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REVIEW ARTICLE

Diagnostic and prognostic biomarkers reflective of cardiac remodelling in diabetes mellitus: A scoping review

Michael Chhor[1] | **William Law**[1] | **Milan Pavlovic**[2] | **Dunja Aksentijevic**[3] | **Kristine McGrath**[1] | **Lana McClements**[1]

[1]School of Life Sciences, Faculty of Science, University of Technology Sydney, New South Wales, Sydney, Australia

[2]Department of Internal Medicine - Cardiology, Faculty of Medicine, University of Nis, Nis, Serbia

[3]Centre for Biochemical Pharmacology, William Harvey Research Institute, Barts and the London School of Medicine and Dentistry, Queen Mary University of London, London, UK

Correspondence
Lana McClements, School of Life Sciences, University of Technology Sydney, Sydney, NSW, Australia.
Email: lana.mcclements@uts.edu.au

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Abstract

Aims: The aim of this scoping review is to evaluate the current biomarkers used in the assessment of adverse cardiac remodelling in people with diabetes mellitus (DM) and in the diagnosis and prognosis of subsequent cardiovascular disease. We aim to discuss the biomarkers' pathophysiological roles as a reflection of the cardiac remodelling mechanisms in the presence of DM.

Methods: We performed the literature search to include studies from 2003 to 2021 using the following databases: MEDLINE, Scopus, Web of Science, PubMed, and Cochrane library. Articles that met our inclusion criteria were screened and appraised before being included in this review. The PRISMA guidelines for Scoping Reviews were followed.

Results: Our literature search identified a total of 43 eligible articles, which were included in this scoping review. We identified 15 different biomarkers, each described by at least two studies, that were used to determine signs of cardiac remodelling in cardiovascular disease (CVD) and people with DM. NT-proBNP was identified as the most frequently employed biomarker in this context; however, we also identified emerging biomarkers including hs-CRP, hs-cTnT, and Galectin-3.

Conclusion: There is a complex relationship between DM and cardiovascular health, where more research is needed. Current biomarkers reflective of adverse cardiac remodelling in DM are often used to diagnose other CVDs, such as NT-proBNP for heart failure. Hence there is a need for identification of specific biomarkers that can detect early signs of cardiac remodelling in the presence of DM. Further research into these biomarkers and mechanisms can deepen our understanding of their role in DM-associated CVD and lead to better preventative therapies.

KEYWORDS

biomarker, cardiac fibrosis, cardiovascular disease, heart failure, metabolomics, scoping review

1 | INTRODUCTION

Cardiovascular disease (CVD) is an umbrella term encompassing any disorder affiliated with the heart and blood vessels, such as coronary artery disease (CAD) and heart failure (HF).[1] CVD is currently the highest cause of mortality worldwide, representing 32% of all deaths globally.[2] For perspective, prevalent cases of CVD have reportedly doubled between 1990 and 2019 from 271 million to 523 million people. CVD resultant deaths have similarly followed this trend and increased from 12.1 million to 18.6 million people between 1990 and 2019.[3] Consequently, it is fast becoming a serious financial and medical burden to the entire population.

Meanwhile, diabetes mellitus (DM) is also a pervasive and deleterious disease. Worldwide, DM affects 422 million people and accounts for 1.6 million deaths a year.[4] There are two key pathological processes that cause the development of DM: inadequate insulin production by beta islet cells of pancreas, and insulin resistance (IR), which results from impaired insulin response in peripheral tissues. DM is a heterogenous disease with multiple organs involved in the aetiology: liver, skeletal muscles, pancreas, kidneys, brain, small intestine, and adipose tissue.[5] Hyperglycaemia associated with DM consequently triggers a surfeit of macro- and microvascular complications.[6]

The risk of CVD morbidity in DM is approximately two-three times more likely compared to those without DM.[7] The Framingham Heart Study concluded that type-2 diabetes mellitus (T2D) independently increases the HF risk up to two-fold in men and five-fold in women compared to matched controls.[8,9] Thus, accelerated HF is a common clinical manifestation of CVD in T2D.[5] DM progression leads to specific changes to myocardial structure, function, and metabolism, collectively defined as diabetic cardiomyopathy (dbCM).[5,10] Hyperglycaemia, insulin resistance as well as lipotoxicity drive numerous fibrogenic pathways, triggering generation of reactive oxygen species (ROS), enhancing neurohumoral responses, stimulating growth factor cascades (i.e., TGF-β/Smad3 and PDGFs), inducing pro-inflammatory cytokines and chemokines, generating advanced glycation end-products (AGEs), stimulating the AGE-receptor for AGE (RAGE) axis, and up-regulating fibrogenic matricellular proteins.[11] Despite DM-triggered fibrogenic signalling sharing common characteristics in multiple tissues, diabetic myocardium develops more pronounced and clinically significant fibrosis.[11]

Myocardial fibrosis plays an essential role in cardiac remodelling and is linked to DM and many CVDs.[12] Its primary culprit is cardiac fibroblast (CF) to myofibroblast (MF) differentiation. CFs are one of the largest cardiac cell populations, responsible for extracellular matrix (ECM) homeostasis, however, once harmed they transform into MFs.[13] This considerably elevates ECM protein levels, which adversely augment ECM heart structure and promote formation of scar tissue.[14] In DM, myocardial fibrosis and cardiac remodelling have become structural hallmarks of a diabetic heart. In fact, in absence of traditional cardiovascular risk factors, including hypertension, valvular disease and overt CAD, dbCM develops.[15] Interestingly, myocardial fibrosis and adverse remodelling are the first signs of dbCM.[15,16]

People with DM show signs of impaired left ventricular (LV) function, thickness, and remodelling, often resulting in LV diastolic dysfunction. Cardiac remodelling is a compensatory process exacerbated when the heart is under duress; however, exact mechanisms have yet to be elucidated. Insulin resistance and AGEs are key mechanisms in this compensation that may explain the development of hypertrophy of the heart in the presence of DM.[17] Conversely, it should be noted that insulin sensitivity and signalling pathways play a significant role in dbCM both exacerbating its progression, but also having cardioprotective mechanisms. Particularly through the activation of the PI3Ka/Akt pathway, the suppression of cardiac ROS, and inflammation in dbCM, insulin signalling exhibit a mechanistic role in the diabetic heart. It should be noted that this evidence stems from animal studies and may not correspond to a human scenario.[18] Thus, the effects of DM on cardiac remodelling evidently contain many complex mechanisms that need to be further studied.

