

*Review Article*

## Advanced Glycation End Products and Diabetes

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### ABSTRACT

Advanced Glycation End products (AGE) are sugar derived substances which increase the effect of hyperglycemia and is a chief cause of the complications of diabetes. It is formed by a sequence reaction known as the Maillard, or browning, reaction which entails non-enzymatic reaction of reducing sugars, ascorbate and other carbohydrates with amino acids, lipids and nucleic acids. The complications seen in diabetes, namely, microvascular and macrovascular damage is attributed to the accumulation of AGEs in tissues. N-carboxymethyllysine(CML) is one of the better characterized end products which has been extensively used as an AGE marker in measurement studies. Foods high in lipid and protein content show the highest AGE levels. Starches, fruits, vegetables, and milk, contain the lowest AGE concentrations. AGE ingestion could be reduced to a great extent by using water based culinary method (steaming, poaching, boiling, and stewing). Methods that accelerate new AGE formation include grilling, broiling, roasting, searing, and frying. Exposure to lower temperatures with more moisture corresponded to lower levels of AGE as opposed to cooking with higher temperatures and lower moisture levels for equal weights. Limiting the consumption of products that lead to higher levels of AGE and modulation of food-AGE content is imperative in management of hyperglycemia in patients suffering from diabetes.

**Keywords:** Advanced Glycation End products AGE Diabetes, N-carboxymethyllysine

### INTRODUCTION

Diabetes mellitus is the most common endocrine disorder. The rate at which the prevalence of diabetes is rising all over the globe is so alarming <sup>[1]</sup> that it is predicted that the total number of people with diabetes would increase from 171 million in 2000 to 366 million in 2030. <sup>[2]</sup>

Diabetes is characterised by macrovascular and microvascular complications, occurrence of which has been associated with increased morbidity and mortality. <sup>[3]</sup>

Chronic hyperglycemia contributes to microvascular complications which are unique to diabetes, <sup>[4]</sup> hence maintenance of tight glucose control is imperative in Type I and Type II diabetes mellitus. <sup>[5,6]</sup>

The concept of glycemic index has been popularly adopted when looking at lifestyle modifications for tight glycemic control. Adoption of foods with low glycemic index has been postulated to help improve blood sugar levels.

But one concept that has hitherto been overlooked is that of "AGE".AGE or

Advanced Glycation End products are sugar derived substances which increases the effect of hyperglycemia, chief cause of the complications of diabetes and their reduction in diet has been shown to have positive impact on health.

This review article focuses on the concept of AGE, factors affecting its formation, its impact on diabetic complications and significance of limiting dietary AGE content for improvement in diabetic health.

### AGE

AGE comprise a heterogeneous group of molecules formed by a sequence reaction known as the Maillard, or browning, reaction first identified in 1912 [7] which entails non-enzymatic reaction of reducing sugars, ascorbate and other carbohydrates with amino acids, lipids and nucleic acids. [8,9]

The formation of AGEs is a part of normal metabolism being extremely accelerated in diabetes. [10,11] Even though the reaction takes place continuously within the body, they become pathogenic if excessively high levels are reached in tissues. [12]

### Formation of AGE

The generation of AGEs takes place through the Maillard reaction initiating with formation of a Schiff base non-enzymatically by attachment of glucose to a free amino acid (mainly lysine and arginine) of a protein, lipid or DNA. The reversible formation of Schiff base is followed by its rearrangement to form a relatively stable Amadori product e.g. haemoglobin A1c (A1C). A series of reactions including successions of dehydrations, oxidation-reduction reactions, and other arrangements lead to the formation of AGEs from the Amadori product. [13,14]

The list of structurally identified AGEs is growing, and N-carboxymethyllysine(CML) is one of the

better characterized end products which has been extensively used as an AGE marker in measurement studies. [10]

The ability of AGEs to alter the chemical and biological properties of native molecules by cross-link formation results in their pathologic effects. [9,15,16]

### Exogenous AGEs/AGE contributed by Diet

Diet also acts as a significant exogenous source of highly reactive AGE. The formation of AGE is an endogenous process, but their concentration can be elevated by exogenous source such as tobacco smoke or food. [17,18]

These dietary AGEs include reactive AGE precursors which on entering the body are converted and absorbed in the gastrointestinal tract (-10%) and delivered to the liver and to other tissues, 1/3 is excreted in the urine, and the rest contributes to AGE-related pathology in diabetes. [9,19,20]

### Factors affecting AGE generation

Several factors are known to affect AGE generation in foods namely nutrient composition, physical parameters (temperature, humidity and pH) and cooking conditions. [18,21]

The average AGE content for each food group classified as per the American Diabetes Association exchange lists is shown in Table 1 and Table 2. [21,22]

**Table 1: AGE content of selected food items based on different cooking methods (AGE content based on CML (carboxymethyllysine) content)**

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

**Table 2: AGE content of selected food items (AGE content based on CML (carboxymethyllysine) content)**

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

As seen from the above Table 1 and 2, there is a clear relation between AGE content and nutrient composition. Foods high in lipid and protein content show the highest AGE levels. Foods that are composed mostly of carbohydrates eg. starches, fruits, vegetables, and milk, contain the lowest AGE concentrations. [22] Among meat products, beef and cheeses followed by poultry, fish, and eggs correspond to highest AGE levels.

AGE ingestion could be reduced to a great extent by using water based culinary method (steaming, poaching, boiling, and stewing) instead of fat based and/or browning methods (frying, broiling, and grilling) as seen from Table 1. [22] Methods that accelerate new AGE formation include grilling, broiling, roasting, searing, and frying. [18,22]

Cooking time plays a less significant role as compared to temperature and methods of cooking. In all cooking methods, exposure to lower temperatures with more moisture corresponded to lower levels of AGE as opposed to cooking with higher temperatures and lower moisture levels for equal weights. [21]

### **Relation between AGE and Diabetes**

The complications seen in diabetes, namely, microvascular and macrovascular damage is attributed to the accumulation of AGEs in tissues. [23] The concentration of exogenous AGE that would be safe and optimal for the intention of disease prevention has yet to be established.

However, reduced levels of oxidative stress, less deterioration of insulin sensitivity and kidney function, and longer life span were observed when AGE in diet was reduced to 50% of usual intake in animal studies. [24]

### **The “AGE-Less” Diet – Lowering the AGE content in Diet**

This relation between AGE and Diabetes emphasizes that limiting the consumption of products that lead to higher levels of AGE and modulation of food-AGE content is imperative in management of hyperglycemia in patients suffering from diabetes.

Thus, increasing the consumption of fish, legumes, low-fat milk products, vegetables, fruits, and whole grains and by reducing intake of solid fats, fatty meats, full-fat dairy products, and highly processed foods significantly reduces the intake of AGE.

Switching to cooking methods such as poaching, steaming, stewing, and boiling that are low AGE generating would be a beneficial option for improvement in health. The use of acidic marinades, such as lemon juice and vinegar before cooking can also be encouraged to limit AGE generation. [8]

### **CONCLUSION**

Thus the evidence suggests that reduction of AGE content in diet is important in maintaining tight glycemic control and would help in improvement of health of diabetic patients. The focus today should be shifted to development of an “AGE-Less” diet in ways described above for optimal management of diabetic complications.

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