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REVIEW ARTICLE

A REVIEW ON EFFECT OF CYSTATIN C IN TYPE 2 DIABETES MELLITUS.

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Abstract

Diabetes mellitus is a metabolic disorder resulting from deficient insulin secretion, inefficient insulin action or both leading to prolongedhyperglycemia. Diabetic problems result from the toxic effects of prolonged hyperglycemia combined with other metabolic imbalances. type 2 diabetes mellitus, formerly called non-insulin-dependent diabetes mellitus, is a serious, costly disease. Treatment prevents some of its devastating complications but does not usually restore normoglycemia or eliminate all the adverse consequence . Cystatin C is a cysteine protease inhibitor with a low-molecular weight that is produced by all nucleated cells at a constant rate. Cystatin C also produce contraindication like it play a major role in the thyroid functions, Kidney,CVS.

Introduction:-

Diabetes is a difficult problem for public health in all over the world. This is a chronic disease in which patients have high blood glucose level because body does not produce enough insulin or cells are not responding effectively. There are two types of diabetes one is insulin dependent or type 1 diabetes and other one is non-insulin dependent or type 2 diabetes. According to data of feb 2011 there are 25.8 million peoples are suffering from Diabetes in United States. Total costs of diabetes, including medical care, disability, and premature death, reached an estimated $174 billion in 2007 in the United States. There are from type 1 diabetes about 10% peoples are suffering.this type of diabetes mostly occurrence in young age. It is insulin depended Insulin is a hormone manufactured by the beta cells of the pancreas, which is required to utilize glucose from digested food as an energy source.[1,16,17] Chronic hyperglycemia is related with micro vascular and macro vascular difficulties that can lead to visual impairment, blindness, kidney disease, nerve damage,Amputations, heart disease, and stroke.[2] Diabetes is strong and has led to screening strategies in diabetic patients even before they are symptomatic. Diabetic patients often are unaware of myocardial ischemic pain, and so silent myocardial infarction and ischemia are markedly increased in this population.[3] Type 2 diabetes is influenced by genetic factors, Aging,Obesity,and peripheral insulin resistance rather then autoimmune processes or viruses[4].In type 2 diabetes, hyperglycemia starts after forties, usually when the kidneys have already suffered the long term consequences of ageing and other recognized promoters of chronic renal injury like arterial hypertension, obesity, dyslipidemia and smoking.Diabetic nephropathy refers to a characteristic set of structural and functional kidney abnormalities in patients with diabetes.[5]

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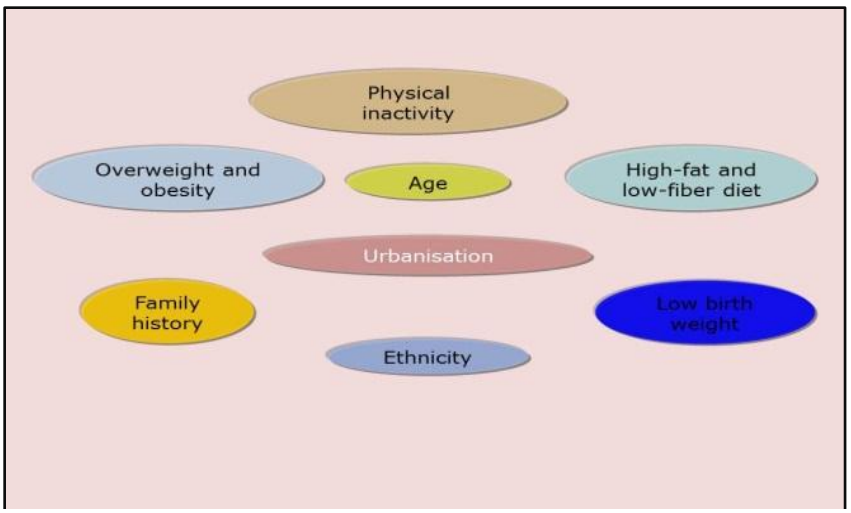

Fig No 1:- Risk factors for type 2 diabetes.

Noninsulin-dependent diabetes mellituss (NIDDM), maturity onset diabetes mellitus there is no loss or moderate reduction in B cell mass; insulin in circulation is low, normal or even high no anti-B-cell antibody is demonstrable; has a high degree of genetic predisposition; generally has a late onset(past middle age).Over 90% cases are type 2 DM.[6]

Insulin:-

Insulin was discovered in 1921. Insulin is synthesized in the B cells of pancreatic islets as a single chain peptide Preproinsulin (110 AA) from which 24 AAs are first removed to produce Proinsulin.[6],[8] insulin is synthesised as a precursor (preproinsulin) in the rough endoplasmic reticulum. Preproinsulin is transported to the Golgi apparatus, where it undergoes proteolytic cleavage first to proinsulin and then to insulin plus a fragment of uncertain function called C-peptide[8].

