IgG Glycation and Diabetes: A Review
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Abstract: Non-enzymatic glycosylation of proteins is one of the important cascades in the pathogenesis of diabetic complications and age accelerating disease. Glycation of IgG is of major value due to its possible influence on the dependency of immunoglobulins and overall immunocompetence. Glycation and fluorescence at 440 nm (excitation at 370 nm) are found to be increased in immunoglobulin G (IgG) from diabetic strongly indicating the presence of IgG-linked advanced glycation end products or Maillard products. i.e. increased non enzymatic IgG-linked advanced glycation end products reduces defense mechanism of immunoglobulin G as Diabetic nephropathy is a major cause of end stage renal disease. Increased excretion of albumin has widely been recognized as an early manifestation of diabetic nephropathy particularly in subjects with diabetes mellitus. Humans have evolved with immune mechanism to protect against age accelerating disease like Diabetes and its complications. These immune system include immunoglobulin G. Browning of proteins are responsible for changes in the functional properties of IgG.

Keywords: IgG, defense mechanism, Maillard products, IgG cross linkage

Table-1: The classification encompasses both clinical stages and etiological types of diabetes mellitus and other categories of hyperglycemia, as suggested by Kuzuya and Matsuda

<table>
<thead>
<tr>
<th></th>
<th>Type 1 Diabetes</th>
<th>Type 2 Diabetes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Etiology</td>
<td>Autoimmune</td>
<td>Peripheral resistance</td>
</tr>
<tr>
<td>Formerly known as IDDMM</td>
<td>NIDDM or “adult onset” diabetes</td>
<td></td>
</tr>
<tr>
<td>Age of onset</td>
<td>Younger</td>
<td>Older</td>
</tr>
<tr>
<td>Obesity</td>
<td>Rare</td>
<td>Common</td>
</tr>
<tr>
<td>Family History/Twin concordance</td>
<td>Rare</td>
<td>Common</td>
</tr>
<tr>
<td>HLA association</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Ketonuria</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Insulin resistance</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Endogenous insulin</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Respond to Oral Agents</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Metabolic labiality</td>
<td>Labile</td>
<td>Not labile</td>
</tr>
</tbody>
</table>

PATHOPHYSIOLOGY:
Diabetes = Hyperglycemia, which is defined as:
--fasting plasma glucose above 126 mg/dl
--oral glucose tolerance test (OGTT) above 200 mg/dl
Pre-Diabetes is defined as:
glucose is a vital source of energy for most living organisms. During fasting, independently of insulin glucose is utilized throughout the body. After ingestion of glucose containing product, blood glucose level rises rapidly stimulates insulin secretion from β cell of pancreas, which consequently increases glucose transport, metabolism and storage by muscle and adipocytes. On the other side, insulin suppresses glucagon secretion and minimizes the serum free acid concentrations, resulting in the sharp decline in hepatic glucose production. With the help of insulin and other enzymes about half of the glucose ingested is converted into energy through the glycolysis and citric acid pathway and about half is stored as fat and glycogen. Insulin production fluctuates within the β cells, irrespective of blood glucose levels. It is temporarily stored within vacuoles and released by the process of exocytose, which is triggered by absorbable glucose. The chief trigger is a rise in blood glucose levels after meal [5].

There are two main types of diabetes, Type I and Type II, described below.[6]

A) Type I Diabetes: (Juvenile Onset Diabetes, Insulin-Dependent Diabetes)

Pathogenesis of type-I diabetes

Type 1 Diabetes Mellitus develops as a result of synergistic effect of genetic, environmental and immunologic factor that ultimately destroys the pancreatic beta cells. Type1 diabetes has a genetic component which must be a present for susceptibility to occur. It is believed that the susceptibility gene resides on the sixth chromosomes, with the major alleles conferring risk being HLA-DR3, HLA-DR4, HLA-DW4, HLA-B8 and HLA-B15. Secondly an environmental insult, such as virus, exposure to an allergen, or both, is believed to initiate the process in genetically susceptible individuals. This external influence precipitates an inflammatory response in the pancreas known as insulitis. [7] The inflammatory response is autoimmune mediated and take place on the surface of insulin producing beta cells such that these cells are no longer recognized by the immune system. Antibiotics against the beta cells are produced, resulting in their destruction and clinical appearance of diabetes. This destruction is thought to occur slowly, over the course of several years in many cases. [7]
Type 2 DM is characterized by three pathophysiologic abnormalities:

