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Myo-Inositol Oxygenase Expression Associate with Oxidative Stress and Renal Function Decline in Patients with Diabetic Nephropathy

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Abstract

Background: Diabetic kidney disease (DKD) is the leading cause of renal failure. The diagnostic preferred, urinary albumin is nonspecific and insensitive. There is urgently want for finding a renal-precise biomarker that could be detectable early sufficient and a capability target for therapeutic intervention.

Method: The expression of Myo-Inositol Oxygenase(MIOX)in kidney tissues from DKD and minimum-change nephropathy patients were detected via immunohistochemistry and the connection between MIOX expression and medical parameters of DKD have been analyzed by Pearson correlation evaluation. Then, the extent of MIOX in both of serum and urine had been tested via ELISA, and the correlation of MIOX in serum and urine and scientific parameters have been also analyzed.

Results: Immunohistochemistry showed that MIOX was localized to the proximal renal tubule and MIOX expression is significantly up regulated in kidney of patients with DKD ,compared with controls($p<0.01$). Moreover, linear regression analysis revealed MIOX expression in the kidney of DKD patients was positively related to tubulointerstitial lesion score, ROS generation, urea nitrogen(BUN), creatinine, blood glucose, glycosylated hemoglobin and 24-hour urine protein. In addition, ELISA analysis showed that the levels of MIOX in serum and urine of DKD patients were significantly increased .The correlation analysis indicated that the expression of MIOX in both serum and urine were also positively related to creatinine, blood glucose, glycosylated hemoglobin, and 24-hour urine protein.

Conclusion: These dates indicate that MIOX is associated with ROS accumulation and kidney injury and plays an important role in the development of DKD. Furthermore, serum or urine MIOX maybe a new diagnostic biomarker and therapeutic target.

Keywords Myo-inositol oxygenase; Tubular; Diabetic nephropathy; Renal function; Oxidative Stress; Biomarker

Introduction

Diabetes mellitus is the maximum common continual disorder characterized by way of Hyperglycemia. Hyperglycemia is a pivotal thing inside the improvement of diabetic headaches such as nephropathy, neuropathy, retinopathy, and cataract.

Recent studies have showed that the myo-inositol (MI) modulated odd metabolism related to the pathogenesis and pathological trade of type-2 and sort-1 diabetes [1,2]. MI is an osmo regulator and a precursor for inositol-primarily based 2d messengers, and is understood additives of endogenous inositol phosphorglycans, which act as insulin mediators [3,4] indicating that strange concentration of MI is associate with expression of DM worry. The enzyme MI oxygenase (MIOX), a 33-kDa nonheme iron protein, is taken into consideration to be the keyregulator of inositol degrees, catalyzing the oxidative conversion of MI to D-glucuronic acid [5, 6] the handiest regarded pathway for MI catabolism [7]. It has been demonstrated that MIOX is a tubular-particular enzyme and almost solely expressed the proximal tubular epithelial cells with improved degrees in diabetic kidney [8] conceivably modulates phosphoinositide signalling critical for various cellular occasions of the renal tubular epithelium. MIOX expression is up-regulated by way of hyperosmotic pressure in renal proximal tubular epithelial cells [9], and in db/db mice, a version for type-2 diabetes, accelerated MIOX hobby is in proportion to increased Hyperglycemia [10]. Therefore, there studies indicate that MIOX may also play an essential function inside the pathogens is process of diabetic nephropathy. Despite the intense mechanistic hobby in MIOX, its glaring importance in diabetes and its complication, and the possibility that MIOX may be of diagnose cost, little is thought of its impact on diabetic sufferers. Here, we describe that MIOX expression is up-regulated in renal tissue, serum and urine of diabetic kidney sickness (DKD) sufferers. Crucially, MIOX has effective dating with numerous clinical parameters, which indicate that MIOX may be a brand new diagnostic biomarker and therapeutic goals of DKD.

Methods Participants

15 DKD patients and 15 non-DKD controls (minimal-change nephropathy as control group) were. The DKD patients contain 8 males and 7 females, aged 32-55years(mean:45.6±0.7years);control group contains 9 male and 6 females, aged26-45 years(mean: 23.9±1.2 years). They were diagnosed Um Alqura University, according to the World Health Organization diagnostic criteria for type2 diabetes. All patients did not use adrenal cortical hormone, immune inhibitors and ACEI/ARB drugs. Preparation of kidney biopsy and all the blood and urine collection were authorized by the Institutional Human Experimentation Ethics Committee, Um-Alqura University.