Hence, this scoping review aims to provide an assessment of current biomarkers available that can be utilised in the detection of myocardial fibrosis/remodelling and,

What's new?

Cardiovascular disease (CVD) is still the biggest killer with increasing incidence, and people with diabetes mellitus (DM) have a two-three-fold increased risk of CVD. Cardiac remodelling is an early sign of deteriorating cardiac health; however, the mechanisms are poorly understood and can differ in the presence of DM. In this scoping review, we assessed publicly available data on all biomarkers of adverse cardiac remodelling in people with DM. We identified fifteen reliable biomarkers that could also represent viable therapeutic targets for adverse cardiac remodelling in people with DM. Timely diagnosis of early cardiac changes could significantly improve the quality of life of people with DM with a potential to prevent or delay heart disease.

diagnosis and prognosis of subsequent CVD or cardiovascular complications. Through assessing the viability of these biomarkers, efficient diagnostic, prognostic and therapeutic interventions could be developed to detect or stop the progression of myocardial fibrosis/remodelling in its early stages. This could aid early detection of myocardial fibrosis/cardiac remodelling to stop its permanent damage, and most importantly attenuate the development of lethal CVDs, such as HF, particularly in people with DM.

2 | METHODS

2.1 | Research question

The purpose of this scoping review is to appraise the current biomarkers used in the diagnosis of cardiac remodelling and prognosis of CVD, linking their pathophysiological roles as a reflection of the underlying mechanisms.

2.2 | Identification of studies

This scoping review was conducted following the PRISMA guideline for Scoping Reviews.[19] The following search term sets were used:

Set (A): biomarker OR marker OR markers.

Set (B): cardiac remodelling OR remodelling OR cardiac remodeling OR remodeling.

Set (C): diabetes or diabetes mellitus.

The following databases: MEDLINE, Scopus, Web of Science, PubMed, and Cochrane library. All searches were conducted from June to September 2021 by investigators MC and WL.

2.3 | Study selection

2.3.1 | Inclusion criteria

Studies that were included had the main aim of assessing cardiac remodelling using a biomarker in people with DM. This includes studies that did not focus solely on DM but had a subpopulation of people with DM within the study. Studies that did not have a control group of people without DM were also selected. Only studies written in the English language were included.

2.3.2 | Exclusion criteria

Studies that were excluded did not examine people with DM or have a biomarker measure indicative of cardiac remodelling. Further studies that were excluded were review articles, articles not in English, and case reports.

2.4 | Data extraction

Following full-text screening, papers that met the selection criteria were scanned for extraction. The following details were extracted: Year, Author, Country, Patient Characteristics, Patient numbers with DM or in the control group, Mean Age, Biomarker, Biomarker Classification, and Level of Evidence. No review protocol was available specific to the purposes of this scoping review, hence biomarker classification and the level of evidence were appropriated as per a scoping review conducted by De Luca Canto et al. 2015.[20] The biomarker clinical application was classified as: (1) potential biomarker(s) of cardiac remodelling; (2) inconclusive biomarker of cardiac remodelling, and (3) evidence not supportive as potential biomarker of cardiac remodelling. The level of evidence was classified as A (well-designed prognostic or diagnostic studies on relevant population), B (prognostic or diagnostic studies with minor limitations, overwhelmingly consistent evidence from observational studies) or C (observational studies [case–control and cohort design]).

3 | RESULTS

3.1 | Study selection

Two independent investigators, MC and WL, identified 4400 papers using the search terms set in the five databases outlined in the methodology. After removing any duplicate papers, a total of 1774 papers remained for Title and Abstract screening. Following the initial screening, 127 papers remained for full-text screening. Of those papers, 43 were included in our data extraction displayed in Table 1. The remaining 84 articles were excluded for: not relating to the topic, not including a biomarker, not written as an article, not in English, inaccessible, and with insufficient data. This process is visualised in Figure 1, with a PRISMA flow chart diagram depicting the search process.

3.2 | Study characteristics

Studies were extracted for descriptive data and displayed in Table 1, with a total of 43 studies that were included. The year of study ranged from 2003 to 2021. It was determined from our investigation that the origin country of study had a widespread reach, being conducted in over 24

TABLE 1 Descriptive characteristics of included cardiac remodelling studies.

