The Dual Disease Burden of Hypertension and Diabetes

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Abstract

Hypertension and diabetes are among the most common non-communicable diseases worldwide with a global prevalence of 22% and 9%, respectively. In Singapore, the prevalence of both diseases is higher at 23.5% and 11.3%, respectively, and similar trends are evident in much of Asia. There is an even higher prevalence of hypertension among diabetics, likely contributed to by inappropriate activation of the renin–angiotensin–aldosterone system (RAAS), altered sodium transport, a complex interaction of hyperinsulinemia and insulin resistance with obesity, RAAS, arterial baroreceptor reflex impairment, leading to an activated sympathetic nervous system, and the coexistence of kidney damage accelerated by hypertension. While angiotensin-converting enzyme inhibitors (ACEi) or angiotensin II receptor blockers remain the mainstay of treatment for the comorbidities of hypertension and diabetes, various guidelines are inconsistent with blood pressure thresholds and treatment goals. Shared lifestyle factors in the etiology of hypertension and diabetes do provide further opportunities for non-pharmacologic intervention. Taken together, strategies that incorporate early diagnosis of diabetes and hypertension and its complications, disease self-management and education, and optimal medical and lifestyle management will reduce the burden of complications from these dual conditions.

Key words: Cardiovascular disease, diabetic kidney disease, renin–angiotensin–aldosterone system, vascular complication

Introduction

Hypertension and diabetes are common chronic diseases and contribute to significant morbidity and mortality worldwide. Hypertension is estimated to have caused 10.7 million deaths globally in 2015.¹ If left uncontrolled, hypertension causes stroke, ischemic heart disease, cardiac failure, atrial fibrillation and flutter, dementia and cognitive impairment, chronic kidney disease (CKD), and end-stage renal failure (ESRF). Diabetes is also a well-recognized cause of premature death and disability, increasing the risk of cardiovascular disease, kidney failure, blindness, and lower-limb amputation. Diabetes was considered directly responsible for 1.5 million deaths in 2015.¹ Its impact is expected to increase in the future as in recent decades, the prevalence of diabetes has been increasing globally and has been particularly accelerated in low- and middle-income countries. Further, hypertension and diabetes are among the most common non-communicable diseases across developed to developing countries, from Europe to Asia and to Africa, and from the elderly to the young. Driven by economic development, nutrition transition, and increasingly sedentary lifestyles, we face a threat from the dual disease burden of both hypertension and diabetes globally.

As in much of the developed world, non-communicable diseases are the leading cause of death in Singapore, with diseases of the heart and hypertensive diseases; cerebrovascular diseases (e.g., stroke); kidney (CKD) and disorders of the urinary system; and diabetes representing 2nd, 4th, 5th, and 6th leading causes of death in 2016.² Diabetes has an additive impact on mortality by contributing to 1 of 2 heart attacks, 2 in 3 cases of kidney failure, and 2 of 5 strokes in Singapore.³

Apart from the association of hypertension and diabetes with mortality through complications as listed above, both these conditions contribute significantly to disability-adjusted life years (DALY), a measure of a combination of years of life lost due to premature mortality, and from years lived with disability (any short-term or long-term health loss). In Singapore, a total of 399,675 life years were lost due to all mortality and ill-health in 2010. Diabetes

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Prevalence of Hypertension and Diabetes in Singapore and Asia

The global prevalence of raised blood pressure (defined as systolic and/or diastolic blood pressure (DBP) ≥140/90 mmHg) in adults aged 18 years and above was around 22% in 2014. The global prevalence of diabetes (defined as a fasting plasma glucose value >7.0 mmol/L [126 mg/dl] or being on medication for raised blood glucose) was estimated to be 9% in 2014. Of note, the prevalence of diabetes has increased exponentially throughout the world, with that among adults over 18 years of age increasing from 4.7% in 1980 to 8.5% in 2014. In Asia, the prevalence of hypertension and diabetes from Singapore, Malaysia, Japan, and Thailand is summarized and compared in Table 1.

