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Short Communication

# Clinical association between the metabolite of healthy gut microbiota, 3-indolepropionic acid and chronic kidney disease

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## SUMMARY

*Background & aims:* Emerging evidence indicates that gut microbiota serves an important role in the development and progression of chronic kidney disease (CKD). Changes to the gut microbial flora can cause the generation of uremic toxins, which contribute to chronic kidney injury. The aim of the current study was to explore the clinical association between metabolites and CKD.

*Methods:* Between August 2013 and January 2015, a two-phase case–control study was conducted to analyze the clinical association between metabolites and CKD in a community health program. The first phase of the study was a prospective case–control survey designed for comparing the differences in the metabolome profile of patients with ($n = 10$) and without ($n = 10$) estimated glomerular filtration rate (eGFR) rapid decline (a yearly decline >20%). The second phase of the study was a cross-sectional case–control study, which checked and compared the metabolites, indoxyl sulfate and p-cresol sulfate levels between healthy subjects ($n = 144$) and CKD patients ($n = 140$).

*Results:* In the first phase of the study, it was revealed that IPA levels of patients with rapid renal function decline were significantly reduced compared with the control patients ($n = 10$ for each group). The second phase furthered checked and compared the IPA, indoxyl sulfate and p-cresol sulfate levels between healthy subjects ($n = 144$) and CKD patients ($n = 140$). The results showed that the average level of indoxyl sulfate (2738.2 *vs.* 541.0 ng/ml, $P < 0.01$) and p-cresol sulfate (1442.8 *vs.* 1394.6 ng/ml, $P < 0.01$) were significantly higher in the CKD patients, while the average level of IPA was significantly higher (49.8 *vs.* 34.7 ng/ml, $P < 0.01$) in the control patients.

*Conclusions:* Our results suggest that IPA might be an important biomarker and renal protector against the development of CKD.

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## 1. Introduction

The association between gut microbiota and human health is being increasingly recognized. It is now well established that a healthy gut flora is largely responsible for the overall health of the host. Previous studies have shown that the progression of chronic kidney disease (CKD) is related to the composition of a patient's microbiota. CKD triggers intestinal dysbiosis, which results in the production of uremic toxins, including indoxyl sulfate (IS) and p-cresol sulfate (PCS) [1]. IS/PCS may cause the development of

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*Abbreviations:* CKD, chronic kidney disease; IS, indoxyl sulfate; PCS, p-cresol sulfate; eGFR, estimated glomerular filtration rate; MDRD, Modification of Diet in Renal Disease; IPA, indolepropionic acid.

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tubulointerstitial fibrosis and glomerular sclerosis [1]. Accumulating evidence indicates that IS/PCS produced by the gut microbiota, have a significant association with disease progression and outcomes in CKD patients [2].

Previous animal and clinical studies have also indicated that modulation of the gut microbiota could reduce uremic toxin production and delay CKD progression [3]. However, understanding of the association between metabolites in healthy gut microbiota and kidney function are still limited. The purpose of this investigation was to explore the clinical association between metabolites and CKD.

## 2. Methods

### 2.1. Ethics statement

The present study was performed in accordance with the ethical principles of the Declaration of Helsinki, as well as good clinical practice guidelines and local regulatory requirements. Patients were invited to participate in this study on the day of their health screening. Trained physicians evaluated their mental status during the screening and informed them of the consent procedure. Written informed consent was obtained from all subjects prior to their participation. The study was approved by the Institutional Review Board of Chang-Gung Memorial Hospital (IRB no. 100-2243A3).

