BMC Geriatrics

Open Access

The relationship between polycyclic aromatic hydrocarbons exposure and serum klotho among adult population

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Abstract

Background: Klotho is an important factor involving aging process. Recently, polycyclic aromatic hydrocarbons (PAHs) exposure was reported to have adverse impact on DNA methylation associated with aging. The aim of the current study was to determine the relationship between serum klotho and PAHs exposure in an adult population.

Methods: A total of 2597 participants obtained from NHANES 2015–2016 were included in this cross-sectional study. Serum klotho levels were analyzed by enzyme-linked immunosorbent assay (ELISA). PAHs exposure was estimated by urinary sample using liquid chromatography-tandem mass spectrometry. The relationship between serum klotho and exposure to PAHS was analyzed by a multivariable linear regression model.

Results: 2-napthol and 3-fluorene were significantly associated with decreased klotho. After fully adjusting pertinent variables, PAH exposure was significantly associated with decreased klotho, particularly in men.

Conclusion: In the present study we highlighted the significant association between PAHs exposure and serum klotho levels. The importance of environmental effect on aging process and age-related disorders should be paid more attention and clinical intervention is necessary.

Keywords: Polycyclic Aromatic Hydrocarbons, Klotho, Adult

Introduction

Klotho gene mutation was reported to involve many pathways about aging process such as shortened lifespan, vascular calcification, growth retardation, and osteoporosis [1–3]. It encodes a type I transmembranous protein related to β-glucuronidases and divides into α-, β-, and γ-isoforms [4, 5]. α-Klotho has emerged as a powerful regulator of the aging process by regulating many pathways, such as the regulation of phosphate homeostasis, Wnt signaling, and insulin signaling [5]. It is regarded as a crucial role in the pathophysiology of common aging related disorders, including chronic kidney disease, metabolic syndrome, and cardiovascular diseases [6–8].

Polycyclic aromatic hydrocarbons (PAHs) are organic compounds with multiple aromatic rings of only carbon and hydrogen [9]. These pollutants are generated via the insufficient combustion of natural or synthetic organic matter [10, 11], including biomass burning [12], vehicular exhausts [13], and metal emission [14]. They can spread from their source via many media such as air, water [15, 16], and even store in the terrestrial soils [13, 17]. Methods for evaluating PAHs exposure include job exposure matrices in exposure modeling, occupational settings, self-reported exposures, and biomarkers [18–20]. Hydroxylated (OH) PAH metabolites in urinary sample are widely used biomarkers to assess implied human exposure to a number of PAHs [21, 22]. Commonly

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detected urinary metabolites are low-molecular weight PAHs, including naphthalene, fluorene, phenanthrene, and pyrene [23]. Evidence reports that high-molecular weight PAHs with over 4 aromatic rings, especially benzo[a]pyrene, are mainly excreted via feces and are not detectable in urine [24–26].

PAH exposure causes various systemic diseases, including cancer, obstructive lung diseases, and cardiovascular diseases [27–29]. Recently, PAH exposure was suggested to be associated with frailty, including poor muscle strength and altered bone turnover in elder population [30, 31]. PAHs exposure may have adverse impact on aging process by accelerating DNA methylation aging [32]. To the best of knowledge, no previous study has reported the association between exposure to PAHs and klotho either in vivo or in vitro. In our study, we hypothesized that PAHs exposure may be correlated with decreased serum klotho in a cross-sectional analysis of a nationally representative general adult sample in the United States.

Method
Study population
All study information was collected from the National Health and Nutrition Examination Survey (NHANES) 2015–2016. NHANES is a major program of the National Centers for Health Statistics (NCHS). This nationally representative survey engages a variety of health and nutrition measurements of population in United States. A total of 2637 participants included in the NHANES database who had klotho in the serum measured from 2015 to 2016 were included in this study. After excluding those didn't have laboratory data of urinary PAH and complete other examinations, 2597 eligible participants included 1318 men and 1279 women were enrolled in this study. Ethics approval was approved by the Institutional Review Board of the NCHS Ethics Review Board (number: Protocol #2011–17) and study design was confirmed in accordance with the Helsinki Declaration. Participants provided informed consent before enrollment.