As noted [Table 1], in Singapore, the prevalence of hypertension and diabetes was both higher than the global average at 23.5% and 11.3%, respectively. Trends over the years [Table 2] demonstrate that although the prevalence of hypertension remains steady, that of diabetes has increased significantly, and is likely still underestimated considering inclusion of only residents aged 18–69 years in the survey.

Prevalence of Hypertension among Diabetics

Hypertension and diabetes are intertwined conditions, and the prevalence of hypertension among diabetics is consistently higher than that in the general population. In the United States, among adults aged 18 years or older with diagnosed diabetes, 73.6% (95% confidence interval [CI], 69.9%–77.1%) had systolic blood pressure (SBP) of 140 mm Hg or higher or DBP of 90 mm Hg or higher, or were on prescription medications for high blood pressure. In Korea, the prevalence of hypertension in adults with diagnosed diabetes was 55.5%, based on the Fourth Korea National Health and Nutrition Examination Survey; as compared with the general population, the prevalence of hypertension among adults with diagnosed diabetes was higher in all age groups in both genders. In Japan, one study showed that approximately 50% of diabetic patients had hypertension. In Thailand, approximately half the diabetics (49.0%, 95% CI 45.6–52.5) had hypertension and 14.4% (95% CI 13.0–16.0) of hypertensives had diabetes. In Singapore, 86.4% of patients self-reported to have diabetes had hypertension according to one study. In an enterprise-wide diabetes study in Singapore at the National Healthcare Group, one of two public health-care clusters in Singapore spanning across three acute hospitals, nine primary care polyclinics, and national specialty centers serving 2.2 million population, among diabetics under primary care, only 1.5% was considered “diabetes only,” 5.1% was “diabetes and hypertension only,” and 77.7% was “diabetes with hypertension and dyslipidemia.” In other words, 82.8% of diabetics in primary care had hypertension and 79.7% of diabetics under specialists care had hypertension. This high prevalence of hypertension among diabetics, hence, portends a dual risk of end organ damage with its attendant morbidity and mortality.

Pathophysiology of Hypertension in Diabetes and their Relationship to End Organ Damage

Several pathophysiological mechanisms likely contribute to the development of hypertension in diabetes. The renin–angiotensin–aldosterone system (RAAS) may be activated leading to hypertension directly mediated by Angiotensin II. In addition, a complex interaction between obesity, hyperinsulinemia, and insulin resistance, impairment in arterial baroreceptor control...
Table 2: Prevalence of hypertension and diabetes from 1992 to 2010 in Singapore

<table>
<thead>
<tr>
<th>Year</th>
<th>Hypertension (%)</th>
<th>Diabetes (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1992</td>
<td>22.2</td>
<td>8.6</td>
</tr>
<tr>
<td>1998</td>
<td>27.3</td>
<td>9</td>
</tr>
<tr>
<td>2004</td>
<td>24.9</td>
<td>8.2</td>
</tr>
<tr>
<td>2010</td>
<td>23.5</td>
<td>11.3</td>
</tr>
</tbody>
</table>

and an activated RAAS may enhance sympathetic nervous activity and lead to increased peripheral vascular resistance and hypertension.[22] Renal sodium handling differs in diabetes due to upregulation of sodium transporters in the kidneys thereby upregulating RAAS.[21] Moreover, insulin stimulates obesity through fat accumulation, and this leads to obesity-induced hypertension in association with diabetes.[23] Chronic low-grade inflammation and oxidative stress in the adipose tissue lead to increased production of angiotensinogen and angiotensin II with consequent tissue RAAS activation. Angiotensin II exerts many of its detrimental effects through activation of the angiotensin II type 1 receptor, resulting in multiple intracellular events, including the production of reactive oxygen species, reduced insulin metabolic signaling, and proliferative and inflammatory vascular responses, all of which cause endothelial dysfunction, insulin resistance, and hypertension.[24]

