Skin cholesterol adds to Framingham risk assessment

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Introduction It has been demonstrated that skin tissue cholesterol (SkinTc) is associated with angiographic disease. Now, we further delineate the relative risk of multivessel disease (>50% stenosis in at least two vessels) in the conjoint presence of high SkinTc and high traditional risk burden.

Methods Patients scheduled for angiography (N=649) had SkinTc measured immediately prior to the procedure. Patients were classified according to the presence of high (>110) SkinTc and high (>10) Framingham global risk scores. Multivariable logistic regression models were used to estimate relative risk of multivessel disease for patients with isolated high skin tissue cholesterol, isolated high Framingham risk or conjoint high skin tissue cholesterol and high Framingham risk (each compared to neither factor elevated).

Results The mean age was 63 ± 12 years and 33% (n=214) were women. Thirty seven percent (n=237) had angiographically determined multivessel disease. Patients with isolated high SkinTc showed a relative risk of multivessel disease of 1.6 (95% CI=1.0-2.4), while patients with isolated high Framingham risk had an odds ratio of 1.8 (CI=1.0-3.4). However, when both scores were elevated, risk of multivessel disease was increased 4.3 times (CI=2.6-7.2) compared to neither elevated.

Conclusions We see an independent, additive risk of concurrent multivessel disease when Framingham risk and skin cholesterol are both elevated. Skin tissue cholesterol may have value in further stratifying subjects with Framingham scores >10. (Am Heart J 2006;152:694-6.)

Screening individuals for cardiovascular risk is key to targeting resources for prevention. Within the already modest predictive intervals of traditional Framingham risk, new imaging (eg, electron beam computed tomography), and blood (eg, C-reactive protein) opportunities are increasingly used to further refine assessments. The incremental value of such testing modalities, based on cost/benefit analyses, is controversial. Skin cholesterol presents a new approach toward risk assessments. Although safe and inexpensive, skin cholesterol has not been as fully considered for risk prediction in the context of traditional risk (ie, Framingham global risk score). Significant associations between skin cholesterol and vascular disease markers, such as positive stress testing,[1] multivessel angiographic disease,[2] coronary calcium,[3] and carotid intima-media thickness,[4] have been observed, even after adjustment for traditional risk factors. Herein, we evaluate the combined value of traditional risk with or without elevated skin tissue cholesterol (SkinT) measurements toward prediction of multivessel disease in subjects referred for coronary angiography.

Methods

Six hundred forty-nine patients, not receiving lipid-lowering medications, undergoing nonemergency diagnostic catheterization had $SkinT_c$ measured and baseline risk data recorded. The patient population was recruited consecutively from 3 separate sites, 2 in Canada (St Michael's Hospital n = 323; Trillium Health Center n = 179) and 1 in the United States (Cleveland Clinic Foundation, 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 were anginal symptoms (>90%) and positive stress test (>60%, >100% because some had both). The extent of the disease was defined as the number of vessels with ≥50% stenosis. Traditional coronary artery disease (CAD) risk was characterized by the Framingham global risk score as reported by Wilson et al.[5] Institutional review boards approved the study protocols at each site, and all subjects provided informed consent before study enrollment.

Skin tissue cholesterol was measured as previously described within 24 hours of angiography. Briefly, a digitonin-copolymer-horseradish peroxidase conjugate was added to the palm after 1-minute unbound conjugate was removed by blotting, followed by the addition of horseradish peroxidase substrate. After a 2-minute incubation, the hue of the substrate was measured

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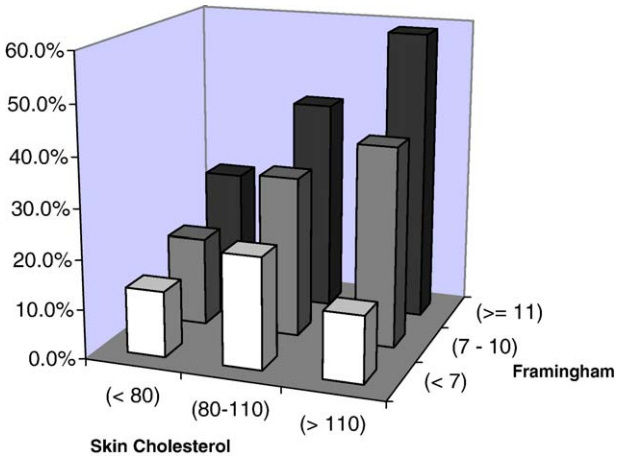
Table I. Presentation characteristics

