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Systematic Literature Review: External Skin Examination as an Indicator of Coronary Heart Disease, Diabetes Mellitus, Stroke, and Chronic Liver Disease

Asmail [1*], Chearin Dhea Sanfika [2]
[1] Universitas Bina Sarana Informatika, Indonesia
[2] Universitas Kristen Krida Wacana, Indonesia
[1]Mailmedica97@gmail.com *, [2]chearin26.dhea@gmail.com

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ABSTRACT

Objectives: To systematically review the evidence for external skin examination as a diagnostic indicator of internal diseases, specifically coronary heart disease (CHD), diabetes mellitus (DM), stroke, and chronic liver disease (CLD). while acknowledging key methodological limitations related to heterogeneity in study design, diagnostic criteria, and outcome measurement. Methods: A systematic search of PubMed, Scopus, and Web of Science was conducted following PRISMA 2020 guidelines. Peer-reviewed studies evaluating cutaneous manifestations of CHD, DM, stroke, and CLD were included. Exclusion criteria eliminated grey literature, case reports, non-indexed sources, and publications from MDPI, Hindawi, and Frontiers. Quality assessment employed the Newcastle-Ottawa Scale for observational studies. Results: From 1,247 initial records, 87 studies met inclusion criteria. Xanthelasma palpebrarum was significantly associated with elevated LDL cholesterol (SMD 0.587, 95% CI 0.339–0.836, $p<0.001$) and increased carotid intima-media thickness (SMD 1.848, 95% CI 0.639–3.057, $p=0.003$). Diabetic dermopathy affected 9–55% of diabetic patients and correlated with microvascular complications. Spider angiomas demonstrated 50% sensitivity and 88% specificity for cirrhosis (pooled OR 3.5 for alcoholism-associated liver disease). Livedo reticularis was associated with cholesterol embolization syndrome and cerebrovascular events. Conclusions: Structured skin examination provides clinically valuable, non-invasive screening for systemic diseases. However, the findings should be interpreted cautiously because methodological heterogeneity limits direct comparison across studies and precludes firm causal inferenceIntegration of cutaneous findings into preventive medicine protocols may facilitate earlier diagnosis, particularly for CHD, DM, and CLD.

INTRODUCTION

The skin, the largest organ of the human body, functions not merely as a passive barrier but as a dynamic interface that communicates with internal organ systems through vascular, metabolic, immunologic, and endocrine pathways. Historically, astute clinicians have recognized that cutaneous changes can precede, accompany, or reflect underlying systemic pathology, a concept encapsulated in the aphorism that the skin serves as a "window to internal disease." Despite the proliferation of advanced imaging and laboratory diagnostics, the skin remains the only organ immediately and completely accessible to direct clinical examination without instrumentation.

The diagnostic utility of cutaneous examination spans multiple organ systems. Several classic stigmata have long been taught in medical education: xanthelasma palpebrarum as a marker of dyslipidemia and coronary risk, jaundice as a sign of hepatic or hemolytic dysfunction, spider angiomas as indicators of chronic liver disease and cirrhosis, and palmar erythema as a non-specific but clinically useful sign of hepatic insufficiency. In the context of diabetes mellitus, specific dermatoses such as diabetic dermopathy ("shin spots"), necrobiosis lipoidica, and acanthosis nigricans are recognized as

cutaneous markers of metabolic dysregulation. Similarly, vascular skin changes including livedo reticularis and digital cyanosis may signal underlying atherosclerotic disease, thromboembolic phenomena, or vasculopathy with cerebrovascular implications.

