Noninvasive Imaging of Endothelial Damage in Patients With Different HbA1c Levels: A Proof-of-Concept Study

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The aim of this study was to compare endothelial permeability, which is considered a hallmark of coronary artery disease, between patients with different HbA1c levels using an albumin-binding magnetic resonance (MR) probe. This cross-sectional study included 26 patients with clinical indication for X-ray angiography who were classified into three groups according to HbA1c level (<5.7% [≤39 mmol/mol], 5.7–6.4% [39–47 mmol/mol], and ≥6.5% [≥48 mmol/mol]). Subjects underwent gadofosveset-enhanced coronary magnetic resonance and X-ray angiography including optical coherence within 24 h. Contrast-to-noise ratios (CNRs) were assessed to measure the probe uptake in the coronary wall by coronary segment, excluding those with culprit lesions in X-ray angiography. In the group of patients with HbA1c levels between 5.7 and 6.4%, 0.30 increased normalized CNR values were measured, compared with patients with HbA1c levels <5.7% (0.30 [95% CI 0.04, 0.57]). In patients with HbA1c levels ≥6.5%, we found 0.57 higher normalized CNR values compared with patients with normal HbA1c levels (0.57 [95% CI 0.28, 0.85]) and 0.26 higher CNR values for patients with HbA1c level ≥6.5% compared with patients with HbA1c levels between 5.7 and 6.4% (0.26 [95% CI −0.04, 0.57]). Additionally, late atherosclerotic lesions were more common in patients with high HbA1c levels (HbA1c ≥6.5%, n = 14 [74%]; HbA1c 5.7–6.4%, n = 6 [60%]; and HbA1c <5.7%, n = 10 [53%]). In conclusion, coronary MRI in combination with an albumin-binding MR probe suggests that both patients with intermediate and patients with high HbA1c levels are associated with a higher extent of endothelial damage of the coronary arteries compared with patients with HbA1c levels <5.7%.

Atherosclerosis is the leading cause of morbidity and mortality among individuals with type 2 diabetes (1). Patients with diabetes have a higher risk of cardiovascular disease compared with patients with diabetes with a similar risk factor burden (2). However, it has been shown that patients with prediabetes conditions, such as impaired fasting glucose and impaired glucose tolerance, are more likely to develop atherosclerosis as well (3). Among these patients, endothelial damage including an increased endothelial permeability is a consistent finding (4,5). Endothelial permeability precedes the manifestation of atherosclerosis, since hyperglycemia leads to increased reactive oxygen species and impaired nitric oxide (NO) production and weakens endothelial repair mechanisms (6). Cardiovascular MRI (CMR) with targeted molecular probes enables the visualization of biological processes that cannot be detected by morphological

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imaging approaches (7–9). The albumin-specific magnetic resonance (MR) probe, gadofosveset trisodium, investigated in this study is clinically approved in the European Union and the U.S. (8,9). After intravenous administration, gadofosveset trisodium reversibly binds to serum albumin. This results in a prolonged serum half-life and an up to 10-fold increase in T1 relaxivity of the probe (8,9). Therefore, this probe can be detected by CMR with a much higher sensitivity compared with other clinically used contrast agents, such as gadovist. Bound to albumin, this probe was shown to have properties comparable with Evans blue dye, which represents a surrogate marker for endothelial permeability in the arterial system (8,9). Prior studies in a murine model of atherosclerosis have demonstrated that gadofosveset trisodium accumulation reflects the degree of endothelial leakiness and gap junction width (8,9).

The aim of this study was to test the potential of gadofosveset trisodium as a novel in vivo biomarker for the evaluation of endothelial permeability in patients with different HbA1c levels.

RESEARCH DESIGN AND METHODS

Study Population

The study population consisted of patients with different HbA1c levels, who were prospectively enrolled between April 2015 and June 2016. Inclusion criteria were age between 18 and 99 years and clinical indication for invasive X-ray coronary angiography (XCA) owing to symptoms of stable coronary artery disease (CAD) or acute coronary syndrome (unstable angina and non-ST elevation myocardial infarction). Patients were stratified into three groups based on HbA1c level: low (<5.7% [<39 mmol/mol]), intermediate (5.7–6.4% [39–47 mmol/mol]), or high (≥6.5% [≥48 mmol/mol]). HbA1c measurements were performed in EDTA anticoagulated blood samples at the time of admission. Hemodynamically unstable patients, such as patients with cardiogenic shock, rising cardiac enzymes or malignant cardiac arrhythmias, or ST elevation myocardial infarction; pregnant women; patients with a history of coronary stenting; patients with renal insufficiency (creatinine clearance <30 mL/min); and patients who were not able to give written consent either because of age (<18 years of age) or because of mental disorders were excluded. Further exclusion criteria involved common contraindication to CMR (allergy to gadolinium-based contrast agents, claustrophobia, or specific metallic items such as cochlear implants, central nervous system aneurysm clips, or pacemakers/defibrillators). Patients underwent a CMR sequence consisting of a native CMR scan and a gadofosveset-enhanced CMR exam (both exams within 24 h). The following day, XCA and optical coherence tomography (OCT) was performed. The study was approved by the local ethics committee for clinical investigations and was performed in accordance with the Declaration of Helsinki. All patients provided written informed consent.

