Anthem

Medical Policy

Subject: Non-invasive Measurement of Advanced Glycation End Products (AGEs) in the Skin
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Description/Scope

This document addresses non-invasive measurement of advanced glycation end products (AGEs) in the skin via photospectroscopy. AGEs have been indicated as mediators of various vascular and cardiac complications in a wide variety of conditions, including diabetes, renal failure, and congestive heart failure.

Position Statement

Investigational and Not Medically Necessary:

Non-invasive measurement of advanced glycation end products (AGEs) in the skin is considered **investigational and not medically necessary** for all indications, including but not limited to diabetes, renal failure, and cardiac disease.

Rationale

Glycation is a major cause of spontaneous damage to proteins in physiological systems. Advanced glycation end products (AGEs) are metabolic byproducts from non-enzymatic glycation of proteins and amino acids. AGEs accumulate in the skin and other tissues over time in people with a wide variety of medical conditions. Measurement of AGEs has been proposed as a biomarker for disease severity and risk prediction in the study of several diseases, including diabetes, renal failure and systemic lupus erythematosus (SLE), as well as in individuals with solid organ transplantation or high risk of cardiovascular events. AGEs are currently measured via skin biopsy. AGEs demonstrate autofluorescence when exposed to particular wavelengths of light; spectrographic noninvasive autofluorescence readers (AFR) have been developed and used to measure AGEs. Currently, there are no Food and Drug Administration (FDA)-approved non-invasive skin AGE devices.

AGE measurement in Individuals with Diabetes

Studies have demonstrated a link between AGEs in the skin and diabetic complications (Beisswenger, 1993a, 1993b; Beisswenger, 1995; McCance, 1993; Sell, 1991; Sell, 1992). Several studies have demonstrated that skin AGEs are correlated with the development of diabetic retinopathy and neuropathy (Genuth, 2005; Monnier, 1999). Using skin samples obtained by punch biopsy, these studies demonstrated a causal and independent link between skin AGEs and the development of diabetic neuropathy and retinopathy. The Monnier study found that long-term intensive treatment of hyperglycemia was associated with lower levels of AGE accumulation in the skin that paralleled HgbA1c reductions as well as the risk of neuropathy and retinopathy. This study also found that quantitation of AGEs provides insight into an individual's glycemic status over a period of several years. The study by Genuth and colleagues provides additional support to the observation that measurement of skin AGEs, specifically $^{\varepsilon}$N-carboxymethyl-lysine (CML) and pentosidine, can be used to assess future risk of neuropathy and retinopathy. Furthermore, these measures are independent of other risk factors and they may have a predictive value of up to 10 years from the time of measurement.

Meerwaldt and others (2004) reported on the results of a non-randomized controlled trial in which the skin AGE concentrations were measured by both biopsy and AFR in 46 diabetic (type 1 and 2) participants and 46 controls. The results of their study found that there was a high correlation between skin AGE autofluorescence and traditional AGE measurements for CML and pentosidine, as well as $^{\varepsilon}$N-carboxyethyl-lysine (CEL), another type of AGE, and Collagen-Linked Fluorescence (CLF), a summary measure of tissue autofluorescence. This study included predominantly Caucasian participants, thus the results of this study cannot be generalized to non-Caucasian populations due to the fact that autofluorescence is significantly affected by skin pigmentation. Another study by this same group in 117 participants with diabetes and 43 healthy controls, all with non-pigmented skin, found a significant correlation of AFR measurements with cardiac mortality in individuals with diabetes (Meerwaldt, 2007).

A study by Maynard et al. (2007) involved 84 glucose testing-naive individuals who underwent AGE and testing for HbA1c, fasting blood glucose (FBG) concentration and oral glucose tolerance testing (OGTT). The purpose of this study was to evaluate skin AGE measurement as a method of detecting undiagnosed diabetes and impaired glucose tolerance. The authors report that the sensitivity of skin AGEs was significantly greater than FBG and HbA1c testing. The AFR device used in this study utilized an algorithm to correct for differences in skin pigmentation during AGE measurements, and their findings were that the sensitivity of their device was not impaired by variation in skin melanin concentrations. However, it must be noted that while the study cohort did have a high percentage of non-Caucasian study participants (46.7%), there was only a small representation of black participants (3.1%). The remainder of this population was Hispanic (36.5%), Native American (4.8%), Asian (0.85%), East Asian (0.28%), and "Other" (1.1%). These results may not be applicable to the general population.

