Review Article

Amadori albumin in diabetic nephropathy

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ABSTRACT

Nonenzymatic glycation of macromolecules in diabetes mellitus (DM) is accelerated due to persistent hyperglycemia. Reducing sugar such as glucose reacts non enzymatically with free €- amino groups of proteins through series of reactions forming Schiff bases. These bases are converted into Amadori product and further into AGEs. Non enzymatic glycation has the potential to alter the biological, structural and functional properties of macromolecules both in vitro and in vivo. Studies have suggested that amadori as well as AGEs are involved in the micro-macro vascular complications in DM, but most studies have focused on the role of AGEs in vascular complications of diabetes. Recently putative AGE-induced patho-physiology has shifted attention from the possible role of amadori-modified proteins, the predominant form of the glycated proteins in the development of the diabetic complications. Human serum albumin (HSA), the most abundant protein in circulation contains 59 lysine and 23 arginine residues that could, in theory be involved in glycation. Albumin has dual nature, first as a marker of intermediate glycation and second as a causative agent of the damage of tissues. Among the blood proteins, hemoglobin and albumin are the most common proteins that are glycated. HSA with a shorter half life than RBC, appears to be an alternative marker of glycemic control as it can indicate blood glucose status over a short period (2-3 weeks) and being unaffected by RBCs life span and variant haemoglobin, anemia etc which however, affect HbA1c. On the other hand, Amadori albumin may accumulate in the body tissues of the diabetic patients and participate in secondary complications. Amadori-albumin has potential role in diabetic glomerulosclerosis due to long term hyperglycaemia and plays an important role in the pathogenesis of diabetic nephropathy. This review is an approach to compile both the nature of glycated albumin as a damaging agent of tissues and as an intermediate diagnostic marker and its potential role in diabetic nephropathy.

Key words: Amadori albumin, diabetic nephropathy, glycated albumin

Introduction

Diabetes mellitus (DM) is a progressive disease resulting from defects in insulin secretion or action, or both. It is characterized by hyperglycemia, often accompanied by glucosuria, polydipsia, polyuria. In type 1 diabetes, there is a complete absence of insulin, which affects metabolism of carbohydrates, fats and proteins. It is an autoimmune disorder afflicting millions of people worldwide. The disease occurs as a consequence of the organ specific immune destruction of insulin producing beta cells in the islets of Langerhans within the pancreas. However, type 2 diabetes is the result of the inability of islet beta cells to produce adequate insulin and has become epidemic. The global prevalence of DM in 2011 was 366 million; however by 2030, it is expected to reach 552 million.[1] Type 2 DM is highly prevalent and accounts for 90–95% of cases. In 21st century, DM will be a huge burden due to its increasing global prevalence and higher frequency of chronic complications affecting various tissues (nephropathy, retinopathy, neuropathy and cardiovascular disease), difficulty in controlling the disease and high cost. Approximately, 15% of type 1 diabetics will develop diabetic nephropathy.[2] Type 2 diabetes because of its prevalence has now become a leading cause of end-stage renal disease (ESRD).

During diabetes, persistent hyperglycemia leads to nonenzymatic glycation of various proteins such as

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hemoglobin, proteins of erythrocyte membrane, insulin, human serum albumin (HSA), high and low density lipoproteins, IgG, IgM, collagen and histones.[3,4] Proteins are glycated, when glucose is chemically bound to amino groups of proteins without the help of enzyme, which causes many structural and conformational changes in protein, and proceeds to various micro-macro complications in diabetic patients.[5] A strong link between Amadori albumin and diabetes specific complications have been demonstrated by studies in humans,[6] animals[7] and cell culture.[8] The goal of this review is to enumerate the importance of Amadori-albumin in the genesis of diabetic nephropathy and to signify the advantages of glycated albumin (GA) as an intermediate index of glycation.