The superimposition of hypertension on diabetes further aggravates microvascular and macrovascular complications through additive mechanisms that include arteriolar and capillary damage resulting subsequently in end organ damage.[25] The pathophysiology of the microvascular disease involves a combination of direct glucose-mediated endothelial damage, oxidative stress due to superoxide overproduction, and the production of sorbitol and advanced glycation end-products.[26] In combination with hypertension, these metabolic injuries cause altered blood flow and change in endothelial permeability, extravasation protein deposition, and coagulation resulting in organ dysfunction.[27] These microvascular complications are best exemplified in diabetic kidney disease (DKD), in which initial local renal damage mediated by metabolic effects from uncontrolled hyperglycemia, compounded by hemodynamic effects from an activated RAAS and impaired afferent arteriolar autoregulation contribute to renal damage. Over time, this local renal damage results in decreased glomerular filtration rate (GFR) and albuminuria. As GFR is reduced, there is further impairment in sodium excretion resulting in increased extracellular volume. In addition, oxidative stress is increased in kidney disease, leading to further endothelial cell dysfunction and vasoconstriction. Systemic RAAS is not appropriately suppressed despite the increased extracellular volume. Angiotensin II increases vasoconstriction through increases in oxidative stress through induction of NADPH oxidase and directly through binding to vascular smooth muscle cells.[28]

These pathophysiologic interactions of hypertension and diabetes underpin the clinical link between hypertension and diabetes in relation to outcomes, especially with regard to renal and cardiovascular damage. In the UK Prospective Diabetes Study, blood pressure control ameliorated cardiovascular complications in patients with type 2 diabetes: Each 10 mmHg decrease in mean SBP was associated with 12% reduction in the risk for any complication related to diabetes, 15% reduction in deaths related to diabetes, and 11% reduction in myocardial infarction.[29] There was also a 13% reduction in microvascular complications with improved blood pressure control in this study; other studies have demonstrated similar benefits with blood pressure control and progression of DKD[30] and retinopathy.[31] The pathophysiologic link between hypertension and diabetes for macrovascular disease includes possibly direct effects of glucose, activation of protein kinase C, endothelial dysfunction from oxidative stress, activation of athero-inflammatory cytokines, and epigenetic changes in vascular endothelial cells.[32] In relation to these macrovascular complications, patients with hypertension and concomitant diabetes, compared to non-hypertensive diabetics were found to have higher rates of cardiovascular death, myocardial infarction, angina pectoris, amputation, and stroke, and independent of other risk factors.[33]

As suggested above, the interaction of hypertension and diabetes is particularly relevant to the development of kidney damage. Globally, diabetes and hypertension are the leading causes of CKD.[34] In Singapore, the crude prevalence of CKD has been reported to be 15.6%,[35] with older age, diabetes, hypertension, and dyslipidemia significantly associated with risk for CKD. Age-standardized prevalence may have better-permitted comparisons between this prevalence in comparison to countries with high incidence of end-stage renal failure (ESRF)[30] in Asia such as Korea,[37] Japan,[38] and Taiwan.[39] From a study done in a primary care cluster in Singapore, the overall prevalence of DKD, which was defined as microalbuminuria (UACR 30–299 mg/g), macroalbuminuria (≥300 mg/g), or renal impairment (estimated glomerular filtration rate eGFR <60 mL/min per 1.73m2), was high at 52.5%. DKD prevalence within ethnic subpopulations was different: 52.2% of Chinese, 60.4% of Malays, and 45.3% of Indians had DKD, respectively. Malays had a 1.42-fold higher DKD prevalence, while Indians had a 0.86-fold lower prevalence.[35] Notably, this high incidence of DKD in primary care translates to a high incidence of ESRF due to diabetes in Singapore. From data from the Singapore Renal Registry, in 2016, among patients initiated on dialysis (including hemodialysis and peritoneal dialysis) 66.6% of ESRF was due to diabetes, this percentage having been increasing steadily from 45.9% in 1999 to 61.8% in 2009.