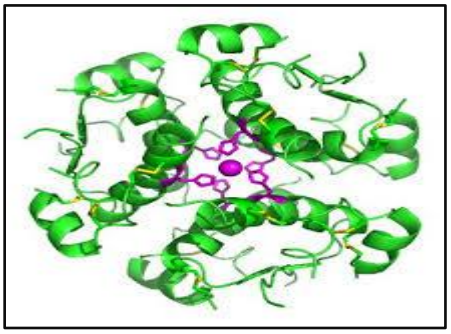

Fig No 2:- Structure of Insulin.

Table 1:- Insulin lowers the concentration of glucose in blood by inhibiting hepatic glucose production andby stimulating the uptake and metabolism of glucose by muscle and adipose tissue .These two important effects occur at different concentrations of insulin.[8]

Liver	Muscle	Adipose Tissue
Inhibits hepatic glucose production	Stimulates glucose uptake	Stimulates glucose uptake
Stimulates hepatic glucose uptake	Inhibits flow of gluconeogenic precursors to the liver	Inhibits flow of gluconeogenic and reduces energy substrate for hepatic gluconeogenesis (nonesterfied fatty acids)

Cystatin C is a low molecular weight protein produced at a constant rate by all nucleated cells. It is freely filtered by glomerulus, completely reabsorbed and catabolized in the proximal tubule[11]. In type 2 diabetes, the pancreas retains some B-cell function but variable insulin secretion is insufficient to maintain glucose homeostasis.[8]Abnormality in

gluco-receptor of B cells so that they respond at higher glucose concentration. Or relative B cell deficiency.[6] Reduced sensitivity of peripheral tissues to Insulin reduction in number of insulin receptors, down regulation' of insulin receptors.[9] Manyhypertensive are hyperinsulinaemic, but normoglycaemic; exhibit insulin resistance associated with dyslipidemia.[6] Serum cystatin C is reported to be modulated by several non-renal factors like steroids, thyroid status, smoking, C-reactive protein and malignancy. Despite these limitations evidence continues to suggest superiority of serum cystatin C when compared with serum Creatinine in patients with early and moderately decreased renal function.[12] [13],

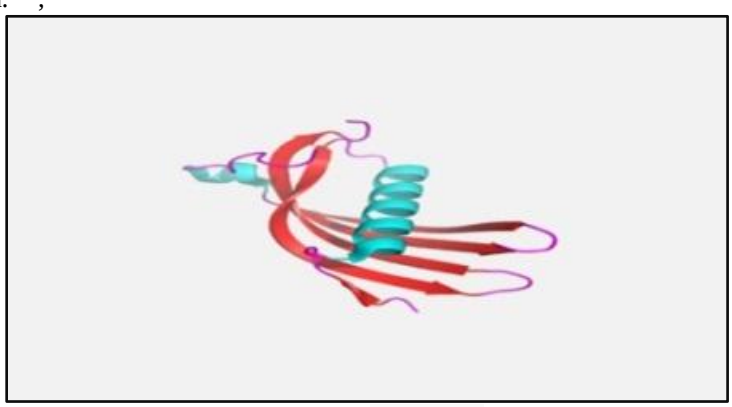

Fig No 3:- Cystatin C

Cystatin C in comparison with serum creatinine can be a useful maker in detecting renal impairment in type 2 diabetes mellitus individuals.[14]cystatin C, in detection of renal disease in type 2 diabetes mellitus. It has been noted that patients with type 2 diabetes and microangiopathy have statistically significant higher levels of cystatin C than healthy individuals. In 52 Caucasian patients with type 2 diabetes, cystatin C was found to be a better marker of kidney disease measured by serum creatinine or Cockcroft and Gault GFR estimation. The study clearly demonstrated that serum concentration progressively increased as glomerular filtration rate decreased [42]. Cystatin C or cystatin 3 (formerly gamma trace,post-gamma-globulin or neuroendocrine basic polypeptide), a protein encoded by the CST3 gene, is mainly used as a biomarker of kidney function. Recently, it has been studied for its role in predicting new-onset or deteriorating cardiovascular disease. It also seems to play a role in brain disorder[10

Biological Functions of Cystatin C:-
In addition to being an inhibitor of papain-like cysteine proteases, cystatin C has recently been shown to inhibit another family of cysteine protease, called the peptidase family C13 with human legumain as a typical enzyme[17]

Distribution of Cystatins in Body Fluids:-
The distribution in body fluids of the different cystatins is remarkably different

Production of cystatin C:-
Determination of the structure of the human cystatin C gene and its promoter has established that the gene is of the house-keeping type, which indicates a stable production rate of cystatin C by most nucleated cell types.

