AGEs: ADVANCED GLYCATION END PRODUCTS

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AGEs = Glucose + Protein

- Glyceraldehyde + glucose + lipids + protein
- Glycolaldehyde + protein + lipid
- Methyl glyoxal + protein + lipid
- Acetaldehyde + protein + lipid

- Formation of AGES pathways
  - Maillard: amino group + glucose → Schiff Base → Amadori product → AGEs
  - Polyol: sorbitol → fructose → oxoaldehydes → AGEs
  - Lipid peroxidation → AGEs

What are AGEs?

- Advanced glycation end products (AGEs) are harmful molecules produced in the body during metabolic processes.
  - AGEs promote
    - Oxidative stress
    - inflammation
    - Apoptosis (cell injury and destruction)
    - Premature aging
    - Cardiovascular disease
    - Fatty liver disease
    - Neurodegenerative disease
    - Hypertension
    - Renal failure
    - Insulin resistance and pancreatic cell dysfunction

Damage by AGEs

- AGEs causes cellular damage, including:
  - Mitochondrial dysfunction
  - Promotion of ROS (reactive oxygen species)
  - Production of Nitrogen Reactive species
  - Nuclear factor kappa beta stimulation (NFk-beta), leading to inflammatory cellular response.
  - Sirtuin-1, aging

  - Extracellular damage affects
    - Maturation of protein in walls
    - Collagen loss
    - Elastic tissue loss

Formation of AGEs pathways

- Maillard reaction
- Polyol pathway (fructose production from glucose)
- Lipid peroxidation (of polyunsaturated fats)

Maillard Pathway

- Amino group of a protein molecule plus glucose combined to make AGEs: Maillard reaction
- Polyol pathway: sorbitol to fructose to oxoaldehyde, results in AGEs
- Lipid peroxidation enhances AGEs

Maillard Reaction

- Maillard reaction is non-enzymatic reaction of
  - carbonyl (sugar) and amino (protein)
  - Sugar and nucleic acids in DNA
  - Sugar and lipids

- Cause impairment of proper protein function and hence cellular metabolic disruption

- RAGEs: Receptors to AGEs, present in all cells of the body

Methlyglyoxal

- Drives Maillard reaction 250 times faster than glucose
- Derived from the breakdown of glycated proteins
- Produced in cooking and storage
- Produced with alcohol consumption and making
- Microbial fermentation

Endogenous AGEs

- Diabetes Mellitus eg Hemoglobin A1C
- CRF (lack of excretion of waste products)
- Liver disease
- Alcohol
- Cigarettes
- High omega 6 fatty acid diet

Endogenous AGEs

- Endogenous AGEs: MOST IMPORTANT TO KEEP GLUCOSE LOW
- Continuous glucose monitoring can most effectively tell you which foods are causing a glucose spike thereby causes AGEs
- Another way to reduce endogenous AGEs is **FASTING**

- AGEs from Exogenous sources: Cooking and storing food and beverages
  - 90% end up in colon, affecting the microbiome
  - 10% are absorbed into the body
  - 30% are excreted in the urine
  - 60% of what is absorbed ends up in the tissues

Inhibitors of AGEs

Synthetic

Metformin
NSAIDs
Benfotiamine
Pyridoxamine
Naringenine
Hesperidin

Natural

Curcumin
Alpha lipoic acid
Flavanoids
Ginko
Celery
Red pepper
Parsley
Chamomile
Mint
Green tea

Exogenous AGEs

- Exogenous AGEs in processed food can take weeks to form products like dicarbonyls (eg. MGO (methyl glyoxal)
- Oxoaldehydes, glycooxidation, lipoxidation
- Reused, reheated old foods
- Processed foods
- Packaged ready made food
- Foods containing HFCS, sugar,
- High temperature, DRY cooking

Exogenous AGEs

- Frying
- Broiling
- Blackening
- Charring
- Baking
- Cereals

Fructose vs Glucose

- **Fructose causes AGEs 7 x FASTER than glucose, and 100% MORE reactive oxygen species**

Damages by AGEs:

- Cellular damage affects
  - Mitochondrial dysfunction
  - Production of reactive oxygen species
  - Production of Nitrogen reactive species
  - Nuclear Factor kappa-Beta stimulation
  - Sirtuim-1 aging
- Extracellular damage
  - Matrix proteins results in collagen loss
  - Elastic tissue loss