The high burden of CKD and ESRF due to diabetes is also reflected across the region. In a study from Asian-Pacific region, DKD was the most common cause of ESRF in 9 of the 12 countries surveyed.[40] Indeed, in international comparisons from the USRDS, 5 Asian countries (Singapore, Malaysia, Hong Kong, Korea, and Taiwan) feature among the top 10 countries with the highest incidence of ESRF due to diabetes in the world.[41] It has been suggested that Asian diabetics exhibit a higher risk
for renal complications than their non-Asian counterparts even after accounting for socioeconomic status. In an international survey, 55% of Asian and 40% of white patients with type 2 diabetes had increased albuminuria. Chinese individuals with impaired glucose tolerance were found to have a high prevalence of albuminuria, with 2-h plasma glucose level as an independent predictor. In observational studies as well as clinical trials, Asian patients with diabetes were more likely to develop ESRF than their white counterparts.\[42\]

In terms of macrovascular complications, cardiovascular disease, a major target organ damage from hypertension and diabetes, is the leading cause of non-communicable disease deaths and responsible for 17.5 million deaths, or 46.2% of the non-communicable disease deaths globally.\[7\] In Singapore, ischemic heart disease caused 17.0% of deaths, in 2016, and was the 3rd leading cause of hospitalization (3.1% discharges) in 2015.\[43\] For diabetes under primary care in 2008, cardiovascular complications were reported among 17.8%.\[20\] From the Singapore Myocardial Infarction Registry, 2016, among these patients with more advanced cardiovascular disease, 75.0% had hypertension, and 50.2% had diabetes.\[44\] Females were more likely to have hypertension (85.6% in females vs. 68.6% in males) or diabetes (59.3% in females vs. 45.8% in males) compared to males. Chinese patients had the highest proportions of hypertensives (75.3% in Chinese vs. 72.6% in Malay vs. 72.7% in Indian), while Indians had the highest proportions of diabetics (76.3% in Indian vs. 66.4% in Chinese vs. 73.0% in Malay).\[45\] As with DKD, the burden of cardiovascular disease has been steadily increasing in Singapore with the age-standardized incidence rate of acute myocardial infarction increasing from 208.9 per 100,000 population in 2007 to 220.8 per 100,000 population in 2016. In a retrospective cohort study involving 34,460 patients in Singapore to identify the prognosis of heart failure (HF) with the effect of multimorbidity focusing on type 2 DM (T2DM) and CKD, the cohort of “T2DM+CKD+HF” had a 56% higher risk of all-cause mortality (HR: 1.56, 95% CI 1.48–1.63) and a 44% higher risk of cardiovascular disease-specific mortality (HR: 1.44, 95% CI 1.32–1.56) compared with patients diagnosed with HF only.\[46\]

Other comorbidities also contribute to the end organ damage from hypertension and diabetes. Both the aging population and obesity play a role for the coexistence of hypertension and diabetes. Singapore has a high prevalence of hypertension among the elderly population as defined by age 60 years and above,\[19\] indicating that more than two-thirds of elderly populations will require antihypertensive treatment. For the elderly >75 years, the prevalence of hypertension was even higher at 83.7% in this study. Another developed country, Korea, showed similar data, with 68.7% of the population above the age of 65 having hypertension.\[47\]