Country	Cohort characteristics	Cases	Control	Mean age	Biomarker	Biomarker classification	Level of evidence
Taiwan	CVD history	505	1416	57.1	NT-proBNP	2	C
International	CVD history	5141/542	8023/350	65/64.7	NT-proBNP (100 ng/L) hs-cTnT (14 ng/L)	1	A
Germany	General	19	858	48	NT-proBNP BNP	1	C
Spain	HF patient	314	562	70.3	NT-proBNP (1720 ng/L), hs-cTnT (16 ng/L), hs-ST2 (50 ng/L)	1	B
Australia	High-risk HF	654	2896	70.4	NT-proBNP	1	A
USA	LVSD outpatient	38/25	37/51	69.3/57.4	Galectin-3 (20 ng/mL)	2	B
Norway	General	380	1678	63.9	cTnT, NT-proBNP, CRP, HbA_{1c}	2	C
USA	General	82	2570	66.9	Ceramides C16:0/C24:0	1	B
Romania	DM/MI patient	45	43	61.3	hs-CRP, EAT	1	A
USA	General	110	638	50	NT-proBNP, hs-cTnT, hs-CRP	3	B
Italy	STEMI patient	12	88	62.5	EAT	3	C
Russia	HF patient	HFpEF: 11, HFrEF: 30	N/A	HFpEF: 57, HFrEF: 63	NT-proBNP, Galectin-3, sST2	1	B
Europe	T1D patient	493	N/A	39.5	TIMP-1, MMP-1, 2, 3, 9, 10	2	B
Italy	T2D patient	51	20	60	miR122-5p	2	C
Sweden	General	116/105	N/A	70.1/77.5	Endostatin, NT-proBNP	3	B

TABLE 1 (Continued)

Country	Cohort characteristics	Cases	Control	Mean age	Biomarker	Biomarker classification	Level of evidence
Japan	HF patient	17	N/A	60.7	NT-proBNP, hs-cTnT	2	C
International	T2D patient	12,310	4182	65.1	NT-proBNP (450 pg/mL), hs-cTnT (3 pg/mL), hs-CRP (0.15 mg/L)	1	A
International	HF in-patient	922	1111	Diabetes: 70.3 Non-diabetes: 70	BNP (500 pg/mL), NT-proBNP (2000 pg/mL), sST2, Galectin-3, hs-CRP	1	B
Denmark	T2D patient	246	N/A	Above median: 58 Below Median: 59	FGF-23 (median 74 ng/L)	2	C
Italy	General	533	1325	N/A	hs-CRP	1	B
CORONA: USA COACH: USA	HF patient	CORONA: 333 COACH: 95	N/A	CORONA: 71.6 COACH: 69.9	Galectin-3 (17.8 ng/mL)	1	B
USA	General	Men: 41 Women: 42	N/A	Men: 87 Women: 78.6	hs-CRP, IL-6, TNFα	2	C
USA	General	Men: 153 Women: 133	N/A	Men: 59 Women: 58	hs-CRP, BNP	2	C
Europe	High risk CVD	310	217	Diabetes: 71.9 Non-diabetes: 73.5	NT-proBNP (125-1000 ng/L), Galectin-3, hs-cTnT	1	A
USA	HF out-patient	117	N/A	56	BNP, MMP-9	1	C
USA	General	87	N/A	56	PIIINP	2	C
Taiwan	General	113	N/A	51.03	hs-CRP, NT-proBNP	1	B
Ireland	High risk CVD	498	N/A	66.2	MMP-9	1	B

(Continues)

TABLE 1 (Continued)

Country	Cohort characteristics	Cases	Control	Mean age	Biomarker	Biomarker classification	Level of evidence
France	T2D patient	91	N/A	Men: 60 Women: 61	BNP	1	A
France	CHF patient	64	92	Control: 56 T2D: 56	PIIINP, PICP, PINP, MMP-1, TIMP-1	2	B
Denmark	T2D patient	60	30	Control:52 T2D: 55	NT-proBNP	1	A
China	CVD patient	DM MACE: 89 DM MACE FREE: 113	748	DM MACE: 63.07 DM MACE FREE: 68.62	hs-ST2, NT-proBNP	1	B
Spain	HF patient	321	N/A	70.2	hs-ST2, NT-proBNP	1	B
Ukraine	T2D patient	186	20	52.49	hs-CRP, Adiponectin, Omentin-1	2	B
Turkey	STEMI patient	71	207	55.3	NT-proBNP	2	B
Netherlands	HF patient	120	N/A	72	Galectin-3	1	B
USA	HF patient	116	132	DM: 69 Non-DM: 74.3	hs-CRP, hs-TnT, NT-proBNP, sST2, PICP, CITP, PIIINP, MMP-2,9, TIMP-1, Galectin-3	2	C

TABLE 1 (Continued)

Country	Cohort characteristics	Cases	Control	Mean age	Biomarker	Biomarker classification	Level of evidence
Greece	LVDD patients	(C) T2DM without LVDD: 48 (D) T2DM with LVDD: 50	(A) Healthy: 42 (B) Non-T2DM with LVDD: 18	A: 55.10 B: 60.33 C: 54.87 D: 56.98	sST2, BNP, hs-CRP	2	B
Egypt	T2D patient	EF < 50%: 46 EF > 50%: 54	50	EF < 50%: 47.71 EF > 50%: 44.89 Control: 45.05	IL-6, NT-proBNP	1	C
China	T2D patient	110	N/A	EF < 50%: 65.71 EF > 50%: 66.29	Ang-II, NT-proBNP	2	C
Denmark	T2D patient	Microalbuminuria = 149, Macroalbuminuria = 563.	703	Control: 64 Microalbuminuria = 66 Macroalbuminuria = 67	Albumin	2	C
Iran	STEMI patient	DM normal {25 (OH)} = 12 DM deficient{25 (OH)} = 26	38	DM normal {25 (OH)} = 63.1 DM deficient{25 (OH)} = 59.6	25 (OH), MMP9	1	B
England	MI patient	ΔEDV </= 0: 22 ΔEDV >0: 24	42	63	VEGFB	2	B

Note: The biomarker clinical application was classified as (1) potential biomarker (s) of remodelling; (2) inconclusive biomarker for remodelling, and (3) evidence not supportive as potential biomarker for remodelling (s). The level of evidence was classified in A (well-designed prognostic or diagnostic studies on relevant population), B (prognostic or diagnostic studies with minor limitations, overwhelmingly consistent evidence from observational studies), C (observational studies [case–control and cohort design]).

