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Journal of Diabetes Science and Technology
1–6
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DOI: 10.1177/19322968241296541
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Advanced Glycation End Products (AGEs) Webinar Meeting Report

Cindy N. Ho, BA[1], Alessandra T. Ayers, BA[1], Paul Beisswenger, MD[2,3], Stuart Chalew, MD[4], Ann Marie Schmidt, MD[5,6,7], Ambarish Pandey, MD, MSCS, FAHA[8], Pankaj Kapahi, PhD[9,10], Alexander Fleming, MD[11,12], and David C. Klonoff, MD, FACP, FRCP (Edin), Fellow AIMBE)[13]

Abstract

The advanced glycation end products (AGEs) Webinar was co-hosted by Diabetes Technology Society and Kitalys Institute on August 8, 2024, with the goal of reviewing progress made in the measurement and use of AGEs in clinical practice. Meeting topics included (1) AGEs as predictors of diabetic nephropathy (DKD), (2) hemoglobin glycation index (HGI) and the glycation gap (GG), (3) formation and structure of AGEs, (4) AGEs as a risk factor of cardiovascular disease (CVD), and (5) approaches to limit or prevent AGE formation.

Keywords
advanced glycation end products, AGE formation, AGE prevention, aging, chronic diseases

Introduction

Moderator: Alexander Fleming, MD

Diabetes Technology Society (DTS), led by David Klonoff, MD and Kitalys Institute, led by Dr Alexander Fleming, MD partnered to host a discussion of AGEs. Advanced glycation end products (AGEs) are a target for slowing the aging process, and preventing and reversing the complications of diabetes and other chronic diseases. Advanced glycation end products are both therapeutic targets and, biomarkers that can have clinical utility in prevention and management of chronic disease. Advanced glycation end products are strongly implicated in the biology of aging, and the development of multiple degenerative diseases and disabilities, including diabetes, atherosclerosis, chronic kidney disease (CKD), and Alzheimer's disease. Increased understanding of AGEs will lead to treatments and diagnostics for slowing and reversing the complications of aging, diabetes, and other chronic diseases.

Section 1: AGEs as Predictors of Diabetic Nephropathy

Panelist: Paul Beisswenger, MD

Major Takeaways

- Advanced glycation end products play a crucial role in the development of diabetic microvascular

[1]Diabetes Technology Society, Burlingame, CA, USA
[2]Geisel School of Medicine at Dartmouth, Hanover, NH, USA
[3]Journey Biosciences, Cleveland, OH, USA
[4]Section Pediatric Endocrinology/Diabetes, School of Medicine, LSU Health, The Children's Hospital of New Orleans, New Orleans, LA, USA
[5]Department of Medicine, NYU Langone Health, New York, NY, USA
[6]Department of Biochemistry and Molecular Pharmacology, NYU Langone Health, New York, NY, USA
[7]Department of Pathology, NYU Langone Health, New York, NY, USA
[8]Division of Cardiology and Geriatrics, Department of Internal Medicine, University of Texas Southwestern Medical Center, Dallas, TX, USA
[9]Buck Institute for Research on Aging, Novato, CA, USA
[10]Juvify Bio, Novato, CA, USA
[11]Kinexum, Harpers Ferry, WV, USA
[12]Kitalys Institute, Charlottesville, VA, USA
[13]Diabetes Research Institute, Mills-Peninsula Medical Center, San Mateo, CA, USA

Corresponding Author:
David C. Klonoff, MD, FACP, FRCP (Edin), Fellow AIMBE, Diabetes Research Institute, Mills-Peninsula Medical Center, 100 South San Mateo Drive, Room 1165, San Mateo, CA 94401, USA.
Email: dklonoff@diabetestechnology.org

complications, with their levels closely linked to individual susceptibility as demonstrated in multiple landmark clinical studies.
- Advanced glycation end product levels can predict the onset of diabetic nephropathy (diabetic kidney disease; DKD) up to 12 years before clinical symptoms appear, offering a significant window for early intervention.
- The ability to measure AGEs and predict DKD risk years in advance, combined with recent pharmacologic and technological advancements, enables proactive intervention and prevention of DKD for the first time in history.

