International Journal of
Diabetes & Clinical Diagnosis

Research Article Open Access

DPP4 Inhibitor Decreases Urinary Albumin Excretion in Association with the Improvement of Glomerular Endothelial Injury in Patients with Type 2 Diabetes

Takayuki Fujita[1*],Hidetsuna Watanabe[2], Yusuke Murata[1], Seiichiro Hemmi[1], Minako Yabuki[1], Yoshinobu Fuke[1], Atsushi Satomura[3], Masayoshi Soma[4]

[1]*Department of Nephrology, Hypertension and Endocrinology, Nihon University School of Medicine, Tokyo, Japan*
[2]*Department of Internal Medicine, SakuboukaiTokiwadaigeka Hospital, Tokyo, Japan*
[3]*Department of Laboratory Medicine, Nihon University School of Medicine, Tokyo, Japan*
[4]*Department of General Medicine, Nihon University School of Medicine, Tokyo, Japan*

Abstract

Background: Glomerular endothelial injury is commonly encountered in diabetic nephropathy, as in type 2 diabetes mellitus (T2DM). Microalbuminuria is associated with endothelial cell dysfunction, and is a significant risk factor for cardiovascular mortality in diabetes. This study was undertaken to study the effect of sitagliptin, a dipeptidyl peptidase-4 (DPP4) inhibitor, on microalbuminuria as a mechanism of improving glomerular endothelial injury in patients with T2DM.

Methods: Sitagliptin, a DPP4 inhibitor, was administered to twenty patients with T2DM, 50 mg/day, for 8 weeks. Plasma levels of glucose, HbA1c, stromal-cell-derived factor-1 alpha (SDF1α), thrombomodulin (TM), serum creatinine, and urinary albumin/creatinine ratio (ACR) were measured at the start and the end of the study. The alteration patterns were statistically compared and analyzed together with their pathologic states. Another nineteen control patients were enrolled in this study.

Results: Sitagliptin treatment resulted in 14% decrease (P=0.0003 vs. control) in HbA1c from 7.2±1.2 to 6.2±1.4%, 74% increase (P<0.0001 vs. control) in SDF1α from 205±70 to 355±80mmol/L, 9% decrease(P=0.0029 vs. control) in TM from 3.2±1.3 to 2.9±1.1FU/mL, 41% decrease (P=0.0095 vs. control) in ACR from 5.5±5.2 to 3.3±4.5mg/mmol. Cr after 8 weeks. Regression analysis revealed a closer relationship between SDF1α and ACR. No remarkable changes were observed in controls. As microalbuminuria represents glomerular endothelial dysfunction, these data suggest the additional effect by DPP4 inhibitor on glomerular endothelial damage.

Conclusion: DPP4 inhibitor decreased urinary albumin excretion in association with the improvement of glomerular endothelial injury in patients with T2DM.

Publication History:

Received: December 26, 2014
Accepted: February 17, 2015
Published: February 19, 2015

Keywords:

Dipeptidyl peptidase 4 inhibitor, Stromal-cell-derived factor 1 alpha, Endothelial dysfunction, Type 2 diabetes mellitus,Urinary albumin excretion

Introduction

Microalbuminuria is a significant risk factor for cardiovascular mortality in diabetes [1]. It remains the best documented predictor for high risk of development of diabetic nephropathy [2]. Urinary albumin excretion is correlated with endothelial dysfunction in diabetes [3]. Endothelial cells are likely to be involved in systemic increases in permeability. In diabetes, the loss of systemic endothelial glycocalyx, a protein-rich surface layer on the endothelium, suggests that damage to this layer represents this missing link [4].The association between endothelial dysfunction and microalbuminuria may underlie the predictability of development of diabetic nephropathy and the greater susceptibility to micro- and macrovascular disease.