Level of urinary PAHs
The urinary hydroxylated polycyclic aromatic hydrocarbon metabolites included 1-naphthalene, 2-fluorene, 2-naphthalene, 1-phenanthrene, 3-fluorene, 3-phenanthrene, 2-phenanthrene, and 1-pyrene. Urinary sample was collected by a well-trained technician under standard protocol and were stored at -20 ℃. The separation and quantification of urinary metabolites was using isotope dilution high performance liquid chromatography-tandem mass spectrometry [33]. To prepare for quality control materials, a known native standard mixture was digested into an anonymous filtered urine pool. The

quality control solution was homogenized for at least 3 h then aliquoted into vials and stored at -70 ℃ [34]. A matrix matched standard calibration curve was used for comparison to target reagents, which was determined from comparative response of native to labelled standards in the urinary samples [33]. These samples were analyzed with one blank sample, one quality control (low), and another quality control (high level) simultaneously in each run. The limits of detection for PAHs metabolites ranged from 0.007 ng/mL to 0.09 ng/mL.

Measurement of serum klotho
Analyses for serum klotho levels were performed by a commercially available enzyme-linked immunosorbent assay (ELISA) kit (Immuno-Biological Laboratories, Takasaki, Japan) according to the manufacturer's protocol. All study samples were examined in duplicate with average of two concentrations used as the final value. Two quality control samples were contained in each plate analyzed in duplicate.

Measurement of covariates
Demographic data, such as age, gender, race/ethnicity, smoking history, and medical histories were obtained from participants' self-reported questionnaires and all data is available on the NHANES database. The participants were classified into different races such as non-Hispanic white and others. Information about medical history, including coronary artery disease, angina, hypertension, and diabetes mellitus were also collected from the participants. Waist circumference was measured in the horizontal plane between the iliac crest and the lowest rib. Laboratory data such as serum creatinine and albumin were analyzed by standard procedures.

Statistical analysis
Statistical estimates were calculated by the Statistical Package for the Social Sciences, version 22.0 (SPSS Inc., Chicago, IL, USA) for Windows. Continuous variables were presented as means and standard deviation, while categorical variables were presented as frequencies and percentage. The differences between the gender groups in terms of demographic information and laboratory data were determined by Pearson chi-square test. A p-value ≤ 0.05 was considered statistically significant. The association between different degree of sarcopenia and higher FRS was analyzed using Logistic regression with an unadjusted and adjusted model for all pertinent variables in the study. Power statistic calculation of FRS was used to estimate the sample size in men and women.

Results

Characteristics of study population

The characteristic information of participants included 2597 eligible participants in this cross-sectional study was demonstrated in Table 1. The mean age was 57.60 ± 10.85 years. The mean level of serum klotho was 861.01 (pg/mL). The mean level of PAHs included 1-naphthol, 2-naphthol, 3-fluorene, 2-fluorene, 3-phenanthrene, 1-phenanthrene, 2-phenanthrene, and 1-pyrene were 43.72, 0.78, 0.29, 0.63, 0.14, 0.21, 0.11, and 0.19 (ug/L), respectively.

Association between PAHs and klotho

Table 2 displayed the association between PAHs and klotho. After adjusting pertinent variables included age, race, waist circumference, creatinine, albumin, medical history, and smoking history, 2-napthol and 3-fluorene were significantly associated with decreased klotho with β values -0.001 (95% confidence interval [CI]: -0.002, 0.000) and -0.026 (95%CI: -0.046, -0.005).

Association between PAHs and klotho in gender difference

The relationship between PAHs and klotho in men and women was demonstrated in Table 3. After fully adjusting pertinent variables, 2-napthol, 3-fluorene, 2-fluorene, and 1-phenanthrene were significantly associated with decreased klotho in men with β values -0.002 (95%CI: -0.003, 0.000), -0.034 (95%CI: -0.059, -0.008), -0.014 (95%CI: -0.027, 0.000), and -0.049 (95%CI: -0.095, -0.004). However, no significant finding between PAHs and kloth was found in women.