		Relationship to $SkinT_c$
N	649	–
Age (y)	64 (55-73)	$r = 0.07$, $P = .10$
Women	33 (214)	N = 123 ± 29; Y = 119 ± 31
LDL-C (mg/dL)	118 (95-140)	$r = -0.03$, $P = .43$
HDL-C (mg/dL)	40 (33-49)	$r = -0.07$, $P = .07$
History of hypertension	56 (364)	N = 118 ± 29; Y = 125 ± 30*
History of diabetes	18 (115)	N = 122 ± 30; Y = 123 ± 27
Smoker (past year)	32 (205)	N = 123 ± 30; Y = 121 ± 29
Framingham global risk score	9 (7-11)	$r = 0.05$, $P = .20$
$SkinT_c$	122 (102-143)	–
Any disease	64 (415)	N = 118 ± 30; Y = 124 ± 30*
Multivessel disease	37 (237)	N = 120 ± 31; Y = 127 ± 28*
History of MI	35 (225)	N = 120 ± 31; Y = 127 ± 28*
History of CABG	8 (50)	N = 121 ± 29; Y = 136 ± 33
History of MI and/or CABG	37 (240)	N = 119 ± 30; Y = 128 ± 29

Categorical measures are shown as percentage and number with characteristic; continuous measures are shown as median and interquartile range. Relationship to $SkinT_c$ shown as unpaired *t* test (categorical measures: present, yes [Y]; not present [N]) or simple correlation (continuous measures). Any disease indicates at least 1 vessel with >50% stenosis; multivessel disease, at least 2 vessels with >50% stenosis. *LDL-C*, Low-density lipoprotein cholesterol; *HDL-C*, high-density lipoprotein cholesterol.
*$P < .05$.

Figure 1



Rate of multivessel disease (>50% stenosis in at least 2 vessels) across the ranges of skin cholesterol and Framingham risk.

directly on the palm with a handheld spectrophotometer. Unbound material was washed from the hand. Cholesterol is assayed only within the stratum corneum. Repetitive readings provide a mean day-to-day coefficient of variation of 3% to 8% with a between-hand average reproducibility of 95%. The entire process requires about 3 to 4 minutes. Although we did not record race, palmar hues do not differ significantly between African Americans and whites (unpublished observations).

Table II. Relative risk (odds ratio, 95% CI, *P* value) of disease by Framingham/$SkinT_c$ status

	Any disease	Multivessel disease
Neither high $SkinT_c$ nor high Framingham	1.00	1.00
Isolated high $SkinT_c$ (>110)	1.41, 0.96-2.07, $P = .08$	1.55, 1.01-2.36, $P = .04$
Isolated high Framingham (≥11)	1.70, 0.92-3.16, $P = .09$	1.80, 0.96-3.37, $P = .07$
High $SkinT_c$ and high Framingham	3.05, 1.77-5.27, $P < .001$	4.27, 2.55-7.16, $P < .001$

Table III. Relative risk (odds ratio, 95% CI, *P* value) of MI, CABG, and MI/CABG by Framingham/$SkinT_c$ status

	MI	CABG	MI/CABG
Neither high $SkinT_c$ nor high Framingham	1.00	1.00	1.00
Isolated high $SkinT_c$ (>110)	1.53, 0.99-2.37, $P = .055$	6.35, 2.84-14.19, $P < .001$	1.82, 1.18-2.80, $P = .006$
Isolated high Framingham (≥11)	1.74, 1.15-2.64, $P = .009$	4.21, 1.82-9.74, $P < .001$	1.90, 1.26-2.87, $P = .002$
High $SkinT_c$ and high Framingham	2.57, 1.35-4.87, $P = .004$	7.98, 2.96-21.52, $P < .001$	2.97, 1.56-5.66, $P < .001$

Statistics

The upper quartile was used to define patients as having elevated Framingham global risk scores (≥11). A cut point of 110 was used to define high $SkinT_c$ based on manufacturer's recommendation (based on internal studies with healthy subjects targeting approximately the top quartile, by PreMD Inc.). Clinically relevant disease was defined as (*a*) stenosis of at least 50% in at least 1 vessel (any disease) and (*b*) stenosis of at least 50% in ≥2 vessels (multivessel disease). Logistic regression techniques were used to estimate the relative risk of CAD for patients with (1) isolated elevated skin cholesterol, (2) isolated elevated Framingham risk, and (3) conjoint elevated skin cholesterol and elevated Framingham risk (odds ratios, 95% CI and *P* values, and area under the receiver operating characteristic curve produced via logistic regression).

