Online edition : ISSN 2188-3610 Print edition : ISSN 2188-3602 Received : January 3, 2020 Accepted : January 31, 2020 Published online : March 31, 2020 doi:10.24659/gsr.7.1_13

Review article Stop the "Vicious Cycle" induced by Glycative Stress.

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Abstract

Glycative stress causes post-translational modifications of protein at the molecular level and increases the risks of various aging-related diseases, such as diabetic complications. There are two representative processes of the unphysiological protein modifications, *i.e.* (1) the carbonylation caused by aldehyde derived from glucose and lipids and the formation of advanced glycation end products (AGEs), and (2) cysteine succination derived from a disorder of the TCA cycle. Endoplasmic reticulum (ER) stress increases in pancreatic β -cells due to the formation of AGEs caused by glycative stress, and causes a reduction in insulin secretion. Lysine and arginine in amino acid sequence of insulin are susceptible to carbonyl modification and are resistant against the enzyme reaction to insulin from proinsulin. As a result, insulin synthetic quantity decreases. Approximately 9% of insulin in serum of patients with diabetes becomes glycated insulin, and it causes the patient's insulin resistance. These findings show that glycative stress is involved not only in diabetic complications, but also the onset and development of diabetes. It has also become clear that there is a "vicious cycle" to increase the onset of diseases caused by glycative stress are increasing worldwide. In order to prevent the onset and development of these diseases related to glycative stress, it is important to (1) implement countermeasures against glycative stress at an early stage and (2) understand the mechanisms of these vicious cycles and prevent them.

KEY WORDS: advanced glycation end products (AGEs), glyceraldehyde, dehydrogenase (GAPDH), TCA cycle, succination

Introduction: What is Glycative Stress?

Glycative stress is the condition where various aldehydes derived from reducing sugars, lipids and alcohol are generated in excess in the living body. These aldehydes react with the substances in the body such as protein and generate carbonyl modified proteins and advanced glycation end products (AGEs), enhance the secretion of inflammatory cytokine by stimulating AGEs/RAGE (receptor for AGEs) signals, and causes various disorders in cells and tissues ^{1, 2)}. Furthermore, glycative stress causes disorders of TCA cycle in mitochondria and causes succination of protein¹⁾. These two reactions are representative modifications after protein translation caused by glycative stress.

The causes responsible for glycative stress are (1) "glucose spike" and (2) dyslipidemia (hyper-triglyceridemia and hyper-LDL cholesterolemia) and (3) excessive drinking.

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What is common to these three causes is aldehyde. There are quite a few people whose blood glucose level becomes higher than 140 mg/dL after a meal even though their fasting blood glucose level is normal. This type of postprandial blood glucose is called a glucose spike and it has become known to accelerate the progression of arteriosclerosis and is closely related to the onset of cerebro-cardiovascular events. Glucose spikes evoke an "aldehyde sparks" and furthermore, a variety of aldehydes with strong reactivity are generated at once by chain reactions^{3,4}.

Glycative stress causes not only diabetic complications but is also involved in the onset and development of various disorders such as cataract (glycated crystallin)^{5,6}), dementia (glycated β amyloid)^{7,8}), osteoporosis (glycated type I collagen)^{9,10}), and skin aging (glycated collagen and elastin) ^{2,11,12}). Furthermore, glycative stress damages the pancreas, kidney, visceral fat and skeletal muscles, and it was found that these vicious cycles cause glycative stress to be further intensified through these disorders. In this report, we will explain the mechanism of these cycles caused by glycative stress.

Vicious Cycles through Pancreas

Insulin is synthesized in pancreatic β -cells in the following process (*Fig. 1*): Initially, it is biosynthesized as pre-proinsulin in the rough endoplasmic reticulum (ER). The "pre" is signal-peptide, and after polypeptide is synthesized and moves to the ER, it is cleaved off and becomes proinsulin. Proinsulin is a peptide combined with chains in the order of B chain, C chain and A chain.

After being carried to Golgi body, proinsulin is cleaved from protease, C-chain (C peptide) is removed and insulin is produced. The structure of human insulin (molecular weight: 5,807) is that where A chain with 21 amino-acid residues and B chain with 30 peptide chains are combined by disulfide bonds. There is one disulfide bond also in the A chain. Synthesized insulin is accumulated in cells and secreted from cells by secretion stimulation.