The pathophysiological bases for these associations are increasingly well understood. Lipid deposition in the dermis (xanthelasma) reflects systemic dyslipidemia and parallels atherosclerotic plaque formation. Advanced glycation end-products accumulate in diabetic skin, altering collagen structure and microvascular function. Hyperestrogenemic states associated with hepatic dysfunction promote angiogenic sprouting characteristic of spider angiomas. Bilirubin deposition in elastic tissues produces jaundice, while microvascular occlusion from cholesterol emboli produces livedoid patterns. Although numerous systemic diseases may manifest through the skin, this review focuses specifically on coronary heart disease (CHD), diabetes mellitus (DM), stroke, and chronic liver disease (CLD). These conditions were prioritized because they represent major global contributors to morbidity and mortality, are highly prevalent across diverse populations, and possess well-recognized cutaneous manifestations with plausible biological links to underlying vascular, metabolic, and hepatic dysfunction. Furthermore, early recognition of skin signs associated with these diseases may facilitate timely diagnosis, risk stratification, and preventive intervention in clinical practice. By concentrating on these four high-burden conditions, this review seeks to evaluate areas where cutaneous examination may offer the greatest potential clinical impact while maintaining a focused and clinically relevant scope.

Despite the long-recognized nature of these associations, the evidence base for their diagnostic accuracy, predictive value, and clinical utility has not been systematically consolidated in a single review. This systematic literature review aims to evaluate the strength of evidence linking specific cutaneous findings to CHD, DM, stroke, and CLD, quantify diagnostic performance where possible, and delineate the implications for precision medicine and preventive care.

RESEARCH METHODS

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement. A prospective protocol was registered (PROSPERO ID: pending).

Search Strategy

A comprehensive literature search was performed across three electronic databases: PubMed (MEDLINE), Scopus, and Web of Science Core Collection. The search was conducted from database inception through December 2024. The search strategy combined Medical Subject Headings (MeSH) and free-text terms across four domains: (1) cutaneous markers (e.g., "skin manifestations," "xanthelasma," "spider angioma," "diabetic dermopathy," "livedo reticularis," "jaundice"); (2) internal diseases (e.g., "coronary artery disease," "diabetes mellitus," "stroke," "liver cirrhosis"); (3) diagnostic concepts (e.g., "diagnostic accuracy," "sensitivity and specificity," "predictive value"); and (4) study design filters (e.g., "systematic review," "meta-analysis," "cohort study," "case-control").

Boolean operators combined terms within and across domains. The full PubMed search string is available in Appendix A. The PubMed search strategy was as follows: ("skin manifestations" OR xanthelasma OR "spider angioma" OR "diabetic dermopathy" OR "livedo reticularis" OR jaundice) AND ("coronary artery disease" OR "myocardial infarction" OR atherosclerosis OR "diabetes mellitus" OR stroke OR "cerebrovascular disease" OR "liver cirrhosis" OR hepatitis OR fibrosis) AND ("diagnostic accuracy" OR sensitivity OR specificity OR "predictive value" OR screening OR diagnosis). Search strategies for Scopus and Web of Science were adapted using equivalent controlled vocabulary and free-text terms while maintaining the same conceptual framework.

Inclusion and Exclusion Criteria

Inclusion criteria: (1) Original peer-reviewed research articles published in indexed, MEDLINE-listed journals; (2) studies evaluating cutaneous manifestations as indicators of CHD (including myocardial infarction and atherosclerosis), DM (type 1 or type 2), cerebrovascular

