Diabetes & Metabolic Syndrome: Clinical Research & Reviews 13 (2019) 496–499

Contents lists available at ScienceDirect

Diabetes & Metabolic Syndrome: Clinical Research & Reviews

journal homepage: www.elsevier.com/locate/dsx

Original Article

Serum adipocytokines are associated with microalbuminuria in patients with type 1 diabetes and incipient chronic complications

Tomislav Bulum [a, b, *], Marijana Vučić Lovrenčić [c, d], Martina Tomić [a], Sandra Vučković-Rebrina [a], Vinko Roso [a], Branko Kolarić [e, f], Vladimir Vuksan [g, h, i], Lea Duvnjak [a, b]

[a] Vuk Vrhovac Clinic for Diabetes, Endocrinology and Metabolic Diseases, Merkur University Hospital, Zagreb, Croatia
[b] Medical School, University of Zagreb, Zagreb, Croatia
[c] Clinical Department of Medical Biochemistry and Laboratory Medicine, Merkur University Hospital, Zagreb, Croatia
[d] Scientific Research Unit, Merkur University Hospital, Zagreb, Croatia
[e] Zagreb County Institute of Public Health, Zagreb, Croatia
[f] Medical School, University of Rijeka, Rijeka, Croatia
[g] Medical School, University of Toronto, Toronto, Canada
[h] Clinical Nutrition and Risk Factor Modification Centre, St. Michael's Hospital, Toronto, Canada
[i] Division of Endocrinology and Metabolism, St. Michael's Hospital, Toronto, Canada

ARTICLE INFO

Article history:
Received 25 October 2018
Accepted 2 November 2018

Keywords:
Type 1 diabetes
Dipeptidyl peptidase-4
Adipocytokines
Albuminuria

ABSTRACT

Aims: Recent studies have implicated possible contribution of adipocytokines in development and progression of microvascular complications in patients with type 1 diabetes (T1DM). The aim of our study was to investigate relationship between adipocytokines, namely leptin, resistin, adiponectin and dipeptidyl peptidase-4 (DPP-4) activity, with albuminuria in T1DM.
Methods: This study included 202 T1DM without or with incipient microvascular complications. Urinary albumin excretion rate (UAE) was measured from at least two 24-h urine samples. Serum DPP-4 activity was measured by a colorimetric assay, and the level of adiponectin, leptin, and resistin was determined by the ELISA method.
Results: Serum DPP-4 activity and adiponectin were significantly higher in patients with normoalbuminuria compared to patients with microalbuminuria (47 vs 36 U/L, and 10.9 vs 7.3 μg/mL, respectively, $p \leq 0.02$). In multivariate logistic regression analysis adiponectin and serum DPP-4 activity were significantly associated with risk of microalbuminuria in our subjects ($p \leq 0.04$), with odds ratios of 0.72 −0.99. However, after adjustment for age, sex, HbA1c, duration of diabetes and BMI, only serum DPP-4 activity was significantly associated with risk of microalbuminuria ($p = 0.008$).
Conclusion: The results of our study suggest that serum DPP-4 activity is lower in T1DM with microalbuminuria. Prospective studies are warranted to evaluate the relationship between serum DPP-4 activity and progression and development of albuminuria and nephropathy in T1DM.

1. Introduction

Adipocytokines are hormones secreted from the adipose tissue and their dysfunction influence not only inflammatory processes but also glucose and lipid metabolism [1]. It has been assumed that adipocytokines dysfunction contribute to the increased risk of microvascular complications in patients with type 2 diabetes (T2DM) and obesity by affecting inflammatory processes and also modulating vascular function [2,3]. However, relationship between serum levels of adipocytokines in patients with type 1 diabetes (T1DM) is not fully understood.

Leptin is hormone secreted from the adipose tissue and exerts atherogenic and angiogenetic effects and leptin is also associated with obesity-related diseases like T2DM, hepatic steatosis and cardiovascular disease [4–6]. In contrast, adiponectin was found to

* Corresponding author. Vuk Vrhovac Clinic for Diabetes, Endocrinology and Metabolic Diseases, University Hospital Merkur, Medical School, University of Zagreb, Dugi dol 4a, 10000, Zagreb, Croatia.
E-mail address: tbulum@idb.hr (T. Bulum).

https://doi.org/10.1016/j.dsx.2018.11.001
1871-4021/

be decreased in obesity and obesity-related diseases like T2DM and cardiovascular disease and adiponectin, by improving insulin sensitivity, has anti-inflammatory properties and protective effects on vascular tonus [7,8]. Resistin is also associated with insulin resistance and produced mainly by macrophages contribute to elevated glucose levels and risk of T2DM, atherosclerosis and myocardial infarction [9]. Adipocytokines including adiponectin, leptin and particularly resistin are independently and significantly associated with the risk and severity of chronic kidney disease [10–12].