Glycative stress also has an effect on β -cells and reduces the synthesis and secretion of insulin¹³⁻¹⁵. Open-chain glucose, open-chain fructose, aldehydes coming from outside the cell and free fatty acids (FFA) are pointed out as factors of glycative stress within cells.

What most often causes small amounts of aldehydes is the formation of various aldehydes (aldehyde spark) that occurs in chain reactions following postprandial hyperglycemia (glucose spike). When this occurs, glyceraldehyde (GA), glycolaldehyde, 3-deoxyglucosome (3-DG), glyoxal (GO) and methylglyoxal (MGO) are synthesized ¹⁶.

While FFA is excessively accumulated in adipocytes as triglycerides in a process leading to obesity, its level in blood is maintained mainly under the lipase control and utilized by each cell and tissue. The phenomenon where excessive FFA impairs the secretion of insulin is called β -cell lipotoxicity ^{17, 18)}. Actually, keto group (C=O) and aldehyde group (-CHO) substances with aggressive-reactivity are synthesized from FFA, which may be protein modification by carbonylation. Carbonylated protein is metabolized furthermore and finally forms AGEs.

Arginine and lysine are susceptible to carbonyl modification among amino acid sequences of insulin, both of which are dibasic amino acids. This is because dibasic amino acids can retain another amino group (-NH₂) even after an amino group was used for peptide bonds. We have a hypothesis that if arginine and lysine at both ends of C-peptide are modified, protease resistance increases, and as a result, C-peptide becomes unable to be disconnected and insulin synthesis decreases.

In the case of patients with type 2 diabetes mellitus (T2DM), because 9% of insulin in the serum changes to glycated insulin, insulin resistance becomes elevated¹⁹). Glycated insulin has no function of uptaking glucose into cells and cannot exert insulin function²⁰.

Furthermore, it is reported that in the conditions where glycative stress is strong because of hyperglycemia or otherwise, a TCA cycle disorder within mitochondria tends to occur. If NAD (nicotinamide adenine dinucleotide) is depleted, the TCA cycle becomes unable to work well



Fig. 1. The structure of insulin, proinsulin and pre-proinsulin.



Fig.2. TCA cycle disorder induced by glycative stress and cysteine succination.

2SC, S-(2-succinyl)cysteine.

and fumarate is accumulated. *Figure 2* shows the forming process of cysteine succination $(2SC)^{1, 21, 22}$. If cysteine, which is supposed to form a physiological disulfide bond, is modified, the protein's three-dimensional structure greatly changes. The reason why fumarate becomes excessive in mitochondria is unknown; it may be because it is more resistant to metabolization than citrate, ketoglutarate, succinate, malate and oxaloacetate.

The protein becomes able to maintain normal threedimensional structure immediately after translation and becomes a mature protein with physiological function by being folded and modified in the ER. However, due to the increase of glycative stress and decrease of chaperone function, abnormal protein increases and synthesis of normal protein is impaired. This is the condition where ER stress advances. It is said that 30% of insulin synthesized in β -cells is produced as ill-folded protein. Chaperone is a generic term used to refer to proteins that combine with unfolded and immature proteins to help them reach a normal condition (physiological condition) where they are appropriately folded.

In the experiment in this research, it was also confirmed that when pancreatic β -cells were given the load of glycative stress, insulin mRNA began decreasing and the syntheses of proinsulin and insulin protein decrease (*Fig. 3*)²³). If the additive amount of AGEs is larger, it causes apoptosis in β -cells.

Figure 4 shows the mechanism of these cycles through the pancreas. If glycative stress becomes strong, the production of AGEs increases, the secretion of insulin decreases, diabetic stage further proceeds and glycative stress becomes stronger. Another cycle shows that if glycative stress becomes strong, the produced amount of glycative insulin increases, insulin resistance becomes more elevated and diabetic stage further proceeds. Glycative stress develops and complicates T2DM through the cycles described above. It is very important to inhibit these cycles with countermeasures against glycative stress.



Fig. 3. Influence of glycative stress on insulin synthesis in the pancreatic β-cells.

RIN-m5F cells are incubated with glycated HSA for 48 hours. Insulin mRNA measured by the real-time PCR method. Results are expressed as mean \pm SD, n = 3. HSA, human serum albumin; PCR, polymerase chain reaction; SD, standard deviation. Data quoted from Reference 23).



Fig. 4. Vicious cycles induced by glycative stress in the pancreas. AGEs, advanced glycation end products; ER, endoplasmic reticulum; T2DM, type diabetes mellitus.