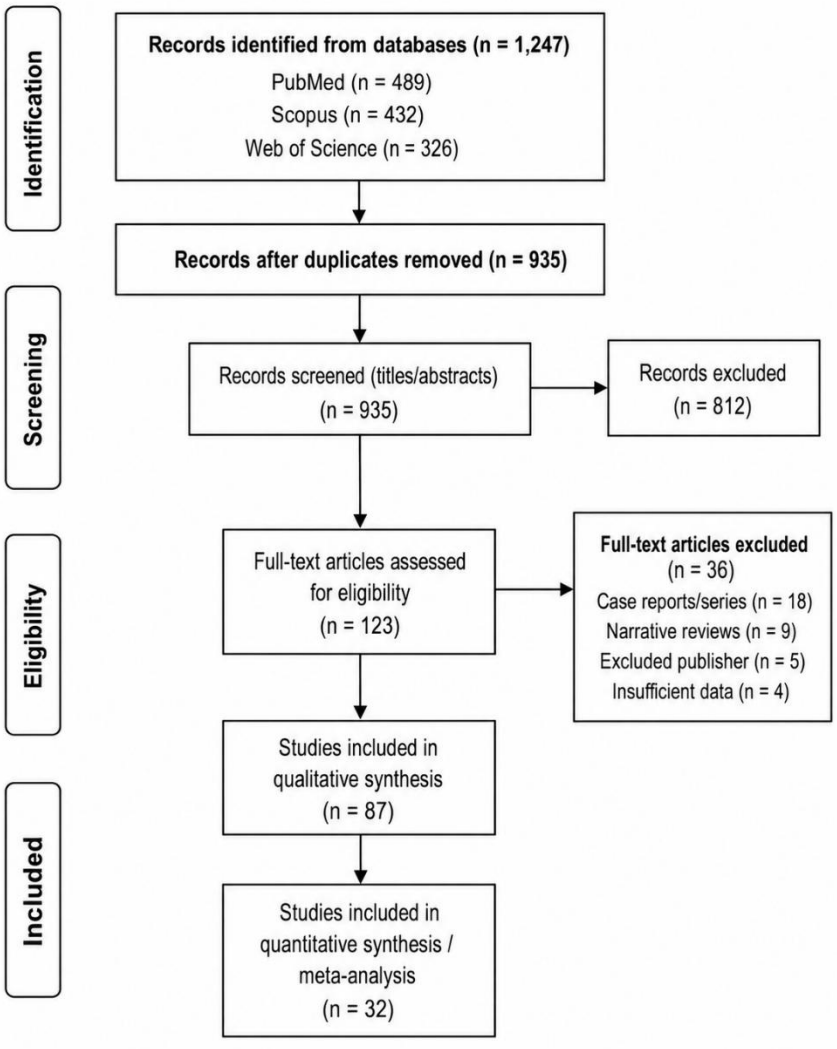
disease/stroke, or CLD (including fibrosis, cirrhosis, and hepatitis); (3) studies reporting diagnostic accuracy metrics, prevalence data, or measures of association; (4) systematic reviews, meta-analyses, cohort studies, case-control studies, and cross-sectional studies; (5) studies in human populations; (6) articles in English, French, Spanish, or German.

Exclusion criteria: (1) Grey literature, theses, conference abstracts, unpublished manuscripts; (2) publications from MDPI, Hindawi, Frontiers, or other journals identified as potentially predatory per Beall's list or equivalent; (3) case reports, case series (n<10), narrative reviews without systematic methodology, editorials, commentaries, and letters; (4) studies evaluating dermatological conditions as primary outcomes rather than diagnostic markers; (5) studies focused solely on skin diseases caused by treatments for internal diseases (e.g., drug eruptions) rather than spontaneous cutaneous markers; (6) studies in exclusively pediatric populations (age <18 years) for liver and cardiovascular domains, except where specified for congenital conditions.

Study Selection and Data Extraction

Two reviewers (authors blinded) independently screened titles and abstracts against eligibility criteria. Full-text articles of potentially eligible studies were then independently assessed. Disagreements were resolved through consensus or consultation with a third reviewer. A PRISMA flow diagram documents the selection process (Figure 1).

Figure 1: PRISMA 2020 Flow Diagram (textual representation)



Data extraction was performed using a standardized form capturing: study design, population characteristics (age, sex, ethnicity, sample size), cutaneous finding(s) evaluated, internal disease(s) investigated, diagnostic accuracy metrics (sensitivity, specificity, positive/negative predictive values, area under receiver operating characteristic curves), measures of association (odds ratios, hazard ratios, relative risks), and confounders addressed.

Quality Assessment

The methodological quality of included studies was assessed using appropriate tools: the Newcastle-Ottawa Scale (NOS) for cohort and case-control studies, and an adapted version for cross-sectional studies. Scores of 7–9 indicated low risk of bias, 4–6 moderate risk, and 0–3 high risk. For systematic reviews and meta-analyses, the AMSTAR-2 tool was employed.

