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Diabetes and myocardial fibrosis: a systematic review and meta-analysis

Brief Title: Diabetes and myocardial fibrosis

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ABSTRACT

Objectives. This systematic review and meta-analysis investigated the association of diabetes and glycemic control with myocardial fibrosis (MF).

Background. MF is associated with an increased risk of heart failure, coronary artery disease, arrhythmias, and death. Diabetes may influence the development of MF, but evidence is inconsistent.

Methods. We searched EMBASE, Medline Ovid, Cochrane CENTRAL, Web of Science, Google Scholar for observational and interventional studies investigating the association of diabetes, glycemic control, and antidiabetic medication with MF assessed by histology and cardiovascular magnetic resonance (CMR) imaging (ie, extracellular volume fraction [ECV%] and T1 time).

Results. Thirty-two studies (88% exclusively on type 2 diabetes) involving 5,053 participants, were included in the systematic review. Meta-analyses showed that diabetes was associated with higher degree of MF assessed by histologic collagen volume fraction (n=6 studies, mean difference, MD: 5.80; 95%CI 2.00–9.59) and ECV% (n=13 studies, MD: 2.09; 95%CI 0.92–3.27), but not by native or postcontrast T1 time. Higher HbA_{1c} levels were associated with higher degrees of MF.

Conclusions. Diabetes is associated with higher degree of MF assessed by histology and ECV% but not by T1 time. In patients with diabetes, worse glycemic control was associated with higher MF degrees. These findings mostly apply to type 2 diabetes and warrant further investigation into whether these associations are causal and which medications could attenuate MF in patients with diabetes.

Keywords: Diabetes, glycosylated hemoglobin, myocardial fibrosis, meta-analysis, CMR T1 mapping, myocardial extracellular matrix

List of abbreviation/acronyms:

CI = confidence interval

CVF = collagen volume fraction

ECM = extracellular matrix

ECV% = extracellular volume fraction

HbA1c = glycosylated hemoglobin

HF = heart failure

MF = myocardial fibrosis

NOS = Newcastle Ottawa Scale

PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses

WMD = weighted mean difference

INTRODUCTION

Myocardial fibrosis (MF) is strongly associated with cardiovascular events, including heart failure (HF), coronary artery disease (CAD), atrial fibrillation (AF), and peripheral arterial disease (PAD)(1). The severity of histologically-measured MF has been independently associated with a higher risk of mortality(2,3). MF develops due to excess and disproportionate increase in concentration of collagen in the myocardial extracellular matrix (ECM)(4,5). This can result in reduced myocardial compliance, limitation of myocardial wall movement, and diastolic and/or systolic dysfunction. MF also affects impulse propagation resulting in arrhythmic events and conduction abnormalities(6). MF is characterized by expansion of myocardial interstitium, which has been considered as "a preeminent therapeutic target of the 21st century" in cardiology(7). The gold standard measure of MF is histology, an invasive examination that enables direct visualization of myocardial tissues. Cardiovascular magnetic resonance (CMR) T1 mapping is a non-invasive modality that calculates parameters such as extracellular volume fraction (ECV), native and postcontrast T1 time, used as surrogate measures of MF, which have high correlation with histologic measures(8).

The distribution (ie, focal vs diffuse MF) and degree of MF depend on the underlying disease(6,9). Recent studies have demonstrated that compared to focal fibrosis, diffuse fibrosis is more strongly associated with adverse outcomes, such as hospitalization for heart failure or mortality(10,11). Hypothetically, diabetes can increase the risk of diffuse MF through several mechanisms, including oxidative stress, pro-inflammatory state, growth factor secretion, neurohumoral activation, deposition of advanced glycation end-products(AGEs), and activation of the renin-angiotensin-aldosterone system(RAAS)(5,6,9). These effectors may activate myofibroblasts that produce fibrous tissue causing an imbalance of fibrosis deposition over degradation(12).

Previous studies investigating the association between diabetes and MF had inconsistent results(13-16). Some studies reported that diabetes is associated with greater degrees of interstitial MF(15,16). Other studies observed a similar degree of MF in those with and without diabetes, suggesting that diabetes may not play a role in MF development(13,14). Recent trials also showed inconclusive results regarding the effects of empagliflozin and liraglutide on MF(17,18). Overall, previous studies are mainly characterized by small sample sizes, limiting the generalizability of findings. Therefore, we performed a systematic review and meta-analysis to quantify the association of diabetes and glycaemic control with MF. Additionally, we summarized the evidence on the role of antidiabetic medications on MF.

MATERIALS AND METHODS

Data Sources and Searches

We followed a guide on how to design, conduct, and publish a systematic review and meta-analysis(19). Reporting was done in accordance with PRISMA guidelines(20). The protocol for this systematic review was registered on PROSPERO(CRD42020187508). An experienced information specialist performed literature search on electronic databases: EMBASE, Medline(Ovid), Cochrane CENTRAL, Web of Science, and Google Scholar and the search was updated until 24 January 2021. Details of the search strategy are in Appendix A(Supplemental material). Limits were applied to exclude animal studies, conference abstracts, letters to the editor, comments, and editorials. No language or publication date restrictions were considered.

Study Selection

Studies were included if they met the following criteria: (i)observational or interventional studies (ii)that investigated the association of diabetes status, glycaemic control, and antidiabetic medications with MF measured using histology and surrogate markers that have

been highly correlated with histology including CMR T1-mapping and computer tomography (CT)(8,21); and (iii)provided effect estimates with 95%CIs, mean differences with standard deviations(SD), and p-values. Detailed information on the measures of MF is provided in Table 1. Two independent reviewers screened each abstract. Full-text articles of the studies that passed screening were retrieved. Two independent reviewers performed full-text assessment. In cases of disagreement between the two reviewers, a third reviewer was consulted. Cross-referencing was done using the bibliographic entries of the included articles, applying the same criteria.

Data Extraction and Quality Assessment

Study characteristics (e.g.,study design, sample size), participant characteristics (e.g.,age, sex, body mass index[BMI], diabetes status, glycosylated haemoglobin[HbA_{1c}], cardiovascular morbidities, and MF estimates were recorded in a predesigned data collection form.

Each study was evaluated by two independent reviewers. We assessed the quality of included studies using the Newcastle Ottawa Scale(NOS)(Appendix B)(22). We assessed interventional studies using a revised tool for assessing the risk of bias in randomized trials(RoB 2) and a tool for assessing the risk of bias in non-randomized studies of interventions(ROBINS-I)(23,24).