Biochemical analysis of blood and urine

The serum liver and renal functions and triglycerides, total cholesterol(TC),high-density lipoprotein cholesterol(HDL-C), low-density lipoprotein cholesterol (LDL-C), and blood glucose levels were analyzed using standard automated enzymatic methods (Hitachi 912 automated analyzer). 24-hour urine specimen was analyzed by automatic urinary sediment analyzer of Kidney Disease Laboratory in

Um-Alqura University to detect the urine sediment and 24 hours urinary protein quantitative.

Morphological analysis of kidney

Human kidney biopsy tissues were obtained from DKD and nondiabetic patients. The4 µm paraffin sections of kidney biopsy were stained with hematoxylin-eosinstaining (HE),periodicacidschiff (PAS), periodic acid–silver methenamine(PASM)and Masson. Tubulointerstitial lesion index was determined by using a semiquantitative scoring system [11].Tubular injury was scored as previously described [12].

Immunohistochemistry

Kidney biopsy was paraffin-embedded and sectioned. After deparaffinization sections were incubated with 3% H2O2 solution to block endogenous peroxidase. Antigen retrieval was carried out using EDTA solution (pH 9.0) for 10 min .Sections were incubated with anti-MIOX antibody (1:100, abcam) overnight at 4 horseradis peroxidase-conjugated secondary antibody and diaminobenzidine(DAB) substrate sequentially. After hematoxylin counter staining and dehydration, the sections were mounted and observed under a Nikon fluorescence microscope. Intracellular generation of O2- was assessed by DHE staining.

ELISA

Standards and samples (100µL/well) are pipetted into the wells where anti- MIOX has been pre-coated at ambient temperature for 1 h and then washed three times with washing buffer (200 µL/well). After removing any unbound substances, a biotin-conjugated antibody specific for MIOX is added to the wells. The plates were incubated at ambient temperature for another 1 h .After washing, avid in conjugated Horseradish Peroxidase (HRP) is added to the wells. Following a wash to remove any unbound avid in-enzyme reagent, a substrate solution is added to the wells and colour develops in proportion to the amount of MIOX bound in the initial step. The colour development is stopped and the intensity of the colour is measured.

Statistical Analysis

Statistical analysis was performed using SPSS 19.0 software. Data was expressed as mean ±SD. Two sample multiple comparisons and a correlation between two variables was analyzed with the t-test and Pearson correlation test, respectively. Significance level P <0.05 was considered statistically significance.

Results

Increased expression of MIOX in renal tissues of patients with diabetic nephropathy. Immunohistochemistry and DHE staining showed a significantly increased MIOX expression and ROS production in the renal tubules of DKD patients compared with that of Non-DKD (Figure 1A-C). Morphological changes in both the glomerular and tubulointerstitial compartments, including mesangial matrix proliferation, Kimmelstiel-Wilson lesions, tubularatrophy and interstitial fibrosis, were highlighted by HE, PAS ,PASM and Masson staining in DKD patients compared with Non-DKD patients (Figure 2A).Interstitial damage score in the kidneys of DKD patients were higher than that in Non-DKD patients (Figure 2B). Further analysis revealed a positive correlation between MIOX expression and the tubulointerstitial damage (Figure 2C).

