DOI: https://doi.org/10.53350/pjmhs22161716

ORIGINAL ARTICLE

Cystatin C and Fibrinogen Plasma Levels as early Predictors of Diabetic Nephropathy in Type II Diabetes Mellitus; a Review Article

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ABSTRACT

Background: Diabetic nephropathy (DN) is a dangerous illness associated with a significant risk for cardiovascular and kidney problems in diabetic patients. Serum cystatin C levels may rise in diabetic individuals with microalbuminuria, and it has been recommended as an endogenous glomerular filtration rate (GFR) marker because of its link to the albumin to creatinine ratio (ACR) in diabetic nephropathy. Uncontrolled diabetes was found to have a greater level of fibrinogen; in diabetic nephropathy, fibrinogen levels are important. In addition, fibrinogen has been associated to inflammation and has been demonstrated to play a crucial pathophysiologic role in the advancement of renal impairment in individuals.

Methods: The author has no intention of commenting on the molecular role of cystatin C, a cysteine protease inhibitor, or the disrupted haemostatics mechanism in fibrinogen-induced diabetes. in this study, which is expected to investigate views on using the cystatin C as well as plasma fibrinogen plasma levels like an early markers of nephrotic syndrome. Therefore, 4 important clinical datasets were reviewed, including the EMBASE, PubMed and The Cochrane Library, Medline, Google Scholar and a few additional related journals datasets, as well as relevant records were collected with high precision.

Conclusion: When compared to the frequently used creatinine-based predictions, cystatin C is a good marker for diagnosing nephropathy in patients with normal albuminuria, and it may enhance the risk prediction in diabetics. Even before the complication of chronic kidney disease symptoms, Cystatin C levels in urine might be raised in diabetic individuals. Additional investigation into cystatin C and fibrinogen functions as early biomarkers, clinical value in screening, involvement in prognosis, decrease of inflammation and prediction of medication clearance, and drug monitoring in type II diabetic, nephropathy is needed.

Keywords: cystatin C, fibrinogen, nephropathy, diabetes mellitus, biomarkers

INTRODUCTION

Diabetes can be said as chronic diseases which require uninterrupted medical treatment to reduce the complication by controlling glycaemia. Insulin shortage, an insulin effect, or a metabolic disease community with hyperglycaemia are all examples of diabetes mellitus.[1]Population expansion, aging, urbanization, and an increased frequency of obesity and physical problems have all contributed to an increase in the prevalence of diabetes. Diabetic mellitus is expected to affect 9.3% of the world's population in 2019, rising to 10.2% by 2030.[2] Renal nephropathy, which comprises a variety of renal disorders, is one of the most prevalent causes of end-stage kidney disease in diabetics. If diagnosed at an early enough level, early management can assist sluggish the succession of diabetic nephropathy and improve patient outcomes. Most of the morbidity and death associated with chronic diabetes mellitus can be attributed to these illnesses. Chronic consequences can include vascular (microvascular and macrovascular) as well as nonvascular (foot ulcer, infections, and dermatologic manifestation).[3-5] This includes microalbuminuria, diabetic retinopathy and diabetic neuropathies, all of which may be microvascular consequences of type II diabetes. Genes make Cystatin C continually and release it into the bloodstream with a half-life of 2 hours and a half-life. A cysteine protease inhibitor, plasma cystatin (CysC), is totally reabsorbed and catabolized by tubular cells after passing through the blood glomerulus (Ccr).[6-9] Compared to P-Cr, it has been found to be more accurate and less complicated in determining GFR.[10]

When blood viscosity is elevated due to an increase in fibrinogen concentration, it plays a significant role in the development of microcirculatory abnormalities among diabetes patients, according to research.[11]

The plasma fibrinogen levels of Type DM 2 patients have been found to be elevated.[12] Many factors, including gender, smoking, age, hypertension, and HbA1c levels, have been a marker to verify plasma fibrinogen. To further understand the haemostatic process in diabetes, more research is needed.[13]

The plasma levels of cystic C and fibrinogen have a vital influence in the management and treatment of diabetes care techniques. Type II diabetics may have an early biomarker for nephropathy in the form of Cystatin C and fibrinogen plasma levels.