Obesity is also strongly associated with hypertension and may be partly explained by the associated increased renal sodium reabsorption and blood volume expansion.\[48\] A 5% increase in body weight (equivalent to a gain of 4 kg in an average man or 3 kg in a woman) was closely correlated with a 20–30% increased odds of being hypertensive on 4-year follow-up.\[48\] Worldwide, the prevalence of obesity has nearly doubled for the past 30 years. In 2014, 11% of men and 15% of women aged 18 years and older were obese. More than 42 million children under the age of 5 years were overweight in 2013.\[37\] In Singapore, among those with body mass index (BMI) of 23.0–27.4 kg m\(^2\), the prevalence of hypertension was 76.3%, and among those with BMI of >27.5 kg m\(^2\), hypertension prevalence was even higher at 87.6%.\[19\] However, obesity not only affects the elderly but also affects young people and adolescents. In Asian and especially Southeast Asian populations, a “metabolically obese” phenotype (i.e., normal body weight with increased abdominal adiposity) has been described. Peoples of South Asian descent appear to be more prone to abdominal obesity and low muscle mass with increased insulin resistance. The increased risk of gestational diabetes, combined with exposure to poor nutrition in utero and overnutrition in later life in some populations, may contribute to the increasing diabetes epidemic through “diabetes begetting diabetes” in Asia.\[42\]

Apart from the burden of end organ damage and its associated morbidity and mortality, costs of health-care become additive with increasing burden of disease. A Canadian study showed that the unadjusted annual incremental direct all-cause health-care costs associated with CKD among cohorts with (a) diabetes only, (b) hypertension only, and (c) both diabetes and hypertension were USD11,814, USD8,412, and USD10,625, respectively.\[50\] These data highlight the need to mitigate the effects of hypertension to reduce the burden of disease.

Management of Hypertension in Diabetes to Ameliorate Risk of Progression of End Organ Damage

Apart from an agreement on the need to control blood pressure to mitigate the risks of high blood pressure on end organ damage, the various guidelines are inconsistent with blood pressure thresholds and treatment goals for control of hypertension in the diabetic patient [Table 3].

Nevertheless, there is general agreement on the preferred treatment of hypertension among diabetics. Angiotensin-converting enzyme inhibitors (ACEi) or angiotensin II receptor blockers (ARB) remain the mainstay of treatment for the comorbidity of hypertension and diabetes. The Heart Outcomes Prevention Evaluation study showed that ACE inhibition in type 2 diabetes reduced the risk of vascular complications.\[29\] American Diabetes Association suggested that an ACEi or ARB, at the maximum tolerated dose indicated for blood pressure treatment, was the recommended first-line treatment for hypertension in diabetics with urine albumin-to-creatinine ratio ≥300 mg/g creatinine or 30–299 mg/g creatinine; if one class was not tolerated and the other should be substituted.\[46\] In the 2017 ACC/AHA guideline, ACEi or ARB was recommended for anti-hypertensive therapy among stable ischemic heart disease, HF with preserved ejection fraction, CKD, diabetes, and for prevention of atrial fibrillation.\[53\] The JNC8 recommended that in the general non-black population, including those with
Table 3: Summary of guidelines for blood pressure control in diabetes

<table>
<thead>
<tr>
<th>Guidelines</th>
<th>General Population</th>
<th>Patients with DM and/or CKD</th>
<th>General Population</th>
<th>Patients with DM and/or CKD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Singapore MOH 2017[52]</td>
<td>Younger than 80 years old: ≥140/90</td>
<td>DM ≥140/80</td>
<td>Younger than 80 years old: &lt;140/90</td>
<td>DM &lt;140/80</td>
</tr>
<tr>
<td></td>
<td>80 years old and above: ≥150/90</td>
<td>CKD ≥130/80</td>
<td>80 years old and above: &lt;150/90</td>
<td>CKD &lt;130/80</td>
</tr>
<tr>
<td>ESC 2013[51]</td>
<td>≥140/90</td>
<td>DM:SBP≥140 and DBP≥85</td>
<td>&lt;140/90</td>
<td>DM: SBP&lt;140 and DBP&lt;85</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CKD: SBP≥140</td>
<td></td>
<td>CKD: SBP&lt;140; &lt;130 with severe proteinuria</td>
</tr>
<tr>
<td>JNC8 2014[54]</td>
<td>&lt;60 years old: ≥140/90</td>
<td>DM and CKD: ≥140/90</td>
<td>&lt;60 years old: &lt;140/90</td>
<td>DM and CKD: &lt;140/90</td>
</tr>
<tr>
<td></td>
<td>≥60 years old: ≥150/90</td>
<td></td>
<td>≥60 years old: &lt;150/90</td>
<td></td>
</tr>
<tr>
<td>KDIGO[55]</td>
<td>-</td>
<td>-</td>
<td>Normal to mild albuminuria: ≤140/90</td>
<td>Moderate to severe albuminuria ≤130/80</td>
</tr>
</tbody>
</table>


