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Ayurveda

CRUCIAL ROLE OF SERUM CYSTATIN-C AS A MARKER FOR EARLY DETECTION OF RENAL DYSFUNCTION IN DIABETES MELLITUS WITH SPECIAL REFERENCE TO *PRAMEHA* IN *AYURVEDA*

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ABSTRACT Diabetes mellitus is a chronic disease characterized by derangements in carbohydrate, fat and protein metabolism. It is a clinical condition characterized by increased blood glucose level (hyperglycemia) due to insufficient or inefficient insulin. It is a most common metabolic disorder in India. Diabetic nephropathy is currently one of the leading causes of morbidity and mortality in diabetic population, accounting for greatest proportion of end stage renal disease worldwide.

In *Ayurveda Prameha* is usually correlated with Diabetes Mellitus with important symptoms like *Prabhoota Mutrata* i.e Increased frequency and quantity of urine and *Avila Mutrata* which means turbid urine. *Prameha* is considered as *Chirakaaleena vyadhi*(chronic disease) which is *Anushangi*[1](recurring) in nature. It is due to vitiation of *tridoshas (vata-pitta-kapha)* especially *Kapha dosha* which can be considered as important components of protoplasm[2] which governs all the activities of body and also symbolizes the physico-biological properties of compounds made through a different combination of *Panchamahabhootas* i.e *Akasha*(space), *Vayu*(electrons), *Teja*(energy), *Jala*(proton) and *Prithvi*(neutron)[3].GFR (Glomerular filtration rate) is considered as the best indicator of overall kidney function and therefore its assessment has become an important clinical tool in daily patient care. A stepwise increase in nitrogenous constituents of blood like urea, creatinine etc and other biochemical parameters like albumin, electrolytes etc also believed to reflect deteriorating kidney function. Cystatin-c[4] is one among Renal Function Tests. It is done to detect chronic kidney dysfunctions. It is considered as better marker for GFR than Serum Creatinine. Even in disease *Prameha*(DM) Renal functions predominantly gets disturbed leading to many future complications. So the pivotal role of serum Cystatin-C as a marker for early detection of renal dysfunction in Diabetes Mellitus will be discussed elaborately which may be beneficial in decreasing the incidence of patients landing up in complications especially related to renal system.

KEYWORDS : Cystatin-C, Diabetes Mellitus, *Prameha*

INTRODUCTION:

Diseases are innumerable with multiple cause and symptoms. History taking, physical examination and also laboratory investigations plays a key role in diagnosis of disease. *Ayurveda* is a comprehensive system of traditional health care deals with the promotion of health, prevention of the disease and effective management of different psychosomatic disorders.

Diabetes Mellitus, one among the group of the clinical presentations explained under the heading of etiopathogenesis and symptomatology of *Prameha* in *Ayurveda*. It comprises group of metabolic disorders in which there is reduced utilization of carbohydrate, and that of lipid and protein enhanced. It is caused by complex interaction of genetics, environmental factors and lifestyle choices, leading to absolute or relative deficiency of insulin. It is a clinical condition characterized by increased blood glucose level (hyperglycemia) due to insufficient or inefficient insulin. Symptoms of Hyperglycemia include polyuria, polydipsia, polyphagia, weightloss etc.

The sedentary lifestyle, earlier age of onset, delayed diagnosis and improper care lead to an increase in morbidity which can be said as diabetic complications like non healing ulcer, nephropathy, retinopathy etc and even mortality. Several complications like Acute life-threatening consequences of uncontrolled diabetes are hyperglycemia with keto acidosis or the non ketotic hyperosmolar syndrome. In long term complications of diabetes skin complications like foot ulcers, gangrene etc are very common and others like loss of vision, nephropathy leading to renal failure, charcot joints and autonomic neuropathy causing gastrointestinal, genitourinary, cardiovascular symptoms and sexual dysfunction. Patients with diabetes have an increased incidence of atherosclerotic cardiovascular, peripheral arterial and cardiovascular disease.

Vivid description of signs and symptoms of Diabetes in *Ayurveda* and its complications has been given by all the classical texts. Most of the classical texts explained complications in brief compared to the exhaustive descriptions of its causative factors and symptoms. When we ponder *Prameha*(Diabetes), Renal system is invariably and also drastically effected which can be understood starting from its causative factors, premonitory symptoms, main symptoms and also its pathogenesis.