Damage by AGEs: Diabetes and the Gut

- Diabetes
  - Insulin resistance
  - Retinopathy
  - Renal failure
  - Small vessel disease
  - cardiomyopathy
- Gut
  - Flora is negatively affected by metabolic endotoxemia
  - Leaky gut
  - Fatty liver disease

Damage by AGEs: Brain and Bones

- Brain
  - Leptin resistance
  - Insulin resistance
  - Small vessel disease
  - Apoptosis of cells
    - Causes degenerative diseases like dementia and movement disorders
- Bones
  - AGEs increase osteoclastic activity

Damage by AGEs: Liver

- Liver damage negatively affects the liver's ability to eliminate AGEs, accumulation of AGEs occurs in any liver disease
- Increase protein kinases, nuclear factor kappa-B
- High omega 6 fatty acids and alcohol, fructose worsen liver injury and increase AGEs

No standard way to measure AGEs, but…

- Natural ways to reduce AGEs include increase intake of
  - Vitamin E
  - Curcumin
  - Alpha lipoic acid
  - Parsley
  - Flavonoids
  - Celery
  - Chamomile
  - Mint

- Synthetic ways to reduce AGEs include; acetylsalicylic acid and metformin, aminoguanidine, pyridoxamine, benfotiamine (a thiamine derivative), ARBs, ACE Inhibitors

High vs Low AGEs

High

- Animal foods
- Processed foods
- Dry/Direct heat cooking
  - Broiling
  - Air frying
  - Grilling
  - Roasting
  - BBQ
  - Baking

Low

- Naturally high carb foods
- Naturally high water content foods
- High phytonutrients
- Raw, uncooked vegetables

Cooking

- Safe way to kill bugs
- Increase flavor
- Easier to digest

Factors that affect the consequences of cooking include:

- Humidity
- Temperature
- PH
- Antioxidants in foods

Cooking Continued…

- Wet cooking (heat via water): Preferred
  - Poaching
  - Stewing
  - Braising
  - Steaming

  - Frying (heat via fat/oil): Avoid
    - Shallow
    - Deep

Cooking Temperatures

- The **higher the temperature,** the higher the AGEs production
- The **longer** the duration, the **more** AGEs produced

- Higher humidity produces less AGEs

- PH must be LOW (marinate food in lemon or vinegar)

- Cooking Methods
  - Boiling – 100 °C, 212 °F
  - Broiling - 225 °C, 437 °F
  - Deep frying - 180 °C, 356 °F
  - Oven frying (air frying) - 230 °C, 446 °F
  - Roasting - 177 °C, 350 °F
  - Microwave – food will only heat to 100 °C, 212 °F (microwave suitable containers)

Cooking Meats

Do's

- Meatballs in stew
- Meat curry
- Chili
- Sous Vide

- Broiled meat has 50% less AGEs than grilled meat

- Microwaved meat has 50% less AGEs

Don'ts

- Dry, processed ground meat ex: hamburgers or sausages, high in AGEs
- BBQ, produces AGEs
- Deep or shallow frying meats in oils/fats, produces AGEs and lipid oxidation
- Roasting, produces AGEs
- Grilling, produces AGEs

AGEs

- Burgers and chicken nuggets: 7,800
- Processed Cheese: 8,700
- Breakfast bar: 2,200
- Tofu: 5,900
- Butter: 26,000 in 3 oz
- Margarine: 7,000
- Peanut butter: 7,000
- Fried chicken: 8,000 (poached is < 1100 and raw chicken is < 800)
- Bacon: fried with no oil 90,000 in 3 oz

Daily recommended AGEs limit:
15,000

Category/Food Item	Cooking Method	AGE (kU/100g)
Beef	Boiled	1538
	Roasted	6071
	Grilled	7416
	Broiled	11270
Poultry	Poached	1101
	Pan fried	4938
	Roasted and BBQ	18520
Salmon	Microwave	912
	Boiled	1082
	Broiled	3347
	Pan-fried	3083
Eggs	Poached	90
	Omelet, Pan	507
	Fried	2749
Cheese	American	8700

Food Group	Food Item	AGE (kU/serving)
Grains	Whole wheat bread	36
	Biscuit, oven baked	441
	Chips	865
Fruits/Vegies	Apple fresh	13
	Apple baked	45
	Eggplant, raw	116
	Eggplant, grilled	256
Milk	Milk, fat free	2
	Milk, whole	12
	Evaporated milk	86

Remember

High temperatures and low moisture leads to more AGEs

Broiling, grilling, frying greater than 177 °C
Not recommended

Cooking Chicken Breast and Eggs

- Chicken Breast
  - 25% less AGEs if steamed/poached
  - Low and slow cooking is better, for example crock pot, pressure cooker, sous vide, and curry.