A vicious Cycle through Visceral Fat Cells

Adiponectin is one of the beneficial substances among biologically active substances (adipocytokine) secreted from the visceral adipose tissue, and it is a protein consisting of 244 amino acids. It exhibits actions including enhancement of fatty acid oxidation, inhibition of hepatic gluconeogenesis and reduction of insulin resistance, performs preventive action against diabetes and prevents arterial sclerosis²⁴⁾. Adiponectin consists of three monomers and forms the structure of three chain helices (trimers) by interaction and is stabilized by disulfide bond of cysteine. The free cysteine of the trimer formed in this way by being disulfide bonded forms hexamers or polymers²⁵⁾. When stress increases, fumarate increased by TCA cycle disorder causes 2SC modification to trimer adiponectin and inhibits the formation of hexamer^{21,22)}. As a result, it becomes difficult for adiponectin to pass through the cell membrane, so its secretion decreases (*Fig. 5*).

Figure 6 shows another vicious cycle through visceral adipose tissue. TCA cycle disorder is caused by glycative stress enhancement within mitochondria, so fumarate is accumulated. As a result, the formation of hexamer is inhibited by 2SC modification, adiponectin secretion decreases and insulin resistance increases, and as a result, glycative stress further increases. The inhibition of the vicious cycle by countermeasures against glycative stress is important for the prevention of the onset and development of metabolic syndrome and T2DM.



2SC, S-(2-succinyl)cysteine. The figure quoted and modified from Reference 21, 22)



Fig. 6. A vicious cycle induced by glycative stress in the visceral adipose tissue. 2SC, S-(2-succinyl)cysteine.

Vicious Cycles through Kidney

The kidney is the most important organ for the clearance of AGEs by playing the role in decomposition and excretion of AGEs. In the process of development of chronic kidney disease (CKD) leading to kidney failure, AGEs increase remarkably in body fluid, cells and tissues, and degenerative changes caused by glycative stress are observed in the body. In the case of dialysis patients, arterial sclerosis mainly comprising ectopic calcification develops, leading to osteoporosis. AGEs remarkably affect skin and muscles, and they present with hardening and pigmentation of skin and skeletal muscle atrophy (sarcopenia)²⁶⁻²⁸.

Recently, the relationship between kidney function decline and cognitive function decline has been clarified ²⁹⁻³¹). The disease rate of cognitive function decline among those with even mild to moderate CKD before dialysis is high. The cognitive function decline of the patients with CKD is often caused by vascular risk factors. Its relationship with neurodegenerative diseases such as Alzheimer's is also becoming clear.

Diabetic kidney disease, among other diabetic complications, interferes with urinary excretion of waste matter from the body, and eventually leads to kidney failure. The essence of the clinical condition is the glycation of proteins forming kidney glomerular basement membrane ^{32, 33)}. The basement membrane includes IV-type collagen and partly consists of proteoglycan. The filtering function deterioration is caused by glycation of basement membrane proteins and the excretion of AGEs lowers as well as waste products, so the accumulation of AGEs in the body increases remarkably. This is also the condition where glycative stress is strong.

The kidney is rich in GAPDH (glyceraldehyde-3phosphate dehydrogenase) and glyoxalase and they play a role as biological defense against glycative stress.

GAPDH exists in large amounts accounting for $10\% \sim 20\%$ of the total amount of proteins within cytoplasm, and it is positioned as the most important defense mechanism

for the organism metabolizing GA^{34,35)}. The kidney is the most important for GA metabolism. Triokinase plentifully exists in kidney phosphorylates GA coming into cells, transforms it to glyceraldehyde-3-phosphatge and keeps it within the cell and does not let it leak out of the cell, so the kidney's capability of retaining GA is very strong compared to other cells (*Fig.* 7)³⁶⁾. GA in cells is changed to 1-3-bisphosphoglycerate by GAPDH, and it becomes lactate through pyruvate following the steps of glycolysis and is then excreted from the cell. However, if the TCA cycle is disrupted by hyperglycemia, fumarate increases and cysteine succination of GAPDH (formation of 2SC-GAPDH) occurs ^{37,38}. As 2SC-GAPDH has no GA metabolic activity, it cannot make GA decomposition, so GA

Glyoxalase plays the role of MGO metabolism. MGO is non-enzymatically conjugated to reduced glutathione (GSH), transformed to lactate by glyoxalase I & II and disconnected from GSH. Glyoxalase exists in abundance in the kidney and is involved in aldehyde metabolism and excretion such as MGO^{39,40}. Glyoxalase activity is lowered along with the development of CKD and the remaining unmetabolized aldehydes accumulate⁴¹. As a result, glycative stress is further increased.