CMR

All subjects were scanned in the supine position in a 3-Tesla MRI scanner (MAGNETOM Skyra; Siemens Healthcare, Erlangen, Germany). Continuous monitoring of vital signs throughout the entire CMR scan was performed with a four-lead electrocardiogram. In patients with elevated troponin levels, a CMR-compatible blood pressure monitor and blood oxygenation sensor was used in addition. Gadofosveset trisodium (dose of 0.03 mmol/kg body wt) was administered intravenously through a catheter in an antecubital vein following the first imaging session. Signal enhancement, as defined by the contrast-to-noise ratio (CNR) (Supplementary Data) of coronary segments was determined according to the nine-segment model. CNR was obtained by dividing the difference in signal intensity (SI) between the coronary segment and blood by the background noise (SI lesion – SI blood)/noise. Segments containing a culprit lesion discovered in XCA were excluded from later analysis. The CMR intensities were set in relation to the intensities from the aorta, i.e., normalized. The goal of this preprocessing step is to make the intensities between the different patients more comparable. Additionally, we extend the model by the available covariates. These are included as additional fixed effects in the model.

XCA and OCT

XCA was performed within 24 h after CMR according to standard techniques via a transradial or transfemoral approach. Whenever possible, two orthogonal views were acquired for all coronary arteries. OCT (Ilumien, OCT system; St. Jude Medical, Minnesota, MN) of the coronary artery with the highest grade of stenosis or the largest amount of plaque was performed after XCA.

OCT Image Analysis

OCT frames were assessed by two experienced readers (M.J. and L.-C.E.), who were blinded to the CMR data sets, using proprietary software (St. Jude Medical). In case of disagreement between the two OCT readers, consensus reading was performed by a third investigator (B.B.). Plaques were evaluated using validated OCT criteria (10). Segments were stratified into two different categories: segments with late atherosclerotic lesions (LALs) (calcified and noncalcified fibroatheroma and calcified and noncalcified thin-cap fibroatheroma) and segments without these high-risk lesions (i.e., early atherosclerotic lesions [EALs], including healthy vessel wall, pathological intimal thickening, and fibrous and fibrocalcific plaque (11).

Statistics

Group differences in MRI signal enhancement were analyzed by hierarchical regression models within a fully Bayesian setup (12). Formulation of these models can be divided into structural and distributional assumptions; i.e., information needs to be provided for effects of interest and covariates as well as for the
likelihood and prior distributions, respectively. In addition, patient-specific variation due to repeated measurements is accounted for by patient-specific intercepts, i.e., random effects. Additional covariates were accounted for by fixed effects. All metrical covariates (age and BMI) have been standardized in order to obtain comparable effect sizes; all binary covariates (CAD, sex, hypertension, and smoking) have been dummy coded.

Student t distribution has been chosen as the likelihood for these models. This choice was made to account for the relatively small sample size and possible outliers. Estimation of the joint posterior distribution of all unknown regression coefficients and parameters was performed by Markov chain Monte Carlo using the probabilistic programming language Stan (13) and its implementation in the R bmrns package (14). Both the choice of the likelihood and the choices of prior distributions were justified by posterior predictive checks.

With respect to baseline characteristics and medical treatment on admission, differences in proportions were assessed using χ^2 tests and differences in continuous variables using the Kruskal-Wallis test or ANOVA as appropriate. The Mann-Whitney U test was applied for comparison of continuous and nonnormally distributed variables (i.e., plaque analysis), respectively. These tests were two sided, and a P value of <0.05 was considered statistically significant. A detailed description of the statistical methods can be found in Supplementary Data.

RESULTS

CMR Analysis

The study included patients with symptoms of stable CAD (n = 17 [65.4%]) and patients with acute coronary syndrome (n = 9, 34.6%). In healthy patients (HbA1c ≤ 5.7% [<39 mmol/mol]; n = 10), patients with an HbA1c between 5.7 and 6.4% (39–47 mmol/mol) (n = 8) and patients with HbA1c levels ≥ 6.5% (≥48 mmol/mol) (n = 8), the total number of coronary segments analyzed were n = 79, n = 65, and n = 62, respectively (combined n = 206 segments). Baseline characteristics are shown in Table 1.