Gerrits (2008) investigated the role of AFR in predicting microvascular complications in 881 individuals with type 2 diabetes. Mean follow-up was 3.1 years. The author found that baseline AFR results were significantly associated with any microvascular complication, neuropathy or microalbuminuria. However, AGE was not found to be significantly associated with the occurrence of retinopathy. This study excluded dark skinned individuals based on limitations of the AFR device's ability to measure accurately in this population.

Lutgers and colleagues (2009) reported on a study involving 973 participants with type 2 diabetes followed for 3 years. The purpose of this study was to evaluate the use of AFR measurement of AGEs for the prediction of cardiac complications in individuals with diabetes. Multivariate analysis found that skin autofluorescence was an independent predictor for fatal and non-fatal cardiovascular endpoints. Additionally, adding AGE data to the UK Prospective Diabetes Study risk engine resulted in the reclassification of 55 of 203 (27%) participants from the low-risk to the high-risk category. The study population of this study was 97% Caucasian, limiting these findings beyond this population.

Neither the American Diabetes Association (ADA) nor the American Academy of Clinical Endocrinologists (AACE) mention the use of AGE measurements in their guidelines for the treatment of diabetes (AGA, 2018; AACE, 2022).

The available evidence evaluating the clinical utility of AGE measurement for identifying individuals with diabetes or impaired glucose

tolerance, and as a tool in predicting the risk of diabetes-related complications is promising; however, the generalizability of the available data is limited. Additionally, there have been no studies demonstrating improved clinical outcomes as a result of this technology.

AGE measurement in Individuals with Renal Failure and Transplantation

It has been proposed that AGEs may play some role in cardiovascular mortality in individuals undergoing renal dialysis. Ueno and colleagues (2008) conducted a non-randomized controlled study of AGE accumulation in 102 Japanese participants with end-stage renal disease (ESRD) and 110 healthy controls. In the ESRD group, the pulse wave velocity, a measure of arterial stiffness, and skin autofluorescence were significantly higher than in the control group and significantly and positively correlated with each other. Multilinear regression analysis found that pulse wave velocity and skin autofluorescence were significant and independent from other factors. The authors concluded that AGE measurement is related to and may play a role in the pathophysiology of arterial stiffness in individuals with ESRD.

In another study, 109 participants undergoing hemodialysis for ESRD had skin AGEs measured non-invasively with AFR and were followed for 3 years (Meerwaldt, 2005). Non-invasive skin AGEs were validated against biopsy results in 29 participants. At 3 years, 42 of the original 109 participants (38.5%) had died. Regression analysis indicated that skin autofluorescence was an independent predictor of overall and cardiovascular mortality. Skin type for the study population was not reported.

Hartog and colleagues (2009) enrolled 302 renal transplant recipients in a study looking at graft loss and AFR measurement. After a mean follow-up period of 5.2 years, statistical analysis found that skin autofluorescence was significantly correlated with graft loss, independent of age, creatinine clearance, protein excretion, high sensitivity C-reactive protein, and human leukocyte antigen-DR mismatching. The authors noted that 7 non-white individuals were excluded from this study, because the AFR devices used had not been validated in individuals with pigmented skin.

The relationship between non-invasively measured AGE concentrations andrenal morbidity and mortality is currently under investigation. To date, there have been no studies demonstrating improved clinical outcomes as a result of this technology.

AGE measurement in Individuals with Systemic Lupus Erythematosus

AGE autofluorescence has been investigated as a means of gauging disease activity and severity in individuals with systemic lupus erythematosus (SLE). One small case-control study found that AFR-measured skin AGEs were significantly higher in individuals with SLE, and that the more active the condition, the higher the AGE measurement (Nienhuis, 2008). These findings were supported by a slightly larger case-control study by de Leeuw and colleagues (2007). In this study, 55 participants with SLE were matched with 55 healthy controls. Skin AGEs were measured by AFR in all study participants. The authors reported that skin AGE concentrations are an independent predictor of disease duration. Measurement of skin AGEs has not been shown to improve outcomes.

AGE measurement in Individuals with Cardiac Disease

There is limited data currently available addressing the measurement of AGEs in individuals with heart disease. Mulder and colleagues (2009) published the results of a study investigating the role of AFR AGE measurement in Caucasian individuals with acute myocardial infarction (MI). Skin AGEs were measured in 201 participants, 88 of whom had ST-elevation MI, 81 who had stable coronary artery disease (CAD), and 32 healthy controls. Measurement in the MI group occurred within 72 hours of the MI event. The authors reported that skin AGEs were significantly elevated in MI individuals compared to individuals with CAD and controls and that elevated AGE measurement in individuals with MI was predictive of future adverse events. No data was provided demonstrating how these findings may impact clinical care.

