Glycated albumin: from biochemistry and laboratory medicine to clinical practice

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Abstract

This review summarizes current knowledge about glycated albumin (GA). We review the changes induced by glycation on the properties of albumin, the pathological implications of high GA levels, GA quantification methods, and the use of GA as a complementary biomarker for diabetes mellitus diagnosis and monitoring and for dealing with long-term complications. The advantages and limits of this biomarker in different clinical settings are also discussed.

1. Introduction

The main functions of albumin include regulation of plasma oncotic pressure, maintenance of acid-base balance, action as a carrier molecule and as an antioxidant system. Adequate plasma levels of albumin (3.5-5.5 mg/dL)~~,~~ as well as the maintenance of its structural integrity~~,~~ are both essential if it is to function properly [1]. One of the main processes affecting the structure of albumin, hence its biochemical and physical properties, is glycation, a non-enzymatic chemical reaction between reducing sugars and/or their degradation products and primary or secondary amine groups on proteins [2,3]. This results in the production of early and advanced glycation end-products (AGEs).

Diabetes mellitus, a metabolic disease characterized by high blood glucose concentration, ~~raising blood glucose,~~ is considered the main pathology associated with ~~high~~ a raise in the levels of glycation products which have been related just to the onset and progression of ~~.~~

~~There appears to be a relationship between glycation products and~~ different detrimental diabetes complications, from cardiovascular pathologies to kidney diseases and blindness [4-6]. Among the different glycated proteins, some studies ascribe a potential pathogenic role only to glycated albumin (GA) [7]. Interest in GA has grown in the last few years, mainly in the field of diabetes monitoring, as a complementary biomarker to blood glucose and glycated hemoglobin (HbA1c) in specific clinical settings in which these molecules do not work properly. In addition, due to the relationship between ~~since~~ glycated proteins ~~play a key role in promoting~~and diabetes-related complications, monitoring GA may be an additional and important toll in controlling ~~the control of~~ the risk of such complications.~~GA has emerged as a marker of diabetes complications.~~

In this review we summarize current knowledge about GA, discussing the biochemical properties of albumin, the effects of glycation on albumin, the pathological implications of high GA levels, the methods of GA quantification and the use of GA as a complementary biomarker for monitoring diabetes mellitus and dealing with its long-term complications ~~of the disease~~.

2. Human serum albumin: biochemical and physiological aspects

Albumin is the most abundant circulating protein, accounting for 50-60% of total plasma proteins. In physiological conditions~~,~~ its levels range from 3.5 to 5.5 g/dL. It is a multifunctional, small (66 kDa),

globular and, negatively charged protein. It comprises a single polypeptide chain of 585 amino acids with abundance of lysine (59) and arginine (24) residues, and containing 35 cysteine residues, 34 of which form 17 disulfide bridges, important for the overall tertiary structure of the protein [1,7]. Cysteine 34 (Cys-34), in contrast, is free and accounts for 80% of total plasma thiol. Cys-34 exists mainly in the reduced form, which gives albumin important antioxidant and scavenging properties. Cysteine 34 (Cys-34), which mainly existsing in the reduced form, gives albumin important antioxidant and scavenging properties and accounts for 80% of total plasma thiol levelss [8].

X-ray crystallographic studies indicated that the protein is organized in three domains (I, II, III), each containing two sub-domains, A and B. Two important ligand-binding sites, Sudlow sites I and II are two important ligand-binding sites , with different but not exclusive affinities. They, have been identified in respectively subdomains IIA and IIIA, respectively [9]. Site I binds mainly large heterocyclic compounds and endogenous substances, including bilirubin and porphyrins. Site II is smaller and less flexible, binds aromatic compounds, such as benzodiazepine and ibuprofen, and is more stereo-specific [10-12]. Also the N-terminal region and Cys-34 are two important binding sites to consider in discussing ligand binding properties of albumin.have binding properties. The N-terminal and Cys-34 also have binding capacity [13].

Drugs like cisplatin, D-penicillamine, and N-acetyl-cysteine, and some metal cations, mainly Au, Ag and Hg, interact with Cys-34. Other ions, such as Cu, Ni and Co, can bind to the N-terminal region. Also inIn this way albumin can , by limitinglimit the availability of these ions, their the interaction between these ions withand oxygen, thus preventing the production of and the generation of reactive oxygen species, albumin exerts antioxidant properties [13].