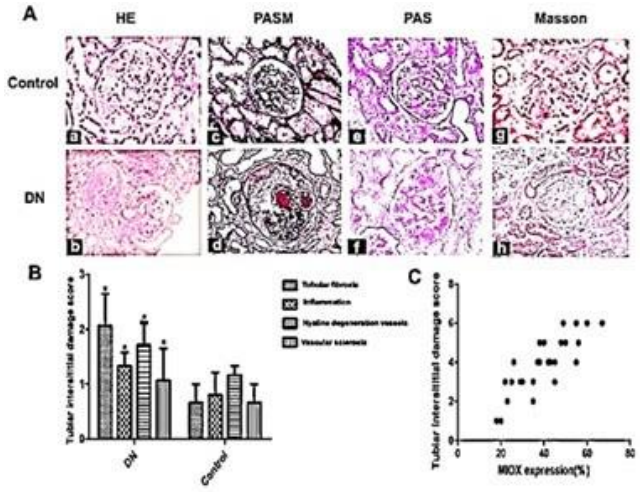

Figure 1: Increased MIOX expression and ROS generation in renal tissues of patients with DN.A. IHC studies revealed increased expression of MIOX in DN patients (FigAa vs. b), increased oxidative stress was seen in kidneys of DN patients, as assessed by DHE (FigAc vs. d); B: Averaged relative intensity following staining of anti-MIOX antibody of kidney biopsies of DN versus Control. C: Quantification of tissues stained with DHE (Fig C).Values are means ± SE. *P < 0.01versus control.

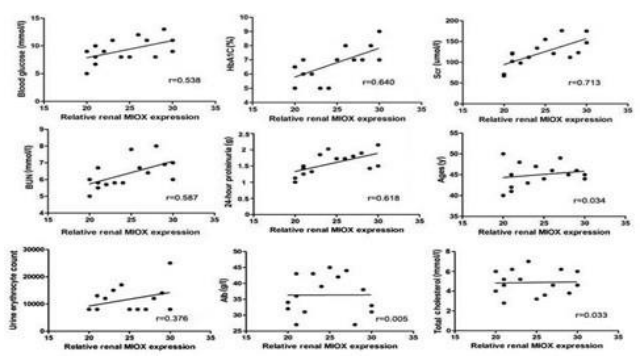

Figure 2: Positive relationship between MIOX expression and tubular interstitial damage. A: HE, PASM, PAS and Massion show mesangial matrix proliferation, Kimmelstiel-Wilson nodules, tubular atrophy and interstitial fibrosis in renal biopsies in patients with DN (Fig Ab,d,f,h); B:Tubular interstitial damage score show higher score in DN patients.

Analysis of the correlation between MIOX expression in the kidney and clinical parameters. Spearman correlation analysis showed that MIOX expression in the kidney tissues in DKD patients was positively correlated with blood glucose, glycosylated hemoglobin, ureanitrogen, creatinine and 24 hours urinary protein, (P< 0.05), however, there were no obvious correlation between MIOX expression and age, serum albumin, urine erythrocyte count and total cholesterol.(Table 1-2, and Figure 3). Increased expression of MIOX in serum and urine of

patients with diabetic nephropathy The results of ELISA showed that the serum concentration of MIOX were 2050.4±160.7 pg/ml and 49.47±3.3pg/ml in in DKD patients and control group, respectively, while the levels of MIOX on urine in the two groups were 2675.3±241.1pg/ml and 73.5±4.8pg/ml, respectively, indicating that the MIOX levels in serum and urinary were increased in DKD patients (Figure 4). Further analysis showed serum MIOX levels is positively correlated with blood glucose, glycosylated hemoglobin, creatinineand24 hour's urinary protein (Figure 5), but no obvious correlation with age, serum albumin, mean blood pressure, urine erythrocyte count and total cholesterol. Furthermore, similar results were observed in that of relationship between urinary MIOX level and clinical parameters (Figure 6).