Human serum albumin; before and after glycation

Human serum albumin is mainly synthesized in the liver, and is the most abundant protein in human circulation. HSA has many physiological and pharmacological functions such as maintenance of colloid osmotic pressure, transport of fatty acids, hormones, drugs and metabolites. HSA also has anti-thrombotic, anti-inflammatory, antioxidant activity and regulates microvascular permeability.[9,10] Some physiological variables such as body mass index or age and pathological conditions such as thyroid dysfunction, Nephrotic syndrome and cirrhosis of the liver alter album metabolism and can affect GA levels.[9] Albumin contains 35 cysteine, 1 tryptophan, 59 lysine and 23 arginine residues among its 585 amino acid residues. Albumin is a lysine rich protein, and it has been proved that specific lysine residues in HSA are involved in nonenzymatic glycation *in vivo*.[11] HSA is more prone to glycation and in conditions of hyperglycemia, it is two to three times more glycated than the rest of the population.[12] Glycation causes alteration in structure and function of HSA.[13] Studies have been shown that antioxidant property of HSA is strongly affected by glycation.[14] An amadori albumin generates oxygen free radicals at potential of Hydrogen 7 and cause lipid peroxidation. Binding affinity of glycated HSA is reduced by 50% for bilirubin and 20% for long chain fatty acid, *cis*-paranaric acid as compared to non glycated HSA.[14] This suggests that the non-enzymatic glycation of HSA will have a depressing effect on drug binding affinity and transport property. Furthermore, Arif *et al.* reported highly immunogenic potential of amadori albumin due to generation of neo-epitopes.[15]

Significance of maillard reaction in diabetes mellitus

The reaction due to Maillard was so named by Prof. Louis Camille Maillard, when he referred to his own studies describing the brown color formed, while heating mixtures of carbohydrate and amines. It was first described during early 20th century. Non enzymatic glycation [Figure 1] ubiquitous chemical modification involves the condensation of the aldehyde group of carbohydrate with either the ε-group of lysine, hydroxylysine, side chains of arginine, histidine and cysteine residues[16] or the alpha amino group of the N-terminal amino acid of proteins.[17] Only open forms of sugars react with proteins, the labile aldimine (Schiff base) is formed (in hours) by attaching protein amino group via nucleophilic attack. This product is reversible and can go back to glucose and protein, or it can form ketoamine that is slightly reversible. This can further undergo intermolecular rearrangement through acid-base catalysis to form 1-amino-1-deoxy fructose (fructosamine), a more stable Amadori product (in days). These sugar-peptide adducts are known as "early glycation products." Both Schiff base and Amadori products *in vivo* predominantly exist in cyclic form.[18] Further, by irreversible chemical reactions involving oxidation and fragmentation [Figure 2], the stable Amadori product gradually evolves to a heterogenous population of still incompletely characterized often fluorescent adducts with new cross links, which are called advanced glycation end products (AGEs).[19] Thus, alpha dicarbonyl compounds and alpha–keto aldehydes formed, respectively, by subsequent degradation of Amadori products and the fragmentation of Schiff base are solely responsible for the formation of inter-intra molecular protein cross-links AGEs.[20] Throughout the 1980s and 1990s a large body of evidence has accumulated implicating AGEs as mediators of various complications of diabetes and aging. The AGEs also interact with various AGE receptors as RAGEs and stimulate signaling pathways that are important to cause long-term complications in diabetic patients.

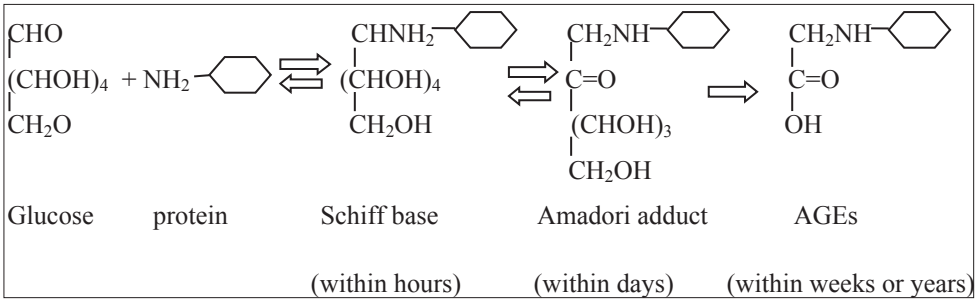

Figure 1: Non-enzymatic glycation of protein by glucose and production of early and late glycation product