Discussion

In the cross-sectional study, we investigated the relationship between exposure to PAHs and serum klotho levels in a nationally representative sample among American population. PAHs such as 2-napthol and 3-fluorene were significantly associated with decreased klotho levels. Especially, this relationship remained significant in men, including 2-napthol, 3-fluorene, 2-fluorene, and 1-phenanthrene, respectively. To the best of our knowledge,

Table 1 Characteristics of Study Population

Variables	Participants ($N = 2597$)
Continuous variables, mean (SD)	
Age (years)	57.60 (10.85)
Waist circumference (cm)	101.56 (15.39)
Creatinine (mg/dL)	0.90 (0.33)
Albumin (mg/dL)	4.23 (0.30)
Klotho (pg/mL)	861.01 (308.09)
1-naphthol (ug/L)	4.37 (51.98)
2-naphthol (ug/L)	7.85 (11.29)
3-fluorene (ug/L)	0.29 (0.59)
2-fluorene (ug/L)	0.63 (1.18)
3-phenanthrene (ug/L)	0.14 (0.29)
1-phenanthrene (ug/L)	0.21 (0.33)
2-phenanthrene (ug/L)	0.11 (0.17)
1-pyrene (ug/L)	0.19 (0.39)
Category Variables, (%)	
Non-Hispanic White	1194 (46.0)
Gender (male)	1318 (50.8)
Coronary heart disease	148 (5.7)
Angina/ angina pectoris	81 (3.1)
Hypertension	647 (23.9)
Diabetes mellitus	408 (15.7)
Smoking	1299 (50.0)

Table 2 Association between PAHs and klotho

Variables	Model 1[a] β[b] (95% CI)	P Value	Model 2[a] β[b] (95% CI)	P Value
	Klotho			
1-napthol	0.000 (0.000, 0.000)	0.766	0.000 (0.000, 0.000)	0.612
2-napthol	-0.001 (-0.002, 0.000)	0.032	-0.001 (-0.002, 0.000)	0.044
3-fluorene	-0.023 (-0.042, -0.003)	0.021	-0.026 (-0.046, -0.005)	0.015
2-fluorene	-0.010 (-0.019, 0.000)	0.057	-0.010 (-0.020, 0.000)	0.071
3-phenanthrene	-0.029 (-0.069, 0.011)	0.159	-0.027 (-0.067, 0.013)	0.185
1-phenanthrene	-0.021 (-0.057, 0.015)	0.249	-0.022 (-0.058, 0.014)	0.227
2-phenanthrene	-0.047 (-0.116, 0.022)	0.183	-0.044 (-0.113, 0.026)	0.219
1-pyrene	0.009 (-0.021, 0.038)	0.562	0.007 (-0.023, 0.037)	0.656

[a] Adjusted covariates

Model 1: unadjusted

Model 2: age, race/ethnicity, congestive heart failure, coronary heart disease, angina, smoking, hypertension, diabetes mellitus, creatinine, waist circumference, albumin

Table 3 Association between PAHs and klotho in gender difference

	Variables	Model 1[a] β[b] (95% CI) Klotho	P Value	Model 2[a] β[b] (95% CI)	P Value
Male	**1-napthol**	0.000 (0.000, 0.000)	0.497	0.000 (0.000, 0.000)	0.379
	2-napthol	-0.002 (-0.003, 0.000)	0.029	-0.002 (-0.003, 0.000)	0.038
	3-fluorene	-0.028 (-0.052, -0.004)	0.023	-0.034 (-0.059, -0.008)	0.009
	2-fluorene	-0.012 (-0.025, 0.000)	0.056	-0.014 (-0.027, 0.000)	0.046
	3-phenanthrene	-0.036 (-0.082, 0.010)	0.129	-0.040 (-0.086, 0.007)	0.093
	1-phenanthrene	-0.046 (-0.091, 0.000)	0.049	-0.049 (-0.095, -0.004)	0.035
	2-phenanthrene	-0.070 (-0.157, 0.016)	0.111	-0.078 (-0.165, 0.009)	0.078
	1-pyrene	0.014 (-0.020, 0.048)	0.410	0.011 (-0.023, 0.046)	0.513
Female	**1-napthol**	0.000 (0.000, 0.000)	0.701	0.000 (0.000, 0.000)	0.815
	2-napthol	-0.001 (-0.002, 0.001)	0.284	-0.001 (-0.002, 0.001)	0.336
	3-fluorene	-0.014 (-0.045, 0.017)	0.381	-0.015 (-0.049, 0.018)	0.376
	2-fluorene	-0.006 (-0.021, 0.009)	0.461	-0.005 (-0.021, 0.011)	0.507
	3-phenanthrene	-0.005 (-0.076, 0.065)	0.881	-0.011 (-0.083, 0.060)	0.756
	1-phenanthrene	0.006 (-0.049, 0.061)	0.839	0.004 (-0.052, 0.059)	0.899
	2-phenanthrene	-0.001 (-0.109, 0.107)	0.985	-0.009 (-0.120, 0.102)	0.870
	1-pyrene	0.006 (-0.046, 0.058)	0.824	0.000 (-0.054, 0.054)	0.997

