Mechanisms of heart failure with preserved ejection fraction in the presence of diabetes mellitus

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A B S T R A C T
Cardiovascular disease (CVD) is the leading cause of death globally. People living with type 2 diabetes mellitus (T2DM) have up to three times higher risk of developing CVD, particularly heart failure with preserved ejection fraction (HFpEF), for which there is no effective treatment. The need for tangible interventions has led to investigations into a number of biomarkers associated with metabolic and vascular dysfunction that could be utilised for diagnostic and treatment purposes. This review discusses the importance and mechanisms of inflammatory and angiogenic biomarkers, which have shown the most potential in the pathogenesis and diagnosis of HFpEF, particularly in the presence of diabetes. In depth “in silico” analysis was also carried out to identify pathogenic pathways associated with HFpEF, both in the presence and absence of diabetes. The results identified mostly inflammatory pathways associated with HFpEF in the presence of diabetes, and a number of pathways related to angiogenesis, remodelling, metabolism as well as inflammation, in the absence of diabetes. The shared and unique pathways identified in HFpEF in the presence and absence of diabetes, should be explored further in order to improve management and outcomes of people living with HFpEF, taking into the account other underlying conditions.

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Introduction

Diabetes and cardiovascular disease

Over the past 40 years there has been a four-fold increase in the incidence of type 2 diabetes mellitus (T2DM) globally.1 According to the World Health Organisation (WHO), the number of people living with diabetes reached 422 million in 2014, where the world population had climbed to 7.2 billion.2 Over the last 20–30 years, sedentary lifestyle choices and the influence of the Western diet,3,4 have led to a global increase in obesity5,6 and subsequent co-morbidities, such as, CVD. Worldwide, CVD is the biggest killer, claiming ~18 million lives annually, equating to 31% of total deaths,6,7 with the incidence of CVD up to three-fold higher in people with diabetes.8,9

Heart failure as a diabetic comorbidity in Australia

Hyperglycaemia, as the major hallmark of diabetes, has been linked to both micro- and macrovascular complications, including coronary artery disease and stroke.10 Poor glycaemic management, therefore, can lead to the development of co-morbidities, such as heart failure (HF), which is associated with high morbidity and poor prognosis.11 Currently, HF is classified as either heart failure with reduced ejection fraction (HFrEF) or heart failure with preserved ejection fraction (HFpEF). It is estimated that approximately 480,000 Australians, 66% of whom are male, are affected by HFrEF, accounting for ~2% of the total population, or 6.3% of people aged 45 years and over. Comparatively, HFpEF is estimated to affect a similar amount of people, although predominating within the female population.12

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While HFrEF has been more closely studied and pharmacologically well managed, HfPEF is still poorly understood and lacking effective treatment strategies. HFrEF is defined as a left ventricular ejection fraction (LVEF) measurement of less than 50%, with or without signs of clinical heart failure. In contrast, defining HfPEF has proven to be much more complicated, as the main marker of cardiac abnormality (LVEF) is, by definition, preserved. As such, the definition of HfPEF (with or without clinical signs of heart disease) is constantly changing and, currently, the diagnosis includes a LVEF of at least 50%, with other evidence such as structural heart disease or diastolic dysfunction. HfPEF is associated with high morbidity, a shortened life expectancy, and a 5-year mortality of newly diagnosed patients that is as high as 50%. This is likely due to the lack of effective interventions and diagnostics for the HfPEF form of the syndrome and a paucity in knowledge in relation to the pathogenesis leading to HfPEF in both people with and without diabetes. Reliable blood-based biomarkers reflective of the cardiac pathology, such as ST2 or hs-CRP, could be beneficial in predicting the risk of HfPEF occurrence and also be utilised in the development of novel therapeutic agents. This review provides a detailed outline of HfPEF occurrence and also be utilised in the development of novel therapeutic agents. This review provides a detailed outline of HfPEF occurrence and also be utilised in the development of novel therapeutic agents.

The pathogenesis of HfPEF in diabetes

HfPEF is classified as a diastolic dysfunction affecting the left ventricle (LV), manifesting as either an impairment of left ventricular relaxation or increased diastolic stiffness, which can be attributed to myocardial hypertrophy, progressive myocardial fibrosis and/or increased cardiac myocyte stiffness. The evident slowed relaxation is due to a loss in flexibility that impacts mid to late diastole, also resulting in elevated blood pressure. The loss of flexibility is due to the re-characterisation of a large sarcomeric protein called titin, which is responsible for recoil, remaining in a compressed state during systole. This occurs through transcriptional and post-translation modifications that results in extracellular matrix accumulation and fibrosis (i.e. an imbalance between depressed collagen degradation and exaggerated collagen synthesis), manifesting in disturbed LV filling and detrimental structural modifications. Furthermore, when stretching of the heart occurs, cardiomyocytes within the ventricles secrete a B-type natriuretic peptide (BNP) that is used as a biomarker for the onset of HfPEF.

