🏆 Best in Category Prize - Male Lower Urinary Tract Symptoms (LUTS) / Incontinence

749

Mitsui T[1], Kira S[1], Ihara T[1], Sawada N[1], Nakagomi H[1], Miyamoto T[1], Takeda M[1]
1. *Department of Urology, University of Yamanashi*

METABOLOMICS APPROACH FOR ASSOCIATION WITH MALE LOWER URINARY TRACT SYMPTOMS: AN IDENTIFICATION OF POSSIBLE BIOMARKERS AND POTENTIAL TARGETS FOR NEW TREATMENTS

Hypothesis / aims of study
Lower urinary tract symptoms (LUTS) are a common complaint in aged males and usually have a major impact on their quality of life (QoL). Looking at pathogenesis of LUTS, although multiple factors, including benign prostatic hyperplasia are associated with symptoms, detailed etiologies of LUTS remain unknown yet. On the other hand, metabolomics analysis enables the detection and semi-quantitative measurement of hundreds of unique metabolites from broad range of metabolic pathways, and these approaches can detect metabolites associated with pathophysiological states. Possible biomarkers in interstitial cystitis were actually detected using metabolomics analysis.(1)(2) In the present study, we identified metabolites from metabolomics approach and investigated association between these metabolites and LUTS.

Study design, materials and methods
A total of 58 male participants without apparent neurological diseases at our outpatient clinic were enrolled in the present study; Age: 71.5+/-4.3 years old, body mass index (BMI): 23.0 +/-2.7. A 24hrs-bladder diary was carried out to assess behavior of micturition, and we used the International Prostate Symptom Score (IPSS) and QOL score to analyze LUTS and QOL. LUTS was defined as a total score of IPSS was 8 and more (LUTS-group), and patients with 7 and less was belong to Control-group. To investigate etiologies of LUTS in males and novel molecular insights into disease pathogenesis, we conducted a comprehensive study of plasma metabolites using capillary electrophoresis time-of-flight mass spectrometry (CE-TOFMS). Metabolites were compared between LUTS- and Control-groups using Mann–Whitney U test, and biomarkers of male LUTS from metabolites in CE-TOFMS were analysed using a multivariable logistic regression analysis to reveal the odds ratio and 95% confidence interval (CI).

Results
Of 58 participants, 32 males were in LUTS-group and the other 23 males in Control-group. A 24hrs-bladder diary revealed that nocturnal urine volume, 24hrs-micturition frequency, nocturnal micturition frequency and nocturia index were significantly higher in LUTS-group. Although there was a trend of lower maximum voided volume and higher nocturnal polyuria index, 24hrs-urine volume was not different between groups. (Table 1) Metabolomics analysis with CE-TOFMS identified 110 metabolites from plasma of participants. In a total of 10 metabolites, there was significant difference or a trend of difference between LUTS- and Control-groups. (Table 2) Regarding these 10 metabolites, a multivariate analysis showed that an increase of Glu and a decrease of Arg and IMP were identified as etiologies of LUTS in males. A decrease of ADP, Asn, Citrulline and Gln was also a possible etiologies of male LUTS. (Table 3)

Interpretation of results
From the present study, some metabolic pathways could be involved in incidence of male LUTS. Particularly, we speculate that central carbon metabolism (Asn, Glu, Gln), urea cycle (Arg, Citrulline) and purine metabolism (ADP, IMP) may be important pathways in etiologies of LUTS in males.

Concluding message
Male LUTS could occur through abnormal metabolism in some pathways. Further studies using metabolomics analysis have a potential to detect new biomarkers and develop potential targets for new treatments.

Table 1 Data in frequent volume chart

	Control	LUTS	P-value
24hrs-urine volume（mL）	1561 +/- 512	1840 +/- 1043	0.3941
Nocturnal urine volume（mL）	473 +/- 143	629 +/- 309	0.0202
24hrs-micturition frequency（times）	7.1 +/- 2.0	11.2 +/- 4.0	<0.001
Nocturnal micturition frequency（times）	0.7 +/- 0.6	2.2 +/- 1.1	<0.001
Maximum voided volume（mL）	365 +/- 134	295 +/- 117	0.0534
Nocturnal polyuria index（%）	31.5 +/- 7.9	35.9 +/- 14.2	0.0959
Nocturia index（times）	1.4 +/- 0.4	2.3 +/- 0.9	<0.001

Table 2 Difference in concentration of substances between control and LUTS

Substances (μM)	Control	LUTS	P-value
ADP	2.21 +/- 1.10	1.68 +/- 0.83	0.0743
ATP	3.38 +/- 1.39	2.75 +/- 1.10	0.0956
Arg	113.5 +/- 22.6	101.8 +/- 17.7	0.0616
Asn	53.0 +/- 9.7	48.7 +/- 8.1	0.0580
Citrulline	43.2 +/- 10.9	38.1 +/- 7.2	0.0823
Gln	710.8 +/- 97.0	662.9 +/- 64.1	0.0470
Glu	40.7 +/- 15.3	50.2 +/- 20.4	0.0382
Glutathione (GSSG)_divalent	0.22 +/- 0.09	0.18 +/- 0.16	0.0223
IMP	1.47 +/- 0.94	0.87 +/- 0.58	0.0092
Ribose 5-phosphate	1.29 +/- 0.20	1.20 +/- 0.17	0.0747

Table 3 The odds ratio associated with a one-unit increase of substances

Substances	Odds ratio	95%CI	P-value
ADP	0.5368	0.2565, 1.0179	0.0570
ATP	0.6643	0.3828, 1.0820	0.1022
Arg	0.9689	0.9374, 0.9979	0.0351
Asn	0.9420	0.8695, 1.0076	0.0835
Citrulline	0.9427	0.8726, 1.0086	0.0885
Gln	0.0519	0.0011, 1.4815	0.0849
Glu	1.0398	1.0032, 1.0843	0.0318
Glutathione (GSSG)_divalent	0.2153	0.0021, 17.601	0.4696
IMP	0.2520	0.0690, 0.7071	0.0068
Ribose 5-phosphate	0.1218	0.0019, 4.8726	0.2789

Covariates: age, BMI, 24hrs-urine volume, nocturnal urine volume

Blue: A decrease in LUTS-group, Red: An increase in LUTS-group.
ADP: Adenosine diphosphate, ATP: adenosine triphosphate, Arg: Arginine, Asn: asparagine, Gln: glutamine, Glu: glutamate, IMP: Inosine monophosphate

References

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