Original Article

Heart Metab. 2019;80:8-12

"Glocalization" of concomitant heart failure and diabetes in Asia

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Abstract: Asia has witnessed significant economic growth and urbanization in the past few decades. In parallel, this has increased the burden of diabetes, obesity, and heart failure (HF). Emerging data has shown that between 40% and 57% of Asian patients with HF have concomitant diabetes. Compared with their Caucasian counterparts, Asian patients with HF have a threefold higher burden of diabetes, are a decade younger, have a lower body mass index, and have greater comorbidity burden. In Asia, there are important differences in clinical correlates and left ventricular remodeling patterns associated with diabetes between HF with reduced ejection fraction (HFrEF) and HF with preserved ejection (HFpEF). Irrespective of the HF subtype, diabetes portends worse quality of life and clinical outcomes. Simultaneously, evidence for a lean diabetic phenotype in HF is accumulating in this region. Given the rich ethnic and regional diversity in Asia, one size certainly does not fit all here. Tailoring therapies and public health policies which cater to these distinct Asian phenotypes is essential for strategic management of concomitant diabetes and HF. This review will explore the epidemiology, clinical correlates, and the unique characteristics of concomitant diabetes in both HFrEF and HFpEF in Asia, with emphasis on the lean diabetic phenotype of HF. ■
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Keywords: Asia; Asian; heart failure; HFrEF; HFpEF; lean diabetes

Introduction

Asia is the most diverse continent,with a "jambalaya" of ethnosociocultural aspects. The tiger economy of Asia has fueled rapid urbanization and epidemiological shifts in the last few decades. This in turn has escalated the prevalence of metabolic syndrome and diabetes in this region. More than half of the global diabetes population (4.7 billion)[1] now resides in Asia, with South-East Asia ranking the highest (78 million).[2] Heart failure (HF) is a common complication in patients with diabetes.[3-6] Among Asian patients with HF, concomitant diabetes portends the worst clinical outcomes, for both HF with preserved ejection fraction (HFpEF) and HF with reduced ejection fraction (HFrEF),[3-6] with key differences in both HF subtypes.[6] Simultaneously, evidence for a lean diabetic phenotype in HF, which has no proven therapy, is accumulating from this region. The management expenditure of diabetes is expected to escalate to $802 billion by 2040.[7] This poses tremendous economic strain on the health care systems across Asia, which are traditionally tailored to be acute, rather than chronic care, models.

This review examines the unique characteristics of concomitant diabetes in HFrEF and HFpEF in Asia, with emphasis on the lean diabetic phenotype.

Epidemiology of diabetes with heart failure in Asia

Population-based data on concomitant diabetes and HF from Asia is scarce. Regional registries of HF patients in Asia have documented a remarkably high prevalence of diabetes in 34% to 47% Asia-wide, with the exception of Japan and Korea.[8] The Asian Sudden Cardiac Death in Heart Failure (ASIAN HF) Registry (11 Asian regions: Taiwan, China, Hong Kong, India, Thailand, Japan, Korea, Singapore, Malaysia, Indonesia, and the Philippines) reported a striking 42.5% prevalence of diabetes among patients with HF, with a threefold higher risk of developing diabetes among those from higher- (vs lower-) income countries (Singapore, Taiwan, South Korea, Hong Kong, Japan).[9] Compared with White Europeans with HF, South-East Asians have a ~threefold higher prevalence of diabetes (57% vs 24%).[3] Patients with HFpEF (ejection fraction [EF]>50%) had a higher prevalence of diabetes (45.0% vs 40.2%) than HFrEF (EF<40%).[6] *Table I* summarizes key findings among HFrEF and HFpEF patients with diabetes.