Molecular biology:-
The cystatin superfamily encompasses proteins that contain multiple cystatin-like sequences. Some of the members are active cysteine protease inhibitors, while others have lost or perhaps never acquired this inhibitory activity. There are three inhibitory families in the superfamily, including

Type 1 cystatins (stefins),
Type 2 cystatins and the kininogens.

The type 2 cystatin proteins are a class of cysteine proteinase inhibitors found in a variety of human fluids and secretions, where they appear to provide protective functions.

Cystatin C is a non-glycosylated, basic protein (isoelectric point at pH 9.3).The crystal structure of cystatin C is characterized by a short alpha helix and a long alpha helix which lies across a large antiparallel, five-strandedbeta sheet. Like other type 2 cystatins, it has two disulfide bonds[18]

Contraindications:-

Thyroid Function:-

Levels of Cystatin C are sensitive to changes in thyroid function and should not be used without knowledge of the patients thyroid status[19]

Corticosteroids:-

It has been reported that Cystatin C serum concentrations are not affected by standardized high-dose corticosteroid therapy but may be increased in patients with impaired renal function receiving corticosteroids.[20]

Cystatin C in the Diagnosis and Management of Kidney Disease:-

The Infection of Chronic Kidney Disease:-

Recent epidemiological studies in the UnitedStates report that there has been a 40% increase in the prevalence of CKD in recent years with a corresponding doubling of the incidence of end-stage renal disease and a tripling of Americans on dialysis.[15] The occurrence of chronic kidney disease has reached epidemic proportions now affecting 13.8 to 15.8 % of the general population[21]

Neurologic Disorders:-

Mutations in the cystatin 3 gene are responsible for the Icelandic type of hereditary cerebral amyloid angiopathy.[25]The role of cystatin C in multiple sclerosis and other demyelinating diseases (characterized by a loss of the myelin nerve sheath) remains controversial.[26]

cardiovascular Disease:-

Kidney dysfunction increases the risk of death and cardiovascular disease.[32][33] Several studies have found that increased levels of cystatin C are associated with the risk of death, several types of cardiovascular disease (including myocardial infarction, stroke, heart failure, peripheral arterial disease and metabolic syndrome) and healthy aging.[26]

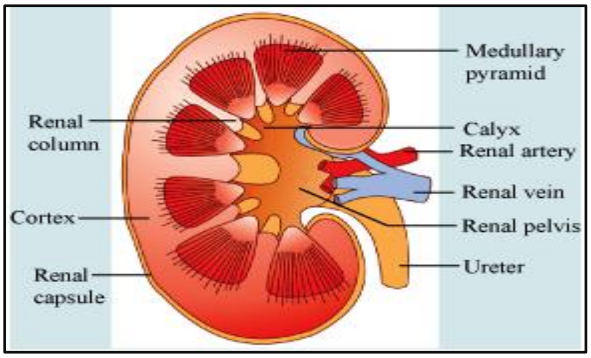

Fig.4:- The kidney has a bean-shaped structure having a convex and a concave border. A recessed area on the concave border is the renal hilum, where the renal arteryenters the kidney and the renal vein and ureter leave[22],[23]

Table 2:- Stage of Kidney Disease NKDEP Classification[24]

Normal	Healthy kidneys GFR > 90 mL/min per 1.73 m^2
Stage 1	Kidney damage with normal or elevated GFR GFR > 90 mL/min per 1.73 m^2
Stage 2	Kidney damage and mild decrease in GFR GFR of 60 -89 mL/min per 1.73 m^2
Stage 3	Moderate decrease in GFR GFR of 30 – 59 mL/min per 1.73 m^2
Stage 4	Severe decrease in GFR GFR <16 – 29 mL/min per 1.73 m^2
Stage 5	Kidney failure - End Stage Renal Disease (ESRD) GFR of <15 mL/min per 1.73 m^2

Discussion:-

Type 2 diabetes affects approximately 8 percent of adults in the . Some risk factors elevated plasma glucose concentrations in the fasting state and after an oral glucose load, over-weight, and a sedentary lifestyle are potentially reversible. We hypothesized that modifying these factors with a lifestyle intervention program or the administration of metformin would prevent or delay the development of diabetes. It is very important in managing diabetes mellitus to detect diabetic nephropathy as early as possible and to prevent its development. The assumption that cystatin C may be a suitable indicator of diabetic nephropathy, we deliberate the level of plasma cystatin C in patients with the non-insulin- dependent type of the disease and analyzed the results in view of parameters routinely used in clinical practice such as albuminuria and plasma creatinine.Plasma cystatin C level shows to be in dependent of gender, weight, infections, dietary factors and liver diseases, but some authors suggest its relation "with age. It was reported that an increase in cystatin C level is accentuated at 50 years of age.

The determination of the plasma concentration of cystatin C may be useful in the detection of incipient nephropathy in patients with non-insulin dependent diabetes mellitus.

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