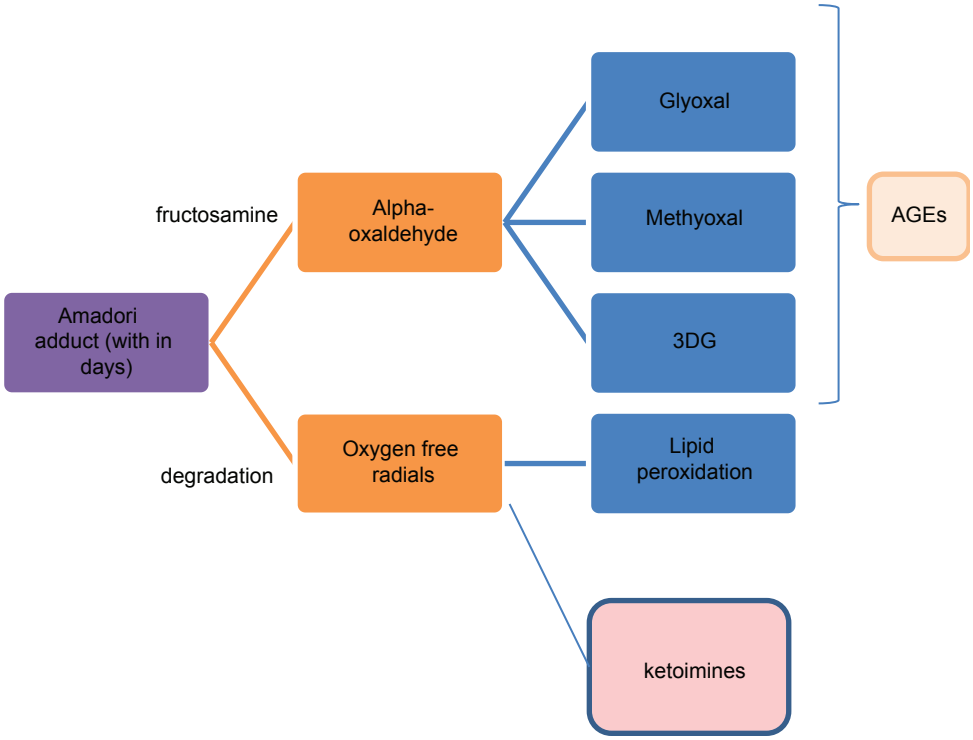

Figure 2: Amadori adduct fate

Stable amadori adduct

Amadori rearrangement is a key early step in the Maillard reaction.[21] The Amadori rearrangement of the Schiff base is believed to occur via an intermediate, open-chain enol form. Formation of the Schiff base from sugar and amine is relatively fast and highly reversible. Formation of Amadori product from the Schiff base is slower but much faster than the reverse reaction, so that the Amadori-glycation product tends to accumulate on proteins. Amadori-products and AGEs are distinct in nature, unlike the Amadori-products, AGEs is irreversible. In addition, the Amadori-modification is also structurally different from those associated with AGEs and Amadori-modified proteins operate through receptors different from that of AGEs. Amadori-albumin is an independent and potent trigger of molecular mediators contributory to diabetic complications. McCance *et al.* reported an independent association of initial amadori adduct with diabetic nephropathy and retinopathy.[22] Animal studies demonstrated that elevated amadori albumin promotes a generalized vasculopathy[23] and has been implicated in the development of diabetic nephropathy[24] and retinopathy.[25] Furthermore, amadori albumin has been reported to be localized in glomeruli of patients with diabetic nephropathy.[26] In addition, various intracellular and extracelluar amadori-glycated lysine-rich protein have potential roles in diabetes, and its related complications [Table 1].