### 2.2. Study subjects

The study design and flow are illustrated in Supplemental Fig. 1. Between August 2013 and January 2015 a community-based cohort study was conducted in Northeastern Taiwan, and community outreach health screening was performed to recruit subjects. A two-phase case–control study was performed. The first phase was a prospective case–control study, which focused on the differences in metabolomic profiles of patients with and without estimated glomerular filtration rate (eGFR) in rapid decline. The eGFR rapid decline (eGFRRD) group ($n = 10$) was defined as having a yearly eGFR decline >20%, while the control group ($n = 10$) was defined as having a yearly eGFR decline <5%. The metabolites that were found to be significantly different between the two groups were validated in the second phase of the study. The second phase was a cross-sectional case–control study, designed to determine the relationship between metabolites and CKD. The CKD group was defined as having an eGFR <60 mL/min/1.73 $m^2$, while the normal group was defined as having an eGFR >90 mL/min/1.73 $m^2$. The eGFR was calculated by the Modification of Diet in Renal Disease (MDRD) GFR equation.

### 2.3. Metabolomic measurements

Metabolomic profiling experiments were performed by the Metabolomics Core Laboratory at the National Taiwan University. There were 382 metabolites in the metabolite library [4]. The serum samples were extracted with 400 μl methanol and analyzed using an Agilent 1290 UHPLC system coupled to a tandem mass spectrometry instrument (6540-QTOF, Agilent Technologies, Inc., Santa Clara, CA, USA). An Acquit HSS T3 column (100 × 2.1 mm, 1.8 μm; Waters Corporation, Milford, MA, USA) was used for the separation and was maintained at 40 °C. A Jet Stream electrospray ionization source with a capillary voltage of 4.0 kV in positive and negative mode was used for sample ionization. The mass spectrometry parameters were set as follows: gas temperature 325 °C; gas flow 5 l min-1; nebulizer pressure 40 PSI; sheath gas temperature 325 °C; sheath gas flow 10 l min-1; and a fragmentor voltage of 120 V. A scan range of 50-1700 m/z was also used.

### 2.4. Serum 3-indolepropionic acid (IPA), IS and PCS analysis

High-performance liquid chromatography was performed at room temperature using a dC18 column (3.0 × 50 mm; Atlantis, Waters). The buffers used were (A) 0.1% formic acid and (B) 1 mM $NH_4OAc$ + 0.1% formic acid in 100% acetonitrile. The flow rate was 0.6 mL/min with a 3.5-min gradient cycling from 90% A/10% B to 10% A/90% B. Under these conditions, IPA, IS/PCS were eluted at 26.65, 2.73 and 2.48 min, respectively. Standard curves for IPA, IS/PCS were set at 1, 5, 10, 50, 250, 500, and 1000 μg/L.

### 2.5. Statistical analysis

The continuous variables are presented as the mean ± standard deviation and were assessed by a student's t-test. Proportions were compared by the chi-squared test. A propensity analysis and matching technique were used to minimize confounding factors. Pairs were matched at one to two with identical propensity scores for age and gender. All statistical analyses were 2-tailed and a P-value <0.05 was considered statistically significant. Data were analyzed using Statistical Package for the Social Sciences software, version 19.0, for Windows (SPSS Inc., Chicago, IL).

## 3. Results

Between August 2013 and July 2014, 2662 participants who completed the baseline survey, including demographic and clinical laboratory data were invited to attend the first phase of the study. Of those invited, 313 attended and successfully completed the one-year follow-up. Participants with diabetes mellitus, malignancy and chronic liver disease were excluded from the study. After matching by age and sex, 20 of the 313 participants were further classified into the eGFRRD ($n = 10$) and control ($n = 10$) groups according to their yearly eGFR decline rate. The characteristics of the first phase study subjects are reported in Table 1. Both groups had similar underlying characteristics, including renal function, blood pressure, lipid profile and glucose level at the start of the study. At the one-year follow-up, the eGFRRD group had significantly lower eGFR levels compared with the control group. A total of 53 metabolites were identified from the metabolic analysis (Supplemental Fig. 2). Among these 53 metabolites, the intensity of histidine, IPA and paraxanthine were significantly different between the eGFRRD and control groups. IPA was the only metabolite which had a significantly different intensity between the two groups at the start of the study and the one-year follow-up (Supplemental Table 1 and Fig. 1).