GFR(Glomerular filtration rate) is considered as the best indicator of overall kidney function and therefore its assessment has become an important clinical tool in daily patient care.GFR is the amount of glomerular filtrate per unit time by all nephrons of both kidneys. Normal value of GFR is 125ml/min. A stepwise increase in nitrogenous constituents of blood like urea, creatinine etc and other biochemical parameters like albumin, electrolytes etc also believed to reflect deteriorating kidney function.

Cystatin-c[5] is also one among RFT. It is done to detect chronic kidney dysfunctions. Since Cystatin-C is a small protein which is produced constantly, freely filtered by glomerulus and also fully reabsorbed and broken down by renal tubules is considered as better marker for GFR than Serum Creatinine. So serum Cystatin-C marker will help in early detection of renal dysfunction in Diabetes Mellitus which will be beneficial in decreasing the incidence of patients landing up in complications especially related to renal system.

(Figure: 1- Structure of Cystatin-C)

AIMS AND OBJECTIVES:

To review the pivotal role of serum Cystatin-C as a marker for early detection of renal dysfunction in Diabetes Mellitus with special reference to *Prameha* in *Ayurveda.*

MATERIAL AND METHODS:

Ayurveda classical and contemporary texts, Text books of Modern medicine, Review articles & journals and other internet sources.

OBSERVATION & DISCUSSION:

The prevalence of diabetes and its complication is increasing all over the world particularly in developing countries. It has emerged as a major public health problem in our country. According to WHO India

had 69.2 million people living with Diabetes in 2015. Nearly 98 million people in India may have type-2 diabetes by 2030. An estimated 422 million people are living with Diabetes in world which is estimated to be 1 in 11 of the world's adult population compared to 108 million in 1980. The global prevalence raised from 4.7% to 8.5% in adult population. 46% of the people with Diabetes are undiagnosed. The figure is expected to rise to 642 million worldwide by 2040.

Diabetes is the major global cause of premature mortality that is widely underestimated, because only a minority of persons with Diabetes dies from a cause uniquely related to the condition. Approximately one half of the patients with type 2 Diabetes die prematurely of cardiovascular cause and approximately 10% die of renal failure. Global excess mortality attributable to diabetes in adults is estimated to be 3.8million deaths[6].

It is a known fact that both Type1 and Type2 DM based on severity and chronicity of hyperglycemia forms the main pathogenic mechanism for several complications including nephropathy, retinopathy, neuropathy etc therefore control of blood glucose level constitutes the mainstay of treatment for minimising development of these complications.

As a consequence of hyperglycaemia every tissue and organ of the body undergoes biochemical and structural changes which account for major complications in Diabetes which may be acute metabolic or chronic systemic. These complications may be broadly divided into 2 major groups: Acute metabolic complications and late systemic complications. Renal involvement is a common complication and a leading cause of death in Diabetes which is classified under late systemic complications.

Recognition of the complications of Diabetes :

In 1936, Kimmelstiel & Wilson's article on a kidney lesion that seemed pathognomonic for the diabetes rounded out the early description of the diabetes complications. Implicit in many of the discussions in these monographs, particularly those on pathology, diabetic coma & retinopathy was concomitant presence of the severe macrovascular disease. The suggestion of the high incidence of the coronary artery disease emphasized in these publications was clearly substantiated in Bell's monumental study on atherosclerosis.

The distinction between what is now known as Type-1 and Type-2 Diabetes was first clearly made by Sir Harold Percival(Harry) Himsworth & published in Jan 1936.

Brief history of Cystatin C

Cystatin-C was discovered in 1961 as an alkaline protein in normal cerebrospinal fluid. It is a 13-kDa, non-glycosylated basic protein belonging to the cystatin super family of cystine proteinase inhibitors. Grubb and Lofberg first reported its amino acid sequence. They noticed it was increased in patients with advanced renal failure. It was first proposed as a measure of glomerular filtration rate by Grubb and co workers in 1985. Use of serum creatinine and cystatin c was found very effective in accurately reflecting the GFR in a study reported in July5, 2012 issue of the New England Journal of medicine[7].

