Hypertension and Chronic Disease Burden

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Abstract

Lifestyle-related non-communicable chronic diseases are the major causes of morbidity and mortality in both developed and developing countries. The major inter-related chronic diseases that have an impact on the population include hypertension, obesity, dyslipidemia, diabetes, and metabolic syndrome. Hypertension is ranked third in terms of the global burden of disease. It is the predominant risk factor for mortality and makes cardiovascular disease the primary cause of death. While we can identify these conditions and complications, it is not so clear how we can assess the burden of these chronic diseases and their association with hypertension. Despite the development of detection methods and equipment, there are still no good markers to relate the diagnosis and control of hypertension before target organ damage occurs. Recent studies using retinal imaging suggest that it is possible to look at the microvasculature to assess disease burden as a result of hypertension. Hypertensive retinopathy is a complication of hypertension. The eye and kidney have similar structures, so there is a close relationship between retinal vessel changes and heart, cerebrovascular, and kidney diseases. Retinal vessel changes reflect the burden of hypertension on these chronic diseases. We can infer the damage of end organs and provide earlier information for the diagnosis and treatment of hypertension.

Key words: Cardiovascular disease, cerebrovascular disease, chronic kidney disease, hypertensive retinopathy

Introduction

Lifestyle-related non-communicable chronic diseases are the major causes of morbidity and mortality in both developed and developing countries. The major inter-related chronic diseases that have an impact on the population include hypertension, obesity, dyslipidemia, diabetes, and the metabolic syndrome.

These diseases are more prevalent worldwide. The estimated global age-standardized prevalence of hypertension in adults aged ≥20 years in 2010 was 31.1%.¹ 39% of adults aged ≥18 years were overweight in 2016, and 13% were obese.² The prevalence of dyslipidemia was 34.0% in China and 15% in America.³,⁴ The total number of diabetics aged 20–79 years worldwide was 425 million in 2017, accounting for 8.8% of the total.⁵ Even more intractable is that these diseases do not exist alone, they interact with one another and damage end organs together, such as the heart, brain, kidney, and eye. It leads to coronary artery disease (CAD), cerebrovascular disease (CVD), chronic kidney disease (CKD), and retinopathy and contributes to the overall chronic disease burden.⁶

Among these chronic diseases, hypertension is the biggest global health challenge due to its high prevalence and resulting target organs damage.⁷ Hypertension affects >1 billion people worldwide, ranking third in terms of the global burden of disease.⁷ It is the predominant risk factor for mortality in both industrialized nations and low- or middle-income countries. Hypertension is responsible for more than half of deaths from stroke, and 45% of deaths from CAD, and, alarmingly, for more than one-tenth of all global deaths.⁸ Hypertension also accounts for up to one-fifth of end-stage renal disease in developing countries⁹,¹⁰ and for CKD affecting 7% of the world’s population.⁹ Therefore, it is necessary to improve the current methods of identification, prevention, and treatment of hypertension and reduce the mortality from its complications.

While we can identify these conditions, it is not so clear how we can assess the burden of these chronic diseases (end-organ damage) and its relationship to hypertension. For example, clinical practice guidelines recommend using urine albumin-to-creatinine ratio as a means to detect target organ damage by...
hypertension but that represents a late sign of damage to the kidney.\textsuperscript{[11]} Thus, to prevent injury and guide clinical treatment, we need better tools to identify the burden of hypertension on end organs. Recent studies suggest that it is possible to use retinal imaging to examine the microvasculature and assess disease burden earlier.\textsuperscript{[12–17]}