1. Impaired insulin secretion
2. Peripheral insulin resistance
3. Excessive hepatic glucose production

**COMPLICATIONS OF DIABETES**

Diabetes mellitus may present with characteristic symptoms such as thirst, polyuria, blurring of vision, and weight loss. In its most severe forms, ketoacidosis or a non–ketotic hyperosmolar state may develop and lead to stupor, coma and, in absence of effective treatment, death.[8] Often symptoms are not severe, or may be absent, and consequently hyperglycemia sufficient to cause pathological and functional changes may be present for a long time before the diagnosis is made.[9,10] The long-term effects of diabetes mellitus include progressive development of the specific complications of retinopathy with potential blindness, nephropathy that may lead to renal failure, and/or neuropathy with risk of foot ulcers, amputation, Charcot joints, and features of autonomic dysfunction, including sexual dysfunction. [11] People with diabetes are at increased risk of cardiovascular, peripheral vascular and cerebrovascular disease. Several pathogenetic processes are involved in the development of diabetes. These include processes which destroy the beta cells of the pancreas with consequent insulin deficiency, and others that result in resistance to insulin action. The abnormalities of carbohydrate, fat and protein metabolism are due to deficient action of insulin on target tissues resulting from insensitivity or lack of insulin.[12]
Glycation is the result of a sugar molecule, such as glucose or fructose, bonding to a protein or lipid molecule without the controlling action of enzyme. All blood sugars are reducing molecules. Glycation may occur either inside the body (endogenous glycation) or outside the body (exogenous glycation). Enzyme-controlled addition of sugars to protein or lipid molecules is termed glycosylation; glycation is a haphazard process that impairs the functioning of biomolecules, while glycosylation occurs at defined sites on the target molecule and is required in order for the molecule to function. Much of the early laboratory research work on fructose glycations used inaccurate assay techniques that led to drastic underestimation of the importance of fructose in glycation.[13].

**Figure-4:** Hyperglycemia and diabetes microangiopathy

**IgG GLYRATION AND DIABETES**

**Glycation**

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**Figure-5:** Biochemical reactions and common advanced glycation end product (AGE) compounds in vivo.

**PROCESS AND EFFECTS OF GLYCATOIN.**

Various studies indicate that glycation of immunoglobulin G (IgG) in vitro leads to IgG fluorescence and polymerization [14], concomitant with marked changes in functional properties of the Fc fragment [15,16]. Glucose is capable of reacting with
proteins, which can also react with DNA and lipids. These chemical reactions called glycation do not involve enzymatic processes. Glycation is thought to contribute to the development of chronic vascular complications of diabetes, non-diabetic nephropathy, vascular disease, Alzheimer’s disease, and aging.

The glycation of proteins leads to covalent cross-linking and abnormal structural stabilization of extracellular matrix proteins. These harmful consequences of this cross-link formation in humans were proposed by Brownlee as an outgrowth of a research effort focused on diabetes. [17]

Cross-links are now considered to be likely causative factors in the development of many age-related and diabetic disorders, particularly those associated with the cardiovascular and renal systems, by causing biochemical and structural alterations on proteins. Recent studies have led to the hypothesis that formation of these amino-sugar structures was a step along a new biochemical pathway in which permanent glucose structures, called "advanced glycosylation end products" (AGEs), were formed on the surface of proteins. [18] These AGEs were able to further interact with adjacent proteins to form permanent links between proteins. Glycation is an unavoidable process of metabolism. In certain physiological states, one or more of the following changes to glycation-related processes occurs, the rate of glycation is increased, the renal clearance of AGEs is decreased and/or the expression of AGE receptors is increased. This may lead to AGE-related basement membrane thickening, AGE-mediated cell activation and amyloidosis.

Figure-6: Cascade of events in cellular injury produced by AGE. Dietary protein is a source of preformed AGE and of amino acids that may form AGE in the circulation, kidney, and possibly other sites.

Amines are indicators of medium-term glycamic control and AGEs are indicators of medium to long-term glycamic control in diabetes mellitus. Some AGEs are risk markers and others are risk factors of disease. [17]

In collagen (the most abundant protein in the body) AGEs form covalent, intermolecular bonds. As depicted luminal narrowing, a major feature in diabetic vessels may arise in part from accumulation in the sub endothelium of plasma proteins such as albumin, low-density lipoprotein (LDL) and immunoglobulin G (IgG). They may get trapped in basement membranes by covalently cross-linking to AGEs on collagen. Glucose, in its aldehyde form reacts with the amino groups of protein to form a Schiff base which rearranges to a stable ketoamine adduct [19] this process, the non-enzymatic glycation of proteins, occurs naturally in the body. Glycation not only affects the structure and function of protein, but also initiates a series of Maillard or browning reactions that eventually lead to cross-linking and denaturation of proteins. The AGE Pathway represents one of several pathological processes believed to be responsible for aging.