A total of 3478 participants attended the second phase of the study between August 2013 and January 2015. Participants with diabetes mellitus, malignancy, chronic liver disease or an eGFR between 60 and 90 mL/min/1.73 $m^2$ were excluded from the study. After age and sex matching of the remaining individuals, a total of 284 subjects were identified and divided into the CKD ($n = 140$) and normal ($n = 144$) groups according to their eGFR. The characteristics of the second phase study subjects are summarized in Table 2. IS/PCS are important representatives of the protein-bound uremic retention solutes. IS/PCS are produced by intestinal bacteria, accumulated in the plasma of chronic kidney disease (CKD) patients. IPA is also an indole-derived tryptophan metabolite and produced by the presence of gut microbiome, *Clostridium sporogene*. Therefore, IS/PCS and IPA were selected for the following study.

The study results revealed that the CKD group had significantly higher IS/PCS levels compared with the normal function group. In contrast, the normal group had significantly higher IPA levels compared with the CKD group (49.8 ± 15.9 *vs*. 34.7 ± 10.8 ng/ml; Fig. 2). The representative results of the IPA analysis of the study subjects is shown in Supplemental Fig. 3.

**Table 1**
Demographic and clinical characteristics for the eGFRRD and control groups at the start of the study and after the one-year follow-up.