Abbreviations: 25 (OH), 25-hydroxy vitamin D; Ang II, angiotensin II; BNP, brain natriuretic peptide; CHF, chronic heart failure; CITP, carboxyl-terminal telopeptide type 1 collagen; CRP, C-reactive protein; cTnT, cardiac troponin T; CVD, cardiovascular disease; DM, diabetes mellitus; EAT, epicardial adipose thickness; FGF-23, fibroblast growth factor-23; HbA_{1c}, haemoglobin A_{1c}; HF, heart failure; hs-CRP, high-sensitivity C-reactive protein; hs-cTnT, high-sensitive cardiac troponin T; IL-6, interleukin 6; LVDD, left ventricular diastolic dysfunction; LVSD, left ventricular systolic dysfunction; MI, myocardial infarction; miR122-5p, MicroRNA-122-5p; MMP, matrix metalloproteinase; NT-proBNP, N-terminal pro b-type natriuretic peptide; PICP, procollagen type 1 carboxy-terminal propeptide; PIIINP, procollagen III N-terminal propeptide; PINP, procollagen type 1 N-terminal propeptide; sST2, soluble suppression of tumorigenesis-2; STEMI, ST-elevation myocardial infarction; T1D, type 1 diabetes mellitus; T2D, type 2 diabetes mellitus; TIMP-1, tissue inhibitor matrix metalloproteinase 1; TNFα, tumour necrosis factor alpha; VEGFB, vascular endothelial growth factor B.

separate countries (Figure 2). The most prevalent country was the USA ($n = 9$) where the most numerous studies were conducted.[21–29] The countries following this were Denmark,[30–32] and Italy[33–35] ($n = 3$); China,[36,37] Europe,[38,39] France,[40,41] Spain,[42,43] and Taiwan[44,45] ($n = 2$). Notably, three studies conducted multicentre studies across the world—categorised at International[46–48] ($n = 3$).

Our searches revealed a total of 15 unique biomarkers used in the detection of cardiac remodelling in DM, where potential biomarkers were described by at least two studies (Table 2). The most studied and represented biomarker was N-terminal (NT)-pro-brain natriuretic peptide (NT-proBNP, $n = 21$).[23,29,31,36,37,39,42–56] Many studies had a multi-marker approach where NT-proBNP was included as one of the biomarkers; however, four studies used NT-proBNP as a sole biomarker in detecting signs of remodelling and CVD outcome. The next most studied biomarkers were high-sensitivity C-reactive protein (hs-CRP, $n = 12$)[23,25,26,29,34,46,47,51,57–60] and high-sensitivity cardiac troponin T (hs-cTnT, $n = 8$),[23,29,39,43,46,48,51,54] Galectin-3 (Gal-3, $n = 7$),[21,24,29,39,47,52,61] and soluble suppression of tumorigenesis-2 (sST2) ($n = 7$).[29,36,42,43,47,52,60] The vast majority of the studies included potential biomarkers collected from blood and plasma biomarkers with the exception of two papers, examining epicardial adipose thickness[35,57] as a potential biomarker.

3.3 | Level of evidence and biomarker classification

The assessment of the included studies as per the level of evidence showed 7 studies were classified as 'A', having a well-designed study for the relevant population and sufficient level of evidence provided for the biomarker studied. Most studies were classified as 'B' ($n = 21$) where the diagnostic/prognostic study had minor limitations but consistent evidence. Lastly, 15 studies were classified as

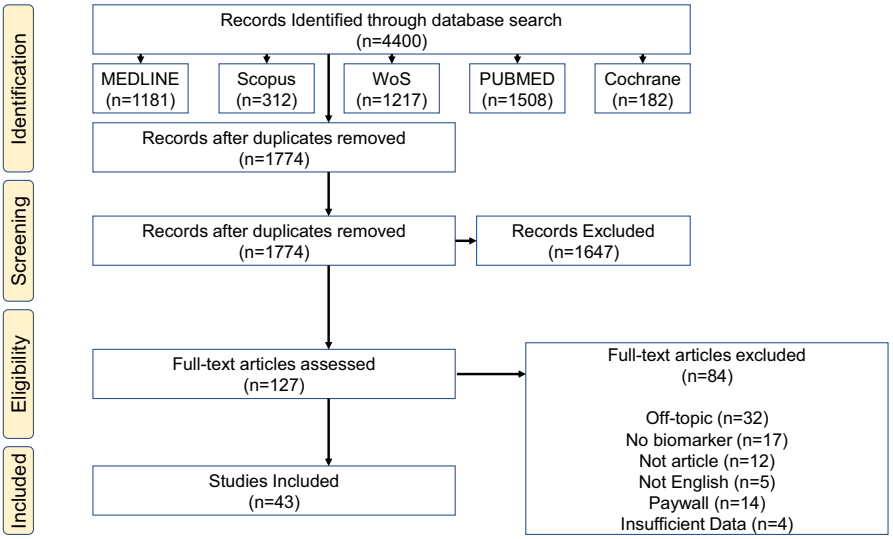

FIGURE 1 PRISMA flow diagram of search process.

