Overview of glycation related diseases

D) Glycation related diseases:

Glycation is a deleterious form of post translational modifications of macromolecules and has been linked to a number of diseases. (Harding et al. 1989).

Cardiovascular Diseases:

The in vivo accumulation of AGE’s over time contributes to changes in function and structure of the cardiovascular system which results in formation of artificial stiffening, endothelial dysfunction and myocardial relaxation abnormalities. Certain mechanisms are responsible for such changes. The collagen undergoes The collagen undergoes additional cross linking by Glycation of its free amino acids. They make the blood vessels stiff. Twenty seven samples of post-mortem aorta were histologically studied from people who suffered from diabetes. A correlation between aortic stiffness and AGE’s accumulation was observed. The reduction of low density lipoproteins uptake by all receptors damages the cardiovascular system. This occurs through Glycation in the phospholipids component of LDL and Glycation of LDL particle on the apolipo protein B. The glycated LDL is more susceptible to cross linking with collagen and arterial walls and it is not taken up in to cells and it accumulates. Foam cell formation also takes place as there is an uptake of macrophages by the modified LDL. Decrease in nitric oxide (vasodilator) activity also contributes to the damage of the cardiovascular system (Sims et. al) year 2010.

Renal Disease:

The patients suffering from Type 2 diabetes exhibit a renal relationship between renal disease and AGE's. In older population, in a study it was demonstrated that in an older population (n = 1008), elevated circulating AGEs were an independent predictor of renal function. The study was carried out in men and women, age 64 and older, participating in the In CHIANTI study in Tuscany, Italy. The results of the study demonstrated an elevated plasma concentration of CML independently associated with chronic kidney disease and the estimated glomerular filtration rate (an index of kidney function) at baseline, after three and six years of follow-up. These findings suggest that the potential adverse effects of AGEs on the kidney are applicable to the general population of older community-dwelling adults. In another study of 548 women from the Women's Health and Aging Study I in Baltimore, 51. 6% of women had decreased glomerular filtration rate, which was associated with increased serum levels of CML and sRAGE. However, more follow-up studies on the elderly population are needed to establish if high levels of CML could predict decreased in renal function (Semba et al 2010).

Alzheimer's disease:

Oxidative stress has being identified as primary risk factor in Alzheimer's disease although a definitive etiology is unknown. The presence of AGE's and aging are a threat through their role in pro. oxidant, inflammatory and chemical actions. A comparison between the brain tissue of the normal control and Alzheimer's disease patient found out the higher RAGE and AGE expression in age matched controls. Also there is evidence that RAGE mediates blood brain barrier transport of amyloid peptides. As a result,

possible links have been described between Alzheimer's disease and diabetes, which include advancing age, hypercholesterolemia and oxidative stress.

Diabetes:

Being an early recognised Glycation product, Haemoglobin A1C works as an indicator to those who all are suffering from diabetes. Hyperglycaemia is apparent in insulin dependant tissues such as endothelial cells, eye lens cells, kidney cells, peripheral neural tissue cells etc, which contributes heavily to Glycation process. Moreover if the proteolytic enzymes undergo Glycation in diabetes, their efficiency reduces, resulting in build up of glycated end products. AGE's delay wound healing associates with diabetes through neurological, vascular or intermediary metabolic modifications.

E) Methods for determination of glycated proteins:

Principles of reaction: A few methods have been described below to determine the presence of glycated proteins.

Binding methods: Ion exchange Chromatography-pk alteration Phenyl Hydrazine Procedure: Nucleophilic attack at the group. Electrophoresis Boronate affinity: Boronate ester formation Immune assay-antigen antibody

Chemical methods: Amino acid analysis (after NaBH4) – Reduction with NaBH4 yields glucitol amino acids Strong acid hydrolysis- Yields furosine, determination with HPLC

Weak acid hydrolysis- Yields hydroxymethylfurfural, determination with thiobarbituric acid

Alkaline solution- Yields reducing activity, determination with red ox indicators (i. e. nitro blue tetrazolium) (J. Clin. Chein. Clih. Bioohem. / Vol. 27, 1989 / No. 9)

Glycated haemoglobin is a well established indicator but not suitable as a diagnostic tool for the exclusion or the detection of diabetes. Instead of the glycated haemoglobin the serum proteins may discriminate better between the normal and the diabetic although the subject is controversial. Serum proteins react faster than the glycated haemoglobin and reflect the changes in glycaemia for a shorter period of time. The laboratory performance for the routine determination of the glycated serum protein is not yet satisfactory as the detection or exclusion of the diabetes in a single sample cannot be established properly. Thus, Glycated serum and glycated protein should be considered as complementary to each other rather than being considered as substitutes.(Schleicher and weiland in 1989)

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