Classically, hypertensive retinopathy (HR) is characterized by retinal vasculopathy in hypertensive patients.\textsuperscript{[18]} Many studies indicate that many of the HR signs are commonly seen in 6–15% of non-diabetic adults aged >40 years.\textsuperscript{[19]} Racial variations in the prevalence of retinopathy show that the highest rates of retinopathy are observed among Chinese (17.2%) and the lowest among White (11.9%) and Black populations (13.9%).\textsuperscript{[11]} HR is the result of a combination of many factors such as age, diabetes, and vascular endothelial dysfunction. These are also common risk factors of CAD, CVD, and CKD.\textsuperscript{[12,21]} The Keith-Wagener-Barker classification of HR in 1934 was defined as four grades of retinal signs: Grade 1 (narrowing), Grade 2 (arteriovenous crossings), Grade 3 (hemorrhages and exudates), and Grade 4 (papilledema). In 2004, Mitchell and Wong simplified the grading system by combining Grades 1 and 2. The three-grade classification accounts for the association between HR and cardiovascular risk.\textsuperscript{[14]} However, seeing retinal signs using physician observation through the performance of fundoscopic examination are non-quantitative and limited by the skills of the attending doctor. Moreover, the fidelity of optimising the management of hypertension through detecting residual endothelial dysfunction requires better tools.

In recent studies, retinal imaging and classification of findings using software were used in place of traditional fundus examination. Quantitative data acquisition and software analysis of retinal vessels in digital fundus photographs can be obtained by non-mydriatic fundus photography.\textsuperscript{[22–25]} As an example, a high-resolution fundus camera with a collection range of 45° was used to collect digital photographs of both eyes centered on the optic disc, and quantitatively analyzed in the range of 0.5–1 disc diameter from the edge of the disc using semi-automatic software, Singapore I Vessel Assessment, version 3.0, Exploit Technologies Private Limited.\textsuperscript{[26]} Based on the modified Knudtson-Parr-Hubbard formula, the diameter of the central retinal artery (central retinal arteriolar equivalent [CRAE]) and central retinal vein (central retinal venular equivalent [CRVE]) was measured. The retinal fractal dimension (Df) was measured in the range of 0.5–2 disc diameter at the edge of the optic disc.\textsuperscript{[26]} In fractal geometry, a Df is a ratio providing a statistical index of complexity comparing how detail in a pattern changes with the scale at which it is measured.\textsuperscript{[27]}

Risk Factors for HR

Many studies have shown that hypertensive patients have different degrees of retinopathy. This is related to age, the degree of elevated blood pressure, and duration of disease. HR is not only the result of hypertension but also closely related to other clinical events and, therefore, is an effective means of assessing the effects of hypertension on chronic disease burden. Risk factors for eye diseases include old age, smoking, hypertension, diabetes mellitus, metabolic syndrome, and obesity.\textsuperscript{[28,29]} They are also the risk factors for hypertension.

Association with Obesity

In adults and children, studies have shown that obesity is a risk factor for diabetic retinopathy (DR) and retinal microvascular changes.\textsuperscript{[26,30,31]} Another study shows that higher body mass index was associated with a higher incidence of diabetes but a lower incidence of DR over a 6-year period in Asian Malays and Indians.\textsuperscript{[32]} Among different eye diseases, obesity has been linked with age-related cataract, glaucoma, age-related maculopathy, and DR. However, the nature and strength of these associations remain to be determined. Studies to date have not found a consistent pattern of association between obesity and risk of age-related maculopathy or DR. Thus, although obesity may be a risk factor for many ocular conditions, the present literature is inadequate to establish any convincing associations.\textsuperscript{[33]}

Retinal Vessels and Dyslipidemia

Many clinical trials performed in diabetic patients demonstrate that dyslipidemia is an important factor in the development of DR.\textsuperscript{[34]} In the Madrid diabetes study, higher low-density lipoprotein (LDL) cholesterol level increased the 4-year risk for DR by 8-fold in Type 2 diabetes.\textsuperscript{[35]} The severity of retinopathy was positively associated with triglycerides, apolipoprotein (Apo) B, and the Apo B-to-Apo A1 ratio and negatively associated with high-density lipoprotein (HDL) cholesterol and Apo A1.\textsuperscript{[36,37]} Hence, lipid-lowering medication is an adjunctive therapy for DR. Longitudinal studies in patients with Type-1 diabetes found modest impact of increased total cholesterol and HDL on the incidence of DR.\textsuperscript{[38]} Changes in the circulating levels of lipids are not unlikely associated with DR progression.\textsuperscript{[39]} Higher levels of total and LDL cholesterol were found to be protective of any retinopathy.\textsuperscript{[40,41]}