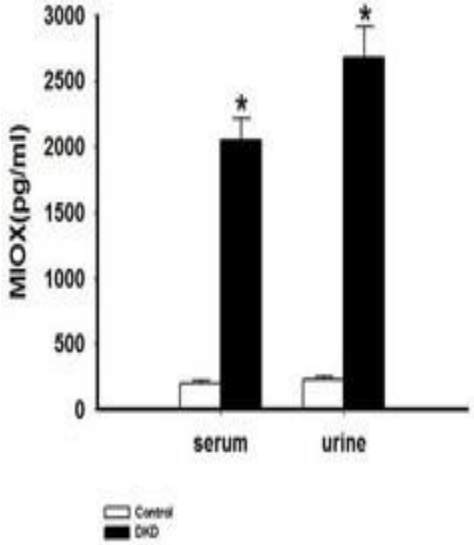

Figure 3: Relationship between MIOX expression in the kidney and clinical parameters. Spearman correlation analysis showed that MIOX expression in the kidney tissues in patients with diabetic nephropathy was positively correlated with blood glucose(r= 0.538, P=0.039) , and glycosylated hemoglobin(r= 0.64, P=0.01), urea nitrogen(r= 0.587, P=0.021), creatinine(r= 0.713, P=0.003) and24 hours urinary protein(r= 0.618,P=0.014),however, there were no obvious correlation between MIOX expression and age(r= 0.034,P=0.903), serum albumin(r= 0.005,P=0.985), urine erythrocyte count(r= 0.376,P=0.168),total cholesterol (r= 0.033,P=0.906).

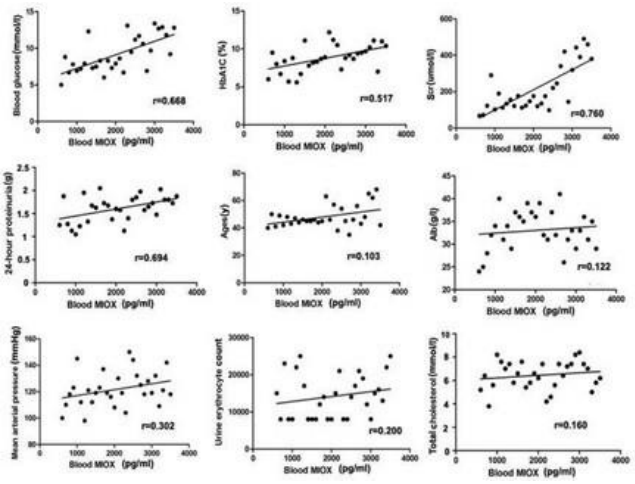

Figure 4: Increased expression of MIOX in serum and urine of patients with diabetic nephropathy. The results of ELISA showed that the levels of serum MIOX in patients with diabetic nephropathy and normal control group were 2050.4±160.7 pg/ml and 49.47±3.3pg/ml respectively, and the levels of urine MIOX in these two groups were 2675.3±241.1pg/ml,73.5±4.8pg/ml, respectively. The serum and urinary MIOX levels in DN groups were significantly higher than that of in control group, Values are means ±SE,*P < 0.01versus control.

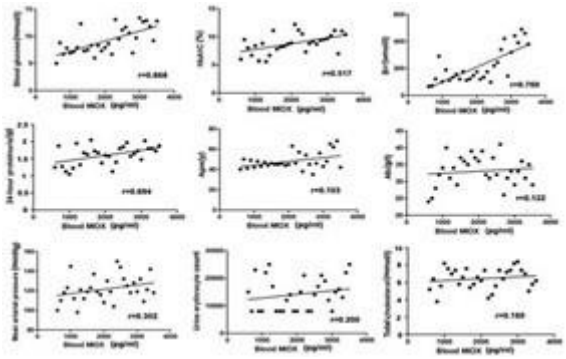

Figure 5: Relationship between MIOX expression in serum and clinical parameters. Spearman correlation analysis showed serum MIOX levels is positively correlated with blood glucose(r= 0.668, P=0.031), glycosylated haemoglobin (r= 0.517, P=0.014), creatinine (r= 0.760, P=0.042),and24 hours urinary protein(r= 0.694, P=0.001),but no obvious correlation with age(r= 0.103, P=0.727), serum albumin(r= 0.122, P=0.522), mean blood pressure(r= 0.302, P=0.105), urine erythrocyte count(r= 0.200, P=0.288) and total cholesterol (0.06).