Vascular endothelial dysfunction is repaired by endothelial progenitor cell (EPC). EPCs are stimulated by stromal-derived factor-1α(SDF-1α), a substrate of dipeptidyl peptidase-4 (DPP4), as well as incretin [5,6]. However, EPCs are reduced in patients with diabetes mellitus complicating cardiovascular disease [7]. Therefore, we hypothesize that inhibition of DPP4 would protect cleavage of SDF1α and endothelial injury, resulting in the decrease of albuminuria. Thrombomodulin (TM) is widely distributed on the endothelium of arteries and kidney [8]. Plasma TM is known as a marker for acute endothelial injury [9]. Urinary 8-hydroxydeoxyguanosine (8-OHdG) is a biomarker of oxidative stress in diabetic nephropathy [10]. Therefore, we measured these markers for glomerular endothelial damage. In this study, we have examined whether a DPP4 inhibitor, sitagliptin, would mitigate the progression rate of diabetic nephropathy via the glomerular endothelial repair by measuring the alteration of microalbuminuria after administration for eight weeks.

Materials and Methods

Study design and patients

Thirty nine patients (mean±SD: 65±14 years of age) who were previously diagnosed with and were being treated for type 2 diabetes mellitus (T2DM) were enrolled in this prospective cohort case-control study. Those with macroproteinuria and macroangiopathies were excluded. Patients having a ratio of urinary excretion of albumin/creatinine (ACR) of less than 100 mg/g. Crwere divided into the following two groups. In the DPP4-inhibitor group, patients accepted to attend this study and to have an additional medication for the improvement of their insufficient glycemic control. In the non-inhibitor group, patients also accepted to attend this study, but did not accept to have an additional medication. There were no statistical differences between the DPP4 inhibitor group (n=20) who had sitagliptin administered and the Non-inhibitor group (n=19) who had not additional medication but received the repeated education of

***Corresponding Author:** Dr. Takayuki Fujita, Department of Nephrology, Hypertension and Endocrinology, Nihon University School of Medicine, 30-1 Oyaguchi-kamimachi, Itabashiku, Tokyo, 173-8610, Japan,Tel: 81 3 3972 8111; Fax: 81 3 3972 8311; E-mail: tfujita@med.nihon-u.ac.jp

Citation: Fujita T, Watanabe H, Murata Y, Hemmi S, Yabuki M, et al. (2015) DPP4 Inhibitor Decreases Urinary Albumin Excretion in Association with the Improvement of Glomerular Endothelial Injury in Patients with Type 2 Diabetes. Int J Diabetes Clin Diagn 2: 110. doi: http://dx.doi.org/10.15344/2394-1499/2014/110

energy restriction by a dietician instead of the additional medication. Patients enrolled to non-inhibitor group were encouraged to improve their insufficient glycemic control. There were 14 out of 39 patients who were undergoing lipid-lowering therapy using statins, and 39 patients were undergoing anti-hypertensive therapy using angiotensin II receptor 1 blocker. All continued their therapy as normal throughout this study. Calcium channel blockers or diuretics were used to treat 24 out of 39 patients. Sulphonylureas were used on 12 patients, and biguanide was used on 14 patients. Precise data in each group are presented in Table 1. The other drugs that function in controlling glycemia were not used. Patients with T2DMwho were not on any oral glucose lowering agents were also excluded. In the DPP4 inhibition group, 50 mg/day of sitagliptin was administered to 20 patients, and a 30 kcal/kg of dietary education was given to the 19 patients in the Non-inhibitor group. This study was pre-checked and permitted by the IRB committee in our hospital. All subjects agreed to attend this study at thetime of sample collection again.

		Non-inhibitor group	DPP4 inhibitor group	(p Value)
N		19	20	
Age	[years]	64±15	67±10	
Sex	[male/total]	14/19	14/20	
Medication				
Angiotensin II receptor blockers	[/total]	19/19	20/20	
Calcium channel blockers	[/total]	12/19	12/20	
Diuretics	[/total]	6/19	6/20	
Sulfonylureas	[/total]	6/19	6/19	
Biguanides	[/total]	8/19	6/19	
α-glucosidase inhibitor	[/total]	9/19	10/20	
stains	[/total]	7/19	7/20	
Systolic blood pressure	[mmHg]	126±11	132±16	(0.2659)
Diastolic blood pressure	[mmHg]	79±9	79±7	(0.6168)
Body mass Index	[Kg/m2]	25.879±3.6	26±3.8	(0.7369)
HOMI-IR		2.63±2.29	2.54±2.98	(0.4133)
Hemoglobin A1c[NGSP]	[%]	7.28±1.44	7.24±1.22	(0.7924)
LDL-cholesterol	[mmol/L]	2.79±0.7	3.15±0.78	(0.3576)
Triglyceride	[mmol/L]	1.22±0.69	1.63±0.82	(0.1403)
eGFR	[mL/min]	73.99±25.9	68.9±19.9	(0.5593)
Albumin/creatinine ratio	[mg/mmolCr]	4.68±3.85	3.51±5.18	
Median(interquartile range)		2.36(0.97-7.00)	3.81(1.75-6.78)	(0.1326)

Table 1: Clinical Characteristics of 39 patients with type 2 diabetes.

