantly associated with increased all-cause mortality [relative risk (RR)=2.1, 95% CI: 1.3–3.5 in men; RR=3.2, 95% CI: 1.9–5.4 in women] and increased CVD mortality (RR=3.2, 95% CI: 1.4–7.1 in men; RR=8.5, 95% CI: 2.8–25.2 in women). The risk of heart failure increased by 40% in the presence of DM, and the age-adjusted odds ratio for the development of heart failure was 2.8 (95% CI: 2.2–3.6) in patients with DM compared with nondiabetic patients. In the National Health and Nutrition Examination Survey cohort [29], ischemic heart disease mortality increased 11% from the 1971 to 1975 cohort followed up through 1986 compared with the 1982–1984 cohort followed up through 1992. At a population level, 26.3% of strokes are attributable to DM [46], and a greater than two-fold risk for ischemic stroke has been observed consistently among those with DM, with a 50% increased risk of hemorrhagic stroke [47]. There is also strong evidence that the mortality rate after MI is higher in diabetic patients than in nondiabetic patients [48–51]. The cardiovascular death rate could be 4.4-fold increased in those diabetic patients presenting none of the classical risk factors (hypertension, hypercholesterinemia, or smoking) compared with age-matched control individuals [52].

However, many studies have argued whether DM is a CHD or CVD risk equivalent. Evidence supporting DM as a CHD equivalent [53,54] shows that DM without prior MI and prior MI without DM indicate similar risk for CHD death in men and women [55]. Compared with women with no DM or CHD at baseline, age-adjusted RR of overall mortality was 3.39 (95% CI: 3.08–3.73) for women with a history of DM and no CHD at baseline, and 3.00 (95% CI: 2.50–3.60) for women with a history of CHD and no DM at baseline [56]. Although some studies reported opposite results, one meta-analysis [57] of 13 studies involving 45 108 patients showed many of those with DM to have lower CHD event rates than persons with known CHD, and another study [58] describing global CVD risk in US adults also indicated that nearly half of women and a third of men with DM are at a low or intermediate CVD risk. Findings [59] from National

Health and Nutrition Examination Survey show the mean Framingham and UKPDS 10-year risk for CHD to be 12.6 and 11.6%, respectively, also confirming that many persons with DM do not reach CHD risk equivalent.

PAD is another manifestation of generalized atherosclerosis, and epidemiological evidence has confirmed an association between DM and increased prevalence of PAD [60,61]. Individuals with DM have a two- to four-fold increase in the rates of PAD [62] and have rates of abnormal ankle-brachial indices ranging from 11.9 to 16% [63,64]. Patients with DM more commonly develop the systematic forms of PAD, intermittent claudication, and amputation [65]. DM is also the most common cause of nontraumatic lower limb amputation in the US [66], and more than 80 000 lower limb amputations in DM patients are performed each year alone [67]. One study [68] using data from Action in Diabetes and Vascular Disease: Preterax and Diamicon Modified Release Controlled Evaluation (ADVANCE) trial indicated that patients with major PAD had increased rates of all-cause mortality [hazard ratio (HR): 1.35, 95% CI: 1.15–1.60] and major macrovascular events (HR: 1.47, 95% CI: 1.23–1.75).

There are, however, ethnic differences in CVD and DM prevalence by race/ethnicity. According to Heart Disease and Stroke Statistics 2016 Update [2], the prevalence of heart disease (includes CHD, angina pectoris, MI, or any other heart condition or disease) among non-Hispanic White, Black or African Americans, Hispanics or Latinos, Asians, American Indians or Alaska Natives, and native Hawaiians or other Pacific Islanders were 11.1, 10.3, 7.8, 6.0, 13.7, and 19.1%, respectively. Other studies concluded a similar finding that after adjusting for multiple cardiovascular risks and confounders African Americans, Asians, and Hispanics had a lower risk of incident CVD than non-Hispanic White [69,70]. However, the prevalence of DM was significantly higher among South Asians (those who live in or have their roots in India, Pakistan, Sri Lanka, Bangladesh, Nepal, Bhutan, or the Maldives) compared with other US ethnic groups [71], and India alone accounts for a fifth of the CHD deaths worldwide [72]. A recent randomized population-based study [73] of South Asians in the USA reported an overall type 2 DM prevalence of 17.4%, and the rate greatly exceeded those in non-Hispanic White (7.8%), non-Hispanic Black (13%), and Hispanic Latinos (10.2%). In absolute terms, South Asia had the largest estimated increase in deaths from cardiovascular disease, reporting more than 1.7 million more deaths in 2013 than in 1990, with the change representing an increase of 97.4% [74].