Diabetes and its complications cost thousands of lives and billions of dollars annually, yet health care providers cannot predict who will develop these complications until they become clinically apparent—often too late for preventive action. Consequently, providers cannot individualize treatment or apply newer therapies until damage has already become irreversible. Patients, unaware of their individual risk, often become complacent about treatments and lifestyle changes

Preventing diabetic complications is further complicated by the variable susceptibility among individuals, even when they achieve the same level of glycemic control.[1] This variability makes it difficult to identify high-risk individuals and apply effective preventive treatments early, potentially missing critical windows for prevention.

Glycative stress is caused by glycation of proteins, lipids, and nucleic acids, and is a major cause of diabetic complications.[2] The stress results from the activation of reactive sugar-derived molecules that lead to the accumulation of toxic AGEs. In this process, intracellular and extracellular proteins and lipids become glycated, which can lead to DKD and other vascular damages.[3]

Cellular production of these reactive sugars increases significantly in DKD progressors compared with non-progressors in diabetes.[4,5] Advanced glycation end products may potentially hasten declining kidney function in patients with CKD and are independently correlated with all-cause mortality.[6] Higher levels of AGEs are also associated with an increased risk of adverse renal outcomes.[7] Measurement of circulating AGEs levels can improve prediction of CKD independently from traditional risk factors such as creatinine clearance and has predicted CKD up to 12 years before clinical onset in type 2 diabetes (T2D).[8]

In patients with T2D, measurement of AGEs by mass spectrometry and use of a proprietary composite test combining concentrations of up to five soluble AGEs established an early predictive test for DKD. This commercially available test[9] has shown a stronger correlation with predicting future decline in renal function when added to traditional risk factors compared with measuring the risk factors alone.[9] This composite score, compared with any individual AGE concentration has improved prediction in two different long-term studies of patients with T2D.[8,9] In adults with T2D, increased levels of soluble receptors for AGEs (as well as AGEs themselves) are independently associated with new or worsening CKD disease and mortality.[10,11]

Autofluorescence in skin may reflect AGEs accumulated in tissues where they can exert harmful effects.[3] Elevated concentrations of circulating AGEs,[3] however, measured by mass spectrometry is more precise and specific, and might be more modifiable and therefore more responsive to therapeutic interventions.[12]

Section 2: Hemoglobin Glycation Index and the Glycation Gap

Panelist: Stuart Chalew, MD

Major Takeaways

- *Glycation gap (GG).* Glycation gap is the observed discordance between an individual's assayed hemoglobin A1c (HbA1c) and the HbA1c predicted from that individual's mean blood glucose (MBG) level based on a population regression model of HbA1c on MBG.
- *Hemoglobin glycation index (HGI) and complications.* Glycation gaps can be quantified by the HGI. The HGI is highly correlated with HbA1c, but statistically independent of MBG. Hemoglobin glycation index permits comparison of HbA1c levels between individuals and groups as if their MBGs were the same. Hemoglobin A1c and HGI appear to contain more information predicting development and progression of chronic complications than MBG alone.
- *Advanced glycation end products.* Advanced glycation end products, as estimated by skin autofluorescence (SAF), are correlated with HbA1c and HGI but independent of MBG.

Glycation Gap

Consistent between-individual differences in HbA1c at the same MBG have long been noted. Such variation gives rise to the concept of GGs, which is the discordance between an individual's assayed HbA1c from the average population HbA1c expected for that individual's preceding MBG. Glycation gap can be quantified by the HGI = (individual's assayed HbA1c–predicted HbA1c from that individual's MBG).[13-15] Predicted HbA1c is calculated from a population regression equation of HbA1c on MBG (some have calculated GG using fructosamine in place of MBG).[15] Hemoglobin glycation index is highly correlated with HbA1c, but statistically independent of MBG.[13,14] An individual's HGI is fairly

stable over time. Hemoglobin glycation index permits comparison of HbA1c levels between individuals and groups as if their MBGs were the same.[13] With caveats, the availability of the glucose management index (GMI) facilitates the calculation of HGI from continuous glucose monitor data, HGI = (assayed HbA1c–GMI).[16]