| Variables | Start of the study | | | One-year follow-up | | |
|---|---|---|---|---|---|---|
| | CG(n = 10) | eGFRRD (n = 10) | P-value | CG (n = 10) | eGFRRD (n = 10) | P-value |
| Male (%) | 4 (40) | 4 (40) | 1.00 | 4 (40) | 4 (40) | 1.00 |
| Age (year) | 62.9 ± 8.4 | 62.6 ± 13.4 | 0.87 | 63.5 ± 9.1 | 61.8 ± 12.0 | 0.78 |
| Waist (cm) | 81.5 ± 6.7 | 82.9 ± 7.1 | 0.67 | 83.0 ± 6.1 | 83.4 ± 8.5 | 0.62 |
| Body mass index | 24.4 ± 2.2 | 24.9 ± 3.0 | 0.44 | 25.0 ± 2.6 | 24.9 ± 3.3 | 0.97 |
| Systolic blood pressure (mmHg) | 133.0 ± 20.5 | 135.7 ± 29.3 | 0.90 | 127.0 ± 15.7 | 129.0 ± 16.0 | 0.96 |
| Diastolic blood pressure (mmHg) | 75.6 ± 15.9 | 82.1 ± 16.4 | 0.60 | 78.1 ± 11.5 | 76.0 ± 13.3 | 0.90 |
| **Blood** | | | | | | |
| White blood cell (1000/uL) | 6.5 ± 1.7 | 7.0 ± 2.9 | 0.78 | 6.1 ± 2.0 | 6.2 ± 1.8 | 0.87 |
| Hemoglobin (g/dL) | 14.0 ± 1.4 | 14.0 ± 1.3 | 0.84 | 13.9 ± 1.2 | 13.9 ± 1.1 | 0.78 |
| Fasting glucose (mg/dL) | 101.0 ± 18.7 | 105.0 ± 32.4 | 0.83 | 99.7 ± 15.2 | 116.0 ± 29.1 | 0.21 |
| Insulin (mU/L) | 6.1 ± 1.9 | 10.9 ± 12.6 | 0.14 | 6.5 ± 2.2 | 10.5 ± 10.4 | 0.48 |
| HbA1c (%) | 5.7 ± 0.5 | 6.1 ± 0.6 | 0.12 | 5.7 ± 0.6 | 6.3 ± 1.4 | 0.18 |
| Triglyceride (mg/dL) | 114.0 ± 60.8 | 146.0 ± 83.0 | 0.34 | 108.0 ± 38.1 | 131.0 ± 55.9 | 0.27 |
| Total cholesterol (mg/dL) | 200.0 ± 39.3 | 205.0 ± 33.9 | 0.73 | 196.0 ± 34.7 | 217.0 ± 31.9 | 0.29 |
| HDL-C (mg/dL) | 54.8 ± 10.0 | 54.8 ± 15.6 | 0.83 | 56.4 ± 8.3 | 56.4 ± 9.8 | 0.91 |
| LDL-C (mg/dL) | 117.9 ± 32.8 | 121.0 ± 32.6 | 0.97 | 121.0 ± 29.4 | 137.0 ± 25.5 | 0.26 |
| AST (U/L) | 21.8 ± 3.9 | 25.1 ± 8.7 | 0.38 | 24.2 ± 8.7 | 27.9 ± 6.5 | 0.16 |
| ALT (U/L) | 20.7 ± 4.5 | 25.4 ± 13.1 | 0.75 | 21.8 ± 13.0 | 24.3 ± 12.4 | 0.78 |
| Blood urea nitrogen (mg/dL) | 14.6 ± 4.3 | 13.9 ± 4.1 | 0.43 | 16.2 ± 5.0 | 16.4 ± 4.7 | 0.95 |
| Uric acid (mg/dL) | 6.0 ± 1.1 | 5.9 ± 1.4 | 0.99 | 6.2 ± 0.9 | 6.6 ± 1.5 | 0.59 |
| Creatinine (mg/dL) | 0.8 ± 0.1 | 0.8 ± 0.3 | 0.92 | 0.8 ± 0.1 | 1.1 ± 0.4 | **0.03** |
| eGFR (mL/min/1.73m$^2$) | 86.8 ± 10.9 | 88.4 ± 24.4 | 0.84 | 88.8 ± 11.1 | 62.7 ± 19.0 | **<0.01** |
| Calcium (mg/dL) | 9.4 ± 0.2 | 9.4 ± 0.5 | 0.72 | 9.4 ± 0.3 | 9.7 ± 0.5 | 0.16 |
| Sodium (Na, mEq/L) | 141.0 ± 1.9 | 141.0 ± 2.0 | 0.75 | 141.0 ± 1.7 | 142.0 ± 2.0 | 0.52 |
| Potassium (K, mEq/L) | 4.4 ± 0.4 | 4.2 ± 0.3 | 0.17 | 4.2 ± 0.2 | 4.4 ± 0.3 | 0.17 |
| **Urine** | | | | | | |
| Albumin (mg/dL) | 4.9 ± 0.2 | 4.8 ± 0.1 | 0.73 | 4.8 ± 0.3 | 4.8 ± 0.4 | 0.90 |
| Total protein (mg/dL) | 7.2 ± 0.3 | 7.0 ± 0.2 | 0.30 | 7.2 ± 0.4 | 7.2 ± 0.6 | 0.78 |
| Urea nitrogen (mg/dL) | 804.0 ± 339.0 | 692.0 ± 380.0 | 0.51 | 844.0 ± 285.0 | 826.0 ± 334.0 | 0.42 |
| Creatinine (mg/dL) | 169.0 ± 62.9 | 129.0 ± 58.8 | 0.21 | 148.0 ± 57.0 | 224.0 ± 69.5 | **<0.01** |

Abbreviations: CG, control group; eGRRD, estimated glomerular filtration rate rapid decline; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; AST, aspartate aminotransferase; ALT, alanine aminotransferase.

## 4. Discussion

IPA is an aromatic amino acid produced by the microbiota as a byproduct of deamination. Accumulating evidence indicates that IPA has a significant clinical association with several diseases. IPA has been demonstrated to be an inhibitor of beta-amyloid fibril formation and a potential neuroprotectant against Alzheimer's disease [5]. Recent studies indicated that elevated serum IPA were correlated with a lower risk of type 2 diabetes and higher consumption of fiber-rich foods [6].The present study demonstrates that IPA is significantly associated with renal function changes and CKD development. It was found that patients with higher serum IPA levels had a lower risk of rapid renal function decline and