Several studies have shown that DM is a stronger risk factor in women compared with men [75]. Early Rancho Bernardo Study publications noted that men with DM had a 2.4-fold excess risk of ischemic heart disease death compared with men without DM, whereas women who

had DM had a 3.5-fold excess risk compared with women without DM [76]. There is a three-fold excess fatal CHD risk in women with type 2 DM compared with non-diabetic women [77], with a higher adjusted HR of fatal CHD in women with DM (HR: 14.74; 95% CI: 6.16–35.27) compared with men with DM (HR: 3.77; 95% CI: 2.52–5.65) [41]. MI occurs earlier in women with DM compared with men [78], with higher mortality from the MI [79]. In a comprehensive systematic review and meta-analysis using data from 64 cohorts including more than 12 000 strokes, the overall adjusted RR for total stroke associated with DM was 2.28 (95% CI: 1.93–2.69) for women and 1.83 (95% CI: 1.60–2.08) for men [80]. In an observational Japanese study comparing 730 women and men with PAD, women were older and more likely to have DM and hyperlipidemia, as well as more severe PAD [81]. One possible explanation for the sex difference in CVD morbidity and mortality is that high bioavailable testosterone may be harmful for women because of its association with obesity, DM, and metabolic syndrome components [82–84], whereas low total testosterone effects in men may be enacted through different mechanisms.

Economic burden

The healthcare spending continues to outpace gross domestic product (GDP) since 1970. The total healthcare spending was 1.4 trillion in 2001 (14.1% of GDP) and over \$2.2 trillion in 2007 (16.7% of GDP) [85]. It is projected that by 2017 the USA will spend \$4.3 trillion (19.5% of GDP) on healthcare [86].

Because of its adverse effect on people's health, DM also imposes an economic burden on individuals and households affected, as well as on the healthcare system. It is well documented that DM places a substantial burden on the economy of the USA, and the cost associated with DM has increased from \$176 billion in 2007 to \$245 billion in 2012, including \$176 billion direct medical costs and \$69 billion indirect costs because of related disability and lost productivity [87]. Spending on DM accounts for more than one in five US healthcare dollars, and people with DM spend 2.3 times more on healthcare services [87]. The largest components of medical expenditures attributed to DM are hospital inpatient care (43% of total cost), prescription medication to treat complications of DM (18%), antidiabetic agents and DM supplies (12%), physician office visits (9%), and nursing/residential facility stays (8%) [87].

However, CVD costs more than any other diagnostic group, for its annual costs of 316.6 billion in 2011–2012 [2]. Studies have demonstrated that CVD accounts for a large proportion of medical expenditure in diabetic patients [88–90], and the cost was more than double for patients with both CVD and DM (\$10 172/person/year) compared with DM alone (\$4402/person/year) [91]. Specific type of CVD such as heart failure not only has an

immediate influence on costs in the year of diagnosis but also has a continuing influence on costs in subsequent years [92]. The mean annual total cost for patients with both heart failure and DM was triple as the cost for patients with DM alone (\$32 676 vs. \$10 566) [93].

Most patients with type 2 DM require drug therapy in addition to that for glycemic control, including medications prescribed for vascular risk factors. In the USA, the DM attributable cost of outpatient medications, excluding insulin and oral hypoglycemic agents, was estimated to be \$5.5 billion in 2002, or 6% of all DM-related healthcare expenditure [94]. One study [95] reported that nonblood-glucose-lowering medications accounted for 75% of all prescription medication costs, and one-third were attributable to DM. The median annual cost of nonblood-glucose-lowering medications per patient increased from \$220 to \$429 over the follow-up 4 years ($P < 0.001$), whereas the DM attributable contribution increased from \$31 to \$159 per patient ($P < 0.001$).

Cardiovascular disease prevention in persons with diabetes mellitus

The American Heart Association (AHA) and the American Diabetes Association (ADA) have each published guidelines for cardiovascular disease prevention. According to comprehensive risk assessment, primary prevention for CVD in people with DM focused on lifestyle management, BP control, lipid control, blood glucose control, antiplatelet agents use, and tobacco use cessation [96].

Lifestyle measures such as medical nutrition therapy and aerobic exercise have been demonstrated to modify lipids and reduce BP and are integral to the management of glycemia and weight control [97,98]. Eating patterns such as the Dietary Approaches to Stop Hypertension, Mediterranean, vegetarian, low-fat, or low carbohydrate diet are effective for controlling glycemia and lowering CVD risk factors [99]. There is no 'ideal' conclusive eating pattern that is expected to benefit all individuals with DM [100]. The stated goals of nutrition therapy for adults with DM are to attain individualized glycemic and lipid levels, maintain healthy body weight, and to prevent or delay DM complications [99]. Assisting with weight loss of 5–7%, at least 150 min of moderate-intensity aerobic physical activity or at least 75 min of vigorous aerobic exercise per week, spread over at least 3 days/week, with no more than 2 consecutive days without activity is recommended by ADA [101]. The most notable recommendation from recent guideline is a shift from every 90 min to every 30 min of sedentary activities for 3 min or more of light activity, such as walking, leg extensions, or overhead arm stretches, to improve blood sugar management in DM patients [101].