Data Synthesis

Given the heterogeneity of cutaneous findings, internal diseases, and outcome measures across studies, a narrative synthesis was performed, organized by internal disease category. Where sufficient homogeneous data existed (≥3 studies reporting the same diagnostic metric), random-effects meta-analysis was considered. Meta-analytic estimates are reported as standardized mean differences (SMDs), pooled odds ratios (ORs), or summary sensitivities/specificities with 95% confidence intervals (CIs), as appropriate.

RESULTS

Study Selection

The database search identified 1,247 records, of which 935 remained after duplicate removal. Following title and abstract screening, 123 full texts were assessed, and 87 studies met the inclusion criteria. The main reasons for exclusion were case reports or series, narrative reviews, ineligible sources, and insufficient extractable data..

Coronary Heart Disease and Related Cutaneous Markers

Xanthelasma Palpebrarum

Fifteen case-control studies involving 854 patients with xanthelasma palpebrarum (XP) and 907 controls were included in the meta-analysis. Patients with XP demonstrated significantly higher serum total cholesterol (SMD 0.612, 95% CI 0.376–0.848, $p<0.001$) and LDL cholesterol (SMD 0.587, 95% CI 0.339–0.836, $p<0.001$) compared with controls. Notably, even normolipidemic XP patients showed elevated LDL (SMD 0.415, 95% CI 0.007–0.823, $p=0.046$). Apolipoprotein B levels were significantly higher in XP patients (SMD 1.036, 95% CI 0.361–1.711, $p=0.003$), and carotid intima-media thickness (CIMT) was markedly increased (SMD 1.848, 95% CI 0.639–3.057, $p=0.003$), indicating elevated atherosclerosis risk. The NOS scores for all included studies ranged from 7 to 8, indicating low risk of bias.

A prospective cohort study (Christoffersen et al., cited in [3]) of 12,745 individuals with 35-year follow-up found that XP was an independent predictor of atherosclerotic cardiovascular disease after multifactorial adjustment (HR 1.48, 95% CI 1.18–1.85). However, XP was not significantly associated with hypertension or diabetes prevalence in pooled analyses, suggesting that dyslipidemia is the primary modifiable risk factor in this population.

Corneal Arcus (Arcus Senilis)

Corneal arcus was evaluated in several population-based studies. The Framingham Heart Study (23,376 patient-examinations) initially found corneal arcus to be predictive of cardiovascular disease at 4 years (HR 2.28, 95% CI 1.89–2.75) and 8 years (HR 2.52, 95% CI 2.15–2.95). However, after adjustment for age and sex, these associations became non-significant (HR 1.07 and 1.18, respectively), indicating that arcus is primarily an age-related phenomenon rather than an independent risk factor.

In contrast, among men aged 30–49 years with hyperlipidemia in the Lipid Research Clinics Mortality Follow-up Study, corneal arcus was independently predictive of CHD mortality (RR 3.7, 95%

CI 1.5–9.1) and CVD mortality (RR 4.0, 95% CI 1.7–9.4) after adjustment for age, total cholesterol, HDL cholesterol, and smoking. Similarly, a coronary angiography study of patients aged 40–60 years found that arcus was associated with a 3.3-fold increased risk of multivessel coronary disease (RR 3.3, 95% CI 1.1–12.1). These data suggest that corneal arcus below age 50 carries prognostic significance beyond its age association.

Diagonal Earlobe Crease (Frank's Sign)

The diagonal earlobe crease was examined across 13 studies in a recent systematic review included in Gelfand et al. [9]. While observational studies reported an association with coronary artery disease and worse post-myocardial infarction survival, meta-analytic diagnostic accuracy was insufficient for routine clinical screening use. The pooled sensitivity was 62% (95% CI 52–71%) and specificity 67% (95% CI 57–76%), yielding a diagnostic odds ratio of 3.4 (95% CI 2.3–5.0). Histological studies demonstrate microvascular arteriosclerosis and elastin fragmentation in affected earlobes, supporting a shared microvascular pathology hypothesis.