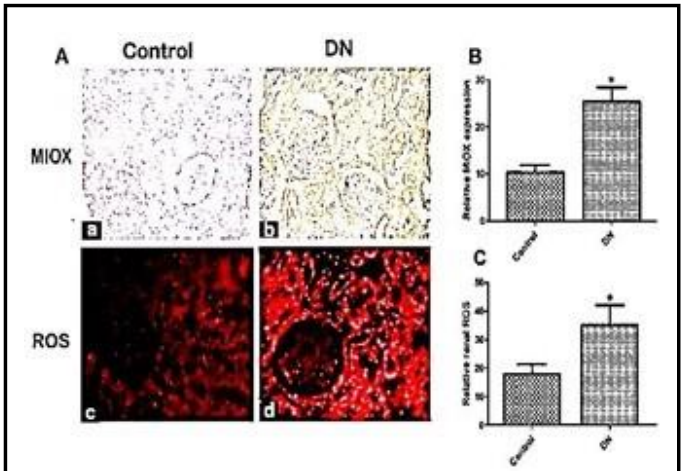

Figure 6: Relationship between MIOX expression in urine and clinical parameters. Further analysis showed urine MIOX levels is positively correlated with blood glucose(r= 0.500, P=0.029), glycosylated hemoglobin(r= 0.543, P=0.002), creatinine(r= 0.570, P=0.001), and 24 hours urinary protein(r= 0.321, P=0.084), however, no obvious correlation with age(r= 0.184, P=0.331), serum albumin(r= 0.106, P=0.579), mean blood pressure(r= 0.232, P=0.217), urine erythrocyte count(r= 0.236, P=0.208) and total cholesterol (r= 0.166, P=0.382).

	DKD(n=15)	Control(n=15)	P
Age(y)	45.6±0.7	23.9±1.2	0.0001
Sex(m/f)	08-Jul	09-Jun	>0.05
Body weight(g)	62.7±2.3	58.5±2.6	0.23
BG (mmol/l)	9.2±0.5	5.1±0.2	0.0001
HbA1C(%)	7.8±0.4	---	---
Alb(g/l)	36.3±1.6	31.3±0.9	0..01
Total cholesterol (mmol/l)	6.3±0.3	7.3±0.4	0.06
Creatinine (umol/l)	122.3±8.2	110.1±5.1	0.22
BUNmmol/l	6.3±0.2	5.9±0.3	0.24
Urine protein (/24h	2.4±0.2	3.4±0.3	0.009
Urine erythrocyte count	11470±1257	15000±1624	0.096
MBP(mmHg)	119.8±3.2	116.3±1.6	0. 31

Table 1: Clinical Characteristics of the Patients x±sby univariate analysis.

By Univariate Analysis		
	r	p
Age(y)	0.034	0.903
Alb(g/l)	0.005	0.985
Urine proteing/24h	0.618	0.014
Creatinine(umol/L)	0.713	0.003
BUNmmol/L	0.587	0.021
BG(mmol/l)	0.538	0.039
HbA1C(%)	0.64	0.01
Total cholesterol(mmol/l)	0.033	0.906
Urine erythrocyte count	0.376	0.168

Table 2: Obvious correlation between MIOX expression and age, serum albumin, urine erythrocyte count and total cholesterol.

Discussion

The observations described in the previous section highlight two major aspects of this investigation. First, MIOX expression is increased in kidney tissues, serum and urine of patient with DKD, which indicated that MIOX may be involved in renal tubular injury of DKD. Second, serum and urine MIOX may be as a new biomarker of monitoring DKD progress or become new targets for therapy. The pathogenesis of diabetic nephropathy is very complicated, Polyols, including MI, have been confirmed in the etiology of diabetes mellitus. Depletion of MI from tissues are involved in diabetic complications, such as nephropathy, retinopathy, neuropathy, and diabetic cataract [3,13-17]. MIOX is known as a key member that catalyzes the first committed step of the only pathway of MI catabolism [7]. MIOX belongs to the family of aldo-keto reductase (AKRs), which include more than 60 members, at present[18].

MIOX was mainly expressed in the proximal tubules of kidney, and lower levels of MIOX were also observed in extra-renal tissues, such as nerve, retina [8]. MI have been implicated in the regulation of various signalling pathways in various diseases, including diabetic mellitus, which indicates that MIOX may be involved in the renal tubules injury of Diabetes .Gaut and his colleagues confirmed that MIOX localized to the proximal renal tubule [19]. Furthermore, Prabhu et al [9] present evidence that depletion of MI in high glucose condition is mediated by the increased expression of MIOX, which is induced by sorbitol, mannitol, and xylitol via the glucuronate-xylulose pathwayin a porcine renal proximal tubular epithelial cell line, LLC-PK [19]. In this study, for the first time, we detected that overexpression of MIOX in renal tubules of patients with DKD(Figure 1 A), which is consisted with what Nayak and Lu have reported, that is MIOX expression, was markedly increased in renal tubules in db/db mice and rats with diabetic nephropathy [10,20]. In addition, D-glucose could induce a dose-dependent increase in MIOX expression and its enzymatic activity in LLCPK cells, a kidney epithelial cell line. The increase in activity was in proportion to serum glucose concentration, which implied that MIOX may play an important role in the progress of diabetic nephropathy, however, the detailed mechanism need to be further exploited. As we known that overproduction of ROS is a commonly event in hyperglycemia situation.