The impact of elevated BP is a risk factor for both microvascular and macrovascular disease in DM;

however, the question of what systolic and diastolic BP goals should be targeted is not completely answered by currently available outcome trial. Prior guidelines had suggested that the goal BP in patients with DM was less than 130/80 mmHg [102,103]. The Hypertension Optimal Treatment trial randomized patients with diastolic BP of 100–115 mmHg to diastolic BP targets of up to 90, 85, and 80 mmHg. In the group randomized to a diastolic target of up to 80 mmHg, the risk of major cardiovascular events was halved compared with the group with a target of up to 90 mmHg [104]. The Appropriate Blood Pressure Control in Diabetes trial indicated that an intensive BP control (mean BP: 128/75 mmHg) slowed the progression to diabetic nephropathy, decreased the progression of diabetic retinopathy, and diminished the incidence of stroke [105]. It was not until the findings of Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial that challenging the prevailing concept that the lower the BP the better. ACCORD confirmed that patients with type 2 DM had no significant cardiovascular benefit and experienced more drug side effects at a mean attained systolic pressure of 119.3 compared with 133.5 mmHg [106]. A meta-analysis of randomized trials of adults with type 2 DM comparing intensive blood pressure targets (upper limit of 130/80 mmHg) with standard targets (upper limit of 140–160/85–100 mmHg) found no significant reduction in mortality or nonfatal myocardial infarction. Major guidelines published after ACCORD raised the blood pressure target in diabetic patients to less than 140/90 mmHg [107–109].

LDL cholesterol is identified and is the primary target of lipid-lowering therapy by both ADA and AHA. The new American College of Cardiology/AHA cholesterol guidelines indicate that patients with DM between 40 and 75 years of age with LDL-C between 70 and 189 mg/dL should be treated with a moderate-intensity statin [110]. Studies showed that a 33–40% reduction in LDL cholesterol is associated with a 31–37% reduction in combined cardiovascular end points [111,112]. A meta-analysis involving 18 686 individuals with DM demonstrated a 21% proportional reduction in major vascular events per 1 mmol/L reduction in LDL-C (RR: 0.79, 95% CI: 0.72–0.86) [113]. In individuals with DM who are over the age of 40 years, without overt CVD, but with one or more major CVD risk factors (cigarette smoking, hypertension, low HDL-C < 40 mg/dL and family history of premature CHD), the primary goal is an LDL-C level of less than 100 mg/dL [110].

Certainly, glucose control is crucial for diabetic patients and it also reduces microvascular complications. After adjustment for other CVD risk factors, an increase of 1% in A1c was associated with an increased risk of 18% in CVD events [114] and 37% in retinopathy or renal failure [115]. The uncertainty of effects of more intensive glycemic control on CVD outcomes was addressed by three large trials among DM patients: the ACCORD trial [116],

the ADVANCE trial [117], and the Veterans Affairs Diabetes Trial [118]. All three studied type 2 DM elder patients aged 60–68 years with known CVD or CVD risk factors to compare the effects of two levels of glycemic control (median A1c: 6.4–6.9% in the intensive arms versus 7.0–8.4% in the standard arms) on macrovascular outcomes. However, none of these trials could demonstrate any significant reduction in the primary combined cardiovascular end points. Thus, the ADA recommends an A1c target of less than 7.0% in general, but suggests targeting an A1c as close to normal as possible without causing significant hypoglycemia in individual patients [119,120].

Antiplatelet agent (aspirin) is widely regarded as the most effective intervention in reducing CVD [121,122], but the use of aspirin for the primary prevention of CVD events in patients with DM remains controversial. Currently available evidence on aspirin for CVD prevention includes three trials [123–125] conducted specifically in DM patients and six other trials [104,126–130] in general population, and no single trial provides definitive results. A meta-analysis containing data from all nine trials found that aspirin was associated with a 9% decrease in risk of CHD events (nonfatal and fatal MI) (RR: 0.91, 95% CI: 0.79–1.05) and a 10% decrease in the risk of stroke (RR: 0.90, 95% CI: 0.71–1.13), but neither was statistically significant [131]. The most recent guidelines [120] suggest aspirin therapy for primary prevention in patients with DM who have a 10-year risk of CVD greater than 10%. This also includes most men older than 50 years of age and most women older than 60 years of age who have at least one additional risk factor (family history of CVD, hypertension, smoking, dyslipidemia, or albuminuria). Aspirin should not be recommended for CVD prevention in men younger than 50 years of age or most women younger than 60 years of age who are at a low risk for CVD (10-year risk <5%) because the increased bleeding risk likely offsets the potential benefit of aspirin treatment.

Smoking is another modifiable risk factor for macrovascular disease both in general population and for patients with DM [132,133]. Smoking cessation with a long-term follow-up demonstrated a reduction in mortality rate with a trend toward reduction of CVD deaths [134]. All patients with DM should be advised to quit cigarette smoking.

Conclusion

The prevalence of DM is increasing rapidly worldwide and not only the disease itself but also its major complications, CVDs, throw a big threat to human being. Appropriate prevention should be conducted to benefit patients' life quality and release huge economic burden for the country.

Acknowledgements

Conflicts of interest

There are no conflicts of interest.

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