Value are expressed as mean±SD, P value: statistical difference vs. Non-inhibitor group, ACR Values are additionally expressed in median and extremes No statistical significance in values between DPP4 inhibitor group vs. Non-inhibitor group HOMA-IR: Homeostasis model assessment of insulin resistance, NGSP: revised by the National Glycohemoglobin Standardization Program, LDL-cholesterol: Low density lipoprotein-cholesterol, eGFR: Estimated glomerular filtration rate

Biochemical measurements

The following markers were measured before and after this study, and the data were examined with their clinical parameters. HbA1c, SDF1α and TM in plasma, and urinary 8-OHdGwere measured at the start and at the end of the study, and homeostasis model assessment of insulin resistance (HOMA-IR), estimated GFR (eGFR) and ACR were calculated simultaneously. Each of the parameters were measured by the following assays: plasma glucose and creatinine by enzymatic assay, Immuno-reactive insulin (IRI) by electrochemiluminescence immunoassay, HbA1cby high performance liquid chromatography and revised by the National GlycohemoglobinStandarization Program (NGSP) , SDF1α and 8-OHdG by emzyme-linked immunosorbent assay, TM by enzyme immunoassay, urinary albumin by turbidimetric immunoassay. HOMA-IR, ACR, and eGFR were calculated from the following formulas: HOMA-IR=glucose x IRI/405; ACR=albumin/creatinine; eGFR (male)= 194 xScr-1.094 xage-0.287; eGFR (female)= eGFR (male) x0.739. Other mediators were usually determined at the central laboratory department of our hospital. Plasma samples were collected at the time the patient visited the hospital and were stored at −80°C until used. Urine was collected by the patient early in the morning and brought to the hospital on the same day, and the urine samples were also stored at −80°C until used.

Statistical analysis

All values are presented as the mean ± standard deviation for continuous variables. ACR values are also provided in median with interquartile range, because ACR varies out of normal distribution. Mann-Whitney U test was used for the comparisons, and multivariate regression analysis was used for correlations.A p value of < 0.05 was considered statistically significant. Calculations were performed with commercial software, JMP ver.6.0.3 (SAS Institute Japan, Tokyo, Japan).

Results

Alterations in SDF1α and other parameters by DPP4-inhibitor

Administration of sitagliptin for 8 weeks resulted in 14% decrease in HbA1c(NGSP) from 7.2±1.2 to 6.2±1.4%, 74% increase in SDF1α from 205±70 to 355±80 mmol/L, 9% decrease in TM from 3.2±1.3 to 2.9±1.1FU/mL, 31% decrease in 8-OHdG from 40.0±13.9 to 27.6±10.4ng/μmolCr, and 41% decrease in ACR from 5.51±5.18 to 3.25±4.46 mg/mmolCr. Additional dietary education showed 0% decrease in HbA1c, 2% increase in SDF1α, 3% decrease in TM, 1% decrease in 8-OHdG, and 7% increasein ACR (Table 2). The DPP4 inhibitor group showed improvement of endothelial damage, glycemic control, and microalbuminuria. The non-inhibitor group showed no remarkable changes in these markers. A significant increase of SDF1α and a significant decrease ofACR after the eight-week sitagliptin treatment were recognized (SDF1α P<0.0001, ACR: P=0.0402), and the alteration degree of SDF1α provided larger than that ofHbA1c. Statistical differences in the alteration rates of each marker comparing the DPP4 inhibitor group and the non-inhibitor group were recognized in SDF1α (P<0.0001), TM (P=0.0143),HbA1C (P=0.0003), eGFR (P=0.0004),8-OHdG (P=0.0009), and ACR (P=0.0007) (Figure1). As microalbuminuriaand 8-OHdG represent glomerular endothelial dysfunction, these datawould suggest the additional effect by DPP-4 inhibitor on glomerular endothelial injury concurrent with improved glucose metabolism.