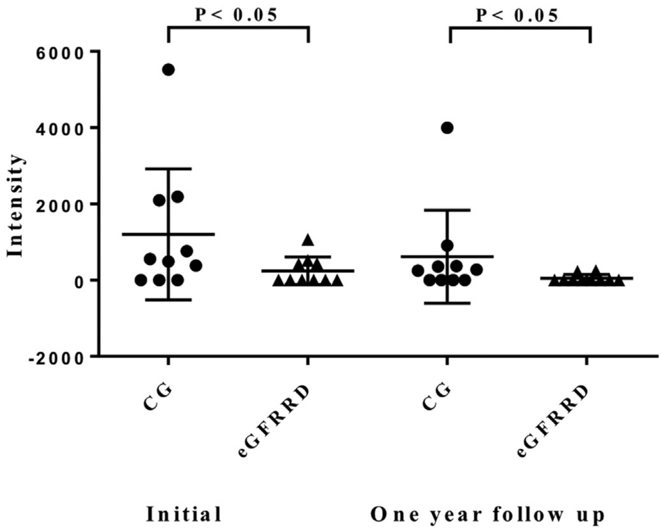

**Fig. 1. Significant difference of serum 3-indolepropionic acid levels between the control group (CG, n = 10) and estimated glomerular filtration rate rapid decline (eGFRRD, n = 10) group.** The results indicated that subjects with rapid renal function decline had significant decreased serum 3-indolepropionic acid intensities at the start and the end of the study when compared with control subjects.

**Table 2**
Clinical characteristics of study subjects for the 3-indolepropionic acid, indoxyl sulfate and *p*-cresol sulfate analysis.

| Variable | NG (n = 144) | CKD (n = 140) | P-value |
|---|---|---|---|
| Male (%) | 58 (40.3) | 56 (40) | 0.99 |
| Age (years) | 71.9 ± 10.0 | 73.8 ± 9.2 | 0.22 |
| Body mass index | 25.1 ± 3.3 | 24.6 ± 3.8 | 0.39 |
| Waist (cm) | 85.3 ± 12.9 | 89.1 ± 10.5 | 0.05 |
| eGFR (ml/min/1.73 m$^2$) | 90.7 ± 18.7 | 30.7 ± 14.6 | **<0.01** |
| Blood urea nitrogen (mg/dL) | 14.5 ± 3.6 | 41.8 ± 36.1 | **<0.01** |
| Creatinine (mg/dL) | 0.8 ± 0.2 | 2.9 ± 2.6 | **<0.01** |
| Inorganic phosphorus (mg/dL) | 3.6 ± 0.48 | 4.2 ± 1.24 | **<0.01** |
| Calcium (mg/dL) | 9.3 ± 0.3 | 9.2 ± 0.8 | 0.10 |
| Sodium (Na, mEq/L) | 141.0 ± 1.5 | 140.0 ± 3.1 | **0.03** |
| Potassium (K, mEq/L) | 4.3 ± 0.4 | 4.6 ± 0.6 | **<0.01** |
| Uric acid (mg/dL) | 5.8 ± 1.4 | 7.1 ± 2.5 | **<0.01** |
| Albumin (g/dL) | 4.6 ± 0.3 | 4.2 ± 0.3 | **<0.01** |
| Fasting glucose (mg/dL) | 98.5 ± 9.9 | 100.0 ± 10.3 | 0.25 |
| HDL-C (mg/dL) | 56.5 ± 16.5 | 49.0 ± 14.5 | **<0.01** |
| LDL-C (mg/dL) | 120.0 ± 35.0 | 99.8 ± 47.3 | **<0.01** |
| Total cholesterol (mg/dL) | 203.0 ± 38.8 | 173.0 ± 33.3 | **<0.01** |
| Triglyceride (mg/dL) | 121.0 ± 75.0 | 147.0 ± 85.5 | 0.06 |

Abbreviations: eGFR, estimated glomerular filtration rate; NG, normal group; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.
Values in bold are statistically significant ($P < 0.05$).