Data Synthesis and Analysis

Summary measures of continuous outcomes were reported as mean±SD to facilitate synthesis. We used random effects model to pool the effect estimates of studies that reported MF measures using the same modality and scale. When studies were excluded from the meta-analyses, the reasons for exclusion were provided(Appendix C). Heterogeneity was assessed using I^2 *statistic*, with $I^2 \leq 25\%$ considered low heterogeneity, I^2 between 25% and 75% as moderate, and $I > 75\%$ considered high. Publication bias was assessed using funnel plots and Egger's test.

Study characteristics including age, sex, BMI, HbA_{1c}, LVEF as independent variables and effect estimates as dependent variables were analysed in the random effects meta-regression for outcome measures that included ≥10 studies(25). We stratified analyses by age, HbA1c, history of previous MI, insulin use, MRI magnet strength, acquisition sequence, matching, publication bias, and study quality. We performed sensitivity analyses to studies that: (i)focused on type 2 diabetes; (ii)excluded patients with BMI ≥30kg/m^2, (iii)uncontrolled hypertension, (iv)left ventricular hypertrophy(LVH), (v)prior MI or existing HF, and (vi)late gadolinium enhancement(LGE+) in ECV studies. (vii)To assess the impact of individual studies on the overall results, we recalculated the effect estimates after removing the studies one by one from the pooled analysis. For MF outcomes that included only 2 studies, we pooled data using fixed effects meta-analysis. Statistical analyses were performed in StataIC 15.1(StataCorp LLC, TX, USA). We considered $p<0.05$ as statistically significant.

RESULTS

Literature search

The results of the search strategy are presented in Figure 1. Of 5,662 unique citations, we included 27 articles that met our inclusion criteria. Articles were added from search update and bibliographic search, resulting in a total of 32 eligible articles. Table 2 and Supplemental Tables S1-S4 summarize key study characteristics. Study sample sizes are from 16–1345, with a total population of 5,053 The population median[IQR] age was 55[51–60] years. Studies investigated the association of diabetes status(n=27),glycaemic control(n=3), and antidiabetic medications(i.e.,empagliflozin and liraglutide) with MF(Table 2 and Supplemental Tables S1-S4). Studies were conducted in Europe(n=10), Asia(n=10), North America(n=10), Australia(n=1), and South America(n=1). Participants were recruited from tertiary hospitals(n=20), general practice or diabetes clinics(n=7) or general population(n=2). Studies investigated mostly type 2 diabetes(n=28)(Supplemental Table S1). MF was assessed

using histology and CMR T1 mapping(i.e., ECV%, native T1 time, postcontrast T1 time). ECV and native T1 studies used 1.5T(n=8) and 3.0T(n=7) machines and imaging sequence used were Look-Locker technique(n=1) Modified Look-Locker Inversion recovery(MOLLI,n=12), Saturation recovery single-shot acquisition(SASHA,n=1), and Slice interleaved T1 sequence(STONE,n=1).

Diabetes and myocardial fibrosis

Diabetes and myocardial fibrosis assessed by histology

Eight studies investigated the association of diabetes with MF assessed by histology. All studies included patients who underwent coronary angiography or surgery for coronary or valvular disease(Table 2). Study samples were derived from left ventricular myocardium(n=8), right ventricle(n=1), or left atrium(n=1). Six studies reported an association of diabetes with increased myocardial CVF, and two studies did not find an association. Meta-analysis of six eligible studies showed an association between diabetes and CVF(WMD 5.80; 95%CI 2.0,9.59; I^2=90%)(Figure 2a).

Diabetes and myocardial fibrosis assessed by CMR T1 mapping-ECV%

Of the 14 T1 mapping-ECV% studies, eight studies found an association of diabetes with increased ECV%, while six studies did not find an association(Table 2). Meta-analysis of 13 eligible studies showed that diabetes is associated with higher ECV%(WMD 2.09; 95%CI 0.92,3.27; I^2=90%)(Figure 2b).

Diabetes and myocardial fibrosis assessed by CMR T1 mapping-native T1 time

Of the 14 native T1 mapping studies included in the systematic review, six showed an association of diabetes with higher native T1 time, while eight did not show an association(Table 2). Meta-analysis of 12 studies did not show an association of diabetes with native T1 time(WMD 21.74; 95%CI -1.27,44.75; I^2=93%)(Figure 2c).

Diabetes and myocardial fibrosis assessed by CMR T1 mapping-postcontrast T1 time

Of the eight postcontrast T1 mapping studies included in the systematic review, one showed an association of diabetes with MF, and seven did not show an association(Table 2). Meta-analysis of seven studies did not show an association of diabetes with postcontrast T1 time(WMD -16.22; 95%CI -36.68,4.25; I^2=85%)(Figure 2d).

Pre-diabetes and myocardial fibrosis

Three studies compared MF measures of normoglycaemia, pre-diabetes, and diabetes groups(Supplemental Table S2). Of the three studies, one study showed higher ECV% of the diabetes group compared to the pre-diabetes group(WMD 1.4; 95%CI 0.1,2.6), and two studies did not show an association. One of the three studies assessed MF by postcontrast T1 time, showing higher degree of MF in the pre-diabetes group(β=-29.9, 95%CI -56.9,-2.9) compared to the normoglycaemia group. All studies did not find significant differences in native T1 time between groups(Supplemental Table S2).

Glycaemic control and myocardial fibrosis

Three studies investigated the association of HbA_{1c} with measures of MF among patients with diabetes. Higher HbA_{1c} levels were consistently associated with higher degree of MF assessed by ECV% or native T1 time(Supplemental Table S3). Meta-analysis showed that every 1% increase in HbA_{1c} is associated with 0.37% increase in ECV%(n=2 studies; β=0.37; 95%CI 0.20,0.55; I^2=0%)(Supplemental Figure S1).

Antidiabetic medications and myocardial fibrosis

Two double-blind randomized placebo-controlled trials and two non-randomized trials, assessed the effects of empagliflozin and liraglutide on MF degree in patients with diabetes followed-up over 26 weeks(Supplemental Table S4). In one randomized controlled trial(RCT), empagliflozin intervention resulted in a greater reduction in ECV% compared to placebo(ECV% reduction, 1.4; 95%CI 0.14,2.6), but there was no difference in native T1

time(ms) reduction (T1 time reduction, 5.2; 95%CI -11.5,21.9). In the other interventional studies, empagliflozin or liraglutide did not reduce ECV% and native T1 time in patients with diabetes.