MATERIAL AND METHODS

The goal of this study is to investigate some of the concerns surrounding the use of cystatin C and fibrinogen plasma levels as early nephropathy biomarkers. The author has no plans to discuss the molecular role of cystatin C, a cysteine protease inhibitor, or the disrupted haemostatic mechanism in fibrinogen-induced diabetes. As a consequence, the correct records were picked with remarkable accuracy from four major medical databases, including The EMBASE, PubMed, and The Cochrane Library, as well as Medline, Google Scholar, and a few

other relevant publications. Keywords included "cystatin C, plasma cystatin C, serum cystatin C, fibrinogen, early diabetic nephropathy, and type II diabetes". The keywords were looked up separately or are combined with others. Between August 2000 and January 2020, we looked at articles that were published. To date, 140 studies have been published, according to our research.

At first, a total of 140 records were identified. Due to resemblance and repetition, 51 entries were eliminated, leaving 89 to be kept. 41 further unconnected records were eliminated after the records and their subjects were screened. Then 48 full-text articles that met the criteria were chosen (Figure 1).

Duplicate papers and articles that did not meet the eligibility criteria were eliminated from the study. The writers then personally screened the abstracts of the remaining submissions. The authors attempted to get full papers for all possibly relevant research, and the systematic review included only those that matched the eligibility

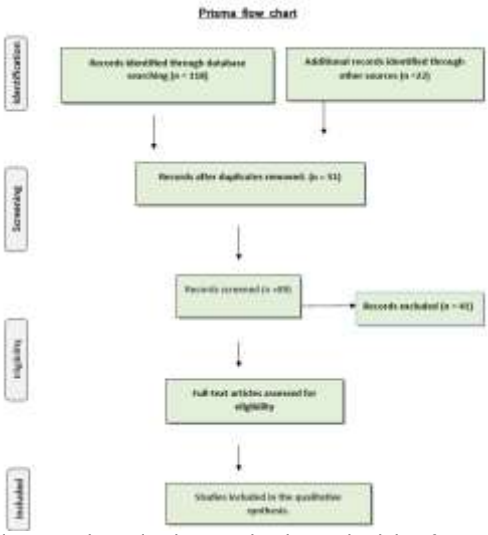

Figure1. The selection mechanism schedule of records relevant to the present study in accordance with the PRISMA technique

Diabetic Nephropathy (DN): Diabetic Nephropathy is one of the major diabetic microvascular complications. In the United States, Diabetes mellitus is a principal foundation for end-stage renal failure. Aging, Sex, ethnicity, and hypertension, hyperglycaemia, and hypercholestermia are all risk factors for nephropathy. Waste removal, blood pressure regulation via fluid and salt management, erythropoietin production (a red blood cell mass regulator), and vitamin D activation are all crucial functions of the kidneys (a co-factor for calcium absorption). Fluid filtration from blood and urine production is required for the kidney's regular functionality. The initial phases of diabetic nephropathy are caused by hypoglycaemia hyper filtration. This in turn results for forming "glomerular hypertrophy" and thickening of basement membrane of kidney. Early nephropathy is also associated with lower afferent and efferent arteriolar resistance, drastically enhanced plasma flow, and a significantly greater glomerular capillary pressure (GFR). As a consequence, the GFR decreases.[14,15]. Inulin or iohexol has extended as the standard benchmark for assessing GFR, but these methods are intrusive, costly, and time-consuming.[16] The occurrence of microalbuminuria is one of the first symptoms of diabetic nephropathy. A urine albumin to creatinine ratio of 2.5-35 mg/mmol in males and 3.5-35 mg/mmol in women, or an albumin excretion rate of 20-200 g/min (30-300 mg/dl), is considered microalbuminuria. In healthy persons without diabetes, urinary albumin excretion seldom exceeds 10 g/min. The kidneys eventually become 'leaky,' allowing more protein, red blood cells, and casts to be excreted. Diabetic nephropathy affects 30-40% of type 1 diabetics and 15-20% of type II diabetics after 20 years (American Diabetes Association, 2003 a). Proteinuria is the inventive indication of diabetic nephropathy, and as kidney function deteriorates, urea and creatinine levels rise in the bloodstream. As a consequence, identifying tiny amounts of urinary albumin by testing urine for microalbumin is an essential method.

A 30g/mg creatinine ‘spot' microalbumin (random sample) is deemed normal.[17] Diabetic nephropathy worsens over time, eventually leading to renal failure.

