Summary and Conclusion

❖ Diabetic Nephropathy:

Diabetic nephropathy is defined as a progressive decline in glomerular filtration rate, accompanied by proteinuria and other end-organ complications such as retinopathy. Diabetic nephropathy progresses to end-stage renal disease via a number of stages including, normoalbuminuria, microalbuminuria/ incipient diabetic nephropathy, macroalbuminuria and finally end-stage renal disease. Indeed, progression to end stage renal disease is enhanced by hyperglycaemia, hypertension and proteinuria, which are all common in diabetes.

Renal disease in diabetic patients is characterised by haemodynamic (hyperfiltration and hyperperfusion) as well as structural abnormalities (glomerulosclerosis, alterations in tubulointerstitium including interstitial fibrosis) and metabolic changes. Within glomeruli, there is thickening of basement membranes, mesangial expansion and hypertrophy and glomerular epithelial cell (podocyte) loss.

In conjunction, disease progression is also seen in the tubulointerstitial compartment causing expansion of tubular basement membranes, tubular atrophy, interstitial fibrosis and arteriosclerosis. To date, the most effective clinical treatments to prevent the progression of diabetic nephropathy are antihypertensives, which target the renin-angiotensin system.

❖ Advanced glycation end products:

Advanced Glycation End-products *(AGEs)* are the result of a chain of chemical reactions after an initial glycation reaction. The intermediate products are known, variously, as Amadori, Schiff base and Maillard products. Side products

generated in intermediate steps may be oxidizing agents (such as hydrogen peroxide), or not (such as beta amyloid proteins).

AGEs may be formed external to the body (exogenously) by heating (e.g., cooking); or inside the body (endogenously) through normal metabolism and aging. Under certain pathologic conditions (e.g., oxidative stress due to hyperglycemia in patients with diabetes), AGE formation can be increased beyond normal levels. AGEs are now known to play a role as proinflammatory mediators in gestational diabetes as well.

❖ *Effects of AGEs:*

AGEs may be less, or more, reactive than the initial sugars they were formed from. They are absorbed by the body during digestion with about 30% efficiency. Many cells in the body (for example, endothelial cells, smooth muscle, and cells of the immune system) from tissue such as lung, liver, kidney, and peripheral blood bear the Receptor for Advanced Glycation End-products *(RAGE)* that, when binding AGEs, contributes to age- and diabetes-related chronic inflammatory diseases such as atherosclerosis, asthma, arthritis, myocardial infarction, nephropathy, retinopathy, and neuropathy. The total state of oxidative and peroxidative stress on the healthy body, and the accumulation of AGE-related damage is proportional to the dietary intake of exogenous AGEs, the consumption of sugars with a propensity towards glycation such as fructose and galactose.

AGEs affect nearly every type of cell and molecule in the body, and are thought to be one factor in aging and some age-related chronic diseases. They are also believed to play a causative role in the vascular complications of diabetes mellitus.

They have a range of pathological effects, including increasing vascular permeability, inhibition of vascular dilation by interfering with nitric oxide,

oxidising LDL, binding cells including macrophage, endothelial, and mesangial cells to induce the secretion of a variety of cytokines and enhancing oxidative stress.

❖ *Anti-AGE Interventions:*

1) Diet and Exercise:

A whole-foods, low-glycemic-index diet is essential to minimize the extent and duration of postprandial surges in blood sugar and triglycerides, and resulting likelihood of AGE formation. Exercise to improve and maintain a healthful BMI, with its positive effects on glucose metabolism, is the second baseline strategy.

2) Older Established Therapies:

A number of established therapies have been shown to decrease AGE formation in vitro including ACE inhibitors, angiotensin receptor antagonists, metformin, peroxisome proliferators receptor agonists, metal chelators and some antioxidants.

3) New Therapeutic Agents:

Several new therapeutic agents that reduce AGE formation and/or accumulation have been developed. ALT-711 (alagebrium), the best researched with positive in *vitro, in vivo,* and human clinical trials, appears to provide the highest efficacy and safety of these compounds. Preliminary research on pyridoxamine, benfotiamine (a thiamine derivative) and LR-90 (methylene bis) suggests they may also provide benefit.