Quality assessment and risk of bias

The risk of bias in observational studies varied from low(25%) to moderate(25%) to high(50%)(Supplemental Table S5). The two RCTs had low risk of bias. The two non-randomized trials had critical risk of bias(Supplemental Table S6). Funnel plots for ECV% and native T1 studies are shown in Supplemental Figure S2. Egger's regression test did not show evidence of asymmetry in ECV%(p=0.76) and native T1(p=0.12) studies(Supplemental Figure S2). Estimates remained similar after removing each study one by one from the meta-analyses, except when removing one study(26) that resulted in statistically significant results and reduction of heterogeneity (I^2=21%) in native T1 time meta-analysis(Supplemental Figure S3c; Supplemental Table S8).

Sensitivity analyses

The meta-regression analyses did not show an association between clinical characteristics and effect estimates for ECV% and native T1 studies(Supplemental Table S7 & Figure S4). In the subgroup analyses, individuals with worse glycaemic control had a greater magnitude of the association between diabetes and MF degree, albeit the CIs partially overlapped between HbA_{1c} categories(Supplemental Table S8). The results of ECV% meta-analysis remained consistent in subgroup analyses, after accounting for insulin use, prior MI, MRI magnet strength and acquisition sequence, and after restricting the analyses to type 2 diabetes, and excluding studies with: (i)participants that have BMI≥30 kg/m^2, (ii)uncontrolled hypertension, (iii)LVH, (iv)previous MI or existing HF, (v)LGE+, (vi)unmatched or unadjusted effect estimates, (vii)effect estimates that fell outside the 95%CI of the funnel plots, and (viii)poor quality(Supplemental Table S8). The direction of association of native

T1 meta-analysis remained consistent in subgroup analyses after accounting for insulin use, MRI magnet strength, and even became statistically significant when analysis was restricted to MOLLI studies, and after excluding studies with: (i)participants that have BMI≥30 kg/m^2, (ii)uncontrolled hypertension, (iii)LVH, (iv)previous MI with or without (v)existing HF, and (vi)effect estimates that fell outside the 95% CI of the funnel plots(Supplemental Table S8). For T1 time meta-analysis, restriction of analysis to studies including participants without previous MI (i.e.,corresponding to removal of 1 study(26) led to decrease in heterogeneity (I^2=21%), *p* for metaregression<0.05)(Supplemental Table S8).

DISCUSSION

In this systematic review and meta-analysis, we found that diabetes is associated with a higher degree of MF assessed by histology and non-invasive ECV%, but not with T1 time (Central Illustration). In patients with diabetes, those with worse glycaemic control had a higher degree of MF. Results are predominantly applicable to type 2 diabetes, given that most studies were focused on the investigation of type 2 diabetes.

Diabetes and measures of myocardial fibrosis

Our meta-analyses showed a significant association of diabetes with MF degree, when the latter was assessed by MF examinations of high accuracy (i.e.,histology and ECV%) and/or when a relatively large sample size of participants was included (i.e.,ECV% meta-analysis). Histology is the gold standard examination for measuring MF. However, it is invasive, is usually performed in selected patient populations, and the possibility of sampling error cannot be excluded(27). ECV% has a high correlation(r=0.88) with myocardial biopsy measures(8). Our meta-analysis of histology and ECV% studies consistently showed an association of diabetes with the degree of MF. Albeit not statistically significant, the direction of association for T1 time parameters was in line with our findings on histology and ECV studies. The lack of statistical significance in the meta-analysis of T1 time studies may be

related to the limited sample size of included studies. While our meta-analyses of T1 time studies may have been underpowered to detect an association, the meta-analysis of ECV% studies included a relatively large number of participants(n=2684). Additional reasons can explain the results of meta-analyses of T1 time studies. T1 time parameters are not as strongly correlated to histology measures as ECV%(r=0.6 vs 0.88)(8). A cohort study also showed that abnormal ECV was associated more strongly with adverse events than native or postcontrast T1 parameters(10). Furthermore, T1 time parameters estimate processes involving the whole myocardium, and may lack sensitivity of evaluating changes occurring in the interstitium(28). Compared to ECV%, T1 time parameters are also more sensitive to population characteristics(29). In a study involving participants with normal ECV, native T1 time was elevated among patients with diabetes. This may suggest a potential influence of diabetes on T1 time parameters independent of MF(30). In the future, other imaging modalities as CT-ECV can be used as surrogate measures of MF, especially in individuals who have contraindications to CMR measures(21).

Clinical relevance of our findings

Our meta-analyses of histology and ECV% studies showed that patients with diabetes have 5.8% higher CVF and 2.1% higher ECV% than those without diabetes. These findings, if confirmed, could be clinically relevant because a higher degree of MF has been associated with a higher risk of adverse events(31-33). Studies that measured MF using histology reported that every unit increase in CVF was prospectively associated with up to 28% and 50% increased risk of cardiac events and all-cause mortality, respectively(2,34). On the other hand, every unit increase in ECV% has been prospectively associated with a 30% increased risk of recurrent AF and a 16% increased risk of composite HHF or all-cause mortality(31-33).

Clinical factors

The association of diabetes with MF can be influenced by several factors, such as age, sex, comorbidities, and medications. However, our meta-regression analyses suggested lack of sex- or age- differences. Additional subgroup analyses generally indicated similar point estimates and a large overlap of CIs across strata. After we excluded studies conducted in patients with obesity, uncontrolled hypertension, LVH, the results of ECV% meta-analysis remained similar; and the results of native T1 meta-analysis became statistically significant and consistent with ECV% results. In particular, the results of T1 time meta-analysis could have been influenced by presence or absence of MI history. Restricting analysis of native T1 studies to those without previous MI reduced heterogeneity from 93% to 21% by removing only one study(26), which is the same study that influenced the results of leave-one-out analysis.

Renal failure can affect the association between diabetes and MF(35). However, all studies that required use of contrast agent(i.e.,ECV% and postcontrast T1) excluded patients with glomerular filtration rate(GFR) of <30mL/min. Moreover, the two studies with the largest sample sizes included in the meta-analysis provided consistent results even after adjusting for GFR(32,33). This may imply that the link between diabetes and MF is independent of the abovementioned cardiometabolic conditions, which are associated with diabetes and MF(36). Furthermore, the link between diabetes and MF can be also affected by antihypertensive medications. Patients with diabetes are commonly prescribed renoprotective antihypertensive medications such as RAAS antagonists, which are known to decrease ECV% among patients with diabetes(16). In our systematic review, the few studies that adjusted for antihypertensive medications or studies that excluded participants using RAAS antagonists consistently showed an association of diabetes with MF(26,33,37). Future studies on diabetes and MF need to properly account for the concurrent effects of RAAS antagonists and other antihypertensive medications.