Table 1: Role of Amadori adduct in diabetes

Early glycated protein	As a causative agent in diabetes mellitus
Human serum albumin	Type 1 and type 2 diabetes with nephropathy and retinopathy
Collagen	Diabetic retinopathy
Immunoglobulins (IgG, IgA, IgM)	Type 1 and type 2 with nephropathy
Plasma proteins	Type 2 diabetes
Lipoproteins (LDL)	Diabetic atherosclerosis
Histone	Diabetes

LDL: Low density lipoprotein

Amadori products are the major form of glycated proteins rather than Schiff base,[27] and are also 2–10 times more than the AGEs.[28] Moreover, the concentration of Amadori-glycated proteins is at least 2% of serum proteins, whereas AGEs are < 0.01%.[29] However, Amadori albumin formation occurs at five time higher rate than amadori-Hb.[30] Studies have shown that Amadori-adducts has an important role in the development of various diabetic complications such as nephropathy, neuropathy, retinopathy and cardiovascular diseases.

Putative role of amadori-albumin in diabetic nephropathy

Diabetic nephropathy is one of the most serious complications associated with DM, and one of the causes of mortality and morbidity in the world. Renal disease will affect 20–40% of diabetics in their lifetime. Diabetic nephropathy involves steadily increasing protein urea accompanied by elevated blood pressure with the

progressive decline in glomerular filtration rate (GFR). Proteinuria is both the consequence of the glomerular damage and cause of further damage since it leads to inflammation and fibrosis in the renal tubules, and a loss of functional nephrons.[31] Glomerulosclerosis is the characteristic feature of diabetic nephropathy, in which there is an increase in extracellular deposits inside the renal corpuscles, with a decrease in surface area available for filtration the glomerular membrane becomes thicker yet leakier.[32] These changes had been attributed to effects on endothelial cells and mesangial cells that support the capillary loops.

Earlier studies strongly suggest the involvement of biochemical disturbance that is caused due to the nonenzymatic glycation of serum proteins such as albumin in the development of diabetic nephropathy. It is revealed that hyperglycemia in streptozotocin or alloxan induced diabetic rats or in human patients with pancreatic insufficiency could cause thickening of the glomerular basement membrane, which may lead diabetic nephropathy.[33] In streptozotocin induced diabetic rats, collagen production in the basement membrane is increased, and the activity of collagen biosynthesis enzymes such as lysyl hydrolylase and glucosyl transferase is enhanced.[34] Amadori modified albumin level is increased in glomerular mesangial and endothelial cells and is a key factor leading to nephropathy in diabetic patients. Due to increasing concentration of Amadori albumin, cell signalling cascade is amplified and modulates pathways that are implicated in the development of diabetic nephropathy[35] such as protein kinase C pathway. Amadori albumin increases the expression of messenger ribonucleic acid encoding the fibrogenic, α1 (IV) collagen, transforming growth factor-β1 (TGF-β1) and its primary signaling receptor, TGF-β type II receptor.[36] As a result the potent cytokines like TGF beta, α1 (IV) collagen and fibronectin secretion is stimulated. These all are significant factors that expand extracellular matrix production in glomeruli and produce glomerular dysfunction and albuminuria[37] and cause diabetic nephropathy [Figure 3]. The hallmark of diabetes nephropathy is albuminiuria and mesangial expansion that can also be generated by the interaction of GA with receptors in the mesangial cells. The functional changes observed in diabetic nephropathy may be the consequence of increased permeability of glomerular basement membrane to glycated proteins. Normally, the glomerular membrane is selectively permeable and presence of molecular charge on the capillary wall, results in the exclusion of some anionic protein and protein larger than 80 kDa in urine.[38] The increased sequestration of endothelial vesicles due to glycosylation of serum albumin may be a mechanism for trans endothelial transport across

