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Research Article

A STUDY SHOWING RELATIONSHIP BETWEEN ACUTE PHASE REACTANTS – HS-CRP, FERRITIN AND IL -6 IN PATIENTS WITH TYPE 2 DIABETES MELLITUS HAVING MICROALBUMINURIA

Mohita Shah* and Prafful Kothari

Department of General Medicine, Surat Municipal Institute of Medical Education and Research, Surat, Gujarat

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ABSTRACT

Background: Poorly controlled blood glucose levels can lead to complications in type 2 diabetes mellitus. The risk of the complications increases with an increase in the duration of hyperglycemia. Acute phase reactants are the markers of inflammation. In our study, we assessed the correlation of the levels of the acute phase reactants – HS-CRP, IL6, Ferritin with an increase in the duration of diabetes mellitus. **Result:** Interpretation of the data suggests that a longer time duration of having diabetes mellitus is directly correlated with increase in inflammation around the kidney as clearly seen by the increasing values of the inflammatory markers taken into consideration in this study which are HR-CRP, IL-6 and Ferritin. **Conclusion:** can be postulated that this pro inflammatory state is responsible for progression of disease and deposition of inflammatory complexes within the kidney. In this study we have taken into consideration patients having diabetes mellitus for upto ten years along with proteinuria as group I and those having for more than 10 years as group II. Inflammatory markers in early type 2 diabetic nephropathy are elevated and are independently associated with urinary albumin excretion. Microalbuminuria not only progresses to macrovascular disease in terms so frank diabetic nephropathy but also is an independent marker for Ischemic heart disease. Thus, its correlation to inflammatory markers may help in early detection and therapy.

INTRODUCTION

Diabetes mellitus (DM) is a heterogenous, metabolic disease which is characterized by hyperglycaemia and long-term complications. The late complications of diabetes are: (a) microangiopathy i.e., abnormalities of the small arteries which include diabetic nephropathy, retinopathy, neuropathy and (b) macroangiopathy i.e. abnormalities of the large arteries which include coronary heart disease and peripheral vascular disease. The risk of the chronic complications increases as a function of the duration of hyperglycaemia. The complications usually become apparent in the second decade of the hyperglycaemia. Acute phase reactants are the markers of inflammation. They are synthesized in response to tissue damage and inflammation.

The activation of the TGF-β1 signalling pathway in the renal system was found to be an intermediary step in diabetic kidney injury [(1)]. TGF-β1 not only stimulates the synthesis of some key components of the ECM, such as type I and type IV collagen, but also decreases matrix degradation by inhibiting the protease activity. Many studies have shown that the outcome of diabetic nephropathy is often linked to the abnormal expression of TGF-β1. Moreover, long-term Diabetic nephropathy, one of leading causes of death in patients with diabetes, is a progressive kidney disease caused by damage to the capillaries in the kidneys' glomeruli. The prevalence of diabetic nephropathy is rising in developed countries, and it was reported to be the primary cause for end-stage renal disease in diabetic patients worldwide. Moreover, the high incidence of diabetic nephropathy, its poor prognosis, and its high cost of treatment has caused it to become a public health issue. Therefore, early diagnosis of diabetic nephropathy is required to promptly intervene and prevent or delay deterioration due to the disease. Currently, microalbuminuria is a widely-used early marker for nephropathy in diabetic patients. However, the sensitivity and accuracy of microalbuminuria as a predictor has been questioned in recent years. Therefore, novel biomarkers with the ability to predict disease progression accurately are needed in clinic practice.

The glomerular capillary wall consists of podocytes (or visceral epithelial cells), glomerular endothelial cells, glomerular basement membranes, and mesangial cells [(2)]. One of the main characteristics of diabetic nephropathy is the expansion of the mesangial matrix which leads to the subsequent accumulation of mesangial cell-derived extracellular matrix (ECM) components. During this process, members of the transforming growth factor-β (TGF-β) family

Corresponding author:* **Mohita Shah
Department of General Medicine, Surat Municipal Institute of Medical Education and Research, Surat, Gujarat

are thought to play an indispensable role. Generally, TGF-β family proteins are essential for regulating cellular growth, differentiation, autophagy, and apoptosis, as well as immune suppression. Upregulation of TGF-β1 expression is reported to be indispensable in fibrosis and in tissue remodeling in various organs during disease progression, including glomerular fibrosis in the kidney. Microalbuminuria not only progresses to macrovascular disease in terms so frank diabetic nephropathy but also is a independent markers for Ischemic heart disease. Thus its correlation to inflammatory markers may help in early detection and therapy.

It is reported that blockade of TGF-β signaling at levels of ligands and receptors by neutralizing antibody or soluble TGF-β receptor (TGFBR2) is effective to relieve DN Targeting TGF-β receptors may be an alternative strategy for the treatment of DN. GW788388, an inhibitor of both TGFBR1 and TGFBR2, has been proven curative to attenuate renal fibrosis. It is possible that several other chemical inhibitors to TGFBR1 (ALK5) may also have therapeutic effects on Diabetic Nephropathy[3].