[a] Adjusted covariates:

Model 1: unadjusted

Model 2: age, race/ethnicity, congestive heart failure, coronary heart disease, angina, smoking, hypertension, diabetes mellitus, creatinine, waist circumference, albumin

no previous study has reported the association between PAH exposure and serum klotho. Our study was the first to investigate the plausible pathway of PAHs exposure involving the aging process.

Klotho gene is reported contributing to anti-aging property by telomerase activation and consequently telomere maintenance [35]. Ullah et al. demonstrated that klotho protein deficiency diminished telomerase activity by impairing the expression of telomeric repeat-binding factor 1, and then led to altered differentiation, cellular senescence, and stem cell apoptosis [36]. Numerous evidence has reported the association between PAH exposure and telomere length. Adli et al. displayed an inverse association between urinary 1-hydroxipayrene level and telomere length in preschool children [37]. An emerging study suggested that everyday life exposure to PAH reduces leukocyte telomere length and mitochondrial DNA copy number [38]. Overall, these studies might support our findings that PAH exposure was associated with reduced serum klotho levels.

Aging is a complicated phenomenon and is influenced by various genetic and environmental factors [39]. Cigarette smoking is regarded as one of the important risk factors of aging process [40]. In a retrospective study included Japanese adults, smokers showed significantly higher serum levels of klotho protein than non-smokers [41]. Kamizono et al. reported cigarette smoking

was significantly associated with plasma α-klotho levels [42]. As one of the possible or known human carcinogens, PAHs are kinds of complex chemical composition released by cigarette smoking [43], and potentially affecting the aging process. Best et al. demonstrated the adverse effect of PAHs exposure on cognitive function among elderly population [44]. Another study also reported exposure to PAHs correlated with functional dependence among older people in the United States [39]. Recently, a variety of evidence suggested that the states of DNA methylation play an important role in gene regulation associated with aging process [45]. In a vitro study, Duca et al. demonstrated that PAH exposure affected DNA and RNA methylation in a rat model [46]. Li et al. reported that PAH exposure was associated with acceleration of DNA methylation in a population-based study [32]. Hypermethylation of klotho promoter decreases the expression of klotho protein in the progress of chronic kidney disease [47]. Genetic silencing of klotho in young muscle progenitor cell induce mitochondrial DNA damage and decreased cellular bioenergetics leading to aging process of muscle regeneration [48].

PAHs are well-known endocrine disrupting toxicants and reproductive chemicals [49]. Zhang et al. demonstrates that high-molecular weight PAHs can activate their endocrine-disrupting effects by androgen or

estrogen receptors, with structure-dependent agonistic or antagonistic effects [50]. Drwal et al. provides evidence of cell specific effects of low-molecular weight PAHs on proliferation, the cell cycle, and hormone secretion [51]. Highly prevalent low-molecular weight PAHs are recognized as inhibitors of gap junctional intercellular communication (GJIC) in some types of cells [52]. GJIC is suggested a key driver of endocrine function in testis, which makes testicular GJIC as a target for PAHs [53]. In a recent study, PAHs are considered an important risk factor leading to reproductive dysfunctions in men through impaired testicular GJIC [54]. Accordingly, the sex-specific impact of PAHs may elucidate the significant change with serum klotho in men of our study.

There are some limitations should be concerned when interpreting our results. First, the cross-sectional design of this study prevented the identification of causal nature between PAHs exposure and serum klotho. PAH metabolite biomarkers display recent exposures rather than long-term exposures. Second, this study assessed serum klotho levels only over the short term. The long-term effect of PAH exposure on klotho will need to be elucidated in the future. Last, the mechanisms of PAH exposure on serum klotho levels are still unknown. Further long-term examination are needed to provide more evidence of air pollution control and prevention of aging acceleration.

Conclusion
In the present study, we demonsrtrated that PAH exposure was associated with decreased serum klotho levels, highlighting the negative impact of PAH exposure on aging. Future studies are warranted to investigate the potential mechanisms of klotho gene expression and clinical significance influenced by such environment-related effects.

Declarations

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