Albumin is also considered the major Zn binding protein in plasma, although the nature and location of the binding is still not clear. The ability to bind iron is weaker [14,15]. The protein also contains seven binding sites for fatty acids [10,16].

In addition to these functions as an important antioxidant and binding protein, albumin is responsible for maintaining colloid osmotic pressure and is involved in acid-base homeostasis [1]. Any pathological condition that lowers circulating albumin levels, or any change in the protein structure - affecting its biochemical and physical properties - mightay result in a loss of functions [10].

3. Glycation

Glycation is a non-enzymatic reaction between reducing sugars or their degradation products and free amino groups of proteins. The formation of glycated products is quite complex but, according to a more simplified view, it is often described as a chemical process that proceeds ~~The process proceeds~~ through three ~~broad~~ main ~~reaction~~ stages: initial, intermediate and late. In the initial stage, the amino-carbonyl interaction results in the formation of an intermediate aldimine (Schiff base). The intermediate stage involves chemical transformation of this early glycation product into a more stable ketoamine (Amadori product, e.g. fructosyl-lysine) and the last stage is the formation of irreversible AGEs, due to oxidation, degradation and other cross-linking reactions. It is still not known whether AGE products are primarily formed by oxidation of Amadori fructosyl or by free carbonyls (non-fructosyl glycation modifications).

To go deeply into the glycation process, it is possible to find a very detailed description of the chemistry of the glycation process in a review by Cho focused on the mechanistic profile of the glycation pathways [17]. ~~Cho has provided a very detailed description of the chemistry of the glycation process in a review focused on the mechanistic profile of the glycation pathways~~ According to this, ~~Seven are main stages utilized by Cho for describing~~ the formation of glycated products is divided into seven major stages. ~~In t~~This scenario ~~is~~ clearly suggests ~~evident~~ not only the complexity of the glycation process but also the redundancy of some stages, the possibility of generating the same AGEs through different chemical pathways and the difficulty of conceiving any single strategy for the prevention and management of AGE formation, that is considered one leading cause of various health complications. Please refer to the review by Cho [17] to find additional information on the chemistry of ~~each of the seven stages of~~ the glycation process.

~~[17]. According to this, the complex process of glycation can be divided into seven major stages. Stage (i) refers to the formation of the intermediate Schiff base and its rearrangement into the Amadori product. Stage (ii) deals with the transformation of the Amadori product into different AGEs through non-oxidative and oxidative reactions. Stage (iii) involves the degradation of the Schiff base to produce glyoxal and glyoxal-protein adducts which are further transformed into AGEs, like pentosidine and N^{ε}-carboxymethyl-lysine (CML), regardless of the Amadori pathway. Stage (iv) involves auto-oxidative glycosylation leading to the formation of novel sugar molecules, like arabinoses, which have lost one atom in their carbon chain. In stage~~

~~(v) the arabinoses generated in stage (iv) are transformed into AGEs. Stage (vi) involves glucose~~

~~In pathological conditions such as diabetes mellitus, the high glycemia promotes the formation of high levels of glycated proteins and AGEs [2,18,19]. Glycation is certainly detrimental to proteins because it affects both their tertiary structure and all the functions closely related to protein conformation [20]. Glycated proteins may also, *per se*, exert damaging effects, thus contributing to the onset and progression of different pathology-related complications [21,22].~~

~~Among different glycated proteins, HbA1c is already used in clinical practice as a biomarker for both diabetes mellitus diagnosis and monitoring. Other specific glycated proteins may therefore be worth investigating as potential biomarkers in specific clinical settings, but to date GA is the only other glycated protein used as an indicator of glycemic control.~~

4. Glycated albumin: structural modification and pathological implications

Albumin is more sensitive to glycation than other proteins, mainly because of its high concentration and long half-life (about 21 days) and also due to the~~, besides the~~ large number of lysine and arginine residues which may be involved in the formation of early and advanced glycation products [1,18,19] . Among the 59 lysines in albumin, only ~~a~~ few of them are real targets of the modifications found in GA. Lysine 525 is the main target site of glycation. Other important glycation sites include lysine 439, 199, 51, 378, 545, 12, 233, 276, 281, 317, 323 and also the N-terminus [20-25]. Probably the accessibility of these sites, the local acid-base catalysis effect and the pKa of each amine group are the main factors in the susceptibility of these residues.