Risk of Complications

A large number of studies indicate that HbA1c and HGI (because of its strong relationship with HbA1c) are better predictors of micro and macrovascular complications than MBG alone.[13,14] In one study of patients with type 1 diabetes, the third of the population with highest HGIs had three times the risk of retinopathy and six times the risk of nephropathy compared with the third of patients with lowest HGIs even though the MBGs of the three groups were similar.[13] Patients with high HGI are more prone to hypoglycemia during therapy. This is especially frequent in African heritage individuals who have higher HGIs compared with white European heritage individuals[16] and greater risk of severe hypoglycemia during treatment.[17]

Advanced glycation end products

The mechanism/s underlying GGs and relationship to complications are at present unclear. Of interest, both HbA1c and HGI but not MBG are correlated with levels of tissue AGEs as estimated by skin intrinsic fluorescence.[18] Advanced glycation end products have been proposed as a mechanism for diabetes complications. Potentially, between-individual differences in hemoglobin glycation in addition to MBG may be an early predictor of AGE accumulation and higher risk for diabetes complications.

Section 3: Formation and Structure of AGEs

Panelist: Ann Marie Schmidt, MD

Major Takeaways

- Advanced glycation end products develop and accumulate in many pathological settings in vivo, such as diabetes, aging, inflammation, neurodegeneration, obesity, and hypoxia and ischemia/reperfusion injury.
- Advanced glycation end products interact with their chief cell surface multi-ligand receptor, receptor for advanced glycation end products (RAGE) is a key mechanism by which AGEs mediate their pathogenic effects in vivo.
- The interaction of the cytoplasmic domain of RAGE with the formin (a cytoskeleton protein in eukaryotic cells), DIAPH1, is important for RAGE signaling. Small molecule antagonism of the RAGE–DIAPH1 interaction has demonstrated efficacy in reducing RAGE-dependent pathobiologies in vivo and may form the basis for a novel class of therapeutic agents for AGE-RAGE-related disorders.

The interaction of AGEs with cell surface receptors, the best-characterized of which is the multi-ligand RAGE, is a chief means by which AGEs exert pathobiological effects. Receptor for advanced glycation end product is expressed in cell types such as immune and vascular cells, neurons, cardiomyocytes, podocytes, and adipocytes. Increased tissue and plasma/serum content of AGEs in diabetes, obesity, aging, inflammation, and neurodegeneration accompanies the augmented expression of RAGE in affected tissues.[3] Ligand–RAGE interaction activates a host of signal transduction cascades to amplify inflammation and oxidative stress and thwart homeostatic functions. Genetic deletion of *Ager* or pharmacological antagonism of RAGE protects from the pathological effects of RAGE ligands in in vivo models of disease,[19] such as the macrovascular and microvascular complications of diabetes, obesity, inflammatory conditions and sepsis, neurodegeneration, including Alzheimer's disease and amyotrophic lateral sclerosis, and aging.

The discovery that the cytoplasmic domain of RAGE binds the formin homology (FH1) domain of Diaphanous 1 (DIAPH1) and that this interaction was important for RAGE signaling was essential to discover the precise means by which RAGE exerts its pathological actions upon ligand engagement.[20] Analogous to findings in mice devoid of *Ager*, mice devoid of *Diaph1* are protected from complications of diabetes, ischemia/reperfusion injury, neointimal expansion after endothelial denudation injury to the femoral artery and atherosclerosis in mice. Structural biology studies have characterized the means by which the intracellular domain of RAGE is engaged with DIAPH1. Collectively, this work set the stage for the cytoplasmic domain of RAGE–DIAPH1 interaction as a platform for screening for small molecule antagonists for therapeutic development.

Novel small molecule antagonists of RAGE–DIAPH1[21] have been developed that demonstrate potent antagonism of this interaction and are effective in cellular models of ligand-RAGE-mediated cellular stress. In vivo, these small molecules have afforded benefit in multiple RAGE-related models of disease. Work is underway to refine these small molecules for testing in clinical trials.

Section 4: AGEs as a Risk Factor of Cardiovascular Disease

Panelist: Ambarish Pandey, MD, MSCS, FAHA

Major Takeaways

- Advanced glycation end products are suggested to contribute to the etiology of CVD and are associated

with increased risk of myocardial infarction (MI) and heart failure (HF), with a greater risk among those with diabetes.
- Advanced glycation end products predispose to adverse CV events through development of subclinical CVD and contribute to tissue stiffness through formation of crosslinks, triggering inflammation through interaction with RAGE.
- Advanced glycation end products accumulate in tissues over time, especially under conditions of hyperglycemia, renal insufficiency, and smoking.

