**Serum aryl hydrocarbon receptor ligand activity is associated with insulin resistance and resulting type 2 diabetes**

Eun Roh\*1,2,5, Soo Heon Kwak\*1, Hye Seung Jung1, Young Min Cho1,2, Youngmi Kim Pak3, Kyong Soo Park1,2,5, Seong Yeon Kim1,2, Hong Kyu Lee4

1Department of Internal Medicine, Seoul National University Hospital, Seoul 110-744, Korea;

2Department of Internal Medicine, Seoul National University College of Medicine, Seoul 110-744, Korea;

3Department of Physiology, Kyung Hee University College of Medicine, Seoul 130-701, Korea;

4Department of Internal Medicine, Eulji University College of Medicine, Seoul 139-711, Korea;

5Department of Molecular Medicine and Biopharmaceutical Sciences, Graduate School of Convergence Science and Technology and College of Medicine, Seoul National University Seoul 110-744, Korea.

\*These authors contributed equally to this work.

**Keywords:** Persistent organic pollutants; Dioxins; Aryl hydrocarbon receptor; Insulin resistance; Type 2 diabetes

Corresponding author and persons to whom reprint request should be addressed:

Kyong Soo Park, MD, PhD

Department of Internal Medicine

Seoul National University College of Medicine

101, Daehak-ro, Jongno-gu, Seoul 110-744, Korea

Phone: +82-2-2072-2946

Fax: +82-2-762-9662

e-mail: kspark@snu.ac.kr

**Supplementary Material**

Supplementary Table 1. Baseline characteristics of the whole population before matching.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | NGT (n = 88) | IGT (n = 154) | T2DM (n = 95) | *P* |
| Age (years) | 57.8 ± 8.8 | 57.5 ± 9.3 | 58.4 ± 11.0 | 0.776 |
| Sex (M/F) | 52/36 | 78/76 | 49/46 | 0.421 |
| Body mass index (kg/m2) | 23.7 ± 2.2† | 24.1 ± 2.6 | 24.6 ± 2.5† | 0.038 |
| Waist circumference (cm) | 87.3 ± 6.1 | 86.1 ± 7.9 | 85.8 ± 6.8 | 0.378 |
| Systolic blood pressure (mmHg) | 124 ± 12 | 122 ± 15‡ | 127 ± 14‡ | 0.034 |
| Diastolic blood pressure (mmHg) | 78 ± 12 | 77 ± 11 | 78 ± 11 | 0.430 |
| Fasting plasma glucose (mmol/l) | 5.0 ± 0.5\*† | 5.4 ± 0.6\*‡ | 6.9 ± 1.8†‡ | <0.001 |
| Hb A1c (%)a | 5.5 (5.3, 5.5)\*† | 5.9 (5.7, 6.0)\*‡ | 6.6 (6.3, 7.0)†‡ | <0.001 |
| HbA1c (mmol/mol)a | 36.6 (34.4, 36.6)\*† | 41.0 (38.8, 42.1)\*‡ | 48.6 (45.4, 53.0)†‡ | <0.001 |
| Fasting plasma insulin (pmol/l)a | 65 (52, 88) | 74 (54, 96) | 78 (62, 102) | <0.001 |
| Total cholesterol (mmol/l) | 5.1 ± 0.8 | 5.1 ± 1.0 | 4.9 ± 0.9 | 0.316 |
| Triglyceride (mmol/l)a | 1.1 (0.8, 1.7) | 1.3 (0.9, 1.8)‡ | 1.5 (1.1, 2.2)‡ | 0.018 |
| HDL cholesterol (mmol/l)a | 1.4 (1.2, 1.6) | 1.3 (1.2, 1.6) | 1.3 (1.1, 1.5) | 0.454 |
| LDL cholesterol (mmol/l) | 3.0 ± 0.8 | 3.1 ± 0.9 | 2.9 ± 0.8 | 0.111 |
| HOMA-IRa | 2.0 (1.6, 2.8)† | 2.4 (1.7, 3.3)‡ | 3.4 (2.3, 4.6)†‡ | <0.001 |
| HOMA-β (%)a | 129 (95, 197)\*† | 102 (79, 147)\*‡ | 71 (51, 100)†‡ | <0.001 |

Data are means ± standard deviation (for normal distribution) or median (interquartile range).

aThese variables were log transformed before analyses.

\**P* <0.05 for NGT vs. IGT; †*P* <0.05 for NGT vs. T2DM, ‡*P* <0.05 for IGT vs. T2DM.

Supplementary Table 2. The proportion of NGT, IGT and T2DM according to the serum TCDDeq quartiles.

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | TCDDeq quartiles  (serum TCDDeq concentrations (pmol/l)) | | | | *P* |
| 1st quartile  (31.7–48.2) | 2nd quartile  (48.3–58.4) | 3rd quartile  (58.5–75.0) | 4th quartile  (75.1–271.3) |
| NGT | 26 (35.1) | 27 (36.5) | 20 (27.0) | 10 (13.5) | <0.001 |
| IGT | 37 (50.0) | 25 (33.8) | 36 (48.6) | 32 (43.2) |
| T2DM | 11 (14.9) | 22 (29.7) | 18 (24.3) | 32 (43.2) |
| Total | 74 (100) | 74 (100) | 74 (100) | 74 (100) |

Data are n (%).

TCDDeq concentrations were log transformed before analyses.

Supplementary Table 3. Association of T2DM and serum TCDDeq quartiles after stratification by age and BMI.

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  |  |  | | TCDDeq quartiles  (serum TCDDeq concentrations (pmol/l)) | | | | |  |
|  |  |  | | | 1st quartile  (31.7–48.2) | 2nd quartile  (48.3–58.4) | 3rd quartile  (58.5–75.0) | 4th quartile  (75.1–271.3) | *P* |
|  | | |  | | 74 | 74 | 74 | 74 |  |
| Age | | |  | |  |  |  |  |  |
|  | <60 years | |  | |  |  |  |  |  |
|  |  | | Cases/n | | 4/37 | 10/36 | 7/36 | 19/41 |  |
|  |  | | OR (95% CI) | | Referent | 3.4 (0.9–12.4) | 1.6 (0.4–6.2) | 7.7 (2.2–26.8) | 0.002 |
|  | ≥60 years | |  | |  |  |  |  |  |
|  |  | | Cases/n | | 7/37 | 12/38 | 11/38 | 13/33 |  |
|  |  | | OR (95% CI) | | Referent | 2.1 (0.7–6.1) | 1.7 (0.6–5.2) | 2.9 (1.0–8.5) | 0.091 |
| BMI | | |  | |  |  |  |  |  |
|  | <25 kg/m2 | |  | |  |  |  |  |  |
|  |  | | Cases/n | | 8/49 | 12/47 | 10/48 | 21/48 |  |
|  |  | | OR (95% CI) | | Referent | 1.8 (0.6–4.8) | 1.4 (0.5–3.9) | 4.4 (1.6–11.5) | 0.005 |
|  | ≥25 kg/m2 | |  | |  |  |  |  |  |
|  |  | | Cases/n | | 3/25 | 10/27 | 8/26 | 11/26 |  |
|  |  | | OR (95% CI) | | Referent | 4.1 (0.9–17.5) | 2.9 (0.6–12.8) | 5.5 (1.3–23.3) | 0.045 |

TCDDeq concentrations were log transformed before analyses.

All odds ratios were adjusted for age and BMI.

OR, odds ratio; CI, confidence interval