All proteins in the body are subjected to these reactions, but long-lived proteins such as collagen, which represents over 30 percent of body protein, accumulate chemical damage with age. The increased rate of glycation of collagen during hyperglycemia is implicated in the development of complications of diabetes, such as blindness, renal and vascular disease.
GLYCATION AND PROTEIN CROSS-LINKING

Since the early 1900s, scientists have known that heating the proteins in the presence of sugars results in the formation of new cross-linked chemical bonds.[18] This reaction is the process by which toast and many baked or cooked foods turn brown. Maillard, and later Amadori, described this formation of complexes between sugars and the amino acids of proteins that were believed to cause the toughening and discoloration of food during the cooking process and after prolonged storage. Proteins cross-linked with sugars are considered to be causative factors in many age-related and diabetic disorders. Glycation of proteins is implicated in diabetes.[20] Glucose and other saccharine are important glycating agents, but the most reactive glycating agents are the α-oxoaldehydes, glyoxal, methylglyoxal and 3-deoxyglucosone. Cross-linking potency is variable among the sugars, with a rank order of glucose < fructose < ribose, and phosphorylated sugars being more potent than their unphosphorylated counterparts.[21]

Early glycation adducts (Schiff’s base, fructosamine) and advanced glycation adducts (AGEs) are formed. Cross-linked proteins appear to be involved in both diabetes and senescence. The sugar-protein complex is able to initiate a chain reaction that ends in forming reversible intermediate substances in a few days. These substances dehydrate, condense and reorganize themselves after a few weeks and become the irreversible components of AGEs. The AGEs induce irreversible cross-links between molecules and thus alter their chemical and biological properties. Most of the carbohydrate-derived products which accumulate in tissue proteins with age and accumulate at an accelerated rate in diabetes are products of both glycation and oxidation reactions.

Figure-7: Glycation induces cross linking proteins

Age-corrected levels of glyoxidation products in collagen correlate with the severity of diabetic complications.[22] Also, cross-linking of collagen proteins, for example, contributes both to the rigidity and the loss of elasticity of tissues, and to the thickening of capillary walls observed in diabetes and during the aging process. This protein modification is also responsible for crystalline lenses becoming opaque in cataracts, a degenerative disease that is also frequent in diabetic or aged persons. With respect to the biological activity of IgG from diabetics, it is shown that the certain functional properties of the Fc region of IgG are impaired, i.e. there is a decrease in binding of protein A andfixation of complement to the Fc fragment, which probably contributes to the increased susceptibility to infections, known to occur in poorly controlled diabetics [23]. The reasons for the changes in the functional properties are unknown. Interaction with protein A and fixation of complement depend on the integrity of the region 230 to 270 of the heavy chains [24], allowing structural changes of the Fc fragment as a prerequisite for complement binding. One might speculate that oxidation of amino acids in the Fc region by free radical mechanisms is responsible for damage of the complement binding site, leading to an alteration of biological activity.

The glycation of nuclear acids may be the cause of DNA mutations and could alter its capacity for replication and transcription. In addition to the cross-
linking of long-lived molecules, AGE is able to stick the rapidly renewable plasma molecules together, whether albumin, antibodies, or LDL cholesterol. The cross-linking of proteins and the trapping of various molecules by the AGES contribute to developing atherosclerosis, kidney, and vascular and neurological diseases in both diabetes and the aging process. Also glycation substances may be involved in the pathogenesis of Alzheimer’s disease, since an accumulation of these substances is observed at the sites of neuronal degeneration during the course of this disease.[25] The body does have a defense against cross-linked proteins. The immune system has macrophages with special receptors for AGES. The macrophages engulf AGES and eventually the products are excreted in the urine.[26] Future research could involve the identification of critical AGEs and AGE receptors involved in protein cross-linking and cell activation. It seems important to characterize their participation in disease mechanisms and to develop therapeutic agents to counter glycation-mediated pathogenesis. Interestingly, carnosine, (beta-alanyl-L-histidine) a naturally occurring molecule is an aldehyde scavenger and appears to be protective against some cross-linking. [27] Also, ethanol consumed in small quantities appears to protect mice hemoglobin against AGE products. [28] The company (Alteon) is developing pharmaceutical compounds that interfere with the cross-linking process or even break existing cross-linked proteins. One such "AGE breaker", ALT-711 is awaiting FDA approval for human use.

REFERENCES