The MIOX expression also up-regulated in cells treated with oxidants H2O2 and methylglyoxal, whereas reduced MIOX expression was observed when treated with antioxidants N-acetylcysteine, β-naphthoflavone, and tertiary butyl hydroquinone [21]. In this study, it is confirmed that ROS production was significantly increased in the kidney of patients with DKD by DHE staining and the increased

MIOX expression parallel to ROS production in diabetic kidney (Figure 1), promoting that the increased MIOX may relate to enhanced ROS production in DKD. So what is the relationship between MIOX and tubular interstitial injury in kidney of DKD? Study has shown that overexpression of MIOX induced up-regulation of alpha-SMA and fibronectin expression, and down-regulation of E- cadherin expression, while decreased alpha-SMA and fibronectin expression were observed by blocking MIOX with antisense oligonucleotide (ODN) in normal NRK-52E cells. This suggests that increased expression of MIOX in diabetic kidneys may contribute to tubulointerstitial injury and the development of diabetic nephropathy.

In addition, Xie et al [21] also found that MIOX expression was increased in diabetic mice and in LLC-PK(1) cells under high-glucose ambience. What's more, an increased expression of fibronectin was observed in LLC-PK (1) cells transfectedwithpcDNA3.1-RSOR/MIOX and in the kidneys of db/db mice having high levels of MIOX. NADH/NAD (+) ratio increased in pcDNA3.1-RSOR/MIOX transfected cells. These studies suggest that MIOX modulates various downstream pathways affected by high-glucose ambience, and conceivably it plays a role in the pathobiology of tubulointerstitium in diabetic nephropathy [22]. Our study showed that tubular interstitial injury score were positively correlated with MIOX protein expression (Figure 2 C), which indicated that MIOX involved in the oxidative stress pathways affected by Hyperglycemia and conceivably it plays an indispensible role in the pathobiology of tubulointerstitium in diabetic nephropathy. Furthermore, there is an interesting finding that increased MIOX expression in diabetic kidney is not only associated with blood glucose, HbA1C in DKD patients but also significantly correlated with BUN, serum creatinine and 24-hour urine protein (Figure 3).In clinical, BUN, creatinine, 24-hour urine protein are as markers of glomerular injury.

Howeve r,glomerular injury is usually accompanied by tubulointerstitial injury [23]. In addition, several early studies surprisedly found that tubular and interstitial injury are the major contributors to loss of renal function by analyzing renal biopsy specimens, even in primary glomerular diseases [24-26]. These studies found that renal function is better correlated with scores for tubular atrophy and interstitial expansion than with scores for glomerular injury. There is also strong evidence that glomerular injury with proteinuria can cause tubular injury [27]. Thus we can infer from above that MIOX not only presents the tubular injury but also can be an early marker of kidney injury. While in this study, no obvious correlation with age, serum albumin, urine erythrocyte and total cholesterol was observed (Figure 3).which may imply that MIOX is not involved in inflammation and lipid metabolic disorder in patients with DKD. These data further indicate that MIOX has an important effect on the pathogenesis of diabetic nephropathy and is a specific protein of tubular injury, which provide new clues to measure serum and urine MIOX levels. As mentioned above, tubulointerstitial injury is an early major feature of diabetic nephropathy and an important predictor of renal dysfunction. The renal tubule in diabetes is subject to both direct and indirect pathogenetic influences as a consequence of its position in the nephron and its resorptive function, renal function correlates more with the degree of tubulointerstitial injury than that of the glomerular lesions. Therefore, to find an early renal tubular injury marker will play an important role in the early diagnosis of diabetic nephropathy.

