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Glycated Albumin, An Early Biomarker of Several Pathologies

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ABSTRACT

The role of glycated albumin is determinant for early diagnosis in several pathologies. Obviously, it is with glycated hemoglobin elective for Diabetes diagnosis but the ratio albumin glycated and hemoglobin glycated could support the in vitro diagnosis in several pathologies of CNS such as Parkinson Alzheimer diseases and Epilepsy.

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Human serum albumin, produced as preproalbumin is modified as mature albumin and secreted by the hepatocytes controlled by the gene localized on chromosome 4 [1,2]. It is present largely in human blood, about 50% of the others circulating protein displaying a concentration ranging from 30 g/L to 50 g/L in non-pathological subjects. On the contrary, its Molecular weight is 67 KDa resulting lower than other proteins [3].

Are present 585 aa constituting III domains each of them sub classified in two domains, A and B [2]. These domains give an alpha helix structure. Among Domains A and B are reported 17 bounds Cyst-Cyst whereas Cyst 34 is unbounded. This protein folding permits to react versus pH changes and other biophysical changes [4]. Useful oncotic pressure is due to electrical point (pI) of the protein giving a distributed negative charge [5,6]; moreover, albumin binds reversibly metabolites, ions, fatty acid, bilirubin and drugs regulating the drug delivering [7-9]. Finally, albumin modulates the oxidative stress in plasma acting with free Cyst-34 [10,11].

Non-Enzymatic Glycated Albumin

The high albumin serum concentration and the moderate half-life (t1/2 = 21 days) with respect the other serum proteins is highly sensitive to direct glycation reaction. This is Maillard's reaction is glucose and free amine group of albumins giving a labile intermediate "Shiff base" that rearranges itself (Amadori mechanism) giving fructose-amine derivatives displaying moderate stability [12,13]. Both Shiff base and fructose-amine derivatives are the preliminary products of glycated albumin [14]; however, the last one could give heterocycles such as piranosyl- and furanosyl-adducts [15]. Other pathways could give, due to several oxidative or cleavage or re-modelling processes, stable compounds so called AGE (Advanced Glycation End product) [16].

Albumin with respect to Hemoglobin is more sensitive to Amadori reaction that Hemoglobin because the first reacts with free glucose whereas the last one is an intracellular protein. In addition, both albumin short half-life and the availability of albumin N-lysine groups shows leads to consider low the reactivity of N-valine present on β-chain of Hb with respect to N-lysine groups. The glycation rate of albumine is 4.5-fold higher than hemoglobin and the glycated hemoglobin/albumin ratio is 1:2,9 [17]. The most important nucleophilic addition groups of albumins are Lys, and Cyst and arginine although the most important fragment is Lys-525 where about 30% of final product is obtained [18,19]. When Cys 34 is involved, albumin is strongly modified in particular is reduced antioxidative properties of protein depicting a pathologic phenotype of protein [20].

High glycated albumin concentration, due to AGE products, several organs such as coronary arteries, cardiovascular system kidney and CNS could give several diseases due to AGE-RAGE interaction. RAGE are specific AGE receptors localized on endothelial glial system, macrophages and muscle [21]. AGE-RAGE interaction stimulates the kB nuclear factor the modulates proinflammatory molecules IL-1, IL-6, IL-8 TNF-a and compounds involved in atherosclerotic events such as ICAM-1 and VCAM-1. The first most important aspect due to the activation of these pathways is the presence of ROS that leads to complications in particular at middle long term of Diabetes Mellitus. At kidney level, glycated albumin stimulates epithelial cells producing pro-oxidative molecules that are involved in several kidney disease [22,23]. At CNS level AGE compounds stimulates oxidative stress and consequently, the neuro-inflammatory processes. Several diseases seem to be related to the presence of AGE in CNS, such as Parkinson, Alzheimer, Huntington pathology [24,25]. In Alzheimer disease AGE are accumulated in pyramidal neuron where both lysosomes and endosomes could give macro complex with β-amyloid, MAP-tau and APO-E4 molecules. Moreover, glycated albumin could overexpress APP inducing an accumulation of β-amyloid plaques. In Parkinson's disease AGE compounds links α-synuclein producing macro-compounds with high cytotoxicity [26].

Advantages of Glycated Albumin as Early Biomarker

Glycated albumin although is a biomarker almost unknown, is middle term a glycaemic parameter because of its hal-life (T1/2 = 20 days) with respect to HbA1c. In fact, glycated albumin early gives the status of glycemic compensation and so is useful in monitoring fast changes of glycaemic parameter [27,28]. In addition, considering that the glycosylation reaction is easier with albumin than haemoglobin could be considered a specific biomarker in cardiovascular risk [29]. Moreover, as previously illustrated, promotes inflammatory steps endothelial dysfunction the renal fibrosis and atheroma plaques [29,30]. The most important parameters employed in evaluating diabetic patients are glycated haemoglobin and plasmatic glucose. The first is a long-term biomarker whereas the last one is for daily evaluation (24 h). However, the glycated haemoglobin values should be actually weighed in patients affected by haemolytic anaemia, in the presence of iron deficiency, and in subject in haemodialysis [31,32].

In fact, in haemolytic anaemia and other pathologies that cause erythrocytes mechanic disruption is possible find lower HbA1C values whereas this value could be higher in iron deficiency anemia or hemoglobin pathologies with respect standard reference. In these pathologies is better albumin glycated instead of corresponding hemoglobin although the first one is not very useful in hyperthyroidism nephrotic syndrome and in obesity because in these conditions an increased metabolism of albumin and therefore of glycated albumin has been observed [33-35]. Considering all these considerations, it would good clinical practice consider GA/HbA1C ratio rather than each single value. In a recent study has been reported that, with respect a control group (2.6± 0.19) this ratio was highest in macrocytic anaemia (3.4 ± 0.50), normocytic anemia (2.8 ± 0.31), in dialysis patients (3.3 ± 0.52), in hypothyroidism (3.0 ± 0.38) chronic live disease (3.0 ± 0.39), live cirrhosis (3.8 ± 0.62) whereas this ratio was lowest in microcytic anaemia (2.5 ± 0.23), nephrotic syndrome (1.6 ± 0.28) and hyperthyroidism (2.2 ± 0.24) [36]. In conclusion, glycated album is useful not only to corroborate and screen diabetes mellitus but also to evaluate the risk in several pathologies. Recently it has been reported that subject with normal glucose tolerance displaying high GA /HbA1c ratio had a higher risk for Alzheimer disease with respect subject with low GA /HbA1c ratio. Similar trend was found in subject with glucose intolerance. Considering this report is possible suggest that GA/HbA1c ratio-but not HbA1c or GA alone might a useful biomarker for AD risk [37].

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