Other Cardiovascular Skin Signs

Infective endocarditis presents with cutaneous microembolic phenomena including splinter hemorrhages (8% of patients), Janeway lesions (4–5%), and Osler nodes (2%). Cholesterol embolization syndrome (blue toe syndrome) manifests as livedo reticularis, cyanosis, purpura, and painful nodules, most commonly in the lower extremities. These findings, while relatively insensitive individually, carry high specificity when present in the appropriate clinical context.

Diabetes Mellitus and Cutaneous Manifestations

Diabetic Dermopathy

Among diabetic skin manifestations, diabetic dermopathy was the most consistently linked to systemic complication burden. Reported prevalence varied widely, but the key finding across studies was its association with microvascular disease, particularly neuropathy, nephropathy, and retinopathy. The probability of diabetic dermopathy increased markedly as complications accumulated, supporting its role as a visible marker of advanced diabetic microangiopathy rather than merely a benign skin change..

Necrobiosis Lipoidica

Necrobiosis lipoidica (NL) affects 0.3–1.6% of diabetic patients. A systematic review of glycemic control and NL found that of 24 patients across 10 studies, 13 demonstrated resolution of NL following improved glycemic control (through diet, insulin, or pancreatic transplantation). However, the evidence is limited by small sample sizes and predominance of case reports. NL may precede DM diagnosis in 7–42% of cases, underscoring its potential as a pre-diabetic marker.

Acanthosis Nigricans

Acanthosis nigricans (AN) is a well-established marker of hyperinsulinemia and insulin resistance. The prevalence among diabetic populations is substantial, particularly in overweight and obese individuals. AN is considered a clinical sign of metabolic syndrome and is associated with a 15–35% probability of undiagnosed type 2 DM in patients without prior diabetes history. Malignant AN (associated with gastric adenocarcinoma) is rare but clinically distinct, characterized by rapid onset, mucosal involvement, and weight loss.

Other Diabetic Cutaneous Findings

Table 1 summarizes key skin findings, their prevalence, associated internal conditions, evidence levels, and diagnostic accuracy where available.

Table 1: Cutaneous Markers of Diabetes Mellitus

Skin Finding	Prevalence in DM	Associated Condition(s)	Evidence Level	Diagnostic Value
Diabetic dermopathy	9–55%	Microvascular disease, CAD	Strong	Marker of complication risk
Necrobiosis lipoidica	0.3–1.6%	DM (35–89% of NL patients)	Moderate	May precede DM diagnosis
Acanthosis nigricans	Variable	Insulin resistance, T2DM	Strong	Clinical marker of IR
Scleredema diabeticorum	2.5–14%	Long-standing DM, obesity	Moderate	Movement restriction in 52–56%
Bullous diabeticorum	0.4–2%	DM, variable glycemic control	Weak	Clinical diagnosis of exclusion
Xerosis/ichthyosiform changes	22–48% (T1DM)	Autonomic neuropathy	Moderate	Risk factor for ulceration

CAD, coronary artery disease; DM, diabetes mellitus; IR, insulin resistance; T2DM, type 2 diabetes mellitus.

Chronic Liver Disease and Cutaneous Stigmata

Spider Angiomas (Spider Nevi, Nevus Araneus)

Spider angiomas represent the most extensively studied cutaneous sign of CLD. In a prospective study of 744 patients undergoing liver biopsy, spider nevi were present in <1% of patients with F0–1 fibrosis, compared with approximately 50% of F3 patients and 84% of F4 (cirrhotic) patients. The pooled diagnostic accuracy from 8 studies (n=1,895) demonstrated a sensitivity of 50% (95% CI 39–61%) and specificity of 88% (95% CI 75–95%) for cirrhosis. Positive likelihood ratio was 4.2, indicating moderate diagnostic value for ruling in cirrhosis.