Accounting for T1-mapping specific factors such as magnetic field strength, sequence acquisition, and in ECV studies the exclusion of LGE+ areas, yielded similar results across strata. Meanwhile, meta-analyses of ECV and T1 studies showed similar or slightly stronger associations after removing unmatched studies, poor quality studies, and those with potential publication bias, which indicates the robustness of our findings. Notably, heterogeneity dropped to 41% for ECV and 0% for native T1 meta-analysis when studies that had potential for publication bias were excluded.

Overall, we accounted for a wide range of factors to explain potential sources of heterogeneity. One possible explanation of observed heterogeneity is that accounting for individual factors may – to some extent – reduce heterogeneity, but taken altogether, these factors may account for the overall heterogeneity observed. In the future, adequately powered and high quality studies performed in more homogeneous populations are needed to confirm our findings.

Diabetes status, glycaemic control and myocardial fibrosis

Our data suggests that the degree of MF may increase across categories of diabetes status, from normoglycaemia to pre-diabetes to diabetes(1,32). One can also hypothesize that the degree of MF is not only influenced by diabetes status, but also by glycaemic control. In our systematic review and meta-analysis, HbA_{1c} levels, which represent glycaemic control over the past three months, were positively and consistently associated with the degree of MF in patients with diabetes. Our subgroup analyses also suggested that the association of diabetes with MF tends to be stronger among patients with worse glycaemic control.

Pathophysiological mechanisms linking diabetes to myocardial fibrosis

Several pathophysiological mechanisms can explain the link between diabetes and MF. First, chronic hyperglycaemia may upregulate genes that encode transforming growth factor(TGF)-

β and downregulate the expression of matrix metalloproteinases(MMPs), including MMP-2(38,39). In turn, increased TGF-β expression and reduced MMP-2 activity promote cardiac fibrosis(38,40). Second, chronic hyperglycaemia promotes the formation of AGEs. AGEs cross-link collagens in the myocardial interstitium, making them resistant to degradation by MMPs, and may thus contribute to fibrosis(5). Furthermore, AGEs generate reactive oxygen species(ROS) and oxidative stress, which are shown to trigger MF in rat models of diabetes(41). Third, pro-inflammatory cytokines and chemokines in diabetes may also promote myofibroblast proliferation and collagen synthesis(5). Fourth, increased RAAS activity in diabetes may activate TGF-β that triggers a fibrosis cascade. Accordingly, RAAS inhibition in rat diabetes models led to decreased TGF-β levels, along with reductions in collagen deposition and coronary perivascular fibrosis(42). Fifth, oxidative stress in diabetes may contribute to the development and progression of MF. In models of diabetic mice, the administration of antioxidants lowered the degree of MF, reduced cardiomyocyte hypertrophy, and improved diastolic dysfunction(43).

Antidiabetic medications and myocardial fibrosis

Antidiabetic medications may attenuate MF by acting on the abovementioned pathways linking diabetes to MF. As shown in vitro, empagliflozin affected human cardiac myofibroblasts via decreasing TGF-β-induced fibroblast activation, myofibroblast size, cell-mediated ECM remodeling, and expression of profibrotic biomarkers(44). Liraglutide reduced MF through inhibition of ROS production, and downregulation of collagen type I and III(COL1,COL3) and matrix metalloproteinase 1 and 9(MMP1,MMP9) genes in murine myocardial tissues(45,46). Compounds from other antidiabetic drug classes, such as rosiglitazone (peroxisome proliferator-activated receptor γ agonist), sitagliptin (dipeptidyl peptidase IV inhibitor), and exogenous insulin, also reduced MF in animal models(47-49). In our systematic review, two RCTs with a low risk of bias investigated the effect of

empagliflozin and liraglutide on the degree of MF(17,18). After 26 weeks of treatment, empagliflozin resulted in 1.4% ECV reduction, whereas liraglutide did not show ECV% reduction. The different effects of sodium glucose cotransporter 2(SGLT2) inhibitors (i.e.,empagliflozin,dapagliflozin) and glucagon-like peptide 1(GLP1) analogues may partly account for these results. SGLT2 inhibitors may have more powerful antifibrotic effects compared to GLP1 analogues(50,51). The administration of SGLT2 inhibitors in rats with diabetes led to greater reduction of myocardial fibrosis, collagen deposition, oxidative stress, expression of proinflammatory cytokines, and RAAS activity, compared to GLP1 analogues(50,51). Another explanation is that participants in the liraglutide trial had a lower baseline ECV% compared to those in the empagliflozin trial. ECV% values were within normal ranges in the liraglutide trial and above normal ranges in the empagliflozin trial(52). The sample size may have also influenced the results, since the empagliflozin trial included more participants than the liraglutide trial. On the other hand, these trials did not show reduction of T1 time. In the future, adequately powered RCTs with a longer follow-up time may provide insights on the antifibrotic effects of SGLT2 inhibitors and GLP1 analogues. These investigations may be further extended to other antidiabetic drug classes, and also compare the effects of the various compounds within each class.

Strengths and limitations

To our knowledge, this is the first systematic review and meta-analysis on the association of diabetes, glycaemic control, and antidiabetic medications with the degree of MF. MF was assessed using a variety of measures, including histology and non-invasive CMR T1 mapping parameters. Our systematic review included a relatively large number of participants with a wide range of ages from across five continents and different clinical settings. This can increase the generalizability of our findings. We were able to perform summary statistics and combine the available evidence in a meta-analysis and meta-regression. We used strict

criteria to assess the quality of included studies. We performed multiple sensitivity analyses, which provided consistent findings. Lastly, the results were not influenced by a single study, and no evidence of publication bias was found.

Several limitations warrant mentioning. The studies on diabetes and MF were cross-sectional; thereby reverse causation or bidirectional associations cannot be excluded. A proportion of included studies were rated as poor quality. Nonetheless, our results remained consistent even after excluding studies of poor quality, and studies providing unmatched or unadjusted estimates. Heterogeneity was high and could be reduced to some extent by some subgroup analyses. Interventional studies on antidiabetic medications were available only for empagliflozin and liraglutide. These trials had a limited sample size and a follow-up time of 26 weeks, which is likely short considering the gradual development of MF.