Cystatin-C test overview:

Test name: Cystatin-C

Reference range: ≤65years 0.50-1.12mg/L
>65years 0.55-1.21mg/L

Specimen required: 1mL serum. Centrifuge within one hour of collection

Estimation of the glomerular filtration rate (GFR) is the most widely used test of renal function and reflects the kidney's ability to clear a particular substance from plasma. GFR is defined as the quantity of glomerular filtrate formed per unit time in all nephrons of both kidneys. The most precise and accurate methods for estimating GFR are based upon determinations of plasma clearance of substances like 51Cr-EDTA, iothalamate or iohexol. These so called "gold standard" methods require injection of an exogenous radioactive or contrast agent and are complex, laborious, expensive and impractical in the clinical setting and for larger research studies. Therefore the measurement of endogenous blood substances to estimate GFR is common practice. For several decades clinicians have relied on measurements of serum creatinine as a rapid first-line test to determine GFR. This test is convenient and cheap, but results are affected by age, sex, muscle mass, diet, race and tubular creatinine secretion particularly when GFR is reduced. Thus, there has been an ongoing search for suitable alternative endogenous markers of GFR.

Cystatin-C unique among cystatins, seems to be produced by all human nucleated cells. It is produced at a stable rate, which is unaffected by inflammatory processes, sex, age, diet, and nutritional status[8]. Only a few circumstances have been identified that have an impact on the production of Cystatin-C, such as very large doses of glucocorticoids and thyroid dysfunction. In the normal kidney, Cystatin-C is freely filtered through the glomerular membrane and then almost completely reabsorbed and degraded by the proximal tubular cells. Therefore, the plasma concentration of Cystatin-C is almost exclusively determined by the GFR, making Cystatin-C an excellent indicator of GFR. Studies of the serum level of Cystatin-C in large patient cohorts have failed to correlate the serum level to any pathophysiological states besides those affecting the GFR.

The interest in Cystatin-C as a marker of renal function has increased tremendously over the last few years and the number of articles and reviews about Cystatin-C continues to grow. Numerous studies and a meta-analysis incorporating 4,492 subject samples, comparing the use of serum Cystatin-C and creatinine as markers of GFR have shown that serum Cystatin-C is clearly superior to serum creatinine as a marker of GFR[9]. Cystatin-C responds more quickly to changes in the GFR than creatinine, which is not a sensitive marker for early decline in GFR. A substantial proportion of patients with reduced GFR display serum creatinine levels within the normal range and even a 50% reduction of GFR is not infrequently associated with a normal concentration of serum creatinine. Cystatin-C is accurate in this "creatinine-blind area" helping the clinician to get an earlier indication of deteriorating renal function, and thus allowing the possibility of taking preventive action. Moreover, Cystatin-C does not have the previously mentioned limitations of creatinine, and its measuremant is a much simpler way of assessing renal function than methods such as iohexol clearance. A particularly important advantage of Cystatin-C as a marker of GFR is that it can also be used to evaluate GFR in patient populations for whom it is difficult to obtain an accurate assessment of GFR based on the creatinine value.

Clinicians need a fast estimate of a patient's renal function to calculate the correct amount of antibiotics or cytotoxic drugs for the individual patient, for instance, before initiating treatment, and also for monitoring patient response during and after therapy. Cancer therapeutics, in particular, have the potential to inflict severe damage to the kidneys. An early indication of renal dysfunction would allow the oncologist to adjust the drug dosage before irreparable kidney damage had occurred. Formulae for estimating the GFR have attracted considerable interest in recent years. Various formulae such as the Cockcroft-Gault and the Modification of Diet in Renal Disease (MDRD) have been suggested for calculating GFR from serum creatinine concentration. These formulae include anthropometric variables such as body weight, gender, age and race to compensate for the inadequacies of creatinine level as a marker of GFR. However, even including these many variables, the formulae have several limitations in estimating the GFR. A new study has been carried out to investigate the possibility of introducing formulae for the estimation of GFR from the serum Cystatin-C concentration without the use of anthropometric variables. Serum Cystatin-C concentrations were measured with the DakoCytomation Cystatin-C Immunoassay for 451 patients. An equation for the conversion of the Cystatin-C concentration in mg/L to GFR in mL/min (determined by iohexol clearance) was established[10]