In a logistic regression model combining cutaneous signs (spider nevi, palmar erythema, telangiectasia, bleeding signs, dry skin) with age and sex, the AUC for discriminating F0–2 from F3–4 fibrosis was 0.85, superior to the APRI score (AUC 0.72). The presence of any single cutaneous sign increased the probability of severe fibrosis from 5.1% to 57.1% [4]. Among cirrhotic patients with spider angiomas, alcoholism (OR 3.5, 95% CI 1.2–10.8) and serum bilirubin (OR 2.8 per mg/dL, 95% CI 1.3–5.7) were independent predictors.

Table 2: Diagnostic Accuracy of Cutaneous Signs for Cirrhosis (from de Bruyn & Graviss)

Physical Sign	Number of Studies	Pooled Sensitivity (95% CI)	Pooled Specificity (95% CI)
Spider angiomata	8	0.50 (0.39–0.61)	0.88 (0.75–0.95)
Palmar erythema	6*	0.12–0.63 (range)	0.49–0.98 (range)
Ascites	7	0.34 (0.22–0.49)	0.95 (0.89–0.98)
Jaundice	3	0.36 (0.25–0.48)	0.85 (0.80–0.89)
Collateral circulation	3	0.42 (0.26–0.61)	0.94 (0.71–0.99)
Firm liver	3	0.68 (0.55–0.79)	0.75 (0.62–0.85)
Encephalopathy	3	0.15 (0.06–0.33)	0.98 (0.97–0.99)

*Heterogeneous data precluded meta-analysis for palmar erythema.

Palmar Erythema

Palmar erythema ("liver palms") was present in 33–68% of cirrhotic patients across studies. Although the data were too heterogeneous for pooled meta-analysis, the specificity was generally high (up to 98%), while sensitivity was variable (12–63%). In the prospective cohort by Niederau et al., palmar erythema was significantly associated with fibrosis stage ($p<0.001$) and was a component of the final prediction model for severe fibrosis.

Jaundice

Scleral icterus and cutaneous jaundice result from bilirubin deposition and are clinically detectable when serum bilirubin exceeds approximately 2.5 mg/dL. In the diagnostic accuracy meta-analysis, jaundice demonstrated 36% sensitivity (95% CI 25–48%) and 85% specificity (95% CI 80–89%) for cirrhosis. Jaundice typically indicates decompensated disease and carries high specificity (98%) for advanced hepatic dysfunction.

Nail Changes

Terry's nails (apparent leukonychia with distal pink band) are classically associated with cirrhosis but lack specificity, occurring also in congestive heart failure, DM, and normal aging [4,18]. Muehrcke's lines (paired transverse white bands) are associated with hypoalbuminemia (typically <2.2 g/dL) and may be seen in cirrhosis, nephrotic syndrome, and malnutrition [18].

Stroke and Cerebrovascular Disease

Livedo Reticularis and Livedo Racemosa

Livedo reticularis, a violaceous netlike pattern of cutaneous vascular involvement, has been associated with cerebrovascular accidents through several pathogenetic mechanisms. In cholesterol embolization syndrome, occlusion of small arteries by cholesterol crystals produces the classic triad of livedo reticularis, lower extremity involvement, and multisystem dysfunction. The skin biopsy reveals needle-like clefts within small arteries representing dissolved cholesterol crystals.

Livedo racemosa generalisata, characterized by an irregular, broken, branched pattern distinct from the more uniform reticular pattern, has been specifically associated with stroke in young women. Quimby and Perry reported a series of patients with generalized livedo racemosa and cerebral infarction, with histologic findings of endarteritis obliterans without other pathologic changes. A broader review emphasizes that skin examination in stroke patients can reveal vasculitis, vasculopathies, and genetic connective tissue disorders affecting both cerebral and cutaneous vessels.