Results

Presentation characteristics are shown for 649 patients scheduled for angiography (Table I). Figure 1 shows that the rate of multivessel disease increases as Framingham risk increases at all levels of skin cholesterol. Moreover, the rate of multivessel disease increases

as skin cholesterol increases in the middle and upper ranges on Framingham risk. Table II shows that the odds ratio for any disease is >3-fold higher for patients with both high $SkinT_c$ and high Framingham compared with patients with neither risk present. The relative risk increases to >4-fold when considering the risk of multivessel disease. In each case, both elevated $SkinT_c$ and elevated Framingham risk confer significant risk when they occur in isolation. Yet, it appears that the conjoint condition confers additive risk. In addition, receiver operating characteristic curves showed an area under the curve of 0.56 for a model with only $SkinT_c$, 0.68 for a model with only Framingham, and 0.77 for a model including both $SkinT_c$ and Framingham.

In this series, 35% (n = 225) had prior myocardial infarction (MI), 8% (n = 50) had prior coronary artery bypass graft surgery (CABG), and 37% (n = 240) had prior MI and/or prior CABG. Subjects with neither elevated Framingham score nor elevated $SkinT_c$ had only a 23% (38/163) rate of MI/CABG compared with a 52% (58/112) rate when both Framingham and $SkinT_c$ were elevated ($P < .001$). Table III shows that patients with both elevated Framingham and $SkinT_c$ had a relative risk of MI almost 3 times that of patients with neither factor elevated, and the relative risk of CABG is approximately 8-fold.

Discussion

In a cohort of subjects referred for coronary angiography, elevated skin cholesterol and high Framingham risk score were at least additive in predicting multivessel disease. The combination of elevated Framingham and $SkinT_c$ demonstrated a 4-fold risk compared with normal or low levels of these 2 markers. Furthermore, multivessel disease was more prevalent in subjects with high $SkinT_c$ in the middle and upper ranges of traditional risk burden. These data are consistent with $SkinT_c$ having value in refining the typical traditional risk characterization using Framingham.

These high-risk subjects from 3 clinical sites, already analyzed to demonstrate the independent value of $SkinT_c$ in predicting multivessel disease and history of MI,[6] were reevaluated to capture the influence of $SkinT_c$ on high or low Framingham risk scores. The presence of high $SkinT_c$ and elevated Framingham risk revealed at least additive risk toward the explanation of multivessel disease. However, there was no evidence of synergism; that is, one factor (either $SkinT_c$ or traditional risk) did not advance or mitigate the risk contribution of the other. These data not only further clarified the independence of this new $SkinT_c$ factor, but also revealed predictive opportunity for concordant assessments.

The basic physiology of skin cholesterol and its association with CAD remains unclear. Tissue cholesterol levels may be more correlated with transport of cholesterol from the serum space or parallel the intrinsic cholesterol synthesis levels, perhaps equivalent in magnitude to those otherwise synthesized in the liver. For now, this empirical relationship, supported by international literature[7,8] and more recent clinical studies[1,2] (eg, independent correlation with multivessel disease based on angiography,[2] association with electron beam computed tomography calcium scores,[3] and correlation to carotid intima-media thickness[4] results), suggests some unique aspect of skin cholesterol to vascular phenotype. In parallel fashion, traditional risk is also at least in part an empiric relationship.[5] We are not clear, for example, on the pathophysiology of age nor sex (2 of the major untreatable parameters defining absolute risk) on the advance of vascular disease.

We appreciate that our study uses a highly select population of subjects, referred for angiography predominantly because of chest pain and/or positive stress testing, both with and without previous history of vascular disease. Although inherent biases could inadvertently mislead the analyses (eg, numerous medications), these would predominantly lessen the influence of a $SkinT_c$ measurement. We found adjustment for medications and history of disease to still permit the $SkinT_c$ disease correlation to be observed.[2] However, large population data will be essential to assure its predictive value.

In summary, these data further define the incremental value of $SkinT_c$ on traditional risk. A testing modality, which is simple and inexpensive, lowers the threshold for attaining a high benefit/cost ratio. In a time of constrained resource, enhanced stratification of traditional risk using modalities such as $SkinT_c$ may offer public benefit.

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