Diabetes and the Eye

Almost all types of eye diseases can occur in patients with diabetes such as fundus bleeding, glaucoma, cataract, vitreous opacity, optic atrophy, and retinopathy. DR, which is different from HR, is characterized by microaneurysm, multiple retinal hemorrhages, microangioma, and neovascularization.\textsuperscript{[42]} It is important for physicians to be aware that some retinal microvascular signs of hypertension may also be seen in other systemic and ocular conditions such as DR and radiation retinopathy.\textsuperscript{[43]}

The incidence of DR increases with the progression of diabetes, it is 44.4% in 5 years and 56% in 7 years.\textsuperscript{[44]} In the Wisconsin epidemiologic study of DR, 3.6% of younger-onset patients (Type 1 diabetes) and 1.6% of older-onset patients (Type 2 diabetes) were legally blind. In the younger-onset group, 86% of
blindness was attributable to DR. In the older-onset group, one-third of the cases of legal blindness were due to DR.\textsuperscript{[12]} In the report of the United Kingdom prospective diabetes study, 22% of patients had developed retinopathy in 6 years. The overall prevalence was 34.6% for any DR in 22,896 individuals with diabetes.\textsuperscript{[31]}

**CAD**

In a study on hypertensive patients, HR is an independent risk factor for predicting CAD.\textsuperscript{[15]} The degree of HR is closely related to the incidence of coronary heart disease.\textsuperscript{[16]} Therefore, fundus screening is recommended as a routine examination for high-risk patients.\textsuperscript{[46]} In hypertensive patients,\textsuperscript{[14]} the degree of progressive HR is commensurate with the degree of atherosclerosis. In patients with severe hypertension, HR is associated with the thickness of aortic plaques.\textsuperscript{[11]} Therefore, HR can be used as an indicator of atherosclerosis. An Italian study of target organ damage in hypertension showed that HR progression was significantly associated with the left ventricular hypertrophy, carotid intima-media thickening, and carotid plaque formation.\textsuperscript{[47]} The Df provides a measure of the microvascular status and has been associated with mortality from coronary heart disease.\textsuperscript{[46]}

**CKD**

HR reflects the degree of kidney disease and is an important predictor of CKD.\textsuperscript{[49]} In hypertension, the severity of HR is often associated with lower glomerular filtration rate.\textsuperscript{[17]} Retinal arteriolar narrowing defined as a CRAE measurement of <144.0 \( \mu \text{m} \) is associated with CKD,\textsuperscript{[24,25]} even among Whites without diabetes and hypertension.\textsuperscript{[50]} There is a correlation between smaller CRAE and CKD,\textsuperscript{[25]} low arteriolar/venous ratio (AVR) (AVR <1.0) and serum creatinine change in 6 years,\textsuperscript{[23]} wider retinal vein (AVR <1.0), and CKD in patients with Type 1 diabetes and Type 2 diabetes.\textsuperscript{[51,52]} Retinal arteriolar narrowing may affect kidney function through microvascular damage resulting from diabetes mellitus,\textsuperscript{[52]} hypertension,\textsuperscript{[28]} and inflammation.\textsuperscript{[53]} In the Singapore prospective study program population, odds ratio comparing the smallest (Quartile 1) with the largest CRAE quartile (Quartile 4) to be 1.42 (95% confidence interval: 1.03, 1.96; \( P_{\text{trend}} = 0.02 \)) for estimated glomerular filtration rate (eGFR) of <60 mL/min/1.73 m\(^2\), and this association was evident in the absence of diabetes and hypertension, suggesting that Df could be an independent marker of CKD.\textsuperscript{[24]}

On the other hand, CKD has adverse effects on both the macrovascular and microvascular circulation. Microvascular changes in the eye can be seen in CKD patients.\textsuperscript{[12,16,54,55]} eGFR <45 mL/min/1.73 m\(^2\) was significantly associated with a 15-year risk of retinal arteriolar narrowing, suggesting that advanced stages of CKD may cause end-organ microvascular damage.\textsuperscript{[50]} In addition, the presence of higher creatinine and CKD was also associated with a significant reduction in CRVE.\textsuperscript{[46,57]}