In addition to early glycation products, AGEs have also been observed in albumin. These are the result of the oxidation/modification of adducts on glycated proteins to form alpha-oxaloaldehydes and their subsequent reaction with arginine and lysine residues in albumin. Some possible AGEs observed in albumin include methylglyoxal-derived hydroimidazolone isomer 1, glyoxal-derived hydroimidazolone isomer 1, tetrahydropyrimidine, N_{ε}-carboxymethyl-lysine, N_{ε}-carboxyethyl-lysine, imidazolone B and pyrraline [26-28]. The kinds of change and the extent of glycation on albumin strongly depend on the amounts of reducing sugars and/or their degradation products and the time available for reaction with albumin. The high reactivity of albumin towards these agents is one of the reasons making ~~why~~ GA ~~is~~ an interesting biomarker for

glycemic control. The pros and cons of using GA for monitoring glycemia and additional reasons why it might be a worthwhile biomarker are discussed in section 6.

Modifications induced by glycation significantly change the structure and ligand binding properties of albumin *in vitro*. Most of the changes in GA occur on several residues near the two Sudlow binding sites I and II, thus suggesting a potential~~n~~ overall alteration of albumin-binding properties. *In vitro* studies on different ligands, such as warfarin, L-tryptophan, sulfonylureas, salicylate, ketoprofen and fatty acids, and those which ~~using~~utilized *in vitro* modified albumin with glycation levels close to those seen in diabetes mellitus~~,~~ confirmed that albumin's binding ability is affected by glycation. In some cases, the effect seems to be minimal, as for warfarin, whereas for other molecules, such as ketoprofen, bilirubin and L-tryptophan, the changes are more marked [29-34]. This means potential change(s) in the therapeutic effects and/or adverse effects for all drugs that bind to albumin, with a large change mainly for agents that work in a relatively narrow range.

Glycation may also promote changes in~~has also been associated with changes to~~ albumin's anti-oxidant and scavenging properties [8]. Although strongly backed by *in vitro* studies, the clinical significance of these findings has not been shown till now. The review by Anguizola et al. [35] provides further details on structural studies of GA, the rate of glycation and modification for human albumin and the effect of glycation on albumin's properties.

In the glycated form, albumin does not simply present changes in its physiological functions but it~~also~~ acquires a pathological phenotype too. High GA levels may induce irreversible damage in the different organs and tissues that are the main targets of complications in diabetes mellitus (such as coronary arteries, cardiovascular system, kidney, eye and nervous system). For example, in the kidney, GA is transported across the glomerular capillaries and taken up by epithelial and mesangial cells where it increases the production of pro-oxidant molecules and contributes to the onset of nephropathy [4,36,37]. In the field of cardiovascular diseases, GA plays a role in the activation and aggregation of platelets, up-regulates the expression of adhesion molecules involved in the formation of atherosclerotic plaques, like ICAM-1 and VCAM-1, and promotes oxidation [38-40]. The activation of the cell-surface receptor for AGE (RAGE) is ~~considered~~ the main mechanism through which GA exerts its damaging effects. In fact, engagement of RAGE leads to the activation of the nuclear transcription factor NF-κB, the production of pro-inflammatory

cytokines and growth factors, apoptosis, oxidative stress and prothrombotic activities, all events which have been associated to pathological consequences of increased levels AGE and GA [41-43].

The increased generation of intracellular reactive oxygen species is also considered one of the main mechanisms leading to the inhibition of glucose uptake both in adipocytes and muscle cells, which in turnthus promotesing insulin resistance [44].

5. Quantification of glycated albumin: methods

GA concentrations can be determined in several ways using colorimetric, enzymatic, chromatographic and mass-spectrometry methods. GA is always expressed as a percentage of albumin. Each test has its pros and cons, related to aspects like ease of use, skills, and instrument-hardware availability.

GA has beingen determined with a high-performance liquid chromatography (HPLC) -method [45,46] that can be used for clinical purposes despite its high cost and the need for skill and know-how. However, the HPLC method is not really useful for routine analysis because of its low throughput [47]. Mass spectrometry (MS) methods are also available but are not currently suitable for clinical purposes, for obvious reasons, mainly method standardization and its complexity.

In the last fifteen years a new and, accurate assay has been developed based on albumin-specific enzymatic protease and ketoamine-oxidase [47,48]. This assay, which allows the direct quantification of GA, is widely used in Japan, China, Taiwan and Korea for diabetes management, but has not yet been approved by the FDA for use in the U.S.A. and is not in use for clinical purposes in Europe either.