Microalbuminuria is a symptom of diabetic nephropathy, which is characterised by glomerular hemodynamic abnormalities that lead to glomerular hyperfiltration and glomerular destruction. Renal impairment will result in lower GFR and end stays if glomerular activity tends to decline overt proteinuria.[1] Angiotensin II has just been discovered, and chemokines can aid in the diagnosis of diabetic neuropathic pain.[18] The best non-invasive technique for early diagnosis of imminent renal illness in non-proteinuric diabetic patients is the albumin excretion rate evaluation; nevertheless, there is still debate over specificity and sensitivity.[19-21]

Cystatin C: Cystatin C is a low-molecular-weight protein that contains 120/122 amino acids and has a molecular weight of 13 kDa. It fits into the cysteine proteinase inhibitors family. Cystatin C is a product of the 'housekeeping' gene, which is generated at a consistent rate right through the human body by all nucleated cells.[22] Cystatin C is only removed from the blood through renal filtration, and it is filtered freely near the glomerular filtration barrier. Its serum levels are unaltered by nonrenal factors. It may be easily filtered at the glomerulus due to its small size.[22] GFR is calculated using serum cystatin C in the same way as blood urea is calculated using nitrogen and creatinine. However, since renal tubules do not resorb or emit it, the optimal endogenous marker should be the one that is closest to it.[23]Cystatin C is concerned in numerous physiological functions, including cellular protein breakdown, enzyme regulation, and a number of pathologic processes. It's present in all bodily fluids and is involved in atherogenesis and arterial wall remodelling. [23-25] It is linked to hyperchromocysteinemia, Alzheimer's disease, leukoencephalopathy with progressive dementia, blood-brain barrier malfunction, and retinal degenerative diseases.[25]

Measurement of cystatin C: The Immunoturbidimetric assay was the most widely used method for measuring serum/urinary cystatin C which particularly measure the latex particle through its enhancement in immunoturbidimetric assay.[26-30] In one study, blood cystatin

C levels were computed by means of the "Dade Behring Cystatin C assay" and the automated "Dade Behring Nephelometer II [BNII]".[31] Particle enhanced nephelometric immune assay, "ELISA [using RD191009100 Human cystatin C ELISA kit], and latex agglutination test" were among the other procedures used.[32-36] The nature of the analysis was not stated in two of the investigations.[37-38] Increasingly, cystatin C assessments utilizing an immunoturbidimetric technique are the method of choice for research. However, no research has been done to compare the efficiency of different cystatin C testing methods in plasma, serum, or urine. Blood cystatin C levels were significantly greater in patients with type II diabetes than in healthy individuals. According to recent researches, increased levels were also detected in those with "normoalbuminuria". The researchers discovered that monitoring blood cystatin C levels is a realistic, applicable and non-invasive approach for detecting renal involvement, and that it may be connected to an increased risk of cardiovascular events in diabetic individuals without nephropathy, especially those with normoalbuminuria. 50 Cystatin C levels were shown to be greatest in type II diabetes individuals without microalbuminuria in another investigation. The researchers also discovered that "cystatin C and cystatin" GFR levels were uppermost and tiniest in type II diabetics with micro albuminuria, which suggest that serum cystatin C quantification could be used to predict the commencement of nephropathy in type II diabetics with normoalbuminuria.[27]

According to another study, estimating cystatin C is a helpful and practical tool for evaluating renal impairment in type II diabetics is yet previous to the expansion of microalbuminuria or early nephropathy.[32]

Cystatin C levels were greater in 45.9% of normoalbuminuric type II diabetics with normal UA and creatinine-based eGFR, indicating that cystatin C levels can be the part of early indication of DN in patients with normal UAE and creatinine-based eGFR. According to the research, even if albuminuria and creatine-based eGFR do not indicate CKD, high levels of cystatin C in diabetics could indicate some degree of renal impairment.[39]

Cystatin C levels were observed to be considerably higher in individuals with microalbuminuria [1.74 0.66] than in those with normoalbuminuria [1.19 0.62]. This suggests that cystatin C is the predictor for preliminary renal injury in individuals even before the micro albuminuria has develops, which is in line with earlier research. The researchers expressed that serum cystatin C may assist in the preliminary recognition of renal impairment in diabetes individuals when used as an independent or combined marker of GFR loss. Despite overwhelming evidence that cystatin C is an excellent biomarker for identifying the onset and development of diabetic neuropathy (DN) in type II diabetics, additional study is required to confirm cystatin C's usefulness in improving patient outcomes.[33]

Fibrinogen: Increased permeability to plasma proteins that aren't readily filtered by the glomerulus, such as albumin and transferrin, as well as increased excretion of extracellular matrix proteins, causes glomerular proteinuria.[40,41]The glomerulus does not frequently filter high molecular weight proteins like type IV collagen and fibronectin from plasma. Their excretion in urine, however, may indicate the pace of matrix synthesis and breakdown in damaged kidneys since they are both elements of the glomerular mesangial matrix and basement membrane.[42-44]

Fibrinogen measurement: In the citrate bulb and Ethylenediaminetetraacetic acid trial, all participants (patients and controls) had their venous blood samples taken and were subjected to fibrinogen levels. Using a Tulip diagnostics' 'FIBROQUANT' test kit and a Behnk coagulometer, the Clauss technique was utilized to calculate fibrinogen levels.[45]

Hyperfibrinogenaemia is associated with low-grade inflammation and elevated cytokines, particularly interleukin-6, which stimulate fibrinogen synthesis by hepatocytes, demonstrating a noteworthy relationship between inflammation and hypercoagulation in DM patients.