Given the sociocultural diversity and diasporic nature of this region, regional and ethnic heterogeneities are rather distinct. The prevalence of diabetes among HF patients is highest in Singapore (58.2%), followed closely by Hong Kong (56.9%), and lowest in China (22.8%).[6] Patients with HF from South East Asia (Thailand, Malaysia, Philippines, Singapore, and Indonesia) and North-East Asia (South Korea, Japan, Taiwan, Hong Kong, China) have the highest (49.3%) and lowest (31.8%) prevalence of diabetes, respectively.[9] Key ethnic differences in HF patients are also noted, with diabetes being least prevalent among Westerners (29.3%), followed by Japanese/Koreans (34.1%), Chinese (42.3%), Indians (44.2%), and most prevalent among Malays (51.9%). Among HF patients, Malay women and Indians with comorbidities (coronary artery disease and hypertension) are particularly at greater risk of developing diabetes.[5]

Comorbidities

Despite a younger age (62 vs 77 years) and lower degree of obesity (19.5% vs 24.8%), there is greater comorbidity burden among Asian patients with HF, compared with their Caucasian counterparts.[3,10] Chronic kidney disease (CKD), hypertension, and coronary artery disease are more common among diabetic patients with HFrEF and HFpEF, compared with nondiabetics of both HF subtypes.[6] Microvascular complications (nephropathy, neuropathy, retinopathy) in diabetes were more prevalent in HFpEF than HFrEF (20% vs 27%) but was similarly associated with worse composite (adjusted hazard ratio [aHR], 1.35, 95% CI, 1.04-1.76) outcomes in both HF subtypes ($P_{interaction}$= 0.112).[11]

Cardiac structural and function changes

Among Asian patients with HF, diabetes is associated with adverse cardiac remodeling (smaller left ventricular [LV] volumes and greater diastolic dysfunction [higher E:e' ratio]), compared with those without diabetes.[6] Diabetes was predominantly associated with preserved LV wall thickness and eccentric hypertrophy among patients with HFrEF, but with increased LV wall thickness and concentric hypertrophy in HFpEF.[6] Intriguingly, among Asian women with HFrEF, diabetes is associated with more concentric remodeling than in men.[4] Differences in diabetes-related remodeling mechanisms could potentially differ between both HF subtypes.[12,13] In HFrEF, diabetes causes increased apoptosis accompanied by fibrosis. In HFpEF, diabetes could potentially cause cardiomyocyte hypertrophy and stiffness following hyperinsulinemia and endothelial dysfunction owing to coronary microvascular disease.[12] Indeed, having a greater number of microvascular complications among HF patients with diabetes is associated with higher LV filling pressures in both HF subtypes, but was also associated with reduced and increased LV hypertrophy in HFrEF and HFpEF, respectively.[11]

Clinical and patient-related outcomes

In both HF subtypes in Asia, diabetes was associated with worse outcomes at 1 year, with 27% and 22% greater adjusted risks of HF rehospitalization and composite outcomes *(Table I)*.[6] Diabetes was associated with a 37% higher univariate risk for all-cause mortality, which was attenuated with multivariable adjustment,[6] possibly attribut-

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able to a short follow-up period.[14] Diabetes also portends worse composite outcomes among women with HFrEF in Asia, despite similar prevalence in both sexes *(Table I).*[4] Whether these sex differences also translate to HFpEF remains to be investigated.

Antidiabetic medication and HF outcomes

Prescription patterns of antidiabetic medications among patients with HF varies vastly across Asia. Metformin was most the commonly used in Asia, except in Japan and China,[15] the latter being possibly related