MATERIAL & METHODS

Inclusion criteria

1. All Patient having microalbuminuria as calculated by urinary ACR
2. GFR>60ml/min/1.73m for >3 months without evidence of kidney damage
3. Age >18years
4. Serum creatinine value of <1.5mg%
5. No Abnormalities detected by USG: Decrease kidney size or loss of cortico-medullary differentiation
6. No Patients with renal arterystenosis
7. No Nephrectomy in 1kidney

Participants after taking their written informed consent. Hemolyzed and lipemic samples were excluded. The blood samples were analyzed for glycosylated hemoglobin by the cation-exchange resin method. In this method, a hemolyzed preparation of whole blood was mixed continuously for 5 minutes with a weakly binding cation exchange resin. During this mixing, the nonglycosylatedhemoglobin binds to the ion exchange resin, leaving the gycosylatedhaemoglobin(GHb) free in the supernatant The percent glycosylated haemoglobin was determined by measuring the absorbances of the GHb fraction and the total haemoglobin fraction. The ratio of the absorbances of the GHb fraction and the total haemoglobin fraction of the control and test was used to calculate the percent glycosylated haemoglobin of the sample. The serum C-reactive protein (CRP) was analyzed by the turbilatexmethod[4] (kit- MERCK laboratory). In this method, the latex particles which were coated with specific human anti-CRP were agglutinated when they were mixed with samples which contained CRP. This agglutination caused an absorbance change which could be quantified by comparison from a calibrator of known CRP concentration.

RESULTS AND ANALYSIS

Biochemical parameters	Normal values	Controls (n=30)	Group I (n=30)	Group II (n=30)
Glycosylated hemoglobin, HbA1c (%)	< 6.5	5.4+0.3	8.8+0.7	9.1+0.8
Serum C –reactive protein (mg/l)	< 1	0.72+0.37	0.95+0.19	6.86+2.89
Urinary albumin (mg/day)	< 30	5+4	19+6	274+78
Ferritin (mcg/ml)	<300	300+50	800+100	1200+100

Interpretation of the data suggests that a longer time duration of having diabetes mellitus is directly correlated with increase in inflammation around the kidney as clearly seen by the increasing values of the inflammatory markers taken into consideration in this study which are HR-CRP, IL-6 and Ferritin.

Thus it can be postulated that this pro inflammatory state is responsible for progression of disease and deposition of inflammatory complexes within the kidney.

In this study we have taken into consideration patients having diabetes mellitus for upto ten years along with proteinuria as group I and those having for more than 10 years as group II. The patients voluntary presented themselves for this study in SMIMER Hospital surat on OPD basis.

From the above table it is also apparent that there may be fluctuations in inflammation in the patients body but a still a constant state of low grade inflammation persists, the correction of this with the help of Anti TGF – May prove to be useful in retarding the progression of disease complications overall by reducing microvascular inflammation in addition special consideration is given to kidney as diabetic nephropathy continues to be a major reason for mortality in chronic diabetes patients closely behind cardiovascular complications

CONCLUSION

The role of inflammatory markers has been severely highlighted and been inflamed during to days pandemic of COVID 19, however these markers and their relations to chronic diseases such as highly prevalent diabetes is not to be forgotten.

Inflammatory markers in early type 2 diabetic nephropathy are elevated and are independently associated with urinary albumin excretion. It is possible to hypothesize on participation of locally released cytokines in development of kidney damage.

This relationship maybe also independent of long term therapy with ACE inhibitors [5]or those patients who had better glycaemic control suggesting a requirement of anti – inflammatory medications (Reno protective effects of anti-inflammatory agents which block the effects of monocyte chemoattractant protein -1 reducing albuminuria have recently been demonstrated) in the treatment of diabetes type 2 to avoid long term renal damage. The TGF-β presents a complex involvement with the pathophysiological progression of the renal disease regarding the inflammatory process. TGF-β is involved in the resolution of renal injury including induction of glomerular capillary formation, apoptosis of mesangial cells, and inhibition of inflammatory cytokines production, such as interleukin-1β and TNF-α. In addition, TGF-β inhibits T cell proliferation and leucocyte infiltration by blocking monocyte chemotactic protein-1 (MCP-1) and adhesion molecules expression.

During the last decades, many treatment strategies have been developed and proven to effectively ameliorate Diabetic Nephropathy clinically. Many drugs targeting diabetes by lowering blood glucose reasonably benefit renal function in DN, e.g., SGLT2 inhibitors empagliflozin and canagliflozin, and DPP-4 inhibitor linagliptin. Furthermore, targeting Diabetic Nephropathy associated risk factors such as hypertension with angiotensin-converting enzyme inhibitors

and angiotensin II receptor blockers and hyperlipidaemia with statins also significantly delays the progression of DN. In addition, the pharmaceutical intervention of particular pathways such as mineralocorticoid receptor signalling, endothelin A receptor signalling, JAK-STAT[6] signalling, and glycolysis is also proven to effectively improve renal function in DN. However, all these treatments have been shown to delay, but cannot prevent, the progression of DN. Therefore, more effective therapeutic drugs for diabetes are urgently needed. Given its critical roles of TGF-β/Smad signalling in the development of DN, TGF-β signal-targeted therapy seems to be promising for the treatment of DN. It is reported that blockade of TGF-β signalling at levels of ligands and receptors by neutralizing antibody or soluble TGF-β receptor (TGFBR2) is effective to relieve DN Targeting TGF-β receptors may be an alternative strategy for the treatment of DN. GW788388, an inhibitor of both TGFBR1 and TGFBR2, has been proven curative to attenuate renal fibrosis. It is possible that several other chemical inhibitors to TGFBR1 (ALK5) may also have therapeutic effects on Diabetic Nephropathy (12).

Microalbuminuria not only progresses to macrovascular disease in terms so frank diabetic nephropathy but also is a independent markers for Ischemic heart disease. Thus its correlation to inflammatory markers may help in early detection and therapy.

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