Elevated skin tissue cholesterol levels and myocardial infarction

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Abstract

Background: Skin cholesterol has been associated with coronary artery disease, extent of angiographic disease and inflammatory markers such as hs-CRP. Based on these findings we sought to determine whether skin cholesterol was associated with myocardial infarction (MI).
Methods: Patients ($N = 649$) underwent diagnostic catheterization and concurrent skin cholesterol measurement. History of MI was determined at the time of hospitalization.
Results: Patients with a history of MI ($n = 225$, 35%) had significantly higher skin cholesterol than those without MI (127 ± 29 versus 120 ± 20, $p = 0.002$). The odds ratio for high skin cholesterol (for MI) was 1.6 (95% CI = 1.1, 2.6; $p = 0.01$) after adjustment for traditional risk and extent of angiographic disease.
Conclusion: Skin cholesterol may indicate increased risk of coronary-related events rather than simply the presence of angiographic narrowing.
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1. Introduction

Skin cholesterol, a surrogate for tissue cholesterol, has long been associated with coronary artery disease (CAD) [1] and more recently with the degree of angiographic stenosis [2]. Further, skin cholesterol has been found to be associated with inflammatory markers (VCAM and CRP) [3]. We would anticipate therefore that skin cholesterol may be associated with acute events, beyond any association with coronary arterial narrowing.

2. Methods

Six hundred and forty-nine patients, not on lipid lowering medications, undergoing non-emergency diagnostic catheterization had $SkinT_c$ measured and baseline risk data recorded. The patient population was recruited consecutively from three separate sites, two in Canada (St. Michaels Hospital (SMH), $n = 323$; Trillium Health Center (THC), $n = 179$) and

one in the United States (Cleveland Clinic Foundation (CCF), $n = 147$). Technicians at each site were trained in an identical manner to measure $SkinT_c$. All catheterization interpretations were performed manually and independently at each site. The major indications for the catheterization was anginal symptoms (>90%) and positive stress test (>60%, >100% because some had both). Institutional Review Boards approved the study protocols at each site and all subjects provided informed consent prior to study enrollment.

Within 24 h prior to the angiographic procedure, $SkinT_c$ measurement was performed. The non-biopsy based skin-cholesterol assay system (cholesterol 1, 2, 3™), which uses a synthetic copolymer conjugated with digitonin and horseradish peroxidase to bind and quantify $SkinT_c$ has been recently described [4]. Cholesterol is assayed only within the stratum corneum. Repetitive readings provide a mean day-to-day coefficient of variation of 3–8% with a between hand average reproducibility of 95%. The entire process requires about 3–4 min.

Extent of disease was defined as the number of vessels with ≥50% stenosis and patients were further classified as having angiographic disease if the extent of disease was at least "one". Traditional CAD risk was characterized by the

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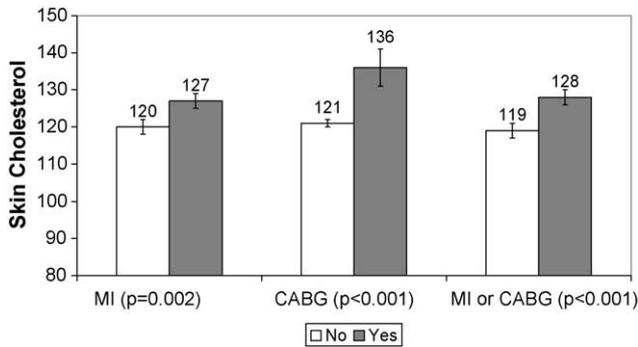*E-mail address:* dennis.sprecher@uphs.upenn.edu (D.L. Sprecher).

Fig. 1. Mean SkinT$_c$ (with standard error) by MI status, CABG status and MI or CABG status.

Framingham global risk score as reported by Wilson et al. [5]. Patients without and with a history of myocardial infarction (MI) (recorded from patient history and chart review) were compared with chi-square tests for categorical measures and unpaired t-tests for continuous measures. High SkinT$_c$ was defined as the upper quartile of the distribution (>143). Logistic regression techniques were used to estimate the relative risk of MI and (since coronary artery bypass surgery (CABG) subjects are enriched with those experiencing recent progressive angina), the combination of MI and/or CABG with odds ratios (OR), 95% confidence intervals (CI) and p-values.

3. Results

Among 649 patients scheduled for angiography, 225 (35%) had a history of MI, 50 (8%) had a history of coronary artery bypass surgery and 240 (37%) had a history of either MI or CABG. Presentation characteristics for patients without and with history of MI are found in Table 1. SkinT$_c$ was significantly higher for patients with history of MI, CABG or either (Fig. 1).

High SkinT$_c$ was associated with an increased rate of prior MI (OR = 1.5, CI = 1.1–2.9, $p = 0.03$). This association remained clear after adjustment Framingham risk and extent of disease (OR = 1.5, CI = 1.0–2.2, $p = 0.05$). The unadjusted OR was 1.7 (CI = 1.2–2.5, $p = 0.003$) for those patients with a history of MI and/or CABG. After adjustment for extent of disease and traditional risk burden the OR for high SkinT$_c$ remained statistically significant (OR = 1.8, CI = 1.2–2.6, $p = 0.005$).

4. Discussion

In our study population of subjects scheduled for angiography, patients with a history of MI had significantly higher skin cholesterol levels. Patients with SkinT$_c$ in the highest quartile were 1.5 times as likely to have had an MI and nearly twice as likely to have had an MI or CABG. These associations remain essentially unaffected by adjustment for extent of disease and traditional risk burden.

Based on the reported modest association between SkinT$_c$ and extent of angiographic disease [2], as well as the association with markers of inflammation (e.g., VCAM [3]), we anticipated a relation between SkinT$_c$ and acute events, outside of the association with extent of disease alone. This would be in line with the known connection between inflammatory markers and acute coronary events [6]. We now know that SkinT$_c$ was correlated with history of MI, even with adjustment for level of angiographic coronary disease. Further, that when adding the subjects with previous CABG (some of whom may also represent recent, more acute conditions), the relation was even stronger.

In previous work [1], the aging of skin and vascular tissue has revealed a temporal concordance, including collagen abnormalities as well as incorporated lipid. Association between vascular disease and both skin cholesterol and ApoB levels has been observed [7]. While the pathophysiology of skin lipid remains to be fully explained [8], the opportunity to use skin bioassay as a surrogate vascular-disease marker appears viable and potentially important for screening algorithms, particularly if it corresponds to plaque stability.

These data suggest that while associated with the degree or presence of angiographic narrowing, elevated SkinT$_c$ may also be associated with coronary-related events.

Table 1
Presentation characteristics by history of myocardial infarction (MI)

| | Prior MI | | p-Value |
	No	Yes	
N	424	225	–
Age	62 ± 11	65 ± 12	0.001
Female	156 (37%)	58 (26%)	0.005
LDL-c (mg/dL)	118 ± 31	115 ± 33	0.24
HDL-c (mg/dL)	44 ± 14	38 ± 12	<0.001
History of hypertension	231 (54%)	133 (59%)	0.26
History of diabetes	58 (14%)	57 (25%)	<0.001
Smoker	125 (29%)	80 (36%)	0.11
Framingham score	8.3 ± 3.3	9.4 ± 3.8	<0.001
Number of vessels with >50% stenosis	0.9 ± 1.0	1.7 ± 1.0	<0.001
LAD > 50%	160 (38%)	143 (64%)	<0.001

Mean ± standard deviation for continuous measures; number and percent for categorical measures.

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