**Table 1** — Baseline patients’ characteristics and medical treatment on admission

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>HbA1c &lt; 5.7 (n = 10)</th>
<th>HbA1c 5.7–6.5 (n = 8)</th>
<th>HbA1c ≥ 6.5% (n = 8)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>63.90 ± 16.21</td>
<td>68.42 ± 11.11</td>
<td>76.50 ± 7.80</td>
<td>0.13</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>7 (70.00)</td>
<td>5 (62.50)</td>
<td>4 (50.00)</td>
<td>0.69</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>80.31 ± 10.12</td>
<td>78.63 ± 23.12</td>
<td>84.62 ± 25.40</td>
<td>0.83</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>27.52 ± 3.81</td>
<td>25.79 ± 5.31</td>
<td>29.38 ± 8.74</td>
<td>0.47</td>
</tr>
<tr>
<td>Risk factors, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>5 (50.00)</td>
<td>3 (37.50)</td>
<td>5 (62.50)</td>
<td>0.82</td>
</tr>
<tr>
<td>Hypertension</td>
<td>8 (80.00)</td>
<td>6 (75.00)</td>
<td>8 (100.00)</td>
<td>0.75</td>
</tr>
<tr>
<td>Smoking</td>
<td>5 (50.00)</td>
<td>3 (37.50)</td>
<td>4 (50.00)</td>
<td>0.84</td>
</tr>
<tr>
<td>Family history of CAD</td>
<td>0 (0)</td>
<td>3 (37.50)</td>
<td>2 (25.00)</td>
<td>0.33</td>
</tr>
<tr>
<td>Laboratory findings</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Troponin T, mg/mL</td>
<td>16.00 (4.00–91.00)</td>
<td>14.50 (6.50–27.00)</td>
<td>37.50 (8.00–67.25)</td>
<td>0.90</td>
</tr>
<tr>
<td>CK, UI/L</td>
<td>150.50 (78.75–176.00)</td>
<td>166.00 (132.75–254.75)</td>
<td>73.50 (42.00–120.50)</td>
<td>0.06</td>
</tr>
<tr>
<td>CK-MB, UI/L</td>
<td>17.00 (13.00–22.00)</td>
<td>22.00 (13.75–31.25)</td>
<td>18.50 (15.75–22.00)</td>
<td>0.93</td>
</tr>
<tr>
<td>Creatinine, mg/dL</td>
<td>0.90 ± 0.26</td>
<td>0.86 ± 0.26</td>
<td>1.08 ± 0.42</td>
<td>0.51</td>
</tr>
<tr>
<td>C-reactive protein, mg/dL</td>
<td>27.86 ± 28.54</td>
<td>27.69 ± 59.62</td>
<td>56.40 ± 121.49</td>
<td>0.22</td>
</tr>
<tr>
<td>Platelets, x 10^12/μL</td>
<td>254.80 ± 56.94</td>
<td>250.13 ± 67.11</td>
<td>251.00 ± 52.20</td>
<td>0.98</td>
</tr>
<tr>
<td>Total cholesterol, mg/dL</td>
<td>180.40 ± 44.40</td>
<td>175.38 ± 29.37</td>
<td>193.29 ± 67.64</td>
<td>0.76</td>
</tr>
<tr>
<td>Triglyceride, mg/dL</td>
<td>132.50 ± 58.22</td>
<td>189.57 ± 170.87</td>
<td>172.00 ± 56.97</td>
<td>0.52</td>
</tr>
<tr>
<td>HDL cholesterol, mg/dL</td>
<td>46.00 ± 14.56</td>
<td>52.00 ± 18.55</td>
<td>41.00 ± 6.84</td>
<td>0.65</td>
</tr>
<tr>
<td>LDL cholesterol, mg/dL</td>
<td>110.60 ± 39.42</td>
<td>96.63 ± 27.64</td>
<td>132.63 ± 55.14</td>
<td>0.23</td>
</tr>
<tr>
<td>HbA1c, %</td>
<td>5.41 ± 0.29</td>
<td>5.99 ± 0.10</td>
<td>7.20 ± 0.98</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Medication</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aspirin</td>
<td>6 (60.00)</td>
<td>6 (60.00)</td>
<td>4 (50.00)</td>
<td>0.58</td>
</tr>
<tr>
<td>Clopidogrel</td>
<td>1 (10.00)</td>
<td>1 (12.50)</td>
<td>1 (12.50)</td>
<td>0.98</td>
</tr>
<tr>
<td>Statin</td>
<td>3 (30.00)</td>
<td>3 (37.50)</td>
<td>3 (37.50)</td>
<td>0.93</td>
</tr>
<tr>
<td>β-Blocker</td>
<td>5 (50.00)</td>
<td>2 (25.00)</td>
<td>4 (50.00)</td>
<td>0.84</td>
</tr>
<tr>
<td>ACEI or ARB</td>
<td>4 (40.00)</td>
<td>5 (62.50)</td>
<td>6 (75.00)</td>
<td>0.31</td>
</tr>
<tr>
<td>Insulin, n (%)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>2 (20.00)</td>
<td>0.18</td>
</tr>
<tr>
<td>OAD, n (%)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>4 (50.00)</td>
<td>0.07</td>
</tr>
</tbody>
</table>