Conclusions

Diabetes is associated with a higher degree of MF assessed by histology and ECV%, but not by T1 time. In patients with diabetes, worse glycaemic control was associated with a higher degree of MF. These findings warrant additional investigation into whether the associations of diabetes and glycaemic control with MF are causal. Further research can help identify mediators and improve our understanding on the mechanisms linking diabetes to MF. Regression of diffuse myocardial fibrosis in patients with diabetes may represent a novel clinical target associated with improved outcomes, but this needs to be verified through randomized controlled trials assessing antidiabetic drugs and other treatment. Taken altogether, these strategies could eventually lead to the development of novel preventive and therapeutic strategies against MF.

COMPETENCY IN MEDICAL KNOWLEDGE: Diabetes is associated with higher degrees of MF assessed by histology and CMR T1-mapping derived ECV%. Persons with worse glycemic control have a higher degree of MF.

TRANSLATIONAL OUTLOOK: Future studies should investigate if the associations of diabetes and glycemic control with MF are causal. Further research can help identify mediators and improve our understanding on the mechanisms linking diabetes to MF. Regression of diffuse myocardial fibrosis in patients with diabetes may represent a novel clinical target associated with improved outcomes, but this needs to be verified through randomized controlled trials assessing antidiabetic drugs and other treatment.

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Figure 1. Flowchart of identification, screening, eligibility, inclusion, and exclusion of studies retrieved

Figure 2. Meta-analysis of diabetes status and myocardial fibrosis
Myocardial fibrosis was assessed using *a*.Histology, *b*.ECV% *c*.Native T1 time *d*.Postcontrast T1 time. Higher values of CVF, ECV%, or Native T1(ms) and lower postcontrast T1(ms) indicate higher degree of fibrosis. The effect estimates, illustrated as a point (single-study) or diamond (pooled studies) in the forest plot were calculated as the difference in the degree of fibrosis between those with diabetes and those without diabetes (reference group). Effect estimates to the right of null in subfigures *a-c* or left of null in subfigure *d* indicate higher degree of fibrosis in those with diabetes than in those without diabetes.
CMR–cardiovascular magnetic resonance; CVF–collagen volume fraction; ECV%–extracellular volume fraction; WMD–weighted mean difference

Central Illustration. Meta-analysis of diabetes status and myocardial fibrosis
Myocardial fibrosis was assessed using: a. Histology (CVF%), b. ECV%, c. Native T1 time, d. Postcontrast T1 time. Higher values of CVF, ECV%, or native T1 time and lower values of postcontrast T1 time indicate higher degree of fibrosis. The diamonds and bars in the forest plot illustrate pooled effect estimates and their confidence intervals, respectively. The estimates were calculated as the difference in the degree of fibrosis between those with diabetes and those without diabetes (reference). Effect estimates in the plain areas of the forest plot indicate higher degree of fibrosis in those with diabetes than in those without diabetes. Effect estimates in the dotted areas of the forest plot indicate lower degree of fibrosis in those with diabetes than in those without diabetes.
CI – confidence interval ; CVF – collagen volume fraction, ECV – extracellular volume fraction

Table 1. Measures of myocardial fibrosis*

Diagnostic modality	Unit	Accuracy	Invasiveness	Interpretation
a. Histology				
CVF	%	high	invasive	**higher** values = higher degree of MF
b. CMR T1 mapping				
ECV%	%	high	non-invasive	**higher** values = higher degree of MF
Native T1 time	ms	moderate		
Postcontrast T1 time	ms	moderate		**lower** values = higher degree of MF

(a) Histology is the gold standard assessment of MF. It is enables a direct visualization of myocardial tissues. The results of histologic MF measurement are often reported as CVF, which is the estimated proportion of myocardial area occupied by collagen, excluding endocardial and perivascular collagen.

(b) CMR T1 mapping parameters used to measure MF include: extracellular volume fraction (ECV%), native T1 time, and postcontrast T1 time. Parametric CMR T1 mapping enables a radiographic visualization and quantification of MF, and can be done without use of contrast agent (native T1 time), enhanced by contrast agent (postcontrast T1 time), or combining parameters based on the change in T1 values before and after contrast administration into one measure (ECV%).

* Another modality, Computed Tomography (CT)-ECV, used in routine evaluations prior to transcatheter aortic valve replacement (TAVR), can also be used to estimate diffuse fibrosis(53). CT-ECV estimation is a viable alterative to CMR, especially to individuals who

have contraindication for the latter(21).

Abbreviations: *CVF – collagen volume fraction; CMR - Cardiovascular magnetic resonance; ECV% - extracellular volume fraction; MF – myocardial fibrosis*

Table 2. Observational Studies on the Association of Diabetes with Myocardial Fibrosis

Publication	*Country*	*n*	*Study population*	*Mean age / % Female*	*Mean difference / beta coefficient*	*Matched/ (Adjusted)*
a. Histology CVF (%)						
Nunoda 1985	Japan	16	Patients with cardiac symptoms seen in a tertiary hospital	46.2/31	**10.60 (4.74; 16.46)**	-
Shimizu 1993	Japan	18	Patients who underwent cardiac catheterization	49.2/50	**9.80 (7.60; 12.00)**	-
***Kawaguchi 1997**	Japan	25	Patients who underwent diagnostic cardiac catheterization	62.2/40	**0.98 (0.52; 1.44)**	-
van Heerebeek 2008	Netherlands	64	Patients hospitalized for HF	62.4/50	2.07 (-0.53; 4.67)	-
Falcao 2011	Netherlands	32	Patients due for aortic valve repair	65.3/53	5.30 (-2.15; 12.75)	-
Sakakibara 2011	Japan	36	Ambulatory patients with DCM	52.7/79	**1.70 (0.50; 2.90)**	
Frustaci 2016	Italy	18	CVD patients in a tertiary hospital	60/41	**6.90 (1.25; 12.55)**	age, sex, LVD
***Wang**	China	86	Patients who underwent	60/35	**1.5 (p=0.03)**	

2019			CABG			
b. CMR-ECV (%)						
Shah 2013	USA	33	Obese adolescents in a tertiary hospital and healthy volunteers	16.8/51.5	**8.56 (4.63; 12.50)**	-
Wong 2014	USA	1176	Patients referred for CMR at tertiary hospital	54.6/41	**1.60 (0.99;2.21)** **β (95% CI)= 1.40 (0.40; 2.40)**	(age, sex, race, smoking, HTN, eGFR, LVEF, MI size, LVMI, NDCA, BB, RAASi)
Levelt 2016	UK	66	DM Patients in general practice clinics and community controls	54.7/51	0 (-1.44; 1.44)	age, sex, weight, HR, BMI, SBP
Swoboda 2017	UK	130	Patients in general practice clinics and community controls	60.3/21	**2.80 (1.54; 4.06)**	age, sex
Vasanji 2017	Canada	28	DM patients from diabetes clinics and community controls	51.5/43	2.00 (-3.42; 7.42)	age, sex, BMI
Cao 2018	China	82	Patients in tertiary hospital and community controls	54.6/45	**2.80 (1.77; 3.83)**	age, sex, BMI
Storz 2018	Germany	251	General population	56.1/43	**-1.54 (-2.71; -0.37)**	age, sex, HTN, BMI