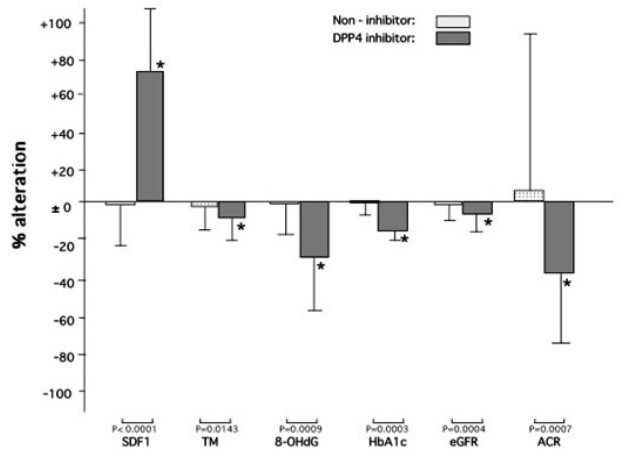

Figure 1: DPP4 inhibitor group shows improvements in endothelial damage, glycemic control, and microalbuminuria. Non-inhibitor group shows no remarkable changes in these markers. Statistical differences in the alteration rates of each marker between DPP4 inhibitor and non-inhibitor groups are recognized in SDF1α, TM, HbA1C, 8-OHdG, eGFR, and ACR. Horizontal bar express standard deviation in each column.

Relationship between %alteration in SDF1α and other parameters

Regression studies revealed a close relationship between the alteration rate of SDF1α and other parameters. Regression coefficients were: R2=0.084477, P=0.0103 between %SDF1α and %HbA1C; R2=0.144209, P=0.0007 between %SDF1αand %TM; R2=0.126208, P=0.0015 between %SDF1α and %ACR (Figure 2a,b,c,d). There was a closer correlation between endothelial damage and glomerular albumin excretion (Figure2d) than between endothelial damage and glycemic control (Figure 2b) in the DPP4 inhibitor group. These data indicate that the improvement of endothelial damage by DPP4 inhibitor develops more clearly than the improvement of glycemic control.

Discussion

In this study, plasmamarkers of endothelial injury and urinary albumin excretion were measured in patients with T2DM. There was a closer relationship between the alteration of endothelial injury and albuminuria than for other glycemic markers. The administration of DPP4 inhibitor was associated with the improvement of endothelial injury and albuminuria as well as glycemic control. Mori et al. also reported that sitagliptin, a DPP4 inhibitor, improved albuminuria in 85 patients with type 2 diabetes after six months [11]. They proposed

Pre-treatment		Non-inhibitor group		DPP4 inhibitor group	
		n=19		n=20	
SDF1α	[Mmol/L]	210.3±69.3		204.5±70.4	
Thrombomodulin	[FU/mL]	3.11±1.04		3.15±1.26	
HOMA-IR		2.63±2.29		2.54±2.98	
Hemoglobin A1c(NGSP)		7.28±1.44		7.26±1.22	
8-hydroxydexyguanosine	[%]	36.7±13.1		40.0±13.9	
eGFR	[Ng/mmolCr]	74.0±25.9		68.9±19.9	
Albumin creatinnine ratio	[mL/min]	4.68±3.85		5.51±5.18	
Median(interquartile range)	[Mg/mmolCr]	2.36(0.97-7.00)		3.81(1.75-6.78)	
Post-treatment			(P value#)		(P value#)
SDF1α	[mmol/L]	207.0±63.4	(0.9302)	355.1±80.1#	(0.0001#)
Thrombomodulin	[FU/mL]	2.99±1.22	(0.7478)	2.88±1.13	(0.4993)
HOMA-IR		2.56±1.65	(0.7258)	2.12±2.67	(0.3049)
Hemoglobin A1c(NGSP)	[%]	7.26±1.25	(0.9766)	6.23±1.42	(0.2050)
8-hydroxydexyguanosine	[ng/mmolCr]	35.9±11.8	(0.8380)	27.6±10.4	(0.5552)
eGFR	[ml/min]	73.6±24.4	(0.8955)	64.7±21.3	(0.3914)
Albumin creatinnine ratio	[mg/mmolCr]	4.99±7.76		3.25±4.46	
Median(interquartile range)		2.41(0.44-5.95)	(0.7042)	2.13#(0.85-3.01)	(0.042#)
%alteration					(P value*)
SDF1α	98±23		174±38*		(<0.0001*)
Thrombomodulin	96±11		91±13*		(0.0143)
HOMA-IR	97±94		83±85		(0.0841)
Hemoglobin A1c(NGSP)	100±7		86±8*		(0.0003*)
8-hydroxydexyguanosine	99±19		69±26*		(0.0009*)
eGFR	99±11		94±10*		(0.0005*)
	107±82		59±39*		(0.0007*)