- Eggs
  - Poached or boiled eggs have less AGEs
  - Pan fried eggs creates AGEs
  - Lightly scrambled eggs are better than fried because they have less AGEs

AGEs in Bread and Cheese

- Bread
  - Crust has AGEs (230-250C)
  - Inside of bread loaf has 10x **less** AGEs
    - Whole wheat vs White flour makes **NO** difference
    - For pastries, add Naringenin hesperetin (flavanoid in citrus, bergamot, tomatoes) to reduce AGEs.
    - Quercetin added to bread reduces AGEs
- Cheese
  - High fat and aged cheeses have more AGEs, likely due to pasteurization and long curing and aging time, higher fat content. Older cheeses continue to make AGEs.

Grains and Legumes

- Cook pasta al dente; Pasta cooked 8 minutes instead of 12 minutes has LESS AGEs
- Rice- cooked for less than 10 minutes has little AGEs
- Instant Pot is highly recommended because of less AGEs and cooking process kills lectins
- Lentils should be soaked overnight, then moist cooked in pressure cooker

Grilled Vegetables

- Don’t blacken vegetables
- Less AGEs in raw states

AGEs in Nuts and Seeds

- Roasting almonds has HIGH AGEs
- Probably the same with other nuts and seeds
- Roasting with sugar or honey is worse

AGEs continued

- High fat spreads like butter, cream cheese, mayonnaise have high AGEs
- Prefer Ghee or refined coconut oil
- Vegetable oils have higher levels too due to an extraction and heat, purification process
- Dry heat prepared crackers, chips and cookies have higher AGEs due to cooking methods and ingredients. Some of these even have AGEs added for taste.

Methyl Glyoxal

- Drives AGEs 250x faster than glucose
- Glycolysis
  - more production
  - Insulin and glucose stimulates more glycated protein breakdown
    - Produces more methyl glyoxal
    - Cooking/storage of foods
    - Alcohol

Methyl glyoxal leads to massive AGEs

Decrease in Type 1 Collagen with loss of elasticity and therefore causes wrinkles

Collagen

- Type IV Collagen in basement membrane
  - Leads to increased permeability, CRF, decreased endothelial adhesion and hence activation of endothelium leading to atherosclerosis
  - Decreased vitronectin, leading to endothelial cell detachment and activation

RAGEs- Receptors of AGES

- On endothelial cells, discovered in 1992
- Receptors are on all cells and belong to immunoglobulin super family
- Bind to AGEs, B-amyloid and others eg DAMPS (damage associated molecular pattern molecules)
- Found on endothelial cells, macrophages, monocytes, lymphocytes, WBCs, microglial cells, astrocytes in high concentration and rapidly impregnated
- Mice with no RAGEs have **no** cardiovascular disease, Alzheimer's dementia, Diabetes complications or even cancer
- Stimulation of RAGEs causes NF kappa-Beta stimulation which causes inflammation.
- Stimulation of RAGEs causes reactive oxygen species

RAGEs Continued

- RAGEs, in low amounts, protect the body, but when overwhelmed, can cause a lot of damage!
- High concentration of RAGEs in lungs in everyone.
- Why?
  - Asthma
  - Pulmonary fibrosis
  - Lung cancer
  - COPD

RAGEs result in increased endothelin-1, vascular cell adhesion, molecule-1, intercellular adhesion molecule, E-selection

RAGEs- Continued

- Increases endothelial permeability with macromolecules and monocytes
- Induce OXLDL receptor production on macrophages and hence increase foam cell production
- AGES reduce NO production (vasodilator)
- AGEs reduce prostaglandin T2 (vasodilator)
- RAGEs are stimulated by HBA1C

Supplements

- Benfotiamine
- Pyridoxamine
- Naringenine
- Hesperidin
- Black Pepper
- Turmeric
- Parsley
- Green tea

Take home points

- Keep your glucose under control
- Avoid Alcohol
- Avoid vegetable seed oils

For exogenous sources of AGEs

- Avoid foods that come with AGEs for example processed foods, ready-made foods
- Learn how to cook your food properly

Remediate with bioflavonoids

Don’t smoke, vent your kitchen

FAST