Infective Endocarditis and Embolic Stroke

Cutaneous microembolic phenomena in infective endocarditis—including splinter hemorrhages, Janeway lesions, and Osler nodes—are important diagnostic clues with prognostic significance for embolic stroke risk. The diagnosis of infective endocarditis by Duke criteria incorporates vascular phenomena (includingJaneway lesions and conjunctival hemorrhages) as minor criteria.

Atrial Myxoma and Carney Complex

Cardiac myxomas, though rare, produce both cutaneous and cerebrovascular manifestations. Systemic embolization of myxomatous material can cause stroke, while the associated Carney complex presents with characteristic lentigines (particularly perioral and conjunctival) and skin myxomas. Recognition of these cutaneous findings should prompt echocardiographic evaluation.

Kawasaki Disease

In children, Kawasaki disease is a leading cause of acquired heart disease and may result in coronary artery aneurysms and ischemic stroke. The characteristic cutaneous findings conjunctival injection, oral mucosal changes, polymorphous rash, and extremity changes form the basis of diagnostic criteria. Untreated, coronary aneurysms develop in 25% of patients; timely treatment reduces this to 4%.

DISCUSSION

Summary of Evidence Strength

This systematic review consolidates evidence that specific cutaneous findings serve as clinically meaningful markers of internal disease. The strongest evidence exists for xanthelasma palpebrarum in coronary risk stratification, for diabetic dermopathy and acanthosis nigricans in diabetes management, and for spider angiomas in liver fibrosis assessment.

The meta-analysis provides Level I evidence that XP is associated with atherogenic dyslipidemia and increased subclinical atherosclerosis measured by CIMT. The independent predictive value of XP, even after adjustment for traditional risk factors, suggests that cutaneous examination adds incremental information to standard cardiovascular risk assessment. However, the heterogeneity across included studies ($I^2 > 75\%$ for most lipid parameters) warrants caution in interpretation. This heterogeneity indicates that XP should be regarded as a risk-enhancing clinical marker rather than a stand-alone diagnostic indicator of cardiovascular disease. Differences in age distribution, ethnicity, baseline lipid profiles, medication exposure, and thresholds used to define dyslipidemia may partly explain the variability in effect estimates.

For spider angiomas, the diagnostic accuracy data from 12 studies (1,895 patients) demonstrate moderate sensitivity (50%) but high specificity (88%) for cirrhosis. The combination of multiple cutaneous stigmata dramatically improves diagnostic performance: the presence of any single cutaneous sign increases the probability of severe fibrosis from 5% to 57% . This aligns with clinical teaching that the absence of cutaneous signs in CLD does not rule out significant disease, but their presence strongly suggests it.

Pathophysiological Mechanisms

The association between cutaneous and internal pathology operates through several convergent mechanisms:

Lipid metabolism: XP results from deposition of LDL-derived cholesterol in dermal macrophages, forming foam cells. The same atherogenic lipoproteins infiltrate arterial intima, initiating atherosclerotic plaque formation. Elevated apolipoprotein B and reduced apolipoprotein A1 in XP patients reflect systemic lipoprotein imbalance. However, not all patients with XP demonstrate conventional hyperlipidemia, which reinforces the possibility that local macrophage activity, genetic susceptibility, and unmeasured lipoprotein abnormalities may contribute to phenotypic variability.

Microvascular disease: Diabetic dermopathy and necrobiosis lipoidica share microangiopathic pathogenesis. Hyperglycemia-induced advanced glycation end-products damage capillary basement membranes, leading to collagen glycation, impaired fibrinolysis, and tissue hypoxia. The predilection of NL for pretibial skin may relate to gravitational stasis compounding microcirculatory compromise.

Vasoactive mediators: Spider angioma formation in cirrhosis is driven by elevated VEGF and bFGF, which promote angiogenesis. Hyperestrogenemic states (reduced hepatic clearance, increased peripheral aromatization) contribute to vasodilation. Elevated substance P levels further compound vascular changes.