However, some studies found that neither baseline CRVE was associated with CKD in either direction.\textsuperscript{[30]} There is no association between CRVE and CKD.\textsuperscript{[24]} Retinal venular dilation may be mediated by endothelial dysfunction\textsuperscript{[12]} and increased inflammatory stress,\textsuperscript{[46,58]} both of which are seen in CKD. Retinal venular dilation and CKD may have shared pathogenic mechanisms, but the evidence is inconclusive.

**CVD**

With antihypertensive drug treatment, there are few patients with Grade 3 HR in clinic. Most Grade 3 HR patients are younger with acute hypertension.\textsuperscript{[30]} This suggests a high risk of hypertensive encephalopathy in the future.\textsuperscript{[39]} HR is not only associated with acute stroke but also related to the occurrence and development of cerebral small vessel disease (SVD). Retinopathy suggests increased risk of SVD in the next 10 years.\textsuperscript{[50]} Especially, the relationship with lacunar infarction is higher than that of non-lacunar infarction.\textsuperscript{[61]} Among them, retinal vascular morphology induced by HR is more significant. Diffuse retinal arteriolar coarcation, arteriovenous crossover sign, and extensive venous dilatation sign were more likely to be detected in patients with acute lacunar infarction.\textsuperscript{[62]} Retinal venectasia is more associated with SVD than retinal arteriostenosis and is a risk factor independent of other CVDs.\textsuperscript{[16,63]} There is also a high association between the diameter of retinal artery and the risk of stroke,\textsuperscript{[22]} retinal microangiopathy, and the occurrence of cerebral microbleeds.\textsuperscript{[54,65]}

**Effects of Blood Pressure Lowering on Retinopathy**

In Type 2 diabetes patients, an intensive combined treatment targeting hyperglycemia, hypertension, dyslipidemia, and microalbuminuria can reduce the risk of retinopathy progression by 55% in the follow-up period of 3.8 years. However, it is not known whether combining blood pressure lowering, glucose control and improving lipid profile can reduce the risk of retinopathy to a greater extent than either treatment alone.\textsuperscript{[60]} The appropriate blood pressure control in diabetes - normotensive study showed a favorable effect, even among patients with long diabetic duration and who had a “normal” blood pressure level.\textsuperscript{[67]} In contrast, in the intensive blood pressure control arm of the ACCORD study, a trend of increased risk for DR progression by 23% at 4 years was seen. The optimal target for blood pressure against retinopathy worsening might not be “the lower the better.”\textsuperscript{[68]} Highlighting that fact that traditional limb transduced blood pressure measurements and management may not provide the full picture, and we need to consider looking at retinal vasculature changes with interventions to optimize treatment.

**Conclusions**

Hypertension and the burden of chronic disease may be characterized by retinal vascular features. The use of fundoscopy to detect HR has been regarded as a part of the standard assessment of hypertension. According to the United States
joint commission on the prevention, detection, assessment, and treatment of hypertension,(89) retinopathy may be an indication of initiation of antihypertensive treatment, even in patients with primary hypertension who do not have evidence of other target organ damages. However, routine clinical application is incomplete due to practical issues of individual clinician physical examination skill, time for dilation of pupils, and interobserver variation. It may be preferable to consider using routine retinal photography coupled with computerized grading to assist the physician in making assessments of hypertension management and its impact on chronic disease burden.

We should pay more attention to the protection from late signs of injury to the heart, kidney, brain, and other target organs by controlling hypertension and assessing control through examination of the retinal vasculature. The clinical evidence suggests that fundus photography should be performed routinely in all hypertensive patients to assess the degree of retinal vascular damage and provide early clues for preventing cardiovascular events, stroke, and kidney damage.(90) It is helpful for the diagnosis and management of hypertension and to assess chronic disease burden before overt clinical signs emerge or end-organ complications arise.

References


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