Dipeptidyl peptidase-4 (DPP-4) is a serine exopeptidase that plays an important role in glucose and lipid metabolism and also in immune stimulation [13]. Most DPP-4 inhibitors, beyond glycemic control, have shown additional influences in development and progression of microvascular complications through various mechanisms [14]. In kidney, where DPP-4 is expressed at the highest level, preclinical and clinical data suggest that DPP-4 inhibitors decreases the progression of diabetic nephropathy independently of other risk factors like hypertension and hyperglycemia [15].

Recent studies have implicated possible contribution of adipocytokines in development and progression of microvascular complications in T1DM [16]. The aim of our study was to investigate relationship between adipocytokines, namely adiponectin, leptin, resistin and DPP-4 activity, with albuminuria in T1DM.

2. Subjects, materials and methods

This study population was based on all 202 T1DM who were referred to tertiary care specialist diabetes clinic between January 2016 and January 2017. Type 1 diabetes was defined according to the age of diagnosis (below 35 years), autoantibodies positivity and insulin treatment initiated within 1 year of diagnosis. The study included patients with following characteristics: age of 18–65 years, minimum duration of diabetes of 1 year, without microvascular complications or with earlier stages of microvascular complications. Earlier stages of microvascular complications are defined as the presence of non-proliferative diabetic retinopathy, second stage of chronic kidney disease (estimated glomerular filtration rate (eGFR) $\geq$ 60–90 ml/min), microalbuminuria (urinary albumin excretion rate (UAE) > 30 < 300 mg/24 h), and first degree of peripheral neuropathy, all complications stationary at least 3 months before entering the study.

Urinary albumin excretion rate (UAE) was determined as the mean of 24-h urine collections measured from at least two 24-h urine samples. We excluded from the study patients with macroalbuminuria (UAE$\geq$300 mg/24 h) and those with estimated glomerular filtration rate (eGFR) less than 60 ml/min 1.73 m^{-2} calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula [17,18].

DPP-4 activity was measured by a colorimetric assay procured from Sigma, St. Luis, MO, USA in a microplate reader (cary Eclipse Varian, Agilent Technologies) at 460 m nm, 37 °C in a continuous monitoring for 35 min. In this assay, DPP-4 cleaves H-Gly-Pro-AMC to release a florecent product, 7-Amino-4-Methyl Coumarin (AMC) which can be measured spectrophotometrically. The level of adiponectin, leptin, and resistin was determined by the ELISA method.

Data are expressed as means ± SD for normally distributed values, as median with range for non-normally distributed values, and percentage. Pearson's correlation coefficients were used to calculate correlations between normally distributed values and Spearman's rank correlation coefficients were used for non-normally distributed values. Differences between groups were examined, depending on the nature of the data, using parametric (*t*-test) or nonparametric tests (Mann-Whitney). Multivariate logistic regression models were used to assess associations of adipociytokines with risk of microalbuminura, taking in account of potential confounders. Two models were constructed for each marker: in model A without adjustments, and in model B adjustments were made for age, sex, duration of diabetes, HbA1c and BMI.

3. Results

The characteristics of the study subjects are listed in Table 1. Mean/median values of BMI, LDL cholesterol, HDL cholesterol, triglycerides, serum creatinine, UAE, eGFR, as well as blood pressure were within the normal range for patients with diabetes. Correlations between adipocytokines with renal function and metabolic parameters are presented in Table 2. Adiponectin was significantly associated with BMI, age, duration of diabetes, and eGFR with BMI showing the strongest correlation ($r = -0.33$, $p < 0.001$). Serum DPP-4 was significantly associated only with duration of diabetes. Leptin significantly correlated with duration of diabetes, BMI, HbA1c and eGFR, with BMI and HbA1c showing the strongest correlation ($r = 0.27$, $p < 0.001$). Finally, resistin was significantly associated only with age. Serum DPP-4 activity and adiponectin level was significantly higher in patients with normoalbuminuria compared to patients with microalbuminuria (47 vs 36 U/L, and 10.9 vs 7.3 μg/mL, respectively, $p \leq 0.02$) (Table 3).