Advanced glycation end products play a significant role as a risk factor for CVD.[22] These heterogeneous compounds result from nonenzymatic reactions between reducing sugars and biomolecules such as proteins, lipids, and nucleic acids. While present in moderate amounts in healthy individuals, AGE formation increases under hyperglycemic conditions. Several cohort studies from Europe and United States have demonstrated associations between AGEs and various cardiovascular outcomes. Higher levels of AGEs, measured through SAF or serum markers, are linked to increased risks of MI, HF, and subclinical cardiovascular disease (CVD). The relationship between AGEs and vascular stiffness, measured by pulse wave velocity (PWV), is also evident.[23] Cross-sectional and longitudinal studies support this association, with the ratio of skin AGE to soluble receptor for AGE (sRAGE) being most strongly associated with PWV changes over time.

Advanced glycation end products enhance cardiovascular risk through several mechanisms, including extracellular protein modification leading to increased vascular stiffness, intracellular protein modification causing cellular stress and apoptosis, and AGE-mediated signaling cascades.[23] The interaction of AGEs with their receptor (RAGE) activates pro-inflammatory, proliferative, fibrotic, and thrombotic pathways, contributing to vascular inflammation and injury. Advanced glycation end products contribute to CVD etiology through various pathways, including the development of subclinical CVD and tissue stiffness.

They accumulate over time, especially in conditions like hyperglycemia, renal insufficiency, and smoking. Given their significant role in cardiovascular risk, anti-AGE therapies are proposed as a promising approach for CVD management and prevention.[24] This research underscores the importance of understanding AGEs in the context of cardiovascular health and potential future therapeutic interventions.

Section 5: Approaches to Limit or Prevent AGEs Formation

Panelist: Pankaj Kapahi, PhD

Major Takeaways

- A combination of nicotinamide, α-lipoic acid, thiamine, pyridoxamine, and piperine (Gly-Low) lowered deleterious effects of glycation by reducing MGO and MGO-derived AGE, MG-H1, in mice.
- Gly-Low supplementation in the diet reduced food consumption by inhibiting Ghrelin, decreased body weight, improved insulin sensitivity, and increased survival in leptin receptor-deficient (Leprdb) and wild-type C57B6/J mice.
- Gly-Low can also mitigate the effects of menopause on food intake, insulin sensitivity and brain aging.

Sweet Sabotage: Role of Methylglyoxal Induced Glycation in Obesity, Insulin Resistance, and Aging

Advanced glycation end products are linked to aging and age-related diseases, exacerbated by the accumulation of methylglyoxal (MGO), a toxic byproduct of glycolysis.[25] MGO is the major precursor of nonenzymatic glycation of proteins and DNA, subsequently leading to the formation of AGEs.[26] Evolutionarily conserved glyoxalases are responsible for α-dicarbonyl compounds (α-DCs) detoxification; however, their core biochemical regulation has remained unclear. We have established a *Caenorhabditis elegans* model, based on an impaired glyoxalase (glod-4/GLO1), to broadly study α-DC-related stress. We show that, in comparison with wild-type (N2, Bristol), glod-4 animals rapidly exhibit several pathogenic phenotypes, including hyperesthesia, neuronal damage, reduced motility, and early mortality.[27] We further demonstrate TRPA-1 as a sensor for α-DCs, conserved between worms and mammals, which activates SKN-1/Nrf via calcium-modulated kinase signaling, ultimately regulating the glutathione-dependent (GLO1) and co-factor-independent (DJ1) glyoxalases to detoxify α-DCs.[28] We identified lipoic acid as a novel activator of TRPA1 that rescues α-DC-induced pathologies in *C. elegans* and mammalian cells.[28] We further examined the potential of combination therapy using other inhibitors of MGO, termed GLYLO, composed of nicotinamide, lipoic acid, thiamine, pyridoxamine, and piperine, to reduce glycation and its detrimental effects. In mouse models in unpublished data, administration of Gly-Low resulted in reduced caloric intake and body weight, improved insulin sensitivity, and extended lifespan. The therapy also extended lifespan when administered in late life, further indicating its potential benefits in ameliorating age-related decline. Gly-Low reprograms metabolism by reducing glycolysis and presumptively enhancing MGO detoxification pathways. The observed reduction in caloric intake and body weight, improved insulin sensitivity, and extended lifespan associated with Gly-Low treatment in this model may result from lowering glycation and AGEs expected from enhancing MGO clearance.[29] The results suggest that Gly-Low could have a role in increasing health span and treating metabolic disorders.