	HFrEF with diabetes (vs HFrEF without diabetes, where appropriate)	**HFpEF with diabetes** (vs HFpEF without diabetes, where appropriate)	**References**
Prevalence of diabetes (%)	40.2	45.0	6
Age (y)	61.9 (10.9)	69.4 (10.8)	6
Men (%)	75.6 - 78.2	50.3	6
Duration of diabetes (y)	9.8 (8.2)	12.0 (8.3)	6
Average BMI (kg/m^2)	25.5 (4.9)	28.4 (6.1)	6
Under- or normal weight*%	31.9	16.8	6
Obesity*%	28.1	49.4	6
Microvascular disease (neuropathy, retinopathy, and nephropathy)%	20	27	11
Correlates of diabetes	Older age, higher BMI, Indian and Malay ethnicity, middle-high income countries, presence of comorbidities (obesity, chronic kidney disease, hypertension, coronary artery disease, prior stroke, peripheral arterial disease), absence of atrial fibrillation	Higher BMI, Malay ethnicity, high-income countries, presence of comorbidities (chronic kidney disease, hypertension, coronary artery disease, microvascular disease [neuropathy, retinopathy and nephropathy])	3, 5, 6
DM medications	Metformin (most common, in absence of renal contraindication), sulfonylurea, insulin, and a dipeptidyl peptidase-4 inhibitor	Metformin, sulfonylurea, insulin, and a dipeptidyl peptidase-4 inhibitor	6, 15
HF medications	Less likely on MRA and RAASi more likely to be on diuretics or β-blockers	Less likely on MRA more likely to be on diuretics or β-blockers	6, 15
LV remodeling	Preserved LV wall thickness smaller LV end diastolic and systolic volumes higher E:e' ratio eccentric hypertrophy	Thicker left ventricular wall smaller LV end diastolic and systolic volumes higher E:e' ratio concentric hypertrophy	4, 6
Quality of life	Worse quality of life with diabetes	Worse quality of life with diabetes; Greater differences in patients with and without diabetes in HFpEF more than in HFrEF	6
Clinical outcomes	Worse 1-year outcomes in both HF subtypes (pooled analysis): all-cause mortality (adjusted hazard ratio [aHR] 1.08 95% CI 0.87-1.35, *P*=0.473), cardiovascular mortality (aHR 1.07 95% CI 0.83-1.36, *P*=0.603), composite outcomes (all-cause mortality/HF hospitalization) (aHR 1.22 95% CI 1.05-1.41, *P*=0.011), HF hospitalization (aHR 1.27 95% CI1.05-1.54, *P*=0.014) $P_{interaction}$ HF subtype and diabetes >0.05 for all		6
Sex differences	Among diabetic women (vs diabetic men): - similar prevalence of diabetes (42 vs 43%) - diabetes at a lower BMI (≥23 vs ≥27.5 kg/m^2) - Greater CKD burden (odds ratio: 1.85 vs 1.32) - Greater concentric remodeling - Worse composite outcomes (aHR 1.79 vs 1.32)	Not available	4

Table I *Key findings of concomitant diabetes among heart failure patients in Asia. BMI, body mass index; CKD, chronic kidney disease; DM, diabetes mellitus; HFrEF, heart failure with reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; LV, left ventricle; MRA, mineralocorticoid receptor antagonist; RAASi, renin-angiotensin-aldosterone system inhibitors. *WHO-recommended Asian cutoffs <18.5, 18.5-23.0, 23.0-27.5, ≥27.5 kg/m^2 for underweight, normal, overweight, and obese respectively*

to the high risk of lactic acidosis in their older patient population.[16] Paradoxically, prescription of sulfonylureas and dipeptidyl peptidase-4 (*DPP-4*) *inhibitors* were common, despite low trial evidence.[15] A number of cardiovascular outcome trials (Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes [EMPA-REG OUTCOME], Canagliflozin Cardiovascular Assessment Study [CANVAS] Program, Dapagliflozin Effect on CardiovasculAR Events [DECLARE-TIMI]) and real-world data [CVD-REAL 2], which included Asian countries, have evidenced that sodium glucose cotransporter 2 inhibitors (SGLT2is) reduce cardiovascular outcomes among diabetic patients with established cardiovascular disease.[17-19] Despite these promising results, the usage of SGLT2is is limited in Asia due to the high associated costs. Of note, appreciable ethnic differences with regards to SGLT2is also exist in published SGLT2i trials. The point estimates for Asians (HR 0.68, 95% CI: 0.48-0.95) and Caucasians (HR 0.88, 95% CI: 0.74-1.04) appeared lower than for blacks (HR 1.48, 95% CI: 0.80-2.02) in EMPA-REG OUTCOME.[19] Conversely, the point estimates for blacks (HR 0.45, 95% CI: 0.19-1.03) and Caucasians (HR 0.84, 95%CI: 0.73-0.96) appeared lower than for Asians (HR 1.08, 95% CI: 0.72-1.64) in CANVAS.[17] Notably, EMPA-REG OUTCOME, CANVAS, and DECLARE-TIMI only had 21%, 13%, and 13% Asians, respectively.[17-19] Therefore, further trial evidence on SGLT2i and a more feasible cost structure are needed for Asian patients with diabetes.