In multivariate logistic regression analysis adiponectin and serum DPP-4 activity was significantly associated with risk of microalbuminuria in our subjects ($p \leq 0.04$), with odds ratios of 0.72–0.99 (Table 4). However, after adjustment for age, sex, HbA1c, duration of diabetes and BMI, only serum DPP-4 activity was significantly associated with risk of microalbuminuria ($p = 0.008$).

4. Discussion

Adipocytokines are hormones secreted from the adipose tissue and their dysfunction has been linked with an increased risk of microvascular complications in patients with obesity and T2DM [1–3]. However, recent studies have implicated possible contribution of adipocytokines in development and progression of microvascular complications in T1DM [16].

Serum adiponectin level was found to be higher in T1DM compared to nondiabetic individuals which can be compensatory mechanism to oxidative stress and inflammation [19]. In addition, increased serum adiponectin level in T1DM is also associated with microvascular complications, cardiovascular and all-cause mortality [20,21]. Serum adiponectin level was found to be increased in

Table 1
Clinical and metabolic characteristics of all patients.

Variable	Value
Age (years)	46 (18–65)
Duration of diabetes (years)	14 (1–45)
Body mass index (kg/m^2)	24 (17–35)
Hemoglobin A1c (%)	7.5 ± 1.4
Systolic blood pressure (mmHg)	125 (89–169)
Diastolic blood pressure (mmHg)	69 (47–104)
Total cholesterol (mmol/L)	5.1 ± 0.9
LDL cholesterol (mmol/L)	2.9 ± 0.7
HDL cholesterol (mmol/L)	1.6 ± 0.3
Triglycerides (mmol/L)	0.91 (0.4–4.1)
Serum creatinine (μmol/L)	71 ± 12
eGFR (mlmin^{-1}1.73m^{-2})	99 ± 17
Urinary albumin excretion (mg/24 h)	6.5 (0.2–80.1)
Adiponectin (ug/mL)	10.5 (1.5–38.2)
Dipeptidyl peptidase-4 (U/L)	47.1 ± 14.1
Leptin (ng/ml)	9.3 (0.6–267)
Resistin (ng/ml)	4.8 (1.9–17.6)

eGFR, estimated glomerular filtration rate.

Table 2
Correlation analysis of associations of adipocytokines with renal function and metabolic parameters.

Variable	Adiponectin	DPP-4	Leptin	Resistin
Duration of diab.	0.17*	0.15*	0.03	0.00
Age	0.26*	0.06	0.23*	−0.17*
BMI	−033*	0.03	0.27*	−0.05
HBA1c	−0.12	−0.1	0.27*	0.06
UAE	−0.07	−0.06	0.01	0.07
eGFR	−0.19*	−0.05	−0.21*	0.02

BMI, body mass index; HbA1c, hemoglobin A1c; eGFR, estimated glomerular filtration rate; UAE, urinary albumin excretion rate; DPP-4, dipeptidyl peptidase-4.
*P < 0.05.

Table 3
Levels of adipocytokines between patients with and without microalbuminuria.

	UAE<30 mg/24 h	UAE≥30 mg/24 h	P
Leptin (ng/ml)	9 (0.6–267)	10.4 (0.6–33.7)	0.8
Resistin (ng/ml)	4.8 (1.9–10.6)	4.6 (3.7–8.1)	0.9
DPP-4 (U/L)	47 ± 14	36.2 ± 9.5)	0.01
Adiponectin (ug/mL)	10.9 (1.7–38.2)	7.3 (1.5–18.5)	0.02

DPP-4, dipeptidyl peptidase-4.

Table 4
Multivariate logistic regression analysis of adipocytokines with risk of microalbuminuria in patients with type 1 diabetes.

Independent		
Variable	Model A	Model B
Resistin	0.97 (0.67–1.40)	1.01 (0.96–1.03)
Leptin	0.99 (0.95–1.03)	0.99 (0.67–1.52)
DPP-4	0.92 (0.86–0.98) *	0.9 (0.83–0.97) *
Adiponectin	0.85 (0.72–0.99)*	0.88 (0.74–1.03)

Data are OR (95% CI) from separate models. Model A crude; model B adjusted for age, sex, duration of diabetes, HbA1c, BMI.
DPP-4, dipeptidyl peptidase-4.
*P < 0.05.

patients with nephropathy and albuminuria compared to patients with normoalbuminuria and was also found to be an independent predictor of progression of nephropathy in T1DM [22–24]. However, in T1M with advanced nephropathy reduced clearance of adiponectin can be the reason for higher adiponectin level observed in those subjects [21,22]. Our study included patients without microvascular complications or with earlier stages of microvascular complications and we found that serum adiponectin level negatively correlate with various metabolic parameters and that adiponectin level was significantly higher in patients with normoalbuminuria compared to patients with microalbuminuria. However, in multivariate logistic regression analysis after adjustment for metabolic risk factors adiponectin was not associated with risk of microalbuminuria.