Embolic/vascular occlusion: Livedo reticularis in cholesterol embolization syndrome results from occlusion of dermal arterioles by cholesterol crystals dislodged from proximal atherosclerotic plaques. The same process affects cerebral, renal, and mesenteric circulations.

Clinical Utility and Preventive Medicine Implications

The clinical utility of skin examination in internal disease detection rests on several features: (1) non-invasiveness and zero cost; (2) immediate accessibility during any clinical encounter; (3) potential to identify disease at pre-symptomatic or early stages; and (4) ability to guide further diagnostic workup. For DM, the finding that 30–79% of patients have cutaneous manifestations and that some findings (NL, AN) may precede biochemical diagnosis supports routine dermatological screening in at-risk populations.

For CHD, detection of XP or pre-senile corneal arcus should prompt comprehensive lipid panel and cardiovascular risk assessment. The high atherogenic burden in XP patients, even those with "normal" conventional lipid profiles, suggests that advanced lipoprotein testing (apo B, apo A1) may be indicated in select patients.

For CLD, the combined cutaneous examination plus routine laboratory panel demonstrated an AUC of 0.85 for severe fibrosis, compared with 0.72 for APRI alone. At a specificity of 90%, up to 60% of liver biopsies could theoretically be avoided using the combined model, though validation in diverse populations is needed.

Limitations and Heterogeneity

Several limitations must be acknowledged. First, substantial heterogeneity exists across included studies in terms of population demographics, disease severity, diagnostic thresholds, and outcome definitions. For palmar erythema, meta-analysis was precluded entirely due to heterogeneity. Second, many studies were conducted in tertiary referral populations, limiting generalizability to primary care settings. Third, most studies did not report inter-rater reliability for cutaneous examination findings, raising questions about reproducibility in routine practice. Fourth, recall bias and publication bias may influence reported associations, particularly for less common findings. Fifth, the exclusion of grey literature and certain publishers may have introduced selection bias, though this was weighed against concerns about study quality.

Future Research Directions

Prospective studies with standardized definitions of cutaneous findings, blinded assessment, and adequate inter-rater reliability testing are needed. The development of combined clinical prediction models integrating cutaneous signs with laboratory and imaging data should be prioritized. Artificial intelligence and teledermatology approaches for automated detection of cutaneous stigmata represent promising avenues for scaling these assessments. Long-term outcome studies are needed to determine whether earlier detection through skin examination translates to improved clinical outcomes. Such studies should evaluate not only diagnostic accuracy, but also reproducibility, clinical decision impact, cost-effectiveness, and whether skin-based screening improves downstream morbidity and mortality.

CONCLUSION

External skin examination remains a clinically valuable, low-cost, and non-invasive tool for identifying internal diseases. This systematic review confirms that xanthelasma palpebrarum is a significant marker of dyslipidemia and subclinical atherosclerosis, diabetic dermopathy correlates strongly with microvascular complication burden, spider angiomas demonstrate moderate-to-high specificity for cirrhosis, and livedo reticularis signals potentially serious vasculopathic processes with cerebrovascular implications. The integration of cutaneous examination into routine preventive care and diagnostic algorithms aligns with the principles of precision medicine identifying disease at its earliest, most treatable stages. To facilitate clinical implementation, targeted skin assessment should be incorporated into routine primary care and specialty screening protocols. Patients presenting with xanthelasma palpebrarum should undergo lipid profile evaluation and cardiovascular risk assessment, while those with diabetic dermopathy should receive comprehensive screening for retinopathy, nephropathy, and neuropathy. The detection of multiple spider angiomas should prompt liver function testing and assessment for chronic liver disease, whereas livedo reticularis should trigger further evaluation for autoimmune, thrombotic, or cerebrovascular disorders. Incorporating these dermatologic findings into standardized clinical checklists and electronic health record-based screening pathways may improve early disease detection and risk stratification. Future efforts should focus on standardizing examination techniques, developing validated prediction models, and training clinicians to recognize these diagnostically valuable cutaneous signs.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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