The study showed that the formula based on Cystatin-C has lower bias and higher accuracy in predicting GFR than the Cockcroft-Gault formula. Thus, Cystatin-C provides a more precise and accurate estimation of GFR, calculated from a single measurement of serum Cystatin-C . Clinical utility in different patient groups in contrast to serum creatinine, serum Cystatin-C is unaffected by muscle mass. This means that selected patient groups, whose muscle mass is either reduced or undergoes rapid change, may particularly benefit from the use of Cystatin-C for estimating the GFR. This is true for children and the elderly. The reference range for serum creatinine increases with age up to the end of puberty and has to be adjusted for gender from puberty onwards. In contrast, the reference range for serum Cystatin-C is identical for men, women and children as the Cystatin-C level is

constant after the age of one and virtually identical to the reference range for adults. In the first years of life, renal function matures physiologically. Accordingly high Cystatin-C concentrations have been found at birth, followed by a rapid decline after birth reflecting maturation of kidney function. Unlike serum creatinine, Cystatin-C can thus be used to assess the GFR of newborns and even of the foetus. GFR decreases with age as the nephrons start to decrease from about the age of 50. At approximately the same age, muscle mass also begins to decline. In the elderly, serum creatinine is notoriously unreliable as an indicator of GFR because the daily production of creatinine is diminished as a result of the reduced muscle mass. Several studies have also shown Cystatin-C to be a superior marker for early detection of renal impairment in elderly people. In a clinical situation, the influence of muscle mass can be essential, for instance when diagnosing reduced GFR in paralysed patients. This has been investigated for patients with spinal cord injury who have varying degrees of muscle atrophy. The results show that Cystatin-C is much more reliable as a marker of renal function for this patient group compared to creatinine[11].

Diabetes is a highly complex disorder with many ramifications and is the commonest cause of kidney failure in younger people globally. Treatment comprises dialysis or kidney transplantation. If early damage to the kidneys can be detected, preventive action can then be taken. Cystatin-C has been reported to be advantageous compared with serum creatinine for the detection of mild diabetic nephropathy, whereas the two markers were equally efficient in detecting advanced diabetic nephropathy[12].

Cystatin-C has been measured before and after chemotherapy in cancer patients. The results show that serum Cystatin-C is a superior marker to serum creatinine for the estimation of GFR, independent of the presence of metastases, and independent of chemotherapy[13]. It has also been shown that Cystatin-C can be used to characterise glomerular function in children with cancer[14].In multiple myeloma, a study has demonstrated no correlation between Cystatin-C and tumour burden.

It has recently been suggested that Cystatin-C could be used as a valuable parameter in the monitoring of pregnancies complicated by pre-eclampsia. Pre-eclampsia is a pregnancy-specific disorder associated with increased foetal and maternal risk. The cause is unknown and delivery is the only definitive cure for this condition. There is a real need for sensitive and specific diagnostic tests for pre-eclampsia. During uncomplicated pregnancy, the renal-flow progressively increases, leading to about 40% higher GFR than in a non-pregnant woman. Pre-eclampsia is characterised by hypertension and renal structural changes, and the kidney function, in particular, is of major concern. Because pre-eclampsia is characterised by a decrease in GFR, kidney function needs to be monitored closely to ensure timely delivery before the development of toxaemia and serious kidney tissue injury. Cystatin-C has been shown to provide superior diagnostic accuracy for pre-eclampsia compared to serum urate and creatinine, and cannot only be used as a marker for impaired renal function, but also for the degree of glomerular endotheliosis (the only consistently found pathological lesion in pre-eclampsia)[15]. Thus, Cystatin-C seems to be useful for optimising the timing of neonatal delivery.

A recent study has indicated that Cystatin-C is more than simply a marker of GFR. In this study the impact of Cystatin-C the prognosis of a large cohort of patients with coronary heart disease (CHD) was evaluated. The data support a potentially important role for cystatin C as a marker for patients with known CHD[16].

The DakoCytomation Cystatin-C Immunoassay is intended for the quantitative determination of Cystatin-C in human serum and plasma by turbidometry and nephelometry[17].