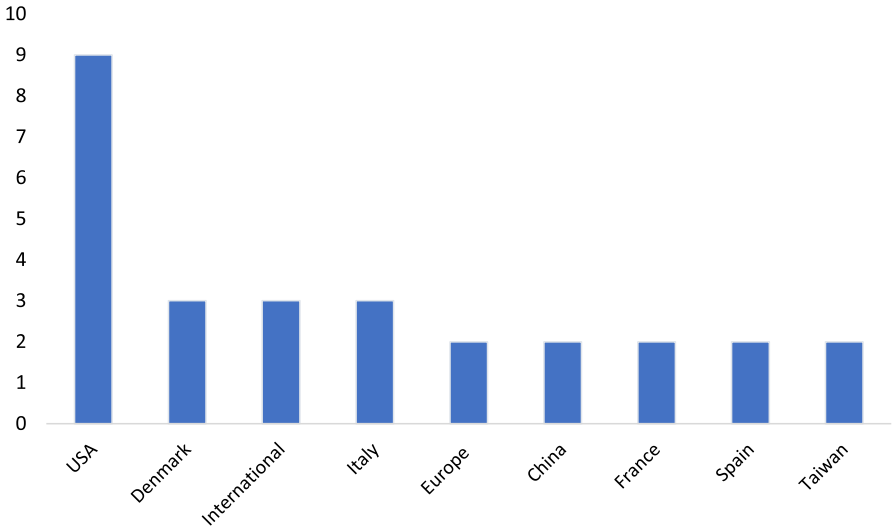

FIGURE 2 Distribution of adult participants according to country of study. United States of America ($n = 9$), Denmark ($n = 3$), International ($n = 3$), Italy ($n = 3$), China ($n = 2$), Europe ($n = 2$), France ($n = 2$), Spain ($n = 2$), Taiwan ($n = 2$). The following countries were not represented in the figure ($n = 1$): Australia, Egypt, England, Germany, Greece, Iran, Ireland, Japan, Netherlands, Norway, Romania, Russia, Sweden, Turkey, and Ukraine.

TABLE 2 Potential biomarkers identified in adults studied.

Biomarker	Number of studies
NT-proBNP	21
hs-CRP	12
MMP-1,2,3,9	10
hs-cTnT	8
Galectin-3	7
hs-ST2	7
BNP	6
PIIINP	3
TIMP-1	3
EAT	2
IL-6	2
PICP	2

Note: The following biomarkers were not presented in the table ($n = 1$): MMP10, 25 (OH), Adiponectin, Ang-II, Ceramide C16:0/C24:0, CITP, Endostatin, FGF-23, HbA_{1c}, miR122-5p, Omentin-1, PINP, TNFα, and VEGFB.

'C', being an observational study with limited evidence provided (Table 1).

In terms of the biomarker classification, 22 studies were classified as (1), where the biomarker studies had the potential to be a reliable biomarker for detecting cardiac remodelling. Furthermore, 18 studies were classified as (2), being inconclusive as a biomarker for cardiac remodelling. Lastly, 3 studies were classified as (3), where insufficient evidence was provided for a biomarker of cardiac remodelling (Table 1).

4 | DISCUSSION

DM is a strong independent factor of CVD development associated with hyperglycaemia that affects heart function and contributes to worse CVD outcome.[49,50] This remains an important factor to account for when determining systemic biomarker concentrations in people with DM and CVD, which often differ from people without DM.[62] Similarly, previous studies have shown that in the presence of DM, there is an up-regulation in inflammatory pathways, not present in people without DM.[39] Inflammation underpins potential mechanisms leading to adverse cardiac remodelling and fibrotic processes in the presence of DM that still need to be fully elucidated.[30,47] The current diagnostic method for detecting cardiac fibrosis relies on invasive imaging methods such as cardiovascular magnetic resonance imaging that includes T1 mapping; however, it can vary in result depending on the practitioner and a patient in question.[14] Often these methods need to be supported with additional assessments to confirm the diagnosis, which highlights the need for more reliable non-invasive methods that could be fulfilled by the emergence of new biomarkers that may be used in tandem with current methods. From the total of 15 biomarkers that were identified as promising within this scoping review, 7 studies were classified in the highest 1A category. This suggests that the quality of biomarkers from these studies is acceptable, and that these biomarkers have high potential of being reliable for cardiac remodelling.

4.1 | NT-proBNP and BNP as a measure of cardiac remodelling

The natriuretic peptide (NP) system has shown to play an important role in the study of cardiac endocrinology with the regulation of circulating active BNP, and the inactive NT proBNP. These peptides are secreted primarily in response to atrial muscle stretch, but can also be influenced by hypoxia, inflammation, angiotensin II (Ang II), and endothelin stimuli.[63] Upon release, BNP binds to the particulate guanylyl cyclase A receptor, followed by the generation of 3′-5′-cyclic guanosine monophosphate. This interaction results in a series of cardioprotective responses such as reduced hypertrophy, fibrosis, and inhibition of the renin-angiotensin-aldosterone system.[64] Circulating levels of NPs typically remain at a low level, but upon stimulus are increased. Clinical data supports this, reporting higher levels of plasma BNP and NT-proBNP in patients with HF, and hence these biomarkers have been the most widely used for the diagnosis and prognosis of HF.[65] In our current study, we found that out of the total 43 studies, 21 measured NT-proBNP concentration as a sole biomarker to determine remodelling or at least as a supplementary measure and six studies measured BNP as a biomarker.

The MESA study examined community patients for the presence of cardiac fibrosis measuring cardiovascular magnetic resonance T1 mapping and NT-proBNP levels. The findings of this study exhibit the relation of NPs and cardiac fibrosis, where a positive relation was found between plasma NT-proBNP levels and the presence of fibrotic changes within the heart. However, in the context of DM, the correlation between NPs and fibrosis displays an inverse relationship between plasma NP levels and insulin resistance across all body weights. The PARADIGM-HF trial measured a series of myocardial fibrosis plasma biomarkers in patients with HF, exhibiting a positive correlation of these biomarker levels to cardiovascular death and hospitalisation. The most notable changes in plasma biomarker concentrations recorded from this study were

suppression of tumorigenesis-2 (ST2), tissue inhibitors of metalloproteinases (TIMP-1), and procollagen type III N-terminal peptide (PIIINP) at baseline; suggesting that TIMP-1 had the strongest prognostic value, exceeding BNP and NT-proBNP. It was also discovered that people with DM had a lower level of NT-proBNP, and significantly higher level of troponin T than people without DM. Out of all the studies included in this review, Lupon et al. 2013[43] provided similar insights and performed a multimarker strategy, reporting a promising diagnostic potential of hs-cTnT and hs-ST2 biomarkers, which performed better together, whereas NT-proBNP was not included in the risk stratification of HF and remodelling. Interestingly, Pecherina et al. 2020[52] suggested that after multi-variate analysis, the prognostic value of NT-proBNP is more reliable for HF symptoms but not for cardiac remodelling.

