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## Urinary type IV collagen excretion predicts an increased urinary albumin-to-creatinine ratio in normoalbuminuric patients with diabetes

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### ABSTRACT

**Aims:** We evaluated whether urinary excretion of type IV collagen (U-COL) may predict an increase in the urinary albumin-to-creatinine ratio (ACR) and what factors regulate U-COL in 145 normoalbuminuric patients with type 2 diabetes. **Methods:** We measured HbA1c, systolic blood pressure (SBP), urinary 8-hydroxydeoxyguanosine (8-OHdG) and monocyte chemoattractant protein (MCP)-1 at start of this study (Baseline), ACR and U-COL in addition to these measurements at one year later (Evaluation-1), and ACR and SBP after two years of the Evaluation-1 (Evaluation-2). The relationships were investigated between the increase of ACR and the U-COL. The effect of angiotensin receptor blockers (ARB) treatment on the correlations between U-COL and ACR at Evaluation-2 on one hand, and between U-COL and percent change of ACR on the other, was also analyzed. Furthermore, we investigated whether the increase in 8-OHdG and in MCP-1 in a year prior to the Evaluation-1 were risk factors of the rise in U-COL levels. **Results:** Both U-COL and SBP at Evaluation-1, but not ARB treatment, were independent risk factors for an increased ACR after 2 years. ARB treatment significantly suppressed the increase in ACR after 2 years in patients with higher U-COL excretion. The percentage changes in 8-OHdG (%8-OHdG) and MCP-1 (%MCP-1) in one year prior to Evaluation-1 measurements are independent risk factors for U-COL. HbA1c and SBP values one year prior to Evaluation-1 are independent risk factors not only for %8-OHdG but also, for baseline U-COL. The % 8-OHdG is an independent risk factor for %MCP-1. **Conclusions:** U-COL may predict an increase in the ACR. The U-COL seems to be increased with oxidative stress and inflammation induced by past hyperglycemia.

### KEYWORDS

Type IV Collagen; Diabetic Nephropathy; Oxidative Stress; Monocyte Chemoattractant Protein-1

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### References

- [1] Moriya, T., Tanaka, K. and Moriya, R. (2000) Glomerular structural changes and structural-functional relationships at early stage of diabetic nephropathy in Japanese type 2 diabetic patients. *Medical Electron Microscopy*, 33, 115-122. doi:10.1007/s007950000010
- [2] Moriya, T., Tanaka, K., Hosaka, T., Hirasawa, Y. and Fujita, Y. (2008) Renal structure as an indicator for development of albuminuria in normo- and micro-albuminuric type 2 diabetic patients. *Diabetes Research and Clinical Practice*, 82, 298-304. doi:10.1016/j.diabres.2008.08.015
- [3] Ziyadeh, F.N. and Wolf, G. (2008) Pathogenesis of the podocytopathy and proteinuria in diabetic glomerulopathy. *Current Diabetes Reviews*, 4, 39-45. doi:10.2174/157339908783502370
- [4] Okonogi, H., Nishimura, M., Utsunomiya, Y., Hamaguchi, K., Tsuchida, H., Miura, Y., Suzuki, S., Kawamura, T., Hosoya, T. and Yamada, K. (2001) Urinary type IV collagen excretion reflects renal morphological alterations and type IV collagen expression in patients with type 2 diabetes mellitus.