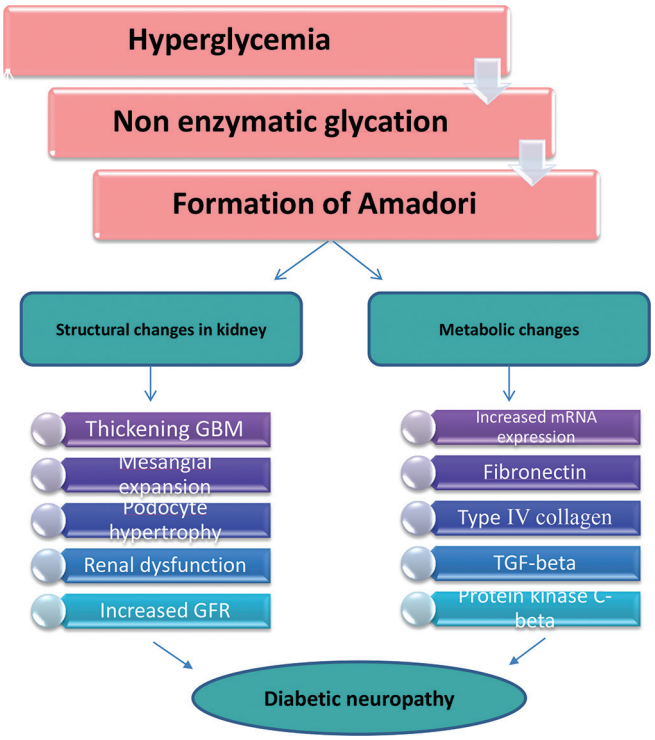

Figure 3: Glucose dependant patho-physiology of glycated albumin

continuous endothelial *in vivo*.[39] *In vitro* studies showed that GA impaired nephrin synthesis through attachment with receptor for advanced AGEs, that is, RAGE. Therefore, nephrin loss and its redistribution in glomeruli is present in both type 1 and type 2 diabetes.[40]

Immunogenic potential of amadori proteins

Most of the earlier studies have documented the presence of autoantibodies against AGE-modified proteins such as IgG, Bovine serum albumin and HSA in diabetic patients.[41,42] However, recently it has been shown that Amadori modified serum proteins are found in greater amount in plasma rather than Schiff base, and are also capable of inducing immune response, when injected in experimental animals. Anti-hexitol lysine IgG, a polyclonal antibody is raised, when well characterized amadori protein is injected in rabbits.[43] Arif *et. al.* reported the highly immunogenic behavior of Amadori albumin and also showed the presence of autoantibodies against amadori albumin in type 1 diabetic patients with or without complications.[15] The presence of autoantibodies against Amadori rich glycated poly L-lysine in the sera of type 1 and type 2 diabetic patients with or without secondary complications, that is, nephropathy, retinopathy and atherosclerosis have been reported.[44] However, further study is required to investigate the presence of autoantibodies against Amadori-glycated proteins in diabetic patients with or without diabetic complications.

Prevention of early glycation

Non enzymatic glycation of serum proteins in the diabetic patients is the major factor responsible for progression of diabetes and their complications. Research has proved that amadori products and/or AGEs both are strongly involved in diabetic secondary complications. There are many chemicals that prevent glycation. GLY-230 (2-[3-chlorophenylamino] phenylacetic acid) reduces GA in the patients and studies in humans showed that ALT-711 (3-phenacyl-4,5-dimethylthiazolium chloride), acts as AGE-cross-link breaker.[45] Aminoguanidine and pyridoxamine are good inhibitors of glycation but have side-effects in humans.

Clinical implications of glycated albumin

Glycated albumin: As a glycemic marker and its utility over other

Glycation of serum proteins, hormones, enzymes and other matrix, intracellular and membrane proteins within the body correlates with blood glucose levels and duration of protein exposure to them. Thus, the relative amount of glycated protein serves as an indirect record of glycemic status over the period of protein turnover.[46] Hemoglobin A1c (HbA1c) and fructosamine are non enzymaticlly glycated proteins that are used to monitor glycemic status in type 2 diabetic patients.[47] They have been commonly used as the primary glycemic control markers, but now GA has gained more attention as a new diabetic marker due to some superiority over HbA1c and fructosamine.