diabetes, initial anti-hypertensive treatment should include a thiazide-type diuretic, calcium channel blocker, ACEi, or ARB; in the population aged 18 years or older with CKD and hypertension, initial (or add-on) anti-hypertensive treatment should include an ACEi or ARB to improve kidney outcomes. This was to apply to all CKD patients with hypertension regardless of race or diabetes status.[54] In Singapore’s hypertension guideline, ACEi or ARB was recommended for HF, previous myocardial infarction, atrial fibrillation prevention, peripheral artery disease, diabetes (with or without albuminuria), and CKD.[56]

The shared lifestyle factors in the etiology of hypertension and diabetes provide an opportunity for additional non-pharmacologic intervention. Indeed, as patients with diabetes are at risk for developing hypertension and its complications, lifestyle management may help prevent or delay a diagnosis of hypertension with the need for pharmacologic therapy.[56] Lifestyle intervention consists of (1) weight loss if overweight or obese; (2) a dietary approaches to stop hypertension-style dietary pattern including reduced sodium and increased potassium intake; increased fruit and vegetable consumption; and (3) increased physical activity (moderately intense physical activity, such as 30–45 min of brisk walking most days of the week).[56] Insufficient physical activity has been shown to contribute to 3.2 million deaths and 69.3 million DALYs each year. Adults who are insufficiently physically active have a higher risk of all-cause mortality compared with those who do at least 150 min of moderate-intensity physical activity per week, or equivalent, as recommended by the World Health Organization (WHO). Globally, in 2010, 23% of adults aged 18 years and over were insufficiently physically active. Women were less active than men, and older people were less active than younger people.[57] Lifestyle intervention is remarkably effective in the primary prevention of diabetes and hypertension and is also pertinent to the prevention of downstream macrovascular complications of the two disorders. Studies have shown that an environment supporting health-promoting behaviors is more likely to enable individuals to adopt and sustain healthy lifestyles by making healthy living more accessible, natural, and effortless.[58]

As a global target, the WHO has advocated for a 25% relative reduction in overall mortality from cardiovascular diseases, a 10% relative reduction in the prevalence of insufficient physical activity, a 25% relative reduction in the prevalence of raised blood pressure, or to contain the prevalence of raised blood pressure, according to national circumstances, and to halt the rise in diabetes and obesity.[59] A recent study has shown that elevated SBP, even as defined by SBP at least 110–115 mm Hg, is a leading global health risk. The estimated annual death rate and DALYs associated with elevated SBP increased significantly over the years.[58] While this study may not translate into clinical practice guidelines for BP threshold, it nevertheless strengthens the case to lower the risk for cardiovascular diseases in those with SBP of 140 mm Hg or higher.[59]

In summary, there is much to be done to reduce the global burden of disease due to hypertension and diabetes. Increasing awareness of the risks of diabetes and hypertension among the young and middle-aged will be of benefit to prevent these dual conditions. Control of hypertension and diabetes, once diagnosed, by all effective means available, including improving uptake of healthy diets, minimizing weight gain or promoting weight loss in overweight and obese individuals, and promoting, uptake, and adherence to drugs as well as management of related complications will mitigate the adverse effects of these dual conditions and reduce end organ damage due to their macrovascular and microvascular complications.
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