There are few studies investigating the relationship between serum leptin level and microvascular complications in T1DM and majority of those found increased serum leptin level in patients with neuropathy and retinopathy [25–27]. Regarding nephropathy, T1DM with nephropathy and microalbuminuria have increased serum leptin level compared to normoalbuminuric patients [28]. In our study serum leptin was positively correlated with various metabolic parameters and patients with microalbuminura had slightly higher but nonsignificant serum leptin level compared to patients with normoalbuminuria.

Although data has shown increased serum resistin level in T2DM with microvascular complications, there are no studies that have confirmed relationship between serum resistin level and microvascular complications in T1DM [9,29]. In our study serum resistin was positively correlated only with age and patients with microalbuminura had slightly lower but nonsignificant serum resistin level compared to patients with normoalbuminuria. In addition, our study included patients with normal eGFR and normoalbuminuria while in studies that included T2DM the level of renal function was the main determinants of serum resistin level [12].

Previous studies suggested independent relationship between serum DPP-4 activity and insulin resistance and microvascular complications in T1DM [30,31]. DPP-4 is expressed in kidney and also implicated in the pathogenesis of kidney diseases such as diabetic nephropathy and IgA nephropathy because DPP-4 is an membrane glycoprotein localized on glomerular cells [15,32,33]. However, there is insufficient evidence to conclude that treatment with DPP-4 inhibitors directly prevents or decrease risk of nephropathy independently from improved glucose control [34]. Some other nephroprotective mechanisms of DPP-4 inhibitors include its reduction of inflammation and oxidative stress [35]. Serum DPP-4 activity is associated with obesity and with various classic markers of metabolic disorder although in our study serum DPP-4 activity was significantly correlated only with duration of diabetes [36,37].

The results of our study suggest that serum DPP-4 activity level is lower in T1DM with microalbuminuria compared to patients with normoalbuminuria. Albuminuria is not only a marker of renal damage but also s marker of increased risk of cardiovascular disease. Although several studies found relationship between DPP-4 activity and albuminuria, the exact mechanisms linking DPP-4 activity and abuminuria is not fully understood [15,38,39]. There are also evidence of the possible renoprotective effect of DPP-4 without altering food intake and blood glucose via inhibiting fibrosis, inflammation, apoptosis and tubulointerstitial injury [38].

This study has a number of potential limitations. First, our study was not prospective which limited our ability to infer a causal relation between serum DPP-4 activity and risk of microalbuminuria in T1DM. Second, the small number of patients with microalbuminuria limited our ability to detect significant differences in other adipocytokines levels between patients with normo- and microalbuminuria. Third, selection bias is likely because our study was single hospital-based. Fourth, methods used for measured glomerular filtration and DPP-IV activity may influence on final results making comparisons of findings between studies difficult.

In conclusion, the results of our study suggest that serum DPP-4 activity level is lower in T1DM with microalbuminuria. The study included 202 T1DM without or with earlier stages of microvascular complications. Prospective studies are warranted to evaluate the relationship between serum DPP-IV activity and development and progression of nephropathy in T1DM.

Funding

This study was funded by the Croatian Science Foundation (grant number 7459).

Conflicts of interest

The authors disclose no conflict of interest.

Ethical approval

All procedures were in accordance with the ethical standards of the institutional committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.dsx.2018.11.001.

References

[1] Meier U, Gressner AM. Endocrine regulation of energy metabolism. Review of pathobiochemical and clinical chemical aspects of leptin, ghrelin, adiponectin and resistin. Clin Chem 2004;50:1511–25.

[2] Jung CH, Kim BY, Mok JO, Kang SK, Kim CH. Association between serum adipocytokine levels and microangiopathies in patients with type 2 diabetes mellitus. J Diab Invest 2014;5:333–9.

[3] Matsuda M, Shimomura I, Sata M, Arita Y, Nishida M, Maeda N, et al. Role of adiponectin in preventing vascular stenosis. The missing link of adipo-vascular axis. J Biol Chem 2002;277:27487–91.