AGE measurement in Individuals with Sarcopenia

Waqas (2022) completed a cross-sectional analysis of the Rotterdam Study to investigate a potential relationship between skin autofluorescence and sarcopenia. The study comprised of 2744 participants. The gait speed of a subset of participants (n=2080) was assessed, which they used for comparison and exploratory analysis. Skin autofluorescence was measured using and AGE Reader™. Severe sarcopenia was analyzed in individuals with gait speed data (n=2080). Nonsignificant association was identified with continuous skin autofluorescence [OR 1.63 (95% CI 0.96, 2.79) with slow gait speed (n=61/2080, 2.9%). Authors concluded further research is important to look at the potential skin autofluorescence in predicting sarcopenia.

Conclusions

At this time, there is insufficient data available demonstrating the clinical utility of non-invasive measurement of skin AGE concentrations. The populations studied thus far have been relatively small and with heterogeneous results. There are several larger studies currently underway in the U.S. and elsewhere evaluating the potential use of AFR. The FDA has not yet approved any AFR devices for marketing in the United States and their use in this country is limited to clinical trials.

Background/Overview

Over the past several decades, many studies have demonstrated a link between advanced glycation end products (AGEs) in the skin and the development of complications in a wide array of conditions including diabetes, lupus, renal failure, and cardiac disease. The current method of AGE measurement involves the use of skin samples obtained by punch biopsy.

Using the fact that several important AGEs autofluoresce at certain wavelengths of light, several groups have undertaken the development of a non-invasive autofluorescence reader (AFR) to measure skin AGE concentrations. To use these devices, an individual places a portion of relatively hair and blemish-free skin onto the device, which then shines several wavelengths of light onto the skin. The reflected light from the fluorescing AGEs is analyzed by a photospectrometer, which quantifies AGE concentrations in the skin. Such non-invasive measurement devices could potentially be used in the physician's office for fast and easy screening and risk assessment for individuals with diabetes and other diseases.

There are currently two AFR devices under evaluation. The first, which is the device used in the majority of peer-reviewed published literature on this topic, is the DiagnOptics AGE Reader™. This device is manufactured in Holland and is not currently available in the U.S. The second device is the Scout DS® which is manufactured in New Mexico and is currently addressed in only one peer-reviewed article. Currently, there are no FDA-approved non-invasive skin AGE devices.

Definitions

Advanced glycation end products (AGEs): Byproducts of a reaction between blood sugars and proteins, lipids and nucleic acids in the body.

Coding

The following codes for treatments and procedures applicable to this document are included below for informational purposes. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement policy. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

When services are Investigational and Not Medically Necessary:

CPT

88749	Unlisted in vivo (eg, transcutaneous) laboratory service [when specified as skin advanced glycation endproducts (AGE) measurement by multi-wavelength fluorescent spectroscopy]

ICD-10 Diagnosis

	All diagnoses

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Index

AGE Reader
Autofluorescence Reader (AFR)
DiagnOptics AGE Reader
Scout DS

The use of specific product names is illustrative only. It is not intended to be a recommendation of one product over another, and is not intended to represent a complete listing of all products available.

Document History

Status	Date	Action
Reviewed	02/15/2024	Medical Policy & Technology Assessment Committee (MPTAC) review. Updated Rationale and References sections.
Reviewed	02/16/2023	MPTAC review. Updated Rationale and References sections.
Revised	02/17/2022	MPTAC review. Updated title from “Endproducts” to “End Products”. Updated References section.
Reviewed	02/11/2021	MPTAC review. Updated References section.
Reviewed	02/20/2020	MPTAC review. Updated References section.
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Reviewed	05/03/2018	MPTAC review. Updated Rationale and Reference sections.
Reviewed	05/04/2017	MPTAC review. Updated Rationale, Background, References, and Index sections.
Reviewed	05/05/2016	MPTAC review. Updated Rationale and Reference sections.
	01/01/2016	Updated Coding section with 01/01/2016 CPT changes, removed 0233T deleted 12/31/2015; also removed ICD-9 codes.
Reviewed	05/07/2015	MPTAC review.
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New	05/13/2010	MPTAC. Initial document development.