Abbreviations

α-DCs, α-dicarbonyl compounds; AGE, advanced glycation end product; CVD, cardiovascular disease; DCCT, Diabetes Complications and Control Trial; DIAPH1, Diaphanous 1; DJ1, co-factor-independent glyoxalase; DKD, diabetic nephropathy; DTS, Diabetes Technology Society; GG, glycation cap; GLO1, glutathione-dependent glyoxalase; GMI, glucose management index; HbA1c, hemoglobin A1c; HGI, hemoglobin glycation index; MBG, mean blood glucose; MGO, methylglyoxal; PWV, pulse wave velocity; RAGE, receptor for advanced glycation end products; SAF, skin autofluorescence; sRAGE, soluble receptor for AGE; T2D, type 2 diabetes.

Acknowledgment

The authors acknowledge Annamarie Sucher-Jones for her editorial expertise.

Declaration of Conflicting Interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: C.N.H. is a consultant for Liom.

ATA is a consultant for Liom.

DCK is a consultant for Afon, Embecta, Glucotrack, Lifecare, Novo, Samsung, Synchneuro, and Thirdwayv.

GAF is an advisor for 180 Life Sciences, 89bio, Adocia, Abbott, AdipoPharma, Aerami, Amolyt, Carthera, Catalyst, Cohen Global, CMC Magnetics, Diasome, Eleos, Entera Bio, Enterin, Glyscend, Hagar, Hogan Lovells, IM Therapeutics, Innoneo, Intarcia, Levicure, Lilly Asia Ventures, Lumos, Mars Symbioscience, Melior, metaLead Therapeutics, Microbiotix, MMD, Modular Medical, New Amsterdam, Northwestern, NuSirt, NuVox, Oramed, Pano, Pasithea, PhylloPharma, Pleiogenix, Recordati, Regor, Remodeless, Renaissance, RenovoRx, Rivus, RxMP, Sera Biopharma, Seraxis, Serpin, SFC Fluidics, Skinject, SROne, Stalicla, Surf Bio, TIXiMED, Veroscience, Verthermia, WaveBreak, Zealand Pharma, and Zucara.

PB is co-founder and Chief Scientific Officer at Journey Biosciences.

SC has nothing to disclose.

AMS holds patents and patent applications with the NYU Grossman School of Medicine for small molecule antagonists of RAGE–DIAPH1.

AP has received grant funding (to the institution) from Applied Therapeutics, Gilead Sciences, Ultromics, Myovista, and Roche; has served as a consultant for and/or received honoraria outside of the present study as an advisor/consultant for Tricog Health Inc., Lilly USA, Rivus, Cytokinetics, Roche Diagnostics, Sarfez Therapeutics, Edwards Lifesciences, Merck, Bayer, Novo Nordisk, Alleviant, Axon Therapies, and has received nonfinancial support from Pfizer and Merck. AP is also a consultant for Palomarin Inc with stocks compensation and has received research support from the National Institute on Aging GEMSSTAR Grant (1R03AG067960-01), the National Institute on Minority Health and Disparities (R01MD017529), and the National Institute of Heart, Lung, and Blood Institute (R21HL169708).

PK is one of the patent holders of GLYLO, a supplement licensed to Juvify Bio by the Buck Institute. PK is also the founder of Juvify Bio.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

ORCID iDs

Cindy N. Ho https://orcid.org/0009-0008-3067-1004
Alessandra T. Ayers https://orcid.org/0009-0000-3054-3207
Paul Beisswenger https://orcid.org/0000-0002-6594-6978
Stuart Chalew https://orcid.org/0000-0002-3914-3127
Ann Marie Schmidt https://orcid.org/0000-0001-8902-070X
Ambarish Pandey https://orcid.org/0000-0001-9651-3836
Pankaj Kapahi https://orcid.org/0000-0002-5629-4947
Alexander Fleming https://orcid.org/0000-0002-6549-0288
David C. Klonoff https://orcid.org/0000-0001-6394-6862

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