From the findings of this study and previous studies, BNPs retain its diagnostic reliability as biomarkers for HF and show potential as biomarkers of cardiac remodelling in the presence of DM, albeit evidence is inconclusive so far based on extensive published research. However, as reported in previous studies, the non-specificity of BNPs may impede its potential as sole biomarkers, making them more beneficial when used in conjunction with other biomarkers of cardiac remodelling.

4.2 | Inflammatory biomarkers of cardiac remodelling

Cardiac fibrosis is inextricably linked to dbCM and HF, where the underlying inflammatory process has shown an important role in its pathogenesis. DM exacerbates the inflammatory response, where a measure of inflammatory mediators at specific points in time can be indicative of the overall condition of the heart.[66]

Gal-3 belongs to the B-galactoside-bindings lectins, with an essential N-terminal domain proteolysed by matrix metalloproteinases (MMP) important for interaction with other intracellular proteins.[67] The ability to interact with other intracellular proteins allows Gal-3 to have a myriad of pleotrophic functions, notably within angiogenesis, inflammation, and fibrosis.[67,68] Gal-3 promotes the chemoattraction of macrophages, fibroblast activity and ECM accumulation, displaying a close association with cardiac remodelling and HF pathophysiology.[68] Gal-3 typically is maintained at low plasma concentration in healthy individuals, however in patients with HF its plasma concentration increases, where its initial anti-necrotic, and anti-apoptotic functions lead to adverse cardiac remodelling and fibrosis over time.[68] Thus Gal-3 has been implicated in the pathogenesis of cardiac remodelling and inflammatory processes and considered a novel biomarker.[67,69] Serum Gal-3 and NT-proBNP concentrations have shown to be increased in HFpEF patients. In measuring ventricular remodelling in HFpEF patients using multivariate analysis, Gal-3 retains its association, whereas NT-proBNP does not and is rather attuned to HF symptoms.[52] This apparent trend of increased Gal-3 levels corresponding with increased CVD risk and mortality was confirmed by Van der Velde et al., 2013.[24] By measuring percentage increase of Gal-3 over 3 months, the study found that an increase of >15% leads to a 50% higher risk of CVD adverse events compared to patients within 15% of their baseline Gal-3.[24] Conversely, De Boer et al., 2011[61] reported that in hospitalised HF patients with DM, Gal-3 plasma concentration doubled, and showed high prognostic value for the primary endpoint of all-cause mortality and HF hospitalisation. Even when adjusted for covariates, including DM, Gal-3 retained promising prognostic value and even when measured at a later time point, it did not impair its prognostic value compared to other studies.[61] Thus, Gal-3 may play an important prognostic role in detecting cardiac remodelling before severe damage or primary CVD mortality is reached, but its potential may be heightened in alliance with other biomarkers.

C-reactive protein (CRP) is a protein produced by hepatocytes within the liver, with serum concentration showing elevated trend under inflammatory conditions and age.[70] Hence, hs-CRP is widely used for its properties as an inflammatory marker, where its sensitivity lies in its ability to accurately detect early, low-grade inflammation.[70,71] In the presence of DM, systematic inflammation is present, which is often chronic and low-grade.[72] Elevated serum CRP is associated with LV dysfunction, increased risk of DM, and it is overall a predictor of CVD risk and mortality.[73,74] The role of CRP in the cardiac remodelling process has further been implicated with studies reporting increased CRP in conjunction with pro-fibrotic and pro-inflammatory properties in Ang II-induced cardiac remodelling through activation of the transforming growth factor-β (TGF-β) and nuclear factor-κB (NFκB) signalling pathways.[75] Hence hs-CRP may have the potential to detect early signs of cardiac remodelling in people with DM and provide tool for risk stratification due to its high sensitivity and possible mechanistic role in cardiac remodelling. Similarly, interleukin-6 (IL-6) is a versatile cytokine embedded within the inflammatory response and pathophysiology of T2D, activating the inflammatory pathways including Janus kinase (JAK) and signal transducers and activators of transcription (STAT).[76,77] The pro-inflammatory properties of IL-6 coincide with the chronic inflammatory disease state of people with DM, further mediating the effects of endothelial dysfunction, a key process in the development of CVD.[78] IL-6 has been reported to be produced by cardiomyocytes

upon myocardial infarction and hypoxia.[76] Though clear relationship between IL-6 in people with DM and related cardiac complications has been found, further studies are needed to understand the exact mechanisms involved.

ST2 is an interleukin receptor-1 (IL-1) family member that binds to the ligand IL-33, both of which play an integral role in the inflammatory and immune response, and have emerged as promising markers of cardiovascular pathophysiology.[79] Both ST2 and IL-33 expression are regulated by the proinflammatory cytokines, IL-6 and tumour necrosis factor alpha (TNF), and impaired cardiac function.[80] Soluble ST2 (sST2) is an isoform of ST2 released by fibroblasts that freely circulate within the blood, and upon binding to IL-33 has cardioprotective and anti-inflammatory properties, preventing the actions of IL-33.[79] Hence sST2 is implicated in the cardiac remodelling process, indicative of fibrosis and hypertrophy.[81] Clinically, sST2 has shown to be a prognostic marker of both acute and chronic HF, where elevated levels have been shown in patients with a higher New York Heart Association (NYHA) functional classification, poor LV function and higher incidence of DM.[79,80] sST2 retains its promising biomarker potential as the influence of comorbidities of CVD, such as DM and hypertension, has shown a less of a confounding effect on sST2 than on NT-proBNP.[43] This presents the possibility of additional mechanisms in which sST2 may function and highlights the advantage of targeting patients with multiple comorbidities, where a combined biomarker strategy holds added potential.