Figure 8 shows the vicious cycles through the kidney. If the condition of strong glycative stress continues, the glycation of glomerular basement membrane protein occurs and AGEs are accumulated, leading to the onset of diabetic nephropathy. If kidney function declines, AGEs clearance also reduces, and as a result, the amount of AGEs in the body further increases. Due to glyoxalase activity reduction caused by the decline of kidney function and 2SC modification of GAPDH, the aldehydes in blood and tissue fluid such as MGO and GA increase and glycative stress further develops. It will be clarified that the cycles of glycative stress through the kidney becomes a great threat against homeostasis maintenance of the body.



Fig. 7. The defense system against glyceraldehyde in the kidney.

GAPDH, glyceraldehyde-3-phosphate dehydrogenase; GA, glyceraldehyde ; GAP, glyceraldehyde-3-phosphate ; 3-PG, 3-Phosphoglycerate; 2SC, S-(2-succinyl)cysteine.



Fig. 8. Vicious cycles induced by glycative stress in the kidney.

AGEs, advanced glycation end products; GAPDH, glyceraldehyde-3-phosphate dehydrogenase; GA, glyceraldehyde; MGO, methylglyoxal.

Vicious Cycles through Skeletal Muscles

The homeostasis of human blood glucose level is maintained within a certain definite range. As blood glucose regulators, gluconeogenesis in the liver, glycogen degradation, glucose uptake in skeletal muscles and adipose tissues and hormonal regulation are identified. Abilities of carbohydrate metabolism and lipid oxidation in skeletal muscles are promoted by continued physical exercise and it becomes possible to flexibly utilize various energy sources on demand. Energy consumption of skeletal muscle is approximately 22% (in the case of a man whose body weight is 70 kg and body fat percentage is 20%)⁴²⁾. Glucose utilization rate in skeletal muscles accounts for 70% of that of healthy people; but it decreases by half in the case of patients with T2DM ⁴³⁾.

Sarcopenia means qualitative and quantitative decline of skeletal muscle caused by aging, and abnormal glucose metabolism is caused by glucose metabolic capacity lowered by quantitative decline ^{44, 45}. Aged diabetic patients tend to be susceptible to sarcopenia, and if they have sarcopenia, vascular management of diabetes becomes difficult ⁴⁶. In animal experiments also, the accumulation of AGEs in connection with aging of skeletal muscles is recognized ⁴⁷, so that it is estimated that glycated actin and glycated myosin are accumulated in skeletal muscles of sarcopenia patients. It is known that the increase of the skin autofluorescence (SAF) has the relationship with the decrease of muscular power by the reports of animal experiments, patients with diabetes and those with sarcopenia ⁴⁸⁻⁵¹, which shows that glycative stress is a great risk for muscle weakness.

Figure 9 shows the vicious cycles through skeletal muscles. Glycation of muscle protein is caused by glycative stress, which cause muscle volume, muscular power and energy

consumption to further decrease. As a result, insulin resistance increases, glucose consumption decreases, spare glucose increases, hyperglycemia is promoted and glycative stress is further strengthened. If skeletal muscle mass decreases due to aging, this vicious cycle is further promoted. In order to reduce glycative stress for health promotion, it is important to maintain muscle mass by muscle load training.

Conclusion

Glycative stress causes modification of proteins and increases the risks of various disorders relating to aging including diabetic complications. As a result, the reduced insulin secretion from β -cells is caused and insulin resistance increases due to glycative insulin formation. It shows that glycative stress is deeply involved not only in the pathogenesis of diabetic complications, but also the onset and development of T2DM, and the existence of vicious cycles impairing health have been clarified. The cases of these cycles in the pancreas, visceral fat, kidney and skeletal muscles are stated in this paper. It is important to take preventative countermeasures against glycative stress and inhibit these cycles in order to prevent the onset and development of age- or T2DM-associated disorders.

Conflict of interest statement

The authors claim no conflict of interest in this study.



Fig. 9. Vicious cycles induced by glycative stress in the skeletal muscle. AGEs, advanced glycation end products.

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