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- [5] Cohen, M.P., Shearman, C.W. and Lautenslager, G.T. (2001) Serum type IV collagen in diabetic patients at risk for nephropathy. *Diabetes Care*, 24, 1324-1327. doi:10.2337/diacare.24.8.1324
- [6] Cohen, M.P., Lautenslager, G.T. and Shearman, C.W. (2001) Increased urinary type IV collagen marks the development of glomerular pathology in diabetic d/db mice. *Metabolism*, 50, 1435-1440. doi:10.1053/meta.2001.28074
- [7] Cohen, M.P., Lautenslager, G.T. and Shearman, C.W. (2001) Increased collagen IV excretion in diabetes. A marker of compromised filtration function. *Diabetes Care*, 24, 914-918. doi:10.2337/diacare.24.5.914
- [8] Elmarakby, A.A. and Sullivan, J.C. (2012) Relationship between Oxidative Stress and Inflammatory Cytokines in Diabetic Nephropathy. *Cardiovascular Therapeutics*, 30, 49-59. doi:10.1111/j.1755-5922.2010.00218.x
- [9] Wu, J., Mei, C., Vlassara, H., Striker, G.E. and Zheng, F. (2009) Oxidative stress-induced JNK activation contributes to proinflammatory phenotype of aging diabetic mesangial cells. *American Journal of Physiology*, 297, F1622-F1631. doi:10.1152/ajprenal.00078.2009
- [10] Lee, H.B., Yu, M.R., Yang, Y., Jiang, Z. and Ha, H. (2003) Reactive oxygen species-regulated signaling pathways in diabetic nephropathy. *Journal of the American Society of Nephrology*, 14, S241-245. doi:10.1097/01.ASN.0000077410.66390.0F
- [11] Ogawa, S., Kobori, H., Ohashi, N., Urushihara, M., Nishiyama, A., Mori, T., Ishizuka, T., Nako, K. and Ito, S. (2009) Angiotensin II Type 1 Receptor Blockers Reduce Urinary Angiotensinogen Excretion and the Levels of Urinary Markers of Oxidative Stress and Inflammation in Patients with Type 2 Diabetic Nephropathy. *Biomarker Insights*, 4, 97-102.
- [12] Ogawa, S., Mori, T., Nako, K., Kato, T., Takeuchi, K. and Ito, S. (2006) Angiotensin II type 1 receptor blockers reduce urinary oxidative stress markers in hypertensive diabetic nephropathy. *Hypertension*, 47, 699-705. doi:10.1161/01.HYP.0000203826.15076.4b
- [13] Araki, S., Haneda, M., Koya, D., Isshiki, K., Kume, S., Sugimoto, T., Kawai, H., Nishio, Y., Kashiwagi, A., Uzu, T. and Maegawa, H. (2010) Association between urinary type IV collagen level and deterioration of renal function in type 2 diabetic patients without overt proteinuria. *Diabetes Care*, 33, 1805-1810. doi:10.2337/dc10-0199
- [14] Taft, J.L., Nolan, C.J., Yeung, S.P., Hewitson, T.D. and Martin, F.I. (1994) Clinical and histological correlations of decline in renal function in diabetic patients with proteinuria. *Diabetes*, 43, 1046-1051. doi:10.2337/diabetes.43.8.1046
- [15] Watanabe, H., Sanada, H., Shigetomi, S., Katoh, T. and Watanabe, T. (2000) Urinary excretion of type IV collagen as a specific indicator of the progression of diabetic nephropathy. *Nephron*, 86, 27-35. doi:10.1159/000045709
- [16] Morii, T., Fujita, H., Narita, T., Shimotomai, T., Fujishima, H., Yoshioka, N., Imai, H., Kakei, M. and Ito, S. (2003) Association of monocyte chemoattractant protein-1 with renal tubular damage in diabetic nephropathy. *Journal of Diabetes and Its Complications*, 17, 11-15. doi:10.1016/S1056-8727(02)00176-9
- [17] Banba, N., Nakamura, T., Matsumura, M., Kuroda, H., Hattori, Y. and Kasai, K. (2000) Possible relationship of monocyte chemoattractant protein-1 with diabetic nephropathy. *Kidney International*, 58, 684-690. doi:10.1046/j.1523-1755.2000.00214.x
- [18] Vlek, A.L., van der Graaf, Y., Braam, B., Moll, F.L., Nathoe, H.M. and Visseren, F.L., SMART Study Group (2009) Blood Pressure and Decline in Kidney Function in Patients With Atherosclerotic Vascular Disease: A Cohort Study. *American Journal of Kidney Diseases*, 54, 820-829. doi:10.1053/j.ajkd.2009.07.007
- [19] Kotajima, N., Kimura, T., Kanda, T., Obata, K., Kuwabara, A., Fukumura, Y. and Kobayashi, I. (2000) Type IV collagen as an early marker for diabetic nephropathy in non-insulindependent diabetes mellitus. *Journal of Diabetes and Its Complications*, 14, 13-17. doi:10.1016/S1056-8727(00)00064-7
- [20] Lee, H.S. (2012) Mechanisms and consequences of TGF- $\beta$  overexpression by podocytes in progressive podocyte disease. *Cell and Tissue Research*, 347, 129-140. doi:10.1007/s00441-011-1169-7
- [21] Cohen, M.P., Lautenslager, G.T. and Shearman, C.W. (2001) Increased collagen IV excretion in