4.3 | Cardiac-specific biomarkers

Troponin is a contractile protein present within skeletal- and cardio-myocytes that facilitate beating of the heart.[82] The most relevant of the isoforms is cardiac troponin in the context of CVD, where it is highly attuned to cardiomyocytes health and indicative of myocardial damage.[82] Hence, the highly specific and sensitive cardiac troponin, hs-cTnT, has been clinically used in the risk stratification for CVD in patients.[83] Given the strong relationship between DM and CVD, studies have reported significantly increased systemic concentrations of hs-cTnT in patients with DM, compared to those without DM.[83] Hs-cTnT measured in HFpEF patients with and without DM,[29] found no-significant differences initially observed between patient groups. However, after 12 months, hs-cTnT was one out of the two biomarkers significantly decreased when the groups were treated with a mineralocorticoid receptor inhibitor, spironolactone.[29] Meanwhile, people with DM and a CVD history with hs-cTnT systemic levels >14 ng/L experienced adverse cardiac outcomes.[48] The findings of this study and previous research indicate the influence of increasing hs-cTnT through coinciding developmental factors of both DM and CVD, such as microvascular disease, ventricular hypertrophy, inflammation, and endothelial dysfunction.[83] This presents the promising biomarker potential of hs-cTnT in elucidating the pathophysiological mechanisms between DM and CVD and detecting the early sign of cardiac remodelling.

Myocardium homeostasis involves the regulation of ECM proteins, namely collagen, for optimal function of the heart. In a disease state, ECM degradation is an integral process in cardiac remodelling aiming to preserve cardiac function through the breakdown of collagen.[84] These homeostatic disruptions result in CVD pathophysiology such as cardiac fibrosis, LV hypertrophy, atherosclerosis, and heart failure.[85] MMPs are a family of endopeptidases with the primary role of cleaving collagen, with 23 total family members.[86] MMP-1, 2, 8, 9, and 14 have been reported to have the ability to cleave collagen in CVD,[84] which align with our findings that identified studies reporting plasma MMP-1, 2, 3, and 9 concentrations to be reflective of early adverse cardiac remodelling. MMP-1 degrades fibrillar collagen, MMP-2 and 9 are involved in the angiogenic processes, and MMP-3 regulates ECM degradation. Hyperglycaemia is a key culprit of DM, where consistently high blood glucose contributes to oxidative stress and increased synthesis of MMP-9.[86]

In relation to MMPs, tissue inhibitors of metalloproteinases (TIMP) play a critical role in the regulation of MMPs and the extent of ECM degradation and structural remodelling.[87] Studies have found that in patients with T2D and hypertension, there is a significant increase in TIMP-1 levels, TIMP-1: MMP-9 ratios, and increased TNF-α.[86]

Given the mechanistic role of MMPs and TIMPs in the structural remodelling of the heart and CVD, they have become a prominent therapeutic target for the treatment of cardiac fibrosis, where their expression is increased in the early fibrosis, preceding scar tissue accumulation.[88]

Thus, both MMPs and TIMP-1 exhibit a strong potential in the early detection of cardiac remodelling in patients with DM.

As described above, cardiac fibrosis is commonly present in many forms of CVDs, where the early stages of cardiac remodelling are influenced by ECM remodelling.[14,84] MMPs have been established as critical regulators of these pathological changes in fibrosis,[86] notably involving excess collagen deposition through fibroblast activation. The major types of collagen present in cardiac muscle are collagen type I and III and account for 85% and 11%, respectively. The ratio of collagen type I to type III has been linked to cardiac fibrosis and underlying structural remodelling, where they can be indicative of the underlying causes.[14] Procollagen type 1 carboxy-terminal propeptide (PICP)

and PIIINP are two collagen peptides extracted from our literature search, and both are associated with production of their respective collagen peptides.[89,90] Previous studies have shown elevated PIIINP levels following myocardial infarction and LV[91] dysfunction, with a poor prognosis.[89,92] Similarly, increased PICP levels have been reported in patients with hypertrophic cardiomyopathy and hypertensive heart diseases but were more significantly elevated in cases of severe cardiac fibrosis.[93,94] However, in T2D, PICP levels were reported to be elevated in the presence of LV diastolic dysfunction compared to the controls.[91] Thus, plasma PIIINP and PICP concentrations have been associated with cardiac remodelling in attenuating the balance between collagen synthesis and degradation.[90] Both these collagen peptide precursors present promising biomarker potential reflective of the early adverse cardiac remodelling through collagen synthesis levels but require further research in people with DM.

4.4 | Metabol(om)ic markers of T2D and CVD: Future perspectives

Although not identified as part of the inclusion criteria of this scoping review, as an emerging field, it is important to consider the potential of metabol(om)ic markers in CVD diagnosis and prognosis in the context of DM. The defining feature of DM is impaired glucose-insulin homeostasis accompanied by obesogenic systemic environment. Over the years, association between circulating amino acids and insulin has been established with some of the amino acids showing an insulinotropic effect. Previous studies have shown a correlation between significant increases in circulating plasma concentrations of leucine, isoleucine, lysine, tryptophan, glutamine, and glycerol, which were identified as the strong metabolic predictors of impaired insulin sensitivity and the incidence of T2D.[95] In the longitudinal Framingham Heart Study, a metabolomic approach was used to measure plasma samples from 200 participants who proceeded to develop DM over a 12-year follow-up. Logistical regression models showed that increase in circulating concentrations of branched-chain amino acids (BCAAs) and aromatic amino acids were associated with future DM.[96] Phenylalanine, tyrosine, and isoleucine have also been reported to predict the onset of CVD.[97] However, the association of these amino acids with early adverse cardiac remodelling/fibrosis or dbCM have not been explored in-depth and this is an area of research that should be addressed in future.