GA definition varies with the assay methods and their target molecules, thus providing different information. HPLC defines GA as the ratio of glycated albumin molecules to total albumin molecules, whereas enzymatic assays and MS measure the concentration as the ratio of glycated albumin amino acids to total albumin [48]. To avoid misinterpretation of results and their clinical meaning, an equation has been developed to match enzymatic assay GA percentages to the HPLC findings [49]. Each of the GA quantification methods previously indicated will indicate how much albumin is glyctaed

~~Other tests can calculate and/or mathematically derive indices of glycation, like the glycated protein ratio [50], aimed at achieving the same clinical utility as GA. However, the GA quantification method is specific for GA and is different from "fructosamine" or total glycated protein methods. These quantify all the~~

~~glycated serum proteins, depending closely on total protein levels, and can be affected by a high serum uric~~ "total glycated protein" which quantify~~. These last, in fact, quantify~~ all serum glycated proteins and they also protein levels, high serum uric acid concentration [50] and unspecific serum reducing activities [51]. There are ~~also~~ other tests which~~that~~ can calculate or mathematically derive indices of glycation, like the glycated ratio [52]. Although these tests aim to achieve the same clinical utility as GA they are totally different from methods performing the specific quantification of GA.

~~Unlike the ketoamine-oxidase method for GA quantification, the assay for total glycated serum protein is approved for use in the U.S.A. but, as already mentioned, is not interchangeable with specific measurement of GA. As a result, although there are FDA-approved tests for fructosamine and total glycated serum proteins, and some commercial laboratories do HPLC assays for GA, there are no FDA-approved commercial assays for GA for use by clinical laboratories in the U.S.A.~~

~~When we qua~~. ~~ntify GA we give a specific information on how much albumin is glycated.~~ This kind of information is thus different from what we can obtain with other tests like "fructosamina" or "total glycated protein" which quantify~~. These last, in fact, quantify~~ all serum glycated proteins and they also be ~~but the results may be~~ strongly affected by total protein levels, high serum uric acid concentration [50] and unspecific serum reducing activities [51]. There are ~~also~~ other tests which~~that~~ can calculate or mathematically derive indices of glycation, like the glycated protein ratio [52]. Although these tests aim to achieve the same clinical utility as GA they are totally different from methods performing the specific quantification of GA.

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~~In the U.S.A, although some commercial laboratories do HPLC assays for GA, there are no FDA-approved commercial assays for GA quantification. This means that also the ketoamine-oxidase method for GA quantification is not yet approved for clinical purpose.~~ At now, the only FDA-approved tests include total glycated serum protein and fructosamine assays that, as already mentioned, are not interchangeable with specific measurement of GA.

6. Glycated albumin as a biomarker in different clinical settings

6.1 GA for screening and monitoring diabetes mellitus

GA is considered useful for assessing the degree of protein glycation directly dependent on glucose exposure. ~~GA is already considered reliable in Asian countries such as Japan, China and Korea where it is measured as an intermediate glycemic control marker. GA is mainly trusted as a marker of glycation in diabetes mellitus management.~~ It is currently used in Asian countries, such as Japan, China and Korea, for diabetes screening, population stratification and classification for the risk of developing diabetes, and for driving therapies [53-55]. Table 1 summarizes the latest studies exploring the ~~-~~GA cut-offs for diabetes diagnosis and monitoring.

The conventional biomarkers employed for screening and monitoring diabetes mellitus include fasting glucose, postprandial glucose and HbA1c. Although these markers provide useful information, in certain clinical conditions they are inadequate. HbA1c is a glycation index that reflects the glycemic status over a period of 120 days, corresponding to the mean lifespan of erythrocytes. Because hemoglobin is found inside these cells, its glycation may be affected by any condition affecting their lifespan (hemolytic anemia, hemorrhage, folate and vitamin B12 deficiency anemia, aplastic anemia, nephropathy) and hemoglobin metabolism (variant hemoglobin, thalassemia) [56-59]. In fact, HbA1c is lower than plasma glucose in all those conditions of shortened erythrocyte lifespan ~~,~~ and is higher when their lifespan is increased. Changes in red blood cell survival are in fact an important determinant of the discordance between HbA1c levels and other measures of glycemic control, both in hematologically normal individuals as well as in people with hematological disorders [60,61]. HbA1c is the result of glycation occurring both on older and new erythrocytes~~,~~ but the reaction is slower on newly formed cells [59,62]. For these reasons, in conditions involving reduced erythrocyte lifespan the ratio of new to old cells will be higher and, as consequence, the HbA1c level will be lower. Unlike HbA1c, GA is not inside the erythrocytes so it is not influenced by their lifespan.

