A REVIEW ON THE EFFECT OF CEROPLASMIN ACTIVITY IN PLASMA OF DIABETIC PATIENTS WITH NEPROPATHY

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ABSTRACT

Oxidative stress is known to be associated with progression of diabetic kidney disease. Ceruloplasmin acts as a pro-oxidant under conditions of severe oxidative stress. Thus, we conducted a longitudinal observational study to evaluate whether the serum ceruloplasmin level of diabetic nephropathy.

Keywords: Oxidative stress, diabetes nephropathy.

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INTRODUCTION

Other longitudinal, observational studies have replicated these results in children and adults, in type 1 and type 2 diabetes, and in individuals from North America, Asia, and Europe. Taken together, these studies provide strong evidence that microalbuminuria may not be the ideal marker of progression after all. Advances in mass spectrometry have enhanced our ability to identify thousands of proteins and peptides in urine in a single analysis—some of which may serve as new markers. This large-scale study of proteins is termed proteomics, whereas the study of naturally occurring peptides generated by endogenous protease activity is termed peptidomics. Urinary proteomics and peptidomics add different dimensions to the investigation of underlying biology. Their application in urine has important clinical implications for diabetic kidney disease, given that urine can be collected noninvasively with relative ease and is directly produced by the kidneys. As such, changes in the relative abundance of urinary proteins and peptides may reflect changes in protein expression, deposition, or turnover in the diabetic kidney.

We reviewed the literature on urinary proteomics/peptidomics, biomarkers, and diabetic kidney disease. We selected the most robust candidate markers at each stage of diabetic kidney disease and then highlighted their roles in biological processes that may contribute to progression from uncomplicated diabetes to incipient diabetic nephropathy to overt diabetic nephropathy. Although reviews on similar topics exist, none integrate findings across studies and assess their biological implications on mechanisms underlying diabetic kidney disease progression. In the present study we study regarding the ceroplasmin activity on type 2 diabetes with nephropathy.

DISCUSSION

Inflammation, similar to coagulation and the regulation of extracellular matrix in uncomplicated diabetes, is linked to the wound healing pathways. In wound healing, macrophages infiltrate the site of injury during inflammation to phagocytose cellular debris, which in turn facilitates the migration and proliferation of other cells. Eventually, inflammation is turned "off" to allow for the resolution of injury through tissue proliferation and remodelling. However, this inflammatory

state is sustained by chronic hyperglycemia, predisposing to progressive diabetic kidney disease. Urinary markers of inflammation include several acute-phase reactant proteins such as α_1-acid glycoprotein 1, haptoglobin, clusterin, α_2-HS-glycoprotein, and mannan-binding lectin serine protease 2.

The transport and metabolism of cholesterols and lipids are regulated, in part, by the apo family.[51]Several members (*e.g.*, apo A, E, H, clusterin/J) were differentially excreted throughout the progression of diabetic kidney disease and significantly contributed to the enrichment of cholesterols and lipids in diabetic nephropathy. Studies have shown that diabetes impairs insulin- and leptin-mediated regulation of cholesterol and lipid, which increases the risk of cardiovascular disease. Interestingly, impaired cholesterol esterification and efflux have been linked to podocyte injury. Cholesterols also play an important role in cell membrane integrity. In diabetes, overexpression of cholesterol in platelet membranes impaired fluidity and in turn heightened platelet sensitivity to thrombin, perhaps contributing to increased thrombosis and vascular injury. There could be an interesting interplay between coagulation, blood vessel development, and cholesterol and lipid regulation. However, unlike other processes, the enrichment of cholesterol and lipid regulation was largely driven by apos as well as other high-abundance plasma proteins. Although these biological processes may reflect systemic changes, these plasma proteins may be detected in the urine as a result of impaired glomerular perm selectivity and tubular reabsorption.

Maintaining ion homeostasis is an important function of the kidney, especially the proximal tubule. These segments are largely responsible for the bulk reabsorption of a variety of electrolytes including sodium, chloride, bicarbonate, and phosphate. Interestingly, iron ion homeostasis emerged as one of the most enriched individual biological processes within the broader cluster of ion homeostasis, a finding that might implicate oxidative stress in incipient diabetic nephropathy. Iron catalyzes the formation of hydroxyl radical, a reactive oxygen species, *via* the Haber–Weiss reaction as a catalyzing agent. Iron metabolism and transport are regulated by haptoglobin and transferrin, which were elevated in the urines of patients with diabetic kidney disease.

Overt Diabetic Nephropathy

The onset of proteinuria, or macroalbuminuria, marks late-stage diabetic kidney disease. Functionally, urinary albumin excretion continues to rise, whereas GFR declines. Structurally, there is evidence of glomerulosclerosis and tubular atrophy. Nearly 10% of patients with diabetes progress further to ESRD and require RRT such as dialysis and transplantation.

Dihazi and colleagues found increased urinary levels of β2-microglobulin and decreased levels of ubiquitin-60S ribosomal

protein L40 from patients with diabetic nephropathy, compared with healthy controls. These proteins are ubiquitously expressed in the body and likely derived from the circulation. As such, their presence in the urine may reflect impaired glomerular perm selectivity. Sharma and colleagues identified a_1-antitrypsin as the primary marker between cases and controls, but were limited by a small sample size of eight patients. The presence of a_1-antitrypsin in urine is consequently not specific to a single stage of diabetic kidney disease. Rao and colleagues focused on low-abundance proteins by immunodepleting albumin, immunoglobin G and A, a_1-antitrypsin, transferrin, and haptoglobin. Transthyretin and a_2-HS-glycoprotein among others were identified as potential markers. Otu and colleagues characterized the urinary proteome for diabetic nephropathy in Pima Indians of Southern Arizona. This particular demographic has been extensively studied for its predisposition to type 2 diabetes and vascular complications. Limitations of this proteomic study include the lack of tandem mass spectrometry, survivor bias, and the questionable stability of urine samples stored for >10 years. Although 50 proteins were differentially excreted in overt diabetic nephropathy, only nine were exclusive to this stage. Consequently, we hypothesize that the biological processes underlying overt diabetic nephropathy were also enriched in previous stages.

Glomerular Dysfunction Predominantly Manifests in Late Disease

Defects in perm selectivity and reabsorption continue to prevail in overt diabetic nephropathy, as exemplified by the increased urinary presence of several carrier proteins (*e.g.*, a_2-HS-glycoprotein, hemopexin, transthyretin) from the plasma compartment.

Underlying Processes in Overt Diabetic Nephropathy Were Likely Active in Previous Stages

In overt diabetic nephropathy, the significantly enriched biological processes included extracellular matrix regulation and metabolism, inflammation, and regulation of the immune response. Interestingly, the number of proteins involved in the regulation of the immune response greatly outnumbered those involved in wound healing, although there is significant overlap between both processes. The immune system plays an integral role in successful wound healing, promoting the infiltration of immune cells into the site of injury and regulating inflammation. For the most part, these biological processes (*e.g.*, extracellular matrix regulation and metabolism, inflammation, regulation of the immune response, and cell adhesion) were also present in the earlier stages, underlining their persistent role in the progression of diabetic kidney disease.

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