ACEI, ACE inhibitor; ARB, angiotensin II receptor blocker; CK, creatinine kinase; OAD, oral antidiabetes drug.
and 0.71 (2.42 to 2.71). With use of a Bayesian framework, there were similar values regarding normalized SIs between the groups in the non–contrast-enhanced sequences (see Fig. 1). With respect to gadofosveset-enhanced sequences, the group with HbA1C levels between 5.7 and 6.4% had an average of 0.30 increased normalized SI (95% CI 0.04, 0.57) compared with the group with HbA1C levels <5.7%. For patients with HbA1C levels ≥6.5%, we recorded an average of 0.57 increased normalized SI (95% CI 0.28, 0.85) compared with the healthy group (HbA1C levels <5.7%). Additionally, we found a 0.26 higher SI for patients with HbA1C level ≥6.5% compared with patients with HbA1C levels between 5.7 and 6.4% (0.26 [95% CI 0.04, 0.57]) (Fig. 1).

The probability that high and intermediate HbA1C levels were associated with higher CNR values compared with low HbA1C levels was 1.00 and 0.99, respectively, whereas the corresponding probability was 0.95 for patients with high versus intermediate HbA1C levels. Corresponding differences were less for the non-contrast-enhanced CMR (Fig. 1).

**Invasive XCA**

In the entire patient cohort, 53.8% of patients had no CAD. These patients were diagnosed with either microvascular disease or noncardiac chest pain (i.e., musculoskeletal).

**CMR Signal Enhancement and Distribution of EALs and LALs**

Contrast-to-noise estimates for EALs and LALs were 2.39 (0.89–3.93) and 3.76 (2.17–5.29), respectively (Fig. 2A). Given the available data, the probability that LALs showed higher mean CNR values, compared with EALs, was 0.93 in gadofosveset-enhanced and 0.40 in native, non–contrast-enhanced CMR (Table 2).

In the subgroup of segments that were visualized on OCT (i.e., culprit vessel), LALs were more common in patients with high HbA1C levels (≥6.5%, n = 14 [74%]; 5.7–6.4%, n = 6 [60%]; and <5.7%, n = 10 [53%]) (Figs. 2B and 3). Probabilities and odds ratios for the presence of LALs are seen in Supplementary Data.

**DISCUSSION**

We demonstrated that patients with low HbA1C levels, <5.7%, showed notably less signal enhancement compared with patients with HbA1C levels above that threshold after application of an albumin-binding MR probe. This probe is considered a surrogate marker of endothelial damage in the arterial system. Notable differences in terms of signal enhancement could already be observed between the low and intermediate HbA1C group. This could be of clinical relevance, as it indicates that patients with slightly elevated HbA1C levels may already have significant vascular impairment and, consequently, an increased risk for CAD.

Additionally, our subanalysis revealed that there was a considerable probability, of 0.93, that LALs, as assessed using invasive OCT, were associated with higher signal enhancement (i.e., CNR values) after application of an albumin-binding probe compared with EALs. Patients with high HbA1C levels are known to have a more aggressive development of atherosclerosis, resulting in a worse cardiovascular outcome (3). In line with...
with this, the percentage of high-risk LALs was highest in patients with high HbA1c levels. In the future, the assumption that gadofosveset trisodium represents a surrogate marker for plaque instability should be validated in larger studies.

Outcome studies have demanoned glycolytic end products, and an enhanced inflammatory transcription factor (nuclear factor-kB) activation lead to increased oxidative stress with reduced NO production/bioavailability (16). As a result, various mediators such as cytokines, growth factors, and procoagulant factors are produced, which further promote inflammation, endothelial permeability, and coagulation. This leads to an imbalance in the vascular hemostasis due to an increased vasoconstriction and impaired vasorelaxation (16,17). These changes in endothelial function occur early during the development
of atherosclerosis, especially in patients with diabetes (16,17). Additionally, in patients with severe diabetes, typical CAD-related symptoms such as chest pain are often masked owing to diabetes neuropathy (18). Therefore, novel diagnostic tools are needed to facilitate the identification of patients at risk for CAD, which may offer a means of monitoring therapy.