A number of studies have investigated kind's ofblood and urine biomarkers for the diagnosis of DKD, including neutrophil gelatinase associated lipocalin (NGAL), and kidney injury molecule 1 (KIM-1).Although substantial progress has been made; no specific, early biomarkers of diabetic nephropathy have translated into clinical practice. When tubular injury occurs, proximal tubular proteins may leak into the extra tubular space and be excreted into urine or reabsorbed into blood. In recent years, Gaut et al [19] identified MIOX as a kidney-specific protein highly concentrated in the proximal tubule. And they found that MIOX was up-regulated in the peripheral blood of patients with acute kidney injury (AKI), which was closely associated with the degree of oliguria. Further analysis showed that in patients with AKI, the time of MIOX began to rise in peripheral blood was earlier than serum creatinine rise, which indicating that serum MIOX can be used as the diagnosis of AKI. In current study, serum and urine MIOX were higher in patients with DKD (Figure 4).And MIOX levels in serum and urine were positively correlated with serum creatinine ,blood glucose and HbA1c (Figure 5 and 6).

Conclusion

Our study provides evidence that detection of peripheral blood and urine MIOX levels might be a new method of diagnosis of DKD. We also found that serum MIOX level was highly related with total cholesterol, which further confirmed that oxidative stress is involved in MIOX expression. However, it is unknown whether MIOX mRNA concentration may change in other tissues following DKD or with other diseases. Additional studies are necessary to investigate the tissue profile of MIOX to explore the renal-specific of MIOX. It remains to be seen whether this intriguing enzyme can fulfill rigorous criteria for translation into clinical practice. To sum up, we demonstrated that MIOX played an important role in kidney injury in DKD patients. MIOX level was increased in the serum and urine of patients with DKD, serum or urine MIOX maybe a new diagnostic biomarker and therapeutic target of DKD. Additional studies are warranted to further investigate the potential of MIOX as an early, kidney specific biomarker of DKDand its potential therapeutic targets.

References

1. Ostlund Jr RE, McGill JB, Herskowitz I, Kipnis DM, Santiago JV, et al. (1993) vchiro-inositol metabolism in diabetes mellitus. Proc Natl Acad Sci USA 90:9988-9992.
2. Kawa JM, Przybylski R, Taylor CG (2003) Urinary chiro-inositol and myo-inositol excretion is elevated in the diabetic db/db mouse and streptozotocin diabetic rat. Exp Biol Med 228: 907-914.
3. Frick W, Bauer A, Bauer J, Wied S, Müller G (1998) Insulin-mimetic signalling of synthetic phosphoinositolglycans in isolated rat adipocytes. Biochem J 336: 163-181.
4. Nascimento NR, Lessa LM, Kerntopf MR, Sousa CM, Alves RS, et al. (2006) Inositols prevent and reverse endothelial dysfunction in diabetic rat and rabbit vasculature metabolically and by scavenging superoxide. Proc Natl Acad Sci USA 103: 218-223.
5. Arner RJ, Prabhu KS, Reddy CC (2004) Molecular cloning, expression, and characterization of myo-inositol oxygenase from mouse, rat, and human kidney. Biochem Biophys Res Commun 324:1386-1392.
6. Yang Q, Bharat D, Jun Wada, Yufeng T, Elisabeth I (2000) Identification of a renal-specific oxido-reductase in newborn diabetic mice. Proc Natl Acad Sci USA 97: 9896-9901.
7. Vaswani L. (2018). Advances in the Diagnosis and Monitoring of Type 1 Diabetes Mellitus. Int J Diabetes Endocrinol 1: 105.