Lean-diabetic phenotype in Asia

Emerging data from the region has highlighted a *sui generis* lean diabetic phenotype among Asian patients with HF. Our rhetorical understanding of diabetes stems from lifestyle changes associated with urbanization and genetic predisposition causing higher prevalence in obesity, glucose intolerance, and subsequently insulin resistance. Lean diabetes occurring among normal or underweight individuals has challenged this conventional paradigm. Population studies from developing nations have evidenced an early age of onset, lack of ketosis upon withdrawal of insulin among malnourished individuals with poor socioeconomic status.[2,20] Compared with Europeans, Indians had strikingly higher prevalence and a three- to fourfold higher risk of diabetes without a corresponding higher risk of being overweight/obese.[21]

Accumulating evidence of lean diabetes among patients with HF is emerging from Asia.[3] In a cross-sectional comparison of Asian and white patients with HF, Asians patients had threefold higher prevalence of diabetes, despite lower body mass index (BMI).[3] The higher burden of diabetes persisted across all BMI categories in Asian patients with HF, including lean and normal BMI categories. Obesity was not as strongly related to diabetes among Asians, compared with whites (odds ratio [OR]: 1.82 vs 3.45).[3] When Asian patients with HF were naturally clustered based on comorbidities, the lean diabetic cluster was associated with the worst quality of life and composite outcomes, with 79% greater risk of hospitalization and mortality at 1 year, compared with young patients with HF.[3,22] Of note, Asian women with HF are more prone to be diabetic at a lower BMI (≥23 vs ≥27.5 kg/m^2), compared with men with HF.[4] Among asymptomatic (without HF) Chinese patients with diabetes, subclinical cardiac remodeling and systolic dysfunction occurred at much lower glycemic cutoffs (compared with universal), and to a more pronounced extent in those who were lean (BMI<23kg/m^2).[23]

Hypotheses surrounding the lean diabetes phenotype include maternal and fetal malnourishment, poor insulin secretion, and unfavorable fat distribution.[3,7] In a population-based study, glucose intolerance in adults was associated with low birth weight at infancy till 2 years of age and subsequent accelerated increase BMI during childhood till adulthood.[24] Mechanistically, a lower number of pancreatic β-cells at birth and poor insulin secretory capacity have also been implicated in lean diabetes. This is in contrast to the poor insulin action suggested in diabetics with higher BMI,[25] suggesting that lean diabetes is potentially a sharp variant of the conventional obesity-related diabetes. Further, Asians are also predisposed to visceral/abdominal fat deposition. A recent study comparing body composition between various ethnicities identified South Asians to have the least favorable body composition (greater visceral and pericardial fat) and adipokine profile compared with others (Whites, Chinese-Americans, African-Americans, and Latinos).[26] This has even prompted the International Diabetes Federation to decide on lower waist circumference cutoffs to diagnose metabolic syndrome in Asians.[27] However, these theories await investigations in HF populations.

Conclusion

Asia harbors the majority of the world's concomitant DM and HF population. Until recently, our knowledge about these coexisting conditions in this region was rather limited. Asian patients with HFrEF and HFpEF are laden with a huge burden of diabetes at a young age, have a high prevalence of comorbidities, and are associated with worse outcomes. In addition to the important ethnic and regional differences, the unique lean diabetic phenotype in this region makes management of these conditions more challenging. Much as we have begun to recognize and appreciate these unique Asian HF and diabetes phenotypes, this evidence merely serves as a maiden voyage for more warranted, deeper explorations to better understand the pathology. ■

Disclosure/Acknowledgments: *CC: No conflict of interest. CSPL: None relevant for the present work. Unrelated to present work: CSPL is supported by a Clinician Scientist Award from the National Medical Research Council Singapore, nonfinancial support from Boston Scientific, nonfinancial support from Bayer, nonfinancial support from Thermofisher, nonfinancial support from Vifor Pharma, other from Bayer, other from Novartis, other from Takeda, other from Merck, other from Astra Zeneca, other from Janssen Research & Development, other from LLC, other from Menarini, other from Boehringer Ingelheim, other from Abbott Diagnostics, from DC Devices, outside the submitted work; in addition, Dr Lam has a patent PCT/SG2016/050217 pending.*

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