Assessment of Coronary Endothelial Permeability in Patients With Elevated HbA1c Levels Using an Albumin-Binding MR Probe

In previous studies, non-contrast-enhanced and contrast-enhanced coronary artery MRI has demonstrated potential for the noninvasive non-radiation-associated evaluation of the coronary artery wall (7–9,19). For contrast-enhanced MRI, T1-weighted inversion recovery-based MR sequences are usually used to visualize and quantify contrast agent accumulation in the coronary artery wall. Previous studies have focused on the use of nonspecific extravascular contrast agents (20,21). This type of contrast agent was shown to accumulate mainly in areas of the coronary arteries with delayed clearance and increased distribution volume as observed in fibrosis or increased neovascularization, which therefore renders clinical interpretation challenging (20,21). In contrast, molecular probes could enable a more specific evaluation of early pathological changes in the coronary artery wall (7–9). Gadofosveset trisodium is such a specific MRI

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**Table 2—Comparison regarding SIs of EALs and LALs in contrast-enhanced (i.e., gadofosveset-enhanced) and native (i.e., non-contrast-enhanced) CMR scans**

<table>
<thead>
<tr>
<th>CMR type</th>
<th>Comparison</th>
<th>Diff</th>
<th>Lower</th>
<th>Upper</th>
<th>$P_{(\text{Diff} &gt; 0)}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Contrast enhanced</td>
<td>LAL vs. EAL</td>
<td>1.36</td>
<td>−0.45</td>
<td>3.10</td>
<td>0.93</td>
</tr>
<tr>
<td>Native</td>
<td>LAL vs. EAL</td>
<td>−0.32</td>
<td>−2.72</td>
<td>2.09</td>
<td>0.40</td>
</tr>
</tbody>
</table>

In this context, we demonstrate the so-called posteriori $P$ values, which report the probability that there is a difference between the groups (rightmost column). For instance, we found that in this study the probability that LAL showed higher mean CNR values, compared with EALs on contrast-enhanced scans, was 0.93. Diff, difference.

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**Figure 3—Representative images of CMR with use of the albumin-binding MR probe for the assessment of endothelial permeability in subjects with different HbA1c levels.** For the presented subject with an HbA1c of 5.4% (A–C), almost no signal enhancement is shown in the left coronary artery (left main [LM], left anterior descending [LAD], left circumflex artery [LCX]), whereas for the patients with an HbA1c level of 6.3% (A’–C’) and an HbA1c level of 7.4%, respectively (A’’–C’’), a stronger probe uptake is demonstrated in the left coronary artery tree. In all three patients, invasive X-ray angiography excluded obstructive coronary artery disease (B, B’, and B”) and OCT revealed healthy vessel wall without the presence of atherosclerotic plaque (C, C’, and C’’).
probe that was initially developed and used as a blood pool agent for high-resolution steady-state angiography (8,9). In subsequent experimental and human studies, it was demonstrated that this probe could also be useful as a surrogate marker for endothelial permeability and damage (8,9).

The direct visualization of endothelial damage and permeability using gadofosveset-enhanced CMR could be regarded as an alternative in vivo parameter for cardiovascular risk prediction in patients with elevated HbA1c levels and monitoring of therapeutic strategies that have positive effects on the endothelium. For instance, therapeutic strategies such as the use of statins, insulin analogs, antihypertensive medication, and hypoglycemic agents have been shown to have a beneficial effect on diabetes associated vascular impairment (16).

This study has some limitations. The main limitation of this study is that endothelial function was not assessed directly, e.g., by invasive measurements. However, previous studies have demonstrated that there is clear evidence that the albumin leakage sign in CMR represents a surrogate marker for endothelial damage (8,9). Only a relatively small number of patients was included in this study. Finally, patients were only categorized based on HbA1c levels and not based on fasting glycemia. However, it has been shown that HbA1c is a well-established parameter for cardiovascular risk stratification (3).

In conclusion, CMR in combination with an albumin-binding probe suggests that intermediate HbA1c levels (5.7–6.4%) and high HbA1c levels (≥6.5%) are associated with a greater extent of endothelial damage of the coronary arteries compared with HbA1c levels <5.7%. Larger studies are needed to evaluate the impact that this in vivo parameter could have on treatment strategies and the associated outcomes of patients.

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References