Table 2: Plasma levels of SDF1α and other parameters in 39 patients with type 2 diabetes.
Values are expressed as mean±SD, ACR values are expressed in median and extremes, #: stastistical difference vs. Pre-treatment , *: stastical difference vs. Non-inhibitor group , SDF1: stromal cell-derived factor 1 alpha, HOMA-IR: Homeostasis model assessment of insulin resistance,
NGSP: Revised by the Glycohemoglobin Standarization Program, eGFR: estimated glomerular filtration rate

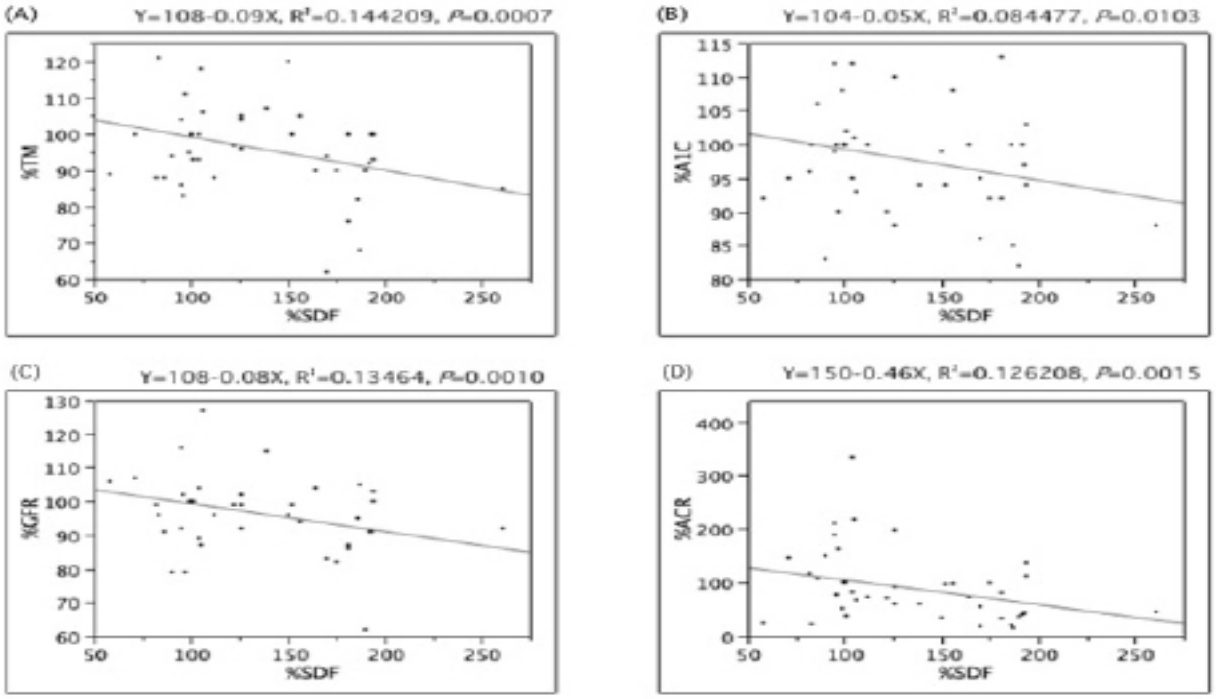

Figure 2: Regression study reveals close relationship between alteration rate of SDF1α and other parameters (A,B,C,D). In the DPP4 inhibitor group, there is a closer correlation between endothelial damage and glomerular albumin excretion (D) than between endothelial damage and glycemic control (B).