Hemoglobin A1c is currently used as the gold standard in the management of diabetes and its secondary complications. Due to longer life span of erythrocytes, the HbA1c test may not be suitable for monitoring short term glycemic status. Thus, HbA1c status shows glucose concentration with broad fluctuations. Besides half-=life of red blood cells (RBC), there are many other factors, that is, uremia, erythropoietin treatment, blood transfusion,[48] abnormalities in hemoglobin metabolism like anemia, decreased renal function, gestational diabetes, ESRD and iron deficiency responsible for the fluctuations in glycemic status. HbA1c is overestimated in uremic patients due to carbamylated hemoglobin. Glycated amino acid may interfere with the test for GA however, the new improved methods employed currently are free of interference by endogenous glycated amino acids and are unaffected by albumin concentration like high performance liquid concentration method and Bromocresol green method etc.[49]

Fructosaime is also similar as GA reflecting the glycemic status over the preceding 2–3 weeks but fructosamine refers to all glycated serum proteins including GA, in serum and GA is a ketoamine formed from a non-enzymatic oxidation of albumin by glucose. Like GA, fructosamine (FA) is not influenced by hemoglobin related disease but strongly influenced by the concentration of serum proteins and low molecular weight substances co-existing in plasma e.g. Bilirubin, hemoglobin and uric acid etc., while GA is not.[50,51]

Non protein diagnostic markers are also available such as 1,5-anhydroglucitol (1,5-AG) and self-monitoring of blood glucose levels in the serum. Under the normal condition, glomeruli filtered 1,5-AG from the blood, and it is completely reabsorbed by the renal tubules in kidney. 1,5-AG is similar in structure with glucose and hence it competes with glucose for reabsorption. As a result, 1,5-AG level is decreased in the plasma, when glucose level is increased approximately 180 mg/dl.[52] Though 1,5-AG shows postprandial excursions more accurately than HbA1c and FA[53] but it does not reflect mean glucose level but provides information of hyperglycemic xcursions.[54]

Many studies have shown that strict glycemic control in diabetic patients, as indicated by lower HbA1c levels may delay the diabetic complications and can improve the quality of life.

Therefore, to overcome the drawbacks of other markers and to achieve a better glycemic status, novel idea of using GA as a glycemic intermediate index has been developed [Table 2].

Non-enzymatic glycation of albumin is a slow oxidative reaction, in which glucose is attached to the free amino groups of albumin to form a stable GA that is a ketoamine.[55] Albumin has a short half-life of 15–20 days. Hence, its measurement provides an index of short term glycation (2–3 weeks). It is not affected by the lifespan of red blood cells or erythropoietin treatment and also not by those diseases that are associated with hemoglobin metabolism. Some reports indicate that HbA1c is not a reliable marker in patients with renal failure and hemodialysis due to either shortening of the life span of erythrocytes or the changing proportion of young to old erythrocytes by

Table 2: Classification of glycemic markers

Classification	Glycemic marker	Glycemic status (days)	References
Long term	HbA1c	120	American diabetes association
Intermediate	GA, FA	18-20	Cohen *et al.* (1999)
Short term	1,5-AG and Apo-B	3-5	Buse *et al.* (2003)

GA: Glycated albumin, FA: Fructosamine, HbA1c: Hemoglobin A1c, 1,5-AG: 1,5-anhydroglucitol, Apo-B: Apolipoprotein B

erythropoietin treatment.[56] Therefore, GA with a shorter half-life than RBC appears to be an alternative marker of glycemic control as it can indicate blood glucose status over a short period and unaffected by RBC life span, anemia, hemoglobinopathies etc., that affect HbA1c. The accuracy of GA compared to HbA1c as indicators of long-term glycemic control in predialysis and dialysis patients has been explored in a number of studies. Good correlations among GA and mean blood glucose were demonstrated in subjects with and without chronic kidney disease (CKD) Stages 4 and 5, including dialysis-dependent subjects. Furthermore, GA was a better indicator of glycemic control in patients on dialysis and predialysis subjects, whereas HbA1c as well as fructosamine, underestimated glycemic control in CKD Stages 3 and 4. Further, the GFR was negatively associated with HbA1c concentrations. Therefore, declining GFR has an impact on and alters the relationship of HbA1c with mean glucose, whereas GA values appear to be unaffected by CKD status. It is therefore, hypothesized that GA may become a better glycemic marker for early improvement in the treatment of diabetes and among diabetic patients with different degree of renal impairment.

