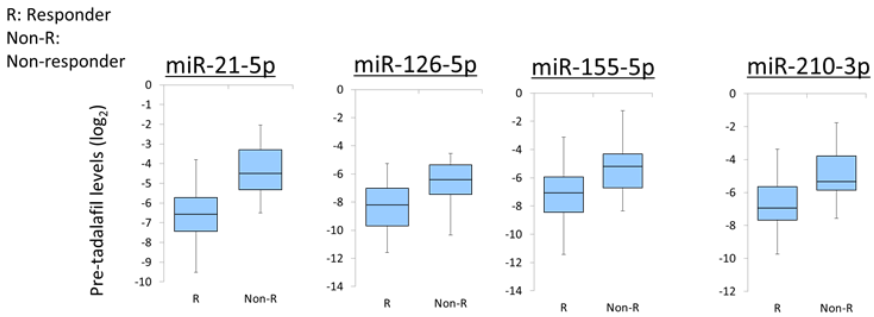
184

Tanaka T[1], Minami A[1], Otoshi T[1], Morimoto K[1], Kuratsukuri K[1], Nakatani T[1]
1. *Department of Urology, Osaka City University Graduate School of Medicine*

THE POSSIBILITY OF URINE MICRORNAS AS A PREDICTIVE BIOMARKER FOR TREATING MALE LUTS/BPH WITH PHOSPHODIESTERASE TYPE 5 INHIBITORS

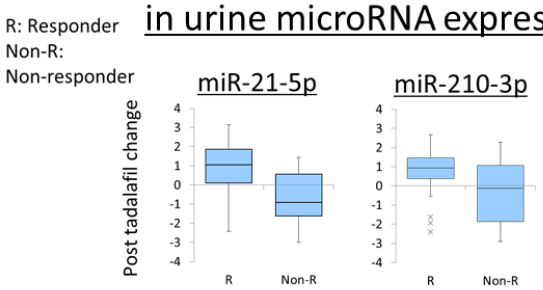
Hypothesis / aims of study
Phosphodiesterase type 5 (PDE5) inhibitors were reported to have some individual actions including the improvement of blood flow of pelvic viscera and suppression of chronic prostatic inflammation except for the release of bladder outlet obstruction through the inactivation of PDE5/ cyclic guanosine 3' 5'- monophosphate (cGMP)/ nitric oxide (NO) pathway. There are only a few reports about conveniently evaluating and predicting the effectiveness of PDE5 inhibitors from the viewpoint of these pathophysiological mechanisms. In this study, we focused on some urine microRNAs that have been shown to regulate the function of endothelial cells via the control of several genes[(1-3)]. We investigated whether the expression pattern of these urine microRNAs is associated with the clinical effects in the male LUTS/BPH patients treated with PDE5 inhibitors.
Study design, materials and methods
This clinical study protocol was approved by the institutional review board of Osaka City University. A total of 70 patients with male LUTS/BPH were enrolled to this study after the agreement with an informed consent. The patients received the administration of a PDE5 inhibitor, tadalafil®, 5mg/ day for 12 weeks and their spot urine was used for measurement of the expression of microRNAs before and at 4 weeks after the treatment. Subjective urinary symptom score (I-PSS and OABSS), QOL and N-QOL index were estimated before and at 4, 8 and 12 weeks after administration of tadalafil. Objective urinary parameters (maximum urinary flow rate; Qmax and average urinary flow rate; Qave) in the uroflowmetry were measured before and at 12 weeks after the treatment. The clinically meaningful improvement (CMI) was defined as (1) ≥25% baseline-to-endpoint total IPSS improvement or (2) ≥2.5ml/s baseline-to-endpoint Qmax improvement. Finally, a total of 55 patients, except for the patients who discontinued the administration, was examined. The compartment of microRNA in each urine sample was collected by the purification kit and followed by the quantification real time RT-PCR using TaqMan Probe. We examined four microRNAs (miR-21-5p, miR-126-5p, miR-155-5p, miR-210-3p) associated with the function of endothelial cells.
Results
Tadalafil 5mg once daily led to CMI in 35 patients (64%) at 12 weeks after the treatment. There are no significant differences between the responders and non-responders regarding the patients' baseline conditions including age, prostate volume, I-PSS, OABSS, QOL and N-QOL index. The baseline expression levels of urine miR-21-5p, miR-126-5p, miR-155-5p and miR-210-3p in the responders were significantly low compared with those in the non-responders. The changes between baseline and 4 weeks in expression of miR-21-5p and miR-210-3p in the responders were significantly high compared with those in the non-responders. In the multivariate regression analysis, the baseline urine miR-21-5p level (P=0.024, OR: 6.2, 95%CI; 0.24-3.4) was positively associated with the clinical response of tadalafil treatment for male LUTS/BPH. Furthermore, the ROC analysis assessing the association urine baseline urine miR-21-5p and response of tadalafil showed AUC of 0.85 (95% CI; 0.74-0.95).
Interpretation of results
Regulation of several endothelium-associated microRNAs expression possibly link to effects of PDE5 inhibitors through the proliferation and protection of endothelial cells.
Concluding message
The urine endothelium-associated microRNA (e.g. miR-21) may be a predictive biomarker for the treatment with PDE5 inhibitors for male LUTS/BPH patients.

Baseline urine microRNA expressions



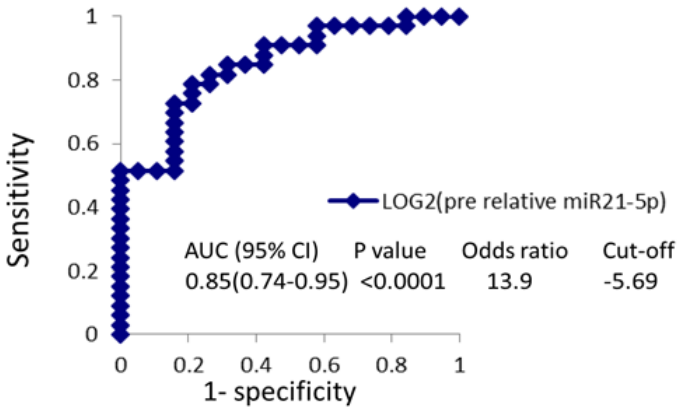
	miR-21-5p	miR-126-5p	miR-155-5p	miR-210-3p
Median Non-R/R (antilog)	0.68	0.78	0.73	0.77
P value	<0.001	0.01	0.006	0.002

Change between baseline-to-4 weeks in urine microRNA expressions



	miR-21-5p		miR-210-3p	
Median fold change (log: post/pre)	1.04	-0.91	0.94	-0.13
P value	<0.01		0.02	

ROC analysis



References

1. Rippe C, Blimline M, Magerko KA, et al. MicroRNA changes in human arterial endothelial cells with senescence: relation to apoptosis, eNOS and inflammation. Exper. Gerontol. 2012; 47: 45–51.
2. Schober A, Nazari-Jahantigh M, Wei Y, et al. MicroRNA-126-5p promotes endothelial proliferation and limits atherosclerosis by suppressing Dlk1. Nat. Med. 2014; 20: 368-376.
3. Fasanaro P, D'Alessandra Y, Di Stefano V, et al. MicroRNA-210 modulates endothelial cell response to hypoxia and inhibits the receptor tyrosine kinase ligand Ephrin-A3. J. Biol. Chemi. 2008; 283:15878–15883.

Disclosures

Funding: no **Clinical Trial:** No **Subjects:** HUMAN **Ethics Committee:** Osaka City University Graduate School of Medicine **Helsinki:** Yes **Informed Consent:** Yes