the mechanism of the reduction could be a direct effect, independently affecting blood pressure, bodyweight and glucose metabolism. In considering the life span of circulating HbA1c, it seems to need more times than our eight-week study for the decrease of plasma HbA1c level by the abnormal glucose metabolism [11]. Saxena et al. reported that SDF1α protected cardiomyocytes from cell death with in 72 hours after hypoxic insult [12]. Our study ended eight weeks after the sitagliptin administration, at which the drug effect might be insufficient to improve abnormal glucose metabolism according to the previous references [11,12]. The time taken for the drug effect suggest that the decrease of albuminuria would be in part due to the improvement of endothelial damage by DPP4 inhibitor.

DPP4 cleaves not only incretin but also SDF1α to lose its bioactivity [5]. SDF1α stimulates EPC mobilization from the bone marrow, and hypoxia-induced SDF1α gradients guide EPC homing to ischemic or injured tissues [6]. EPCs represent the endogenous endothelial regenerative capacity and the ability to form new collateral vessels [7]. SDF1α is reported as cardioprotective after myocardial infarction, and as a marker of severity for atherosclerosis [12]. Endothelial and inducible nitric oxide synthase derived from bone marrow cells play essential roles in the cardioprotective effect that normally occurs after ischemic preconditioning [13]. However, circulating EPCs and their functions are impaired in patients with diabetes mellitus [14]. Reduction of circulating EPCs marks the clinical onset of patients with type 2 diabetes. Both defective mobilization and increased apoptosis may account for this phenomenon [15]. Therefore, DPP4 inhibition is expected to increase SDF1α bioavailability and activity, with the eventual stimulation of EPCs.

Atherosclerotic lesions develop as the result of an inflammatory process initiated by endothelial damage. Chronic low-grade inflammation plays a pivotal role in all manifestations of diabetic complications. Inflammatory processes and immunoregulatory mechanisms contribute to the risk for myocardial infarction and stroke by modulating atherosclerotic plaque growth and complications [16].

DPP4 has been considered to have a role in immunomodulation. Sitaglipin was reported to reduce the number of inflammatory cells. Fadini et al. reported that four-weeks of sitagliptin therapy were also associated with a significant reduction of the pro-inflammatory chemokine, besides increasing EPCs [17]. As atherosclerosis is an immuno-inflammatory disease, it is possible that DPP4 inhibitors modulate responses occurring within atherosclerotic lesions. Sitagliptin also reduced mRNA expression of various inflammatory genes [18]. We provided the improvement of TM and 8-OHdG after the administration of DPP4 inhibitor which would regulate vascular oxidative injury. These data suggest that sitagliptin reduces adipose tissue inflammation, concurrent with improved glucose metabolism, indicating further that DPP4 inhibitors have anti-inflammatory effects.

In this study, possibility for the repair of vascular endothelial damage on glomerulus by a DPP4 inhibitor was proposed. It is noteworthy that the decrease of albuminuria by DPP4 inhibitor in patients with type 2 diabetes was confirmed, because microalbuminuria in patients with type 2 diabetes can predict macroangiopathies in the future. Microalbuminuria is mainly caused by glomerular hyperfiltration and endothelial injury. We did not change patients' anti-hypertensive agents during the study to minimize the effect of glomerular filtration. Increase of glomerular filtration rate would only increase urinary albumin in the sub-microalbuminuric range, as the majority of the excess albumin is reabsorbed by the tubules [19]. Therefore, the glomerular basement membrane might be physically altered. The presence of a significant glomerular endothelial glycocalyx implies that the glomerular endothelium contributes a barrier to macromolecules [20,21].

Reactive oxygen species (ROS) are known to disrupt the glycocalyx [22]. Diabetic patients have decreased systemic glycocalyx volume, and this correlates with the presence of microalbuminuria [23]. Hyperglycemia increases oxidative stress through overproduction of ROS by the mitochondrial electron transport chain. ROS increase activity of nuclear factor κB and oxidative stress, and disrupt the endothelial glycocalyx [24].