Insulin resistance and hyperglycaemia in the periphery have a direct impact on fibrinogen levels, which in healthy persons are linked to insulin and pro-insulin levels.[46]

According to Y. Aso et al. and J. Lin et al., increased coagulability may affect endothelial function, promoting macrovascular disease and aggravating microvascular illness. [47,48]

Increased glomerular basement membrane width, lower albumin to creatinine ratio, and impaired glomerular function in diabetic nephropathy were shown to be evidence of a connection amid plasma fibrinogen and diabetic nephropathy by V.M.Dalla, M.Mussap, et al.[47-49]

Fibrinogen has been related to GBM thickening via endothelial disruption, coagulant activity, and platelet activation, in addition to an inflammatory process. According to a research by Asakawa H et al. and Casale Monferrato, in people with type II diabetes, fibrinogen is an independent predictor of overt nephropathy.[50-51] Other prior studies[52-53], on the other hand, propose a positive feedback loop in which renal insufficiency causes an increase in inflammatory markers (fibrinogen), which leads to renal disease development and an increase in inflammatory markers.

The patient's bulk, in the research by S. Dhwale et al were between the ages of 40 and 60.[54] Group A's microvascular problems included nephropathy (n=17), retinopathy (n=13), and neuropathy (n=4). In a patient with microvascular issues, a patient without microvascular difficulties, and non-diabetic controls, blood fibrinogen levels were 515138.7, 437137, and 30852.65, respectively. Overweight patients had greater blood fibrinogen levels than normal-weight patients in every group. Different albuminuria groups (300 mg/l) had serum fibrinogen values of 439.7135.15, 525.7145.4, and 545.7112.2. The mean fibrinogen level was 541.1121.7 in diabetics with total cholesterol >200. Patients in groups A and B had serum fibrinogen levels of 567.5173.4 and 538.6184.6, respectively, in patients with HbA1C >12%. In both groups, the majority of patients had high fasting blood sugar levels of >126 and a PPBS of >200. The mean fibrinogen levels in patients using insulin, oral hypoglycaemic medicines, and those who did not receive any therapy were 640.8126.4, 449.9145.7, and 419.72 respectively.

Plasma fibrinogen causes death in kidney failure patients in the same way as it does in the universal

populace. The cause for the augmented danger of cardiac mortality in people with CKD is unknown.[55] Much of this increased risk is thought to be due to non-traditional risk factors accumulating with lower kidney function, but this has yet to be validated.[56575859]Current researches have demonstrated that plasma fibrinogen levels are greater in those who have developed end-stage renal failure and have been treated with peritoneal or haemodialysis.[60,61]

To reduce long-term issues, more efforts are urgently required to effectively screen for and diagnose diabetic neuropathy early on. Patient education, dietician roles, and dependable referral channels are all issues that must be addressed in primary care settings. It's critical to start interventions all over the world that empower patients to undertake necessary but difficult lifestyle adjustments while also encouraging them to practice self-care.

CONCLUSION

This study finds that biomarkers that detect disease early on are the most essential, as early detection can help to prevent or delay negative clinical effects. Cystatin C may be a better marker for identifying nephropathy in people with normoalbuminuria than the frequently used creatinine-based predictions, and it may enhance hazard forecast in diabetics. In diabetic patients, cystatin C levels in urine can rise even before the complication of chronic renal disease signs. Uncontrolled diabetes was found to have a greater level of fibrinogen; in diabetic nephropathy, fibrinogen levels are important. In addition, fibrinogen has been associated to inflammation and has been demonstrated to play a crucial pathophysiologic role in the advancement of renal impairment in individuals. In DN patients, a prolonged inflammatory state evidenced by a high serum fibrinogen level is likely to exacerbate disease progression. Furthermore, investigation into the role of cystatin C and fibrinogen as an early biomarker, clinical value as a screening tool, involvement in prognosis, inflammation reduction, medication clearance prediction, and drug monitoring in type II diabetic patients with nephropathy should be done.

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