Furthermore, an inverse association between the circulating aliphatic amino acid glycine concentration and risk of DM has been established.[98] Thus overall, the following amino acids have been identified as potential biomarkers of insulin resistance and DM: glutamate, glutamine, phenylalanine, tryptophan, tyrosine, glycine, isoleucine, leucine, and valine.[95,99] Comparable to BCAAs, the fatty acids (i.e. stearic, palmitic, oleic, linoleic, pentadecanoic, palmitoleic) and intact lipids (triacylglycerides) identified by metabolomics studies have shown potential use as early screening biomarkers for insulin resistance and subsequently DM.

Integration of the findings of GWAS with lipid data has highlighted genes such as *FADS1*, *FADS2*, *ELOVL2*, and *ELOVL6* to be associated with changes in circulating lipid concentrations in patients.[100,101] However, with the discovery of novel gene loci–lipid associations, links to insulin resistance endpoints including CVD will develop.

Further studies have implicated circulating metabolites and their potential role as a serum biomarker for dbCM in patients with DM and diastolic dysfunction. A high body mass index (BMI) and obesity have been correlated with the incidence of DM that is further linked to increases in fatty acid metabolism and impaired diastolic function.[102] Shaver et al. (2016)[102] reported the potential use of the metabolites as a biomarker in patients with diastolic dysfunction and DM compared to healthy controls. In the patient groups with the highest BMIs (DM, DM and diastolic dysfunction) leptin, triglyceride, TNF, and IL-6 concentrations were highest in these groups and inversely correlated with adiponectin levels. In line with these findings, high leptin and triglyceride levels have been associated with DM and fatty acid metabolism, where conversely, adiponectin presents antidiabetic and anti-inflammatory effects.[102] With their present inflammatory role in DM, these biomarkers show a strong potential in detecting cardiac remodelling with supporting echocardiographic data. However, this remains an unexplored research field that is lacking information of how these metabolites can be used as biomarkers of early cardiac changes, including adverse cardiac remodelling especially given their close relationship to inflammatory mechanisms. This field of research should be investigated further given the importance of cardiac metabolism in the development of CVD.

The limitations of this research article may be attributed to the small number of studies including that specifically examining the narrow topic of cardiac remodelling in DM. From the hundreds of research articles screened in this study, only seven studies were found to be of high quality. Further assessment of these biomarkers in a diagnostic or prognostic scope may provide more insight to the quality of their biomarker or therapeutic target potential in cardiac remodelling. Further specification of patient groups, stage of CVD, and cardiac function would bolster the findings of this study, however, were not available in all studies. It is also possible that some biomarkers commonly associated with adverse cardiac remodelling

were not found within our literature search because of the pre-set inclusion criteria, which narrows the range of research articles involving adverse cardiac remodelling. For example, growth differentiation factor 15 (GDF15) is a distant member of the TGF-β family with mechanistic roots in both CVD and DM.[103,104] Despite showing strong prognostic potential as a biomarker for CVD, its role is not well understood currently, hence why GDF15, and other cardiac remodelling-implicated biomarkers were potentially not included. Future inference on this topic would include a systematic review for a more in-depth consideration at the biomarkers mentioned in this study to substantiate their potential as biomarkers of cardiac remodelling in the presence of DM.

5 | CONCLUSION

Cardiac remodelling is inherently tied with cardiovascular outcomes, with DM being one of the main risk factors. The pathogenesis of cardiac remodelling in DM is yet to be elucidated and requires further investigation to understand the mechanisms involved. Through the data collected from this scoping review, it was revealed that NT-proBNP was the most frequently measured biomarker in studies evaluating cardiac remodelling and related CVD outcomes in people with DM. However, the findings and multivariate analysis in the included studies of this scoping review suggest that NT-proBNP, although the standard diagnostic and prognostic biomarker in HF may not be the optimal biomarker in determining signs of cardiac remodelling in the presence of DM. Emerging biomarkers for cardiac remodelling including hs-CRP, hs-cTnT, and Gal-3 being rooted in inflammatory pathways, have shown promising results in the current studies as diagnostic and prognostic biomarkers of adverse cardiac remodelling in DM. Although outside of the scoping review inclusion criteria, with the strong evidence supporting the relationship of certain amino acids and impaired insulin sensitivity, and the emergence of advanced metabolomics technologies, the possibility for the amino acids to be developed as new biomarkers for the early detection of adverse cardiac remodelling and CVD in DM is highly likely. However, further research in larger studies must be conducted to confirm the effectiveness of these emerging biomarkers and understand the mechanisms of cardiac remodelling in DM.

AUTHORS' CONTRIBUTIONS

Conceptualisation, LM and KM; methodology, data extraction, analysis, interpretation, and graphical abstract: MC, WL; contribution to data interpretation and manuscript content: MP and DA; writing—original draft preparation: MC. Manuscript editing: LM, MP, DA, KM. Supervision: LM and KM. All authors read and approved the final manuscript.

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CONFLICT OF INTEREST STATEMENT

The authors declare that they have no competing interests.

DATA AVAILABILITY STATEMENT

I confirm that my Data Availability Statement (pasted below) complies with the Expects Data Policy. The data that support the findings of this study are available from the corresponding author upon reasonable request.

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