GA is also independent of iron deficiency [58,61,63]. In individuals with iron deficiency, HbA1c levels are higher than plasma glucose. This is very likely because cessation of erythropoiesis results in no new unglycated hemoglobin being produced. As a result, the existing hemoglobin becomes older, raising the mean age of circulating erythrocytes, hence also the percentage of glycated hemoglobin in the circulation. ~~Pregnancy is a~~A physiological condition in which HbA1c suffers some limits as an indicator of glycemic pregnancy. During pregnancy HbA1c undergoes a biphasic change: it drops from the first to the second

trimester, due to the decrease in plasma glucose levels, and rises again from the second to the third trimester, probably due to iron deficiency [64]. Unlike HbA1c, GA is not affected by iron deficiency [65,66] and, ~~it is~~ an intermediate-term glycemic marker (this will be~~is~~ discussed in the next section), it enables pregnant with diabetes to maintain stricter glycemic control, important to lower the risk of fetal and maternal complications. GA is also a useful biomarker for monitoring diabetes mellitus in newborns, where HbA1c does not properly reflect the glycemic status on account of the high levels of fetal hemoglobin [67].

Patients with diabetes and end-stage renal diseases under dialysis also cannot be efficiently managed with HbA1c, because of the lower hemoglobin and erythropoietin concentrations and the reduced persistence of red blood cells due to mechanical disruption~~the reduced persistence of red blood cells due to mechanical disruption, hemoglobin concentration and erythropoietin dosage~~ [68,69]. GA may be a better indicator of their glycemic status.

Recent studies have indicated~~suggested~~ GA as a useful diagnostic tool for diabetes screening both in the general population as well as~~nd~~ in individuals with a pre-diabetic condition. The KOPS study [54] suggested the utility of GA in diabetes mellitus diagnosis in the Japanese population. A strong correlation has been found between GA, HbA1c and fasting glucose. GA 15.5% was an optimal cut-off for predicting diabetes (sensitivity 83.3%; specificity 83.3%) (Table 1). In a large cross-sectional Japanese community-based population study [55] GA appeared useful as a screening tool in individuals with fasting glucose between 5.5-6.9 mmol/L and HbA1c <6.5%, in whom the OGTT test was used to diagnose diabetes. Optimal thresholds for diabetes screening were 15.2% for GA and 5.9% for HbA1c in this population. Using these cut-offs, GA and HbA1c had the same sensitivity (62.1%) for detecting diabetes; the specificity was 61.9 % for GA and 66.7% for HbA1c. Sumner et al. [70] suggested that in U.S.-based Africans with pre-diabetes mellitus, diagnosed by ~~-~~a 2h-OGTT test, HbA1c and GA used as single test~~s~~ detected ≤50% of individuals with pre-diabetes. However, combining them made it possible to identify nearly 80%.

6.3 Intermediate-term glycemic status

Compared to HbA1c, GA is considered an intermediate-term glycemic indicator~~,~~ because the turnover of albumin is shorter than the lifespan of erythrocytes (20 *vs.* 120 days). GA also rises sooner than HbA1c when glycemic status worsens. This means that GA is more useful as an indicator of glycemic status in all those

conditions requiring short-term control of changes in glycemia, such as after the start or modification~~s~~ of diabetes treatments [53]. The potential beneficial effects of a dietary strategy and lifestyle changes, often applied as first steps to improve glycemia before any drug therapy, could be monitored by GA too [71,72]. GA seems useful for early monitoring of the worsening of glycemic control in patients after discharge from hospital education programs. Because it rises faster than HbA1c, GA means that countermeasures can be taken promptly [73].

A large rise in plasma glucose in a very short time is sometimes seen in patients with type 1 diabetes. As a result, GA rises more than HbA1c at diagnosis, and the GA/HbA1c ratio may be higher than in patients with untreated type 2 diabetes. A GA/HbA1c ratio ≥3.2 (sensitivity 97%, specificity 98%) was therefore proposed as a cut-off for identifying patients with type 1 diabetes, in which hyperglycemia comes on rapidly, from those with untreated type 2 diabetes [74].

The reason why GA levels rise faster than HbA1c depends closely on albumin's biochemistry, its high glycation speed and its half-life in serum. The glycation speed of albumin is around 4.5 times that of Hb [75].