G-Grade
Table No.1

Category	GFR ml/min/1.73m2	Terms
G 1	≥90	Normal or High
G2	60-89	Mildly decreased
G3a	45-59	Mildly to moderately decreased
G3b	30-44	Moderately to severely decreased
G4	15-29	Severely decreased
G5	<15	Kidney failure

In *Ayurveda* basically 3 types of *Prameha* (Diabetes) has been mentioned in classics has to be understood as *Avasthas* or stages of the disease ultimately landing up in *Madhumeha* mostly correlated to IDDM. In *Madhumeh*a (IDDM) all the *dravadhatus* (Liquified cellular components) in reference to *kapha* (a component of protoplasm) gets excreted through urine. There is a significant change in physical constitution, chemical contents and biochemical properties in such urine. The abnormal metabolic admixture causes urine to become turbid due to the presence of glucose, protein/albumin and even in severe cases ketones.

Upadrava(complication) is one which occurs in the course of some other disease, although it may result from the main disease. The morbid process occurring during a disease may be a minor or major ailment[18]. This episode has been superimposed, altering symptoms and modifying its course as a result disease may become difficult for management. *Acharya Chakrapani* said that the signs and symptoms of a disease which appear at different stages, especially at the later stage of the disease should be considered as the signs and symptoms of the original disease and not as the complications[19]. Different stages of a disease are invariably manifested during the process of pathogenesis and all these stages constitute a disease, but complications may or may not be manifested which represent a distinct stage of development in a disease. But if a disease manifest by powerful *doshas, dushyas* i.e (components of protoplasm) then it is possible that the ailments which constitute complications may also get manifested right from the inception of the disease. *Acharyas* mentioned excess thirst, diarrhoea, loss of compactness of body especially joints, fever, body pain, altered consciousness, cough, dyspnoea, vomiting etc as some of the complications which can be seen in case of patients of Diabetes mellitus. So with the help of Cystatin-C investigation conducted in earlier phase of disease many complications that can be seen in chronic phases of Diabetes can be avoided which will definitely have a overall impact in raising the health standards in an individual.

Correlation of some terminologies mentioned in *Ayurveda* classics:
Table No. 2

Prabhoota Mootrata	Polyuria
Bahvashee	Polyphagia
Trushna	Polydipsia
Alasya	Lassitude
Sthoulya (Margavarana Janya)	Rapid weight gain (especially in early NIDDM)
Krusha (Sahaja)	Rapid weight loss in IDDM
Mootra madhurya	Glycosuria
Tanu madhurya	Hyperglycemia
Beeja, Beejabhaga & Beejabhaga avayava upatapa leading to Prameha arambhaka dosha dushti in Sahaja madhumeha	Genetic susceptibility in the 6th Chromosome leading to IDDM
Kulaja vikara- Pitr Pitamahadi karma	Familial inheritance more in IDDM
Kaphamedokara ahara vihara sevana, Avyayama and Chinta tyaga	Over eating and under activity
Vikara vighata abhava and Sahaja asatmya	Auto immunity
Ksheera, dadhi as Kaphakara ahara	Bovine albumin
Sthoulya upadrava	Obesity leading to NIDDM
Anashana	Malnutrition in infancy predisposes to IDDM
Shoka udwega in Vataja Prameha	Stress leading to IDDM

CONCLUSION:

Initial and rapid determination of renal function followed by timely therapy will help to improve patient care. Cystatin-C can be an excellent marker of renal function, and available evidence demonstrates that serum Cystatin-C is superior to serum creatinine as a marker of GFR, particularly in identifying initial small reduction in GFR. The use of Cystatin-C provides the best possible information on GFR following initial examination of patients whose GFR is of interest, and in situations where gold standard clearance measurements cannot be performed for biomedical or economical reasons.

Multidisciplinary approach towards combating the disease Diabetes is

a need of the time since its morbidity and mortality ratio is going on getting increased even with lot of efforts. It is always better to prevent the disease rather than try to cure it once it has already affected. Genetic, autoimmune etc causes are some exceptions for the same. So having a tool, investigation or any such modalities which will help in detecting the disease or at least contribute in preventing the complication will always be a notable gift to the mankind. A great deal has already been accomplished in establishing a role for routine Cystatin-C determination in many clinical situations. With all these facts considering Cystatin-C as a routine marker can have a great impact in minimizing the mortality rate due to Diabetes complications especially Renal.

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