The presence of HfPEF is more common in diabetes, likely due to the accumulation of adipose tissue and lips within non-adipose tissue that can lead to the development of insulin resistance within myocytes, hepatocytes and adipocytes. T2DM causes endothelial cell dysfunction and hence aberrant angiogenesis, elevating levels of fibrinogen, thrombin, coagulation factors VII & VIII, inflammatory mediators and Plasminogen-Activator Inhibitor Type 1. These factors induce a pro-thrombotic environment within the vasculature by accelerating atherosclerotic plaque formation through chronic inflammation and injury to arterial walls.

Inflammation in HfPEF

As far back as the 1990s, links between increased inflammatory profiles and LV dysfunction have been identified in a number of rat models, suggesting a cause and effect relationship between inflammation and the development of fibrosis. However, the element of time and the inflammatory cascade varies between species, as does the reliance on identifying specific biomarkers at specific time points in disease progression that may be relevant to the overall heart condition. Pentraxin-3 (PTX3) is one such biomarker that has a well-established association with vascular inflammation and, only recently Zlibut et, al. highlighted a role for PTX3 in decreasing nitric oxide (NO) synthesis within endothelial cells, altering their function and inhibiting cell proliferation. Furthermore, correlation between upregulation of the pro-inflammatory cytokine interleukin-6 (IL-6) and PTX3 have also been found in HfPEF, with studies showing that IL-6 forms a cluster with perisinin (involved in vasculature remodelling) and C-reactive protein (CRP), but only within a diabetic environment. This pro-inflammatory state underlying the pathophysiology of HfPEF allows a contrast to be made when compared to the pathophysiology pathway of HfPEF, which shows stronger positive association with NT-proBNP than HfPEF.

Angiogenesis in HfPEF

Aberrant angiogenesis caused by a T2DM-induced pro-thrombotic environment arising from adipose tissue and lipid accumulation, resulting in insulin resistance, also plays an important role in the pathogenesis of diastolic dysfunction and HfPEF. Barroso et, al. recently identified the endogenous angiogenesis inhibitor, endostatin, as a possible biomarker of HfPEF, due to its correlation to the presence and severity of HfPEF, with the evident deterioration of diastolic function correlated with increased endostatin levels. Other angiogenesis biomarkers that have delivered predictive results particular in terms of HfPEF and not HfPEF are the vascular endothelial growth factor co-receptor neuropilin and the remodelling marker osteopontin. Similarly, C-type natriuretic peptide (CNP)-guided therapy as studied by Lok et, al. showed promise in predicting endpoints of patients' re-hospitalisations or all-cause mortality as a result of HfPEF, which was not observed in patients with HfPEF. Higher concentrations of NT-proCNP in HfPEF were observed as a result of these endpoints hence demonstrating strong prognostic biomarker potential of NT-proCNP for HfPEF patients. Furthermore, in the presence of diabetes, there is a direct association between CNP and HfPEF, which is
promising, especially considering its predominant localisation in the endothelium and the detrimental impact diabetes has on inducing endothelial damage.55

**Computational analysis of the literature on HFpEF biomarkers in the presence and absence of diabetes**

A number of “omics” approaches have been employed for biomarker discovery in CVD including genomics, transcriptomics, proteomics and metabolomics in order to understand molecular mechanisms of underlying pathogenesis. The wealth of scientific data available in public repositories can also be helpful to integrate relevant biomarkers in HFpEF and contextualise these into pathogenic biological pathways. Therefore, this study carried out computational analyses of biomarkers identified in the literature to further evaluate pathogenic pathways associated with HFpEF both in the presence and absence of diabetes. For this purpose, a combination of a series of literature queries, public data repositories (Pubtator, Reactome and gProfiler) and in-house developed R scripts were employed. This allowed retrieval and analysis of these biomarkers in the context of pathways/gene sets, similar to what was previously described.56 The retrieval of relevant literature was

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**Fig. 2.** Pathogenic pathways identified using “in silico” analysis of publically available datasets in relation to HFpEF in the presence of diabetes.

**Fig. 3.** Pathogenic pathways identified using “in silico” analysis of publicly available datasets in relation to HFpEF in the absence of diabetes as per the search strategy depicted above.
Conflict of interest

Authors have no conflict of interest to declare.

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