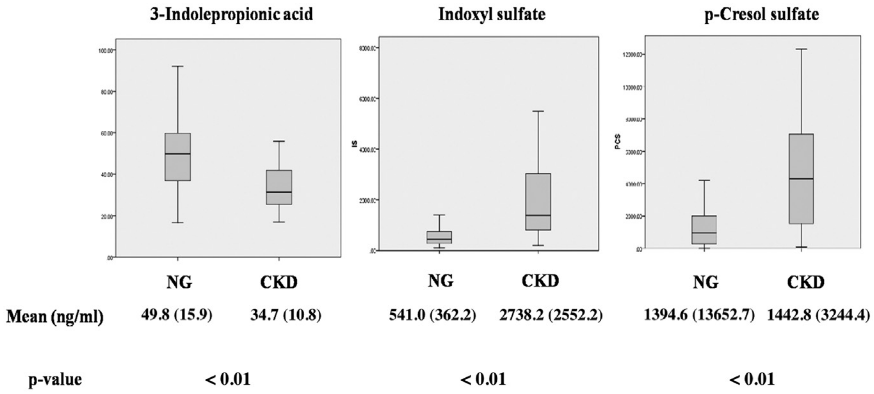

**Fig. 2. Differences of serum 3-indolepropionic acid, indoxyl sulfate, and p-cresol sulfate levels between the normal group (NG, n = 144) and chronic kidney disease (CKD, n = 140) group.** The results revealed that normal renal function associated with increased serum 3-indolepropionic acid levels (mean: 49.8 ng/ml vs. 34.7 ng/ml, $p < 0.01$). In contrast, chronic kidney disease associated with increased serum indoxyl sulfate (mean: 2738.2 ng/ml vs. 541.0 ng/ml, $p < 0.01$), and p-cresol sulfate levels (mean: 1442.8 ng/ml vs. 1394.6 ng/ml, $p < 0.01$). (concentration unit, ng/ml).

developing CKD. The results of the present study suggested that IPA may be an important biomarker and protector against CKD development.

Increased oxidative stress is often observed in CKD patients due to increased reduced antioxidant defenses. Previous studies have found that oxidative stress is significantly associated with increased kidney damage [7]. The putative protective effect of serum IPA on the development of CKD may be explained by its potent anti-oxidative stress capacity, as IPA is a potent scavenger of hydroxyl radicals. In addition, unlike other antioxidants, IPA scavenges radicals without subsequently generating reactive and pro-oxidant intermediate compounds [8]. It has been previously suggested that IPA may play a role in preventing kidney damage associated with oxidative stress by scavenging radicals [9].

Dysbiosis of the gut microbiome impacts the bacterial-mediated production of indole-containing uremic toxins, such as IS/PCS, which are derived from tryptophan. Previous studies indicated that IS/PCS are also renal toxins. Recent studies have reported that IPA could suppress inflammation and kidney fibrosis induced by IS [9]. Organic anion transporter mediated transport of IS/PCS have significant pathological roles in kidney injury [10]. IPA is an organic anion with a similar molecular weight to IS/PCS. Competition for the organic anion transporter between IPA and IS/PCS might be a possible renal protective mechanism of IPA.

In summary, IPA is a metabolite of healthy gut microbiota, which might be an important biomarker and renal protector against the development of CKD.

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## Conflicts of interest

The authors declare that they have no conflicts of interest.

## Author contributions

H.Y.H. was responsible for and the main contributor to the conception of the study, data analysis and writing the manuscript. S.C.Y. was responsible for the study design, data collection and analysis and writing the manuscript. C.J.L. and H.C.P. contributed to the literature analyses, data management, preparation and analysis. C.C.L., S.C.L., Y.T.H. and S.Y.H. contributed to the management, preparation, and interpretation of the data. All authors contributed to and approved the final manuscript.

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## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clnu.2018.11.029.

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