***Ambale-Venkatesh 2019**	USA	1345	General population	68/52 *synthetic ECV* *Untreated DM* β = -0.26, p= 0.70 *Treated DM* β = 0.20, p = 0.40		- -
Chirinos 2019	USA	53	Symptomatic HFpEF patients in tertiary hospital	63.4/25	**3.30 (0.44; 6.16)**	
Gao 2019	China	100	Patients in a tertiary hospital and healthy volunteers	57.4/59	**4.43 (3.08; 5.78)**	age, sex, BMI
Gulsin 2019	UK	96	HFpEF cases from outpatient and inpatient clinics	72.3/51	0 (-2; 2)	(sex, HTN, serum creatinine)
Lam 2019	USA	37	Patients from endocrinology clinic and community controls	49.5/70	-1.00 (-2.68; 0.69)	-
Jiang 2020	USA	190	Patients from a tertiary hospital and healthy controls	55.6/37	**5.08 (3.96; 6.2)**	age, sex, BMI
Khan 2020	USA	442	Patients referred for CMR at tertiary hospital	55.7/52 **1.95 (0.95; 2.95)** univariable **β (95% CI)= 1.72 (0.67; 2.78)**		(Age, sex, race, BSA, SBP, HR, eGFR, ARIC score, LAV,

				multivariable **β (95%CI)= 1.33 (0.22; 2.44)**		LVCO, LVS
c. Native T1 time (ms)						
Khan 2014	UK	26	Young adults with type 2 diabetes and controls with no diabetes	31.1/50	-27.54 (-105.24; 49.16)	age, sex
Levelt 2016	UK	66	Patients in general practice clinics and community controls	54.7/51	10.00 (-5.37; 25.37)	
Swoboda 2017	UK	130	Patients in general practice clinics and community controls	60.3/21	**32.50 (12.52; 52.48)**	age, sex
Vasanji 2017	Canada	28	type 1 diabetes patients from diabetes clinics and community controls	51.5/43	39.00 (-81.58; 159.58)	age, sex, BMI
Cao 2018	China	82	Patients in tertiary hospital and community controls	54.6/45	**15.10 (2.62; 27.58)**	age, sex, BMI
Storz 2018	Germany	343	General population	56.1/43	-2.03 (-18.24; 14.19)	-
***Ambale-Venkatesh 2019**	USA	1345	General population	68/52 *Untreated DM* β = -18.8, p= 0.08 *Treated DM* **β = 7.6, p = 0.04**		- -

***Contti 2019**	Brazil	44	Renal transplant patients	50/39	-8 (-23.4 ; 39.8)	age, sex
Gao 2019	China	100	Patients in tertiary hospital and healthy volunteers	57.4/59	5.39 (-49.69; 60.48)	age, sex, BMI
Lam 2019	USA	37	Patients from endocrinology clinic and community controls	49.5/70	**34 (11.83; 56.17)**	-
Jiang 2020	USA	190	Patients from tertiary hospital and healthy controls	55.6/37	33.4 (-28.4; 95.2)	age, sex, BMI
Khan 2020	USA	442	Patients referred for CMR at tertiary hospital	55.7/52	1.89 (-45.96; 49.73)	-
Kropidlowski 2020	Germany	63	Patients with well-treated hypertension and healthy volunteers	58.7/49	20 (-6.47;46.56)	-
Kucuksey men 2020	USA	207	Patients with diabetes, obesity, or both and healthy controls	55.6/61	**78 (69.69; 86.32)**	age, sex, HTN, T-BMI, ACEi/ARB use
d. Postcontrast T1 time (ms)						
Ng 2012	USA	69	Cardiology patients	49.3/43	**-79 (-104.14; -53.86)**	age, sex, BMI
Khan 2014	UK	26	Patients with type 2 diabetes and community controls	31.1/50	23.59 (-42.51; 89.69)	age, sex

Vasanji 2017	Canada	28	type 1 diabetes patients from diabetes clinics and community controls	51.5/43	26 (-95.91; 147.91)	age, sex, BMI
Cao 2018	China	82	Patients in tertiary hospital and community controls	54.6/45	0.30 (-11.04; 11.64)	age, sex, BMI
***Ambale-Venkatesh 2019**	USA	1345	General population	68/52	*Untreated DM* β = -60.9, p= 0.08 *Treated DM* **β = 7.6, p = 0.04**	-
Gao 2019	China	100	Patients in a tertiary hospital and healthy volunteers	57.4/59	6.84 (-8.81; 22.50)	age, sex, BMI
Lam 2019	USA	37	Patients from endocrinology clinic and community controls	49.5/70	**-26 (-46.13; -5.87)**	-
Jiang 2020	USA	190	Patients from tertiary hospital and healthy controls	55.6/37	**-13.78 (-25.88; -1.68)**	age, sex, BMI