Glycated albumin measurements

Glycated albumin levels are measured as a ratio of total glycated amino acid concentration to albumin concentration. In the old literature, various colorimetric assays were used for the quantification of GA such as thiobarbituric acid and bromcresol green assays[57] but these assays have now been replaced by nitroblue tetrazolium assay[58] and 2-keto-glucose with hydrazine.[59] Presently GA concentration is also measured with several methods including ion exchange chromatography, affinity chromatography and high performance liquid chromatography, immunoassay, enzyme linked immunosorbent assay, enzyme-linked boronate immunoassay and electrochemical methods. These biophysical techniques are specific for measuring glycated amino acids in albumin. In diabetic patients on either Hemodialysis or Peritoneal dialysis, HbA1c values are falsely lower compared to patients without nephropathy. This under estimation in the true glycemic status may result in an inadequate treatment of hyperglycemia. Conversely, carbamylated hemoglobin in the uremic condition may result in an overestimation of glycemic status, thereby, increasing the risk of hyperglycemia. The use of GA rather than HbA1c is being recommended for monitoring glycemic control in patients on dialysis. Currently available data are insufficient to conclude whether GA can replace HbA1c for assessment of glycemic status in diabetic patients with ESRD.[60] Measurement of GA with enzymatic assays is also good and samples for GA measurement can be stored at −80°C for 4 years.[60]

Despite the possible benefits of GA, the lack of normal reference data on GA might limit its use as a diagnostic marker for diabetics. A study has established the reference interval of GA in the Japanese population was 12.3–16.9% and recently Hiramatsu *et al.* reported (2012) in healthy Japanese pregnant women, a reference range of GA 11.5-15.7%.[61] On the other hand a Chinese study reported GA value of 17.1% to be an optimal cutoff in Chinese population for the diagnosis of diabetes.[62] In United States, many laboratories used affinity chromatography to state reference values for GA in the range of 0.6–3.0% and by the enzymatic assay GA reference range came out to be 11-16%[63] [Table 3]. It is also needed to establish a GA reference range among the Indian population with or without diabetes.

Conclusions and Perspectives

Non enzymatic glycosylation is one of the underling modification factors that contribute to the development of diabetic nephropathy. Several studies demonstrated increased serum level of amadori albumin in nephropathy, in glomeruli and the degree of staining was increased with the severity of tissue damage. The highly specific monoclonal antibodies against GA reduced nephropathy in genetic diabetic mice by preventing changes in cultured renal cells and ameliorate the mesangial matrix expansion, proteinuria and renal insufficiency. The underling mechanisms by which glycated serum proteins induce pathological changes in the renal glomerulus are incompletely defined. However, therapeutic strategies that annihilate the effect of amadori albumin are a sensible approach to the treatment of diabetic nephropathy.

Serum albumin has a much shorter half-life (20 days) than hemoglobin and may be more sensitive to changes in glycemia. Therefore, GA, which is not affected by changes in survival times of erythrocytes, and in hemoglobinopathy may be a better marker of monitoring glycemic control. It also provides better information for monitoring short term glycemic control. However, data on Indian population are lacking. Further research is warranted to establish the cut off value in Indian population using control groups.

Table 3: Reference range of GA in different population

Populations	Methods	GA reference range %
American	Enzymatic	11.9-15.8
American	Affinity chromatography	0.6-3.0
Japanese	Enzymatic	12.3-16.9
Japanese pregnant women	Enzymatic	11.5-15.7
Chinese	Enzymatic	17.1

GA: Glycated albumin

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