8. Hankes LV, Politzer WM, Touster O, Anderson L (1969) Myo-inositol catabolism in human pentosurics: the predominant role of the glucuronate-xylulose-pentose phosphate pathway. Ann N Y Acad Sci 165: 564-576.
9. Arner RJ, Prabhu KS, Krishnan V, Johnson MC, Reddy CC (2006) Expression of myo-inositol oxygenase in tissues susceptible to diabetic complications. Biochem Biophys Res Commun 339: 816-820.
10. Gundu HR Rao. (2019). Novel Approaches for the Management of Cardiometabolic Risks Int J Diab Endocrinol 1: 102.
11. Prabhu KS, Arner RJ, Vunta H, Reddy CC (2005) Up-regulation of human myo-inositol oxygenase by hyperosmotic stress in renal proximal tubular epithelial cells. J Biol Chem 280: 19895-19901.
12. Nayak B, Xie P, Akagi S, Yang Q, Sun L (2005) Modulation of renal-specific oxidoreductase/myo-inositol oxygenase by high-glucose ambience. Proc Natl Acad Sci USA 102: 17952-17957.
13. Zhang Z, Sun L, Wang Y, Ning G, Minto AW (2008) Renoprotective role of the vitamin D receptor in diabetic nephropathy. Kidney Int 73: 163-171.
14. Haruna Y, Kashihara N, Satoh M, Tomita N, Namikoshi T (2007) Amelioration of progressive renal injury by genetic manipulation of Klotho gene. Proc Natl Acad Sci USA 104: 2331-2336.
15. Greene DA, Chakrabarti S, Lattimer SA, Sima AA (1987) Role of sorbitol accumulation and myo-inositol depletion in paranodal swelling of large myelinated nerve fibers in the insulin-deficient spontaneously diabetic bio-breeding rat. Reversal by insulin replacement, an aldose reductase inhibitor, and myo-inositol. J Clin Invest 79: 1479-1485.
16. Raccah D, Coste T, Cameron NE, Dufayet D, Vague P (1998) Effect of the aldose reductase inhibitor tolrestat on nerve conduction velocity, Na/K ATPase activity, and polyols in red blood cells, sciatic nerve, kidney cortex, and kidney medulla of diabetic rats. J Diabetes Complications 12: 154-162.
17. Burd JF, Noetzel N, Walsh MJ (2018). Lysulin™: Improvement in Glycemic Control Compared to Type 2 Drugs Int J Diab Endocrinol 1: 103.
18. Cohen AM, Wald H, Popovtzer M, Rosenmann E (1995) Effect of myo-inositol supplementation on the development of renal pathological changes in the Cohen diabetic (type 2) rat. Diabetologia 38: 899-905.
19. Del Monte MA, Rabbani R, Diaz TC, Lattimer SA, Nakamura J, et al. (1991) Sorbitol, myo-inositol, and rod outer segment phagocytosis in cultured hRPE cells exposed to glucose. In vitro model of myo-inositol depletion hypothesis of diabetic complications. Diabetes 40: 1335-1345.
20. Lin LR, Reddy VN, Giblin FJ, Kador PF, Kinoshita JH (1991) Polyol accumulation in cultured human lens epithelial cells. Exp Eye Res 52: 93-100.
21. Pascoal TCL. (2018). The Relationship Between Consumption of Cooked and Grilled Foods in Advanced Glycation End Products in Type 2 Diabetic Patients Int J Diab Endocrinol 1: 104.
22. Danesh FR, Wada J, Wallner EI, Sahai A, Srivastava SK, et al. (2003) Gene regulation of aldose-, aldehyde- and a renal specific oxido reductase (RSOR) in the pathobiology of diabetes mellitus. Curr Med Chem 10: 1399-1406.
23. Gaut JP, Crimmins DL, Ohlendorf MF, Lockwood CM, Griest TA, et al. (2014) Development of an immunoassay for the kidney-specific protein myo-inositol oxygenase, a potential biomarker of acute kidney injury. Clin Chem 60: 747-757.
24. Nayak B, Kondeti VK, Xie P, Lin S, Viswakarma N, et al. (2011) Transcriptional and post-translational modulation of myo-inositol oxygenase by high glucose and related pathobiological stresses. J Biol Chem 286: 27594-27611.
25. Xie P, Sun L, Oates PJ, Srivastava SK, Kanwar YS (2010) Pathobiology of renal-specific oxidoreductase/myo-inositol oxygenase in diabetic nephropathy: its implications in tubulointerstitial fibrosis. Am J Physiol Renal Physiol 298: 1393-1404.
26. Meyer TW (2003) Tubular injury in glomerular disease. Kidney Int 63: 774-787.
27. Schainuck LI, Striker GE, Cutler RE, Benditt EP (1970) Structural-functional correlations in renal disease. II. The correlations. Hum Pathol 1: 631-641.