- [22] Tomino, Y., Suzuki, S., Azushima, C., Shou, I., Iijima, T., Yagame, M., Wang, L.N., Chen, H.C., Lai, K.N., Tan, S.Y. and Kim, M.J. (2001) Asian multicenter trials on urinary type IV collagen in patients with diabetic nephropathy. *Journal of Clinical Laboratory Analysis*, 15, 188-192. doi:10.1002/jcla.1026
- [23] Kado, S., Aoki, A., Wada, S., Katayama, Y., Kugai, N., Yoshizawa, N. and Nagata, N. (1996) Urinary type IV collagen as a marker for early diabetic nephropathy. *Diabetes Research and Clinical Practice*, 31, 103-108. doi:10.1016/0168-8227(96)01210-7
- [24] Doi, T., Mima, A., Matsubara, T., Tominaga, T., Arai, H. and Abe, H. (2008) The current clinical problems for early phase of diabetic nephropathy and approach for pathogenesis of diabetic nephropathy. *Diabetes Research and Clinical Practice*, 82, S21-S24. doi:10.1016/j.diabres.2008.09.013
- [25] Mima, A., Arai, H., Matsubara, T., Abe, H., Nagai, K., Tamura, Y., Torikoshi, K., Araki, M., Kanamori, H., Takahashi, T., Tominaga, T., Matsuura, M., Iehara, N., Fukatsu, A., Kita, T. and Doi, T. (2008) Urinary Smad1 is a novel marker to predict later onset of mesangial matrix expansion in diabetic nephropathy. *Diabetes*, 57, 1712-1722. doi:10.2337/db07-1726
- [26] Matsubara, T., Abe, H., Arai, H., Nagai, K., Mima, A., Kanamori, H., Sumi, E., Takahashi, T., Matsuura, M., Iehara, N., Fukatsu, A., Kita, T. and Doi, T. (2006) Expression of Smad1 is directly associated with mesangial matrix expansion in rat diabetic nephropathy. *Laboratory Investigation*, 86, 357-368. doi:10.1038/labinvest.3700400
- [27] Abe, H., Matsubara, T., Iehara, N., Nagai, K., Takahashi, T., Arai, H., Kita, T. and Doi, T. (2004) Type IV collagen is transcriptionally regulated by Smad1 under advanced glycation end product (AGE) stimulation. *The Journal of Biological Chemistry*, 279, 14201-14206. doi:10.1074/jbc.M310427200
- [28] Lee, E.Y., Chung, C.H., Khoury, C.C., Yeo, T.K., Pyagay, P.E., Wang, A. and Chen, S. (2009) The monocyte chemo-attractant protein-1/CCR2 loop, inducible by TGF-beta, increases podocyte motility and albumin permeability. *American Journal of Physiology—Renal Physiology*, 297, F85-F94. doi:10.1152/ajprenal.90642.2008
- [29] Park, J., Ryu, D.R., Li, J.J., Jung, D.S., Kwak, S.J., Lee, S.H., Yoo, T.H., Han, S.H., Lee, J.E., Kim, D.K., Moon, S.J., Kim, K., Han, D.S. and Kang, S.W. (2008) MCP-1/ CCR2 system is involved in high glucose-induced fibronectin and type IV collagen expression in cultured mesangial cells. *American Journal of Physiology—Renal Physiology*, 295, F749-F757. doi:10.1152/ajprenal.00547.2007
- [30] Nam, B.Y., Paeng, J., Kim, S.H., Lee, S.H., Kim, do. H., Kang, H.Y., Li, J.J., Kwak, S.J., Park, J.T., Yoo, T.H., Han, S.H., Kim, D.K. and Kang, S.W. (2012) The MCP-1/ CCR2 axis in podocytes is involved in apoptosis induced by diabetic conditions. *Apoptosis*, 17, 1-13. doi:10.1007/s10495-011-0661-6
- [31] Lagranha, C.J., Fiorino, P., Casarini, D.E., Schaan, B.D. and Irigoyen, M.C.(2007) Molecular bases of diabetic nephropathy. *Arquivos Brasileiros de Endocrinologia & Metabologia*, 51, 901-912. doi:10.1590/S0004-27302007000600003
- [32] Sanchez, A.P. and Sharma, K. (2009)Transcription factors in the pathogenesis of diabetic nephropathy. *Expert Rev Mol Med*, 11, e13. doi:10.1017/S1462399409001057
- [33] Mima, A., Matsubara, T., Arai, H., Abe, H., Nagai, K., Kanamori, H., Sumi, E., Takahashi, T., Iehara, N., Fukatsu, A., Kita, T. and Doi, T. (2006) Angiotensin II-dependent Src and Smad1 signaling pathway is crucial for the development of diabetic nephropathy. *Laboratory Investigation*, 86, 927-939. doi:10.1038/labinvest.3700445
- [34] Haller, H., Ito, S., Izzo, J.L. Jr., Januszewicz, A., Katayama, S., Menne, J., Mimran, A., Rabelink, T.J., Ritz, E., Ruilope, L.M., Rump, L.C. and Viberti, G., ROADMAP Trial Investigators (2011) Olmesartan for the Delay or Prevention of Microalbuminuria in Type 2 Diabetes. *The New England Journal of Medicine*, 364, 907-917. doi:10.1056/NEJMoa1007994
- [35] Ruggenti, P., Fassi, A., Ilieva, A.P., Bruno, S., Iliev, I.P., Brusegan, V., Rubis, N., Gherardi, G., Arnoldi, F., Ganeva, M., Ene-Iordache, B., Gaspari, F., Perna, A., Bossi, A., Trevisan, R., Dodesini, A.R. and Remuzzi, G., Bergamo Nephrologic Diabetes Complications Trial (BENEDICT) Investigators (2004) Preventing microalbuminuria in type 2 diabetes. *The New England Journal of Medicine*, 351, 1941-1951. doi:10.1056/NEJMoa042167