Adipokines also have the potential to contribute to the development of microalbuminuria. Vascular endothelial growth factor inhibition attenuates glomerular hypertrophy and albumin excretion, and prevents upregulation of endothelial nitric oxide synthase production in glomerular endothelial cells [25]. TNFα increases endothelial permeability and disrupts the glycocalyx [26]. IL-6 levels correlate with albuminuria [27]. Proinflammatory cytokines can cause disruption of the endothelial apical glycocalyx, leading to an increased macromolecular permeation. Therefore, ROS and adipokines have somewhat role in the disruption of endothelial glycocalyx, which may be relevant in pathogenesis of microalbuminuria. It is well-known that TM is produced from the damaged endothelium, and that 8-OHdG is produced in the process of DNA repair after ROS injury. We provide the improvement of TM, 8-OHdG, and urinary albumin excretion suggesting the endothelial repair. In considering the period from the time of DPP4 administration, it is conceivable that the repair of glomerular endothelial damage by DPP4 inhibitor is a candidate in the reduction of microalbuminuria.

Limitation of the Study

The limitations to the present study include the relatively small size and the fact that we did not measure EPC count and endothelial function directly, which would have added to our understanding of the mechanisms associated with urinary albumin excretion and glomerular endothelial damage. We prospectively enrolled patients who had not additional medication to the control. However, the plasma HbA1c level in Non-inhibitor group did not improve in compared with that in DPP4 inhibitor group. Therefore, it is not possible to specifically determine from this study whether the central improvement of albuminuria after the treatment with DPP4 inhibitor is due to the endothelial repair or endothelial dilatation or metabolic improvement. Further research with the use of endothelial-independent vasodilators is needed to clarify this.

In conclusion, DPP4 inhibitors increase plasma SDF1α population and function, resulting in the improvement of microalbuminuria by improving glomerular endothelial injury.

Author Contrubutions

TF wrote the manuscript; TF, HW, YM, SH, and MY performed the research; TF, YM, HW, SH, MY, and YF contributed to the discussion;AS and MS reviewed/edited the manuscript.

Competing Interests

All authors have no potential competing interests to declare associated with this manuscript.

Funding

This work was supported by the constitutional subsidy from Nihon University School of Medecine, Nihon University Itabashi Hospital, and Nihon University Medical Alumni Association.