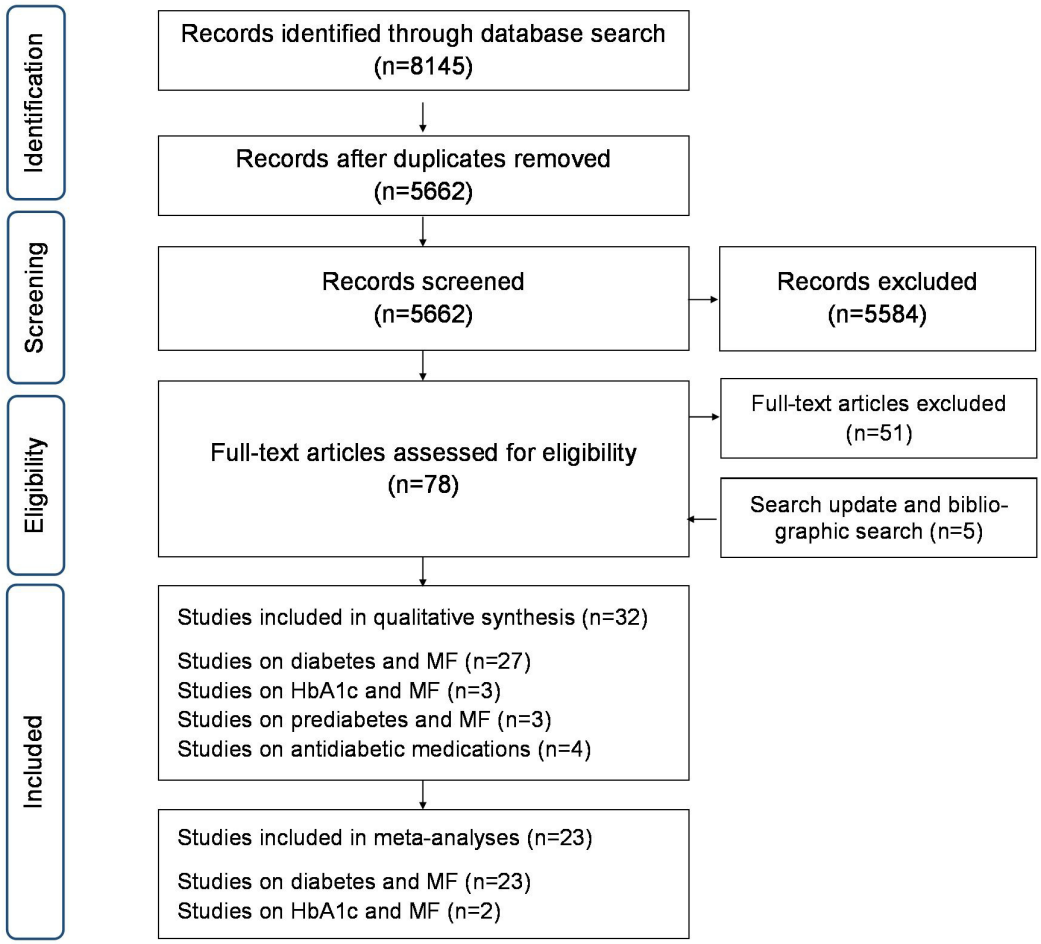
Full references of studies included in the systematic review are listed in the Supplemental material

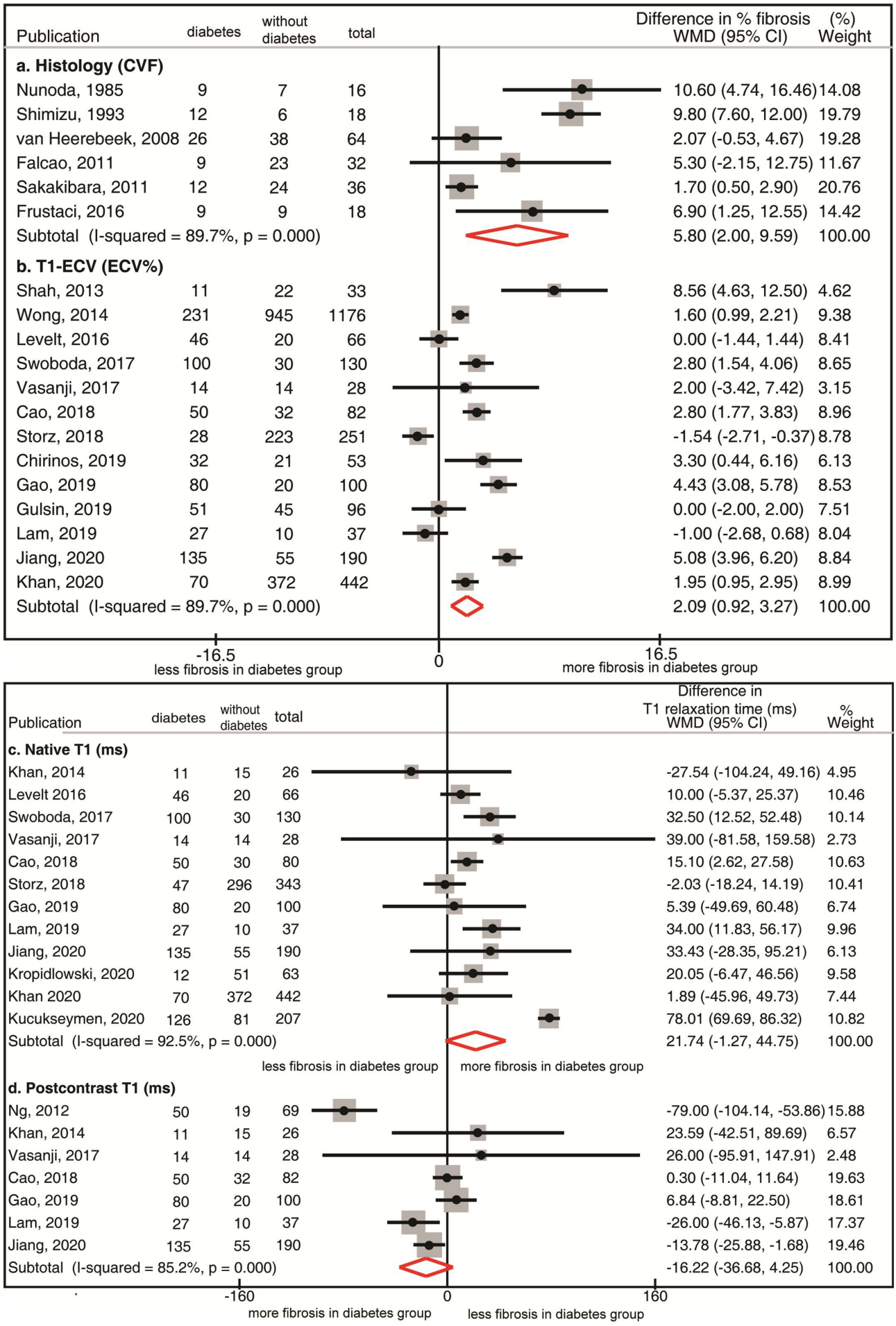
** Not eligible for inclusion in meta-analysis (Reasons for exclusion outlined in Appendix)*

Effect estimates are presented as mean difference and 95% confidence interval or p-value, uncleass otherwise specified. Statistically significant estimates (p < 0.05) are shown in bold. **Effect estimates indicate the difference in the degree of fibrosis between those with diabetes and those without**

diabetes (reference group). Higher values of CVF (%), ECV (%) or native T1 (ms) and lower postcontrast T1 (ms) indicate higher degree of fibrosis.