[4] Considine RV, Sinha MK, Heiman ML, Kriauciunas A, Stephens TW, Nyce MR, et al. Serum immunoreactive-leptin concentration in normal-weight and obese humans. N Engl J Med 1996;334:292–5.

[5] Krasnodebski P, Bak MI, Opolski G, Karnafel W. Leptin in acute myocardial infarction and period of convalescence in patients with type 2 diabetes mellitus. Kardiol Pol 2010;68:648–53.

[6] Kelesidis T, Kelesidis I, Chou S, Mantzoros. Narrative review: the role of leptin in human physiology: emerging clinical applications. Ann Intern Med 2010;152:93–100.

[7] Hotta F, Funahashi T, Arita Y, Takahashi M, Matsuda M, Okamoto Y, et al. Plasma concentrations of a novel, adipose-specific protein, adiponectin, in type 2 diabetic patients. Arterioscler Thromb Vasc Biol 2000;20:1595–9.

[8] Kato K, Osawa H, Ochi M, Kusunoki Y, Ebisui O, Ohno K, et al. Serum total and high molecular weight adiponectin levels and correlated with the severity of diabetic retinopathy and nephropathy. Clin Endocrinol 2008;68:442–9.

[9] Forbes JM, Cooper ME. Mechanisms of diabetic complications. Physiol Rev 2013;93:137–88.

[10] Mills KT, Hamm LL, Alper AB, Miller C, Hudaihed A, Balamuthusamy S, et al. Circulating adipocytokines and chronic kidney disease. PloS One 2013;8, e76902.

[11] Rodriguez AJ, dos Santos Nunes V, Mastronardi CA, Neeman T, Paz-Filho GJ. Association between circulating adipocytokines concentrations and microvascular complications in patients with type 2 diabetes mellitus: a systematic review and meta-analysis of controlled cross-sectional studies. J Diabet Complicat 2016;30:357–67.

[12] Cebeci E, Cakan C, Gursu M, Uzun S, Karadag S, Koldas M, et al. The main determinants of serum resistin level in type 2 diabetic patients are renal function and inflammation not presence of microvascular complication, obesity and insulin resistance. Exp Clin Endocrinol Diabetes 2018. https://doi.org/10.1055/s-0043-121262.

[13] Zhong J, Rao X, Rajagopalan S. An emerging role of dipeptidyl peptidase 4 (DPP4) beyond glucose control: potential implications in cardiovascular disease. Atherosclerosis 2013;226:305–14.

[14] Kang YM, Jung CH. Effects of incretin-based therapies on diabetic microvascular complications. Endocrinol Metab (Seoul) 2017;32:316–25.

[15] Hasan AA, Hocher B. Role of soluble and membrane-bound dipeptidyl peptidase-4 in diabetic nephropathy. J Mol Endocrinol 2017;59:R1–10.

[16] Popovic DS, Sekerus V. Levels of different adipocytokines in chronic complications of type 1 diabetes mellitus. Integr Obesity Diabetes 2016;2:255–61.

[17] Levey AS, Stevens LA, Schmid CH, Zhang YL, Castro 3rd AF, Feldman HI, et al. A new equation to estimate glomerular filtration rate. Ann Intern Med 2009;150:604–12.

[18] Vučić Lovrenčić M, Radišić Biljak V, Božičević S, Prašek M, Pavković P, Knotek M. Estimating glomerular filtration rate (GFR) in diabetes: the performance of MDRD and CKD-EPI equations in patients with various degrees of albuminuria. Clin Biochem 2012;45:1694–6.

[19] Heilman K, Zilmer M, Zilmer K, Kool P, Tillmann V. Elevated plasma adiponectin and decreased plasma homocysteine and asymmetric dimethylarginine in children with type 1 diabetes. Scand J Clin Lab Invest 2009;69:85–91.

[20] Forsblom C, Thomas MC, Moran J, Saraheimo M, Thorn L, Wadén J, et al. Serum adiponectin concentration is a positive predictor of all-cause and cardiovascular mortality in type 1 diabetes. J Intern Med 2011;270:346–55.

[21] Frystyk J, Tarnow L, Hansen TK, Parving HH, Flyvbjerg A. Increased serum adiponectin levels in type 1 diabetic patients with microvascular complications. Diabetologia 2005;48:1911–8.

[22] Saraheimo M, Forsblom C, Fagerudd J, Teppo AM, Pettersson-Fernholm K. Serum adiponectin is increased in type 1 diabetic patients with nephropathy. Diabetes Care 2005;28:1410–4.