References

1. Dinneen SF, Gerstein HC (1997) The association of microalbuminuria and mortality in non-insulin-dependent diabetes mellitus. A systematic overview of the literature. Arch Intern Med 157: 1413-1418.
2. Parving HH, Chaturvedi N, Viberti G, Mogensen CE (2002) Does microalbuminuria predict diabetic nephropathy? Diabetes Care 25: 406-407.
3. Stehouwer CD, Henry RM, Dekker JM, Nijpels G, Heine RJ, et al. (2004) Microalbuminuria is associated with impaired brachial artery, flow-mediated vasodilation in elderly individuals without and with diabetes: further evidence for a link between microalbuminuria and endothelial dysfunction—the Hoorn Study. Kidney Int 92: S42–S44.
4. Satchell SC, Tooke JE (2008) What is the mechanism of microalbuminuria in diabetes: a role for the glomerular endothelium? Diabetologia 51: 714-725.
5. Proost P, Struyf S, Schols D, Durinx C, Wuyts A, et al. (1998) Processing by CD26/dipeptidyl-peptidase IV reduces the chemotactic and anti-HIV-1 activity of stromal-cell-derived factor-1alpha. FEBS Lett 432: 73-76.
6. Ceradini DJ, Kulkarni AR, Callaghan MJ, Tepper OM, Bastidas N, et al. (2004) Progenitor cell trafficking is regulated by hypoxic gradients through HIF-1 induction of SDF-1. Nat Med 10: 858-864.
7. Fadini GP, Sartore S, Albiero M, Baesso I, Murphy E, et al. (2006) Number and function of endothelial progenitor cells as a marker of severity for diabetic vasculopathy. Arterioscler ThrombVasc Bio l26: 2140–2146.
8. Maruyama I, Bell CE, Majerus PW (1985) Thrombomodulin is found on endothelium of arteries, veins, capillaries, and lymphatics, and on syncytiotrophoblast of human placenta. J Cell Biol 101: 363-371.
9. Iwashima Y, Sato T, Watanabe K, Ooshima E, Hiraishi S, et al. (1990) Elevation of plasma thrombomodulin level in diabetic patients with early diabetic nephropathy. Diabetes 39: 983-988.
10. Kanauchi M, Nishioka H, Hashimoto T (2002) Oxidative DNA damage and tubulointerstitial injury in diabetic nephropathy. Nephron 91: 327-329.
11. Mori H, Okada Y, Arao T, Tanaka Y (2014) Sitagliptin improves albuminuria in patients with type 2 diabetes mellitus. J Diabetes Investig 5: 313-319.
12. Saxena A, Fish JE, White MD, Yu S, Smyth JW, et al. (2008) Stromal cell-derived factor-1alpha is cardioprotective after myocardial infarction. Circulation 117: 2224-2231.
13. Urbich C, Dimmeler S (2004) Endothelial progenitor cells: characterization and role in vascular biology. Circ Res 95: 343-353.
14. Fadini GP, Maruyama S, Ozaki T, Taguchi A, Meigs J, et al. (2010) Circulating progenitor cell count for cardiovascular risk stratification: a pooled analysis. PLoS One 5: e11488.
15. Werner N, Kosiol S, Schiegl T, Ahlers P, Walenta K, et al. (2005) Circulating endothelial progenitor cells and cardiovascular outcomes. N Engl J Med 353: 999-1007.
16. Hansson GK (2009) Atherosclerosis--an immune disease: The Anitschkov Lecture 2007. Atherosclerosis 202: 2-10.
17. Fadini GP, Boscaro E, Albiero M, Menegazzo L, Frison V, et al. (2010) The oral dipeptidyl peptidase-4 inhibitor sitagliptin increases circulating endothelial progenitor cells in patients with type 2 diabetes: possible role of stromal-derived factor-1alpha. Diabetes Care 33: 1607-1609.
18. Dobrian AD, Ma Q, Lindsay JW, Leone KA, Ma K, et al. (2011) Dipeptidyl peptidase IV inhibitor sitagliptin reduces local inflammation in adipose tissue and in pancreatic islets of obese mice. Am J Physiol Endocrinol Metab 300: E410-421.
19. Lazzara MJ, Deen WM (2007) Model of albumin reabsorption in the proximal tubule. Am J Physiol Renal Physiol 292: F430-439.
20. Deen WM, Lazzara MJ, Myers BD (2001) Structural determinants of glomerular permeability. Am J Physiol Renal Physiol 281: F579-596.

21. Ballermann BJ (2007) Contribution of the endothelium to the glomerular permselectivity barrier in health and disease. Nephron Physiol 106: p19-25.

22. Henry CB, Duling BR (2000) TNF-alpha increases entry of macromolecules into luminal endothelial cell glycocalyx. Am J Physiol Heart Circ Physiol 279: H2815-2823.

23. Nieuwdorp M, Mooij HL, Kroon J, Atasever B, Spaan JA, et al. (2006) Endothelial glycocalyx damage coincides with microalbuminuria in type 1 diabetes. Diabetes 55: 1127-1132.

24. Vink H, Duling BR (1996) Identification of distinct luminal domains for macromolecules, erythrocytes, and leukocytes within mammalian capillaries. Circ Res 79: 581-589.

25. deVriese AS, Tilton RG, Elger M, Stephan CC, Kriz W, Lameire NH (2001) Antibodies against vascular endothelial growth factor improve early renal dysfunction in experimental diabetes. J Am SocNephrol 12: 993–1000.

26. Friedl J, Puhlmann M, Bartlett DL, Libutti SK, Turner EN, et al. (2002) Induction of permeability across endothelial cell monolayers by tumor necrosis factor (TNF) occurs via a tissue factor-dependent mechanism: relationship between the procoagulant and permeability effects of TNF. Blood 100: 1334–1339.

27. Saraheimo M, Teppo AM, Forsblom C, Fagerudd J, Groop PH (2003) Diabetic nephropathy is associated with low-grade inflammation in Type 1 diabetic patients. Diabetologia 46: 1402-1407.