6.4 Postprandial glycemia

In terms of cardiovascular risk, postprandial glycemia may be a stronger risk factor than fasting glucose, so it needs to be strictly controlled [76-78]. In patients with diabetes, mainly type 1, post-prandial glucose may fluctuate over a wide range. Comparing HbA1c and GA in terms of their ability to distinguish postprandial glucose fluctuations, GA reflects them better [79,80].~~[79,80]: patients with postprandial hyperglycemia have higher GA than HbA1c.~~ Thus, unlike HbA1c, which is mainly ~~reflects the~~an indicator of the mean plasma glucose concentration, GA ~~strongly reflects postprandial glucose and~~ seems a more appropriate ~~indicator~~ biomarker of ~~glycemic control in diabetes~~postprandial glucose levels [53,79,80].

Marked hyperglycemia is also often seen in gastrectomy patients after loading. Their GA/HbA1c ratio is usually ~~was~~ higher than controls, suggesting that GA rises more than HbA1c and seems a better marker for glycemic excursions in these individuals [81].

It is still not clear why GA reflects postprandial glycemia better than HbA1c, but the different glycation rates of the two molecules may be involved.

6.5 GA as a biomarker of complications of diabetes mellitus and other diseases

Most studies focusing on algorithms for patient's follow-up usually compare GA with HbA1c, fasting glucose, OGTT and fructosamine, seeking the best parameter combination with the highest predictive value for diabetes-related complications. As we discussed earlier, GA may be directly implicated in the development of different complications related to diabetes, playing a role as a pathogenic molecule. This has been observed in the onset of nephropathy and in the development of atheromatous plaques. The Atherosclerosis Risk Communities (ARIC) study suggested there might be independent relationships between GA and retinopathy, chronic kidney disease and the incidence of diabetes mellitus. GA was similar to HbA1c in the prediction of retinopathy and chronic kidney disease, but lower than HbA1c for diabetes [82]. In a case-cohort subpopulation of the DCCT/EDIC study GA and HbA1c had similar associations with nephropathy and retinopathy which were strengthened when both measures were considered together, but only HbA1c was associated with the risk of cardiovascular diseases [83]. On the other hand, GA, similar to HbA1c, was further associated with intima media thickness, an indicator of subclinical atherosclerosis, in individuals with and without diabetes, suggesting that it might be also a helpful marker for estimating atherosclerosis risk [84,85].

These data suggest that GA may be an additional aid not only for monitoring and screening diabetes mellitus but also in risk stratification.

6.6 What are the limits of GA?

Undoubtedly in certain specific clinical conditions GA offers some advantages over the classical markers for monitoring glycemic status. In some specific disorders GA levels are either lower or higher than the mean plasma glucose concentration, mainly because of changes in the albumin metabolism. In all conditions with increased albumin catabolism, such as nephrotic syndrome and hyperthyroidism, GA would be lower than blood glucose [86,87]. In obesity too, GA levels would be lower than glycemia because of the increased albumin catabolism promoted by the chronic micro-inflammation [88,89]. A similar alteration has been seen in smokers, patients with non-alcoholic fatty liver disease, hypertriglyceridemia and hyperuricemia [90-92]. In all conditions with reduced albumin metabolism, such as liver cirrhosis and hypothyroidism, GA is higher than blood glucose. In chronic liver diseases (CLD), both GA and HbA1c have some limits for monitoring

the glycemic status. GA is higher than blood glucose because of the reduced albumin synthesis and HbA1c is lower because of the increased erythrocyte catabolism. Simultaneous measurements of HbA1c and GA, and the calculation of CLD-HbA1c (mean of HbA1c and GA/3) wasere proposed as a useful indicator of glycemic control in CLD patients [93-95].

7. Conclusions

GA is an interesting biomarker for diabetes mellitus: 1) as it is an intermediate-term marker of the glycemic status it gives more information than the short-term (glycemia) and long-term (HbA1c) biomarkers currently employed in clinical practice; 2) in specific clinical conditions (altered erythrocyte lifespan, pregnancy and end-stage renal disease) it should be preferred to HbA1c; 3) it is probably also useful for diabetes mellitus screening and risk stratification of diabetes-related complications. Table 2 summarizes the pros and cons of GA use.

In conclusion, the introduction of this biomarker in clinical practice could help clinicians in the early diagnosis of diabetes mellitus, and in planning measures to prevent long-term diabetes complications.

Conflict of Interest: The authors declare that they have no conflict of interest

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