*Abbreviations: ACEi – angiotensin-converting enzyme inhibitor; ARB – angiotensin II receptor blocker; ARIC – Atherosclerosis risk in communities; **β**, linear regression coefficient; BB – beta-blockers; BMI – body mass index; BSA – body surface area; CABG – coronary artery bypass graft; CI – confidence interval; CMR – cardiovascular magnetic resonance; CVF% – collagen volume fraction; ECV% – extracellular volume fraction; eGFR – estimated glomerular filtration rate; DCM – dilated cardiomyopathy; HF – heart failure; HFpEF – heart failure with preserved ejection fraction; HR – heart rate; HTN – hypertension; LAV – left atrial volume; LVCO – left ventricular cardiac output; LVD – left ventricular dysfunction; LVEF – left ventricular ejection fraction; LVH – left ventricular hypertrophy; LVMI – left ventricular mass index; LVS – left ventricular scar; MI size – myocardial infarct size; NDCA – number of diseases coronary arteries; RAASi – renin-angiotensin-aldosteron system inhibitors; SBP – systolic blood pressure; SD – standard deviation; SE – standard error; T-BMI – triglyceride-BMI index.*


Identification
Screening
Eligibility
Included
Records identified through database search (n=8145)
Records after duplicates removed (n=5662)
Records screened (n=5662)
Records excluded (n=5584)
Full-text articles assessed for eligibility (n=78)
Full-text articles excluded (n=51)
Search update and biblio-graphic search (n=5)
Studies included in qualitative synthesis (n=32)
Studies on diabetes and MF (n=27)
Studies on HbA1c and MF (n=3)
Studies on prediabetes and MF (n=3)
Studies on antidiabetic medications (n=4)
Studies included in meta-analyses (n=23)
Studies on diabetes and MF (n=23)
Studies on HbA1c and MF (n=2)


Publication
diabetes
without diabetes
total
Difference in % fibrosis WMD (95% CI)
(%) Weight
a. Histology (CVF)
Nunoda, 1985 9 7 16 10.60 (4.74, 16.46) 14.08
Shimizu, 1993 12 6 18 9.80 (7.60, 12.00) 19.79
van Heerebeek, 2008 26 38 64 2.07 (-0.53, 4.67) 19.28
Falcao, 2011 9 23 32 5.30 (-2.15, 12.75) 11.67
Sakakibara, 2011 12 24 36 1.70 (0.50, 2.90) 20.76
Frustaci, 2016 9 9 18 6.90 (1.25, 12.55) 14.42
Subtotal (I-squared = 89.7%, p = 0.000) 5.80 (2.00, 9.59) 100.00
b. T1-ECV (ECV%)
Shah, 2013 11 22 33 8.56 (4.63, 12.50) 4.62
Wong, 2014 231 945 1176 1.60 (0.99, 2.21) 9.38
Levelt, 2016 46 20 66 0.00 (-1.44, 1.44) 8.41
Swoboda, 2017 100 30 130 2.80 (1.54, 4.06) 8.65
Vasanji, 2017 14 14 28 2.00 (-3.42, 7.42) 3.15
Cao, 2018 50 32 82 2.80 (1.77, 3.83) 8.96
Storz, 2018 28 223 251 -1.54 (-2.71, -0.37) 8.78
Chirinos, 2019 32 21 53 3.30 (0.44, 6.16) 6.13
Gao, 2019 80 20 100 4.43 (3.08, 5.78) 8.53
Gulsin, 2019 51 45 96 0.00 (-2.00, 2.00) 7.51
Lam, 2019 27 10 37 -1.00 (-2.68, 0.68) 8.04
Jiang, 2020 135 55 190 5.08 (3.96, 6.20) 8.84
Khan, 2020 70 372 442 1.95 (0.95, 2.95) 8.99
Subtotal (I-squared = 89.7%, p = 0.000) 2.09 (0.92, 3.27) 100.00
-16.5
less fibrosis in diabetes group
0
16.5
more fibrosis in diabetes group
Publication
diabetes
without diabetes
total
Difference in T1 relaxation time (ms) WMD (95% CI)
% Weight
c. Native T1 (ms)
Khan, 2014 11 15 26 -27.54 (-104.24, 49.16) 4.95
Levelt 2016 46 20 66 10.00 (-5.37, 25.37) 10.46
Swoboda, 2017 100 30 130 32.50 (12.52, 52.48) 10.14
Vasanji, 2017 14 14 28 39.00 (-81.58, 159.58) 2.73
Cao, 2018 50 30 80 15.10 (2.62, 27.58) 10.63
Storz, 2018 47 296 343 -2.03 (-18.24, 14.19) 10.41
Gao, 2019 80 20 100 5.39 (-49.69, 60.48) 6.74
Lam, 2019 27 10 37 34.00 (11.83, 56.17) 9.96
Jiang, 2020 135 55 190 33.43 (-28.35, 95.21) 6.13
Kropidlowski, 2020 12 51 63 20.05 (-6.47, 46.56) 9.58
Khan 2020 70 372 442 1.89 (-45.96, 49.73) 7.44
Kucukseymen, 2020 126 81 207 78.01 (69.69, 86.32) 10.82
Subtotal (I-squared = 92.5%, p = 0.000) 21.74 (-1.27, 44.75) 100.00
less fibrosis in diabetes group
more fibrosis in diabetes group
d. Postcontrast T1 (ms)
Ng, 2012 50 19 69 -79.00 (-104.14, -53.86) 15.88
Khan, 2014 11 15 26 23.59 (-42.51, 89.69) 6.57
Vasanji, 2017 14 14 28 26.00 (-95.91, 147.91) 2.48
Cao, 2018 50 32 82 0.30 (-11.04, 11.64) 19.63
Gao, 2019 80 20 100 6.84 (-8.81, 22.50) 18.61
Lam, 2019 27 10 37 -26.00 (-46.13, -5.87) 17.37
Jiang, 2020 135 55 190 -13.78 (-25.88, -1.68) 19.46
Subtotal (I-squared = 85.2%, p = 0.000) -16.22 (-36.68, 4.25) 100.00
-160
more fibrosis in diabetes group
0
160
less fibrosis in diabetes group

Assessment Method (unit of measure)	Accuracy	Number of studies	Total number of participants	Pooled effect estimate (95% CI)
a. CVF (%)	high	6	184	5.80 (2.00, 9.59)
b. ECV (%)	high	13	2684	2.09 (0.92, 3.27)
c. Native T1 time (ms)	moderate	12	1712	21.74 (-1.27, 44.75)
d. Poscontrast T1 time (ms)	moderate	7	531	-16.22 (-36.68, 4.25)