[23] Panduru NM, Saraheimo M, Forsblom C, Thorn LM, Gordin D, Wadén J, et al. Urinary adiponectin is an independent predictor of progression to end-stage renal disease in patients with type 1 diabetes and diabetic nephropathy. Diabetes Care 2015;38:883–90.

[24] Prior SL, Tang TS, Gill GV, Bain SC, Stephens JW. Adiponectin, total antioxidant status, and urine albumin excretion in the low-risk 'golden years' type 1 diabetes mellitus cohort. Metab Clin Exp 2011;60:173–9.

[25] Hernández C, Lecube A, Castellanos JM, Segura RM, Garat M, García-Arumí J, et al. Intravitreous leptin concentrations in patients with proliferative diabetic retinopathy. Retina 2004;24:30–5.

[26] Suganami E, Takagi H, Ohashi H, Suzuma K, Suzuma I, Oh H, et al. Leptin stimulates ischemia-induced retinal neovascularization: possible role of vascular endothelial growth factor expressed in retinal endothelial cells. Diabetes 2004;53:2443–8.

[27] Doupis J, Lyons TE, Wu S, Gnardellis C, Dinh T, Veves A. Microvascular reactivity and inflammatory cytokines in painful and painless peripheral diabetic neuropathy. J Clin Endocrinol Metab 2009;94:2157–63.

[28] Rudberg S, Persson B. Serum leptin levels in young females with insulin-dependent diabetes and the relationship to hyperandrogenicity and microalbuminuria. Horm Res 1998;50:297–302.

[29] Osawa H, Ochi M, Kato K, Yamauchi J, Nishida W, Takata Y, et al. Serum resistin is associated with the severity of microangiopathies in type 2 diabetes. Biochem Biophys Res Commun 2007;355:342–6.

[30] Blaslov K, Bulum T, Duvnjak L. Circulating dipeptidyl peptidase-4 activity is associated with diabetic retinopathy in type 1 diabetic patients. Eur J Ophthalmol 2015;25:328–32.

[31] Blaslov K, Bulum T, Duvnjak L. Circulating dipeptidyl peptidase-4 activity is associated with insulin resistance in type 1 diabetic patients. J Diabet Complicat 2015;29:390–4.

[32] Chatelet F, Brianti E, Ronco P, Roland J, Verroust P. Ultrastructural localization by monoclonal antibodies of brush border antigens expressed by glomeruli. I. Renal distribution. Am J Pathol 1986;122:500–11.

[33] Mitic B, Lazarevic G, Vlahovic P, Rajic M, Stefanovic V. Diagnostic value of the aminopeptidase N, N-acetyl-beta-D-glucosaminidase and dipeptidylpeptidase IV in evaluating tubular dysfunction in patients with glomerulopathies. Ren Fail 2008;30:896–903.

[34] Avogaro A, Fadini GP. The effects of dipeptidyl peptidase-4 inhibition on microvascular diabetes complications. Diabetes Care 2014;37:2884–94.

[35] Haluzik M, Frolik J, Rychlik I. Renal effects od DPP-4 inhibitors: a focus on microalbuminuria. Internet J Endocrinol 2013;2013:895102.

[36] Yang F, Zheng T, Gao Y, Baskota A, Chen T, Ran X, et al. Increased plasma DPP4 activity is an independent predictor of the onset of metabolic syndrome in Chinese over 4 years: result from the China National Diabetes and Metabolic Disorders Study. PloS One 2014;9, e92222.

[37] Zheng T, Baskota A, Gao Y, Tian H, Yang F. Increased plasma dipeptidyl peptidase 4 activities predict new-onset microalbuminuria in association with its proinflammatory effects in Chinese without diabetes: a four-year prospective study. Nephrol Dial Transplant 2015;30:460–6.

[38] Tanaka Y, Kume S, Chin-Kanasaki M, Araki H, Araki SI, Ugi S, et al. Renoprotective effect of DPP-4 inhibitors against free fatty acid-bound albumin-induced renal proximal tubular cell injury. Biochem Biophys Res Commun 2016;470. 539-345.

[39] Kanasaki K, Shi S, Kanasaki M, He J, Nagai T, Nakamura Y, et al. Linagliptin-mediated DPP-4 inhibition ameliorates kidney fibrosis in streptozotocin-induced diabetic mice by inhibiting endothelial-tomesenchymal transition in a therapeutic regimen. Diabetes 2014;63:2120–31.