中文題目：中老年人血清 Klotho 濃度與死亡風險呈現 U 型相關

英文題目：U-shaped association between serum Klotho levels and mortality risk in middle-aged and older adults

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Background

Alpha-Klotho, or α-Klotho, has been regarded as an anti-aging protein involved in suppressing oxidative stress and inflammation. Emerging research has investigated the roles of Klotho in aging-related disorders such as cancer, cardiovascular disease, and kidney disease. Several studies showed that serum Klotho levels inversely correlated to mortality risk among individuals with advanced kidney disease or renal replacement therapy. However, research on the association of Klotho with the risk of death in general population is relatively lacking. Our study purpose is to investigate the association between serum Klotho level and long-term mortality risk among a nationally representative sample of middle-aged and older adults in the United States.

Method

The study population was recruited from 2007-2016 National Health and Nutrition Examination Survey (NHANES) in the United States. A total of 13583 adults aged 40-79 years with baseline estimated glomerular filtration rate (eGFR) of ≥ 30 mL/min/1.73m^2 were included. Serum levels of soluble alpha-Klotho was measured by a commercially available ELISA kit produced by IBL International, Japan. We grouped the participants by quintile of serum Klotho levels as group 1 (n=2713) with Klotho of < 622 pg/ml (median 537.9, IQR: 475.4 - 582.5 pg/ml), group 2 (n=2731) of 622 ~ < 745 (median 686.7, IQR: 656.9 - 715.4 pg/ml), group 3 (n=2708) of 745 ~ < 870 (median 805.2, IQR: 773.3 - 836.3 pg/ml), group 4 (n=2714) of 870 ~ < 1055 (median 948.6, IQR: 908.0 - 995.6 pg/ml), and group 5 (n=2717) of ≥ 1055 (median 1225.2, IQR: 1129.1 - 1402.2 pg/ml). The survival status was ascertained by linking NHANES data to death records from the National Death Index through probabilistic matching and death certificate review. The follow-up period for each participant is the period between the NHANES baseline examination date and the participant's death date or last date of follow-up (December 31, 2019), whichever came first.

Results

The average age of the study population was 57.6±10.8 years old and 48.5% of them was male, with race/ethnicity distribution of 43.2% Whites, 19.6% Blacks, and 27.4% Hispanics. We observed that individuals with higher serum Klotho levels tended to be younger in age, females, non-smokers, higher in eGFR, lower in prevalence of hypertension, cardiovascular disease (CVD), and previous stroke, and higher in educational attainment. There was no difference in body mass index (BMI), minutes of equivalent combination of moderate- and vigorous-intensity physical activity per week, and family income to poverty ratio. By multiple linear regression, our results showed that females, individuals with higher Hemoglobin (Hb) level, higher eGFR, and those with diabetes or history of hepatitis C virus (HCV) infection positively correlated to higher serum levels of Klotho. In contrast, smokers, non-Hispanic Whites, individuals with higher BMI, higher serum albumin, older age, or lower

educational attainment were associated with lower serum levels of Klotho. Hypertension, CVD, previous stroke, and physical activity minutes per week were not significantly associated with Klotho level.

During a median follow-up of 99.0 months (interquartile range: 68.0-129.0 months), a total of 1490 participants died (11.8 per 10000 person-months), of whom 332 died from CVD and 433 died from cancer. Our crude analysis showed that group 1 correlated to higher risk of all-cause mortality compared with group 2, group 3, group 4, and group 5. By Cox regression analysis with adjustment for age and sex, our results showed that group 2 (HR: 0.80, 95% CI 0.69-0.93, $p<0.01$), group 3 (HR: 0.76, 95% CI 0.65-0.89, $p<0.001$), and group 4 (HR: 0.71, 95% CI 0.61-0.84, $p<0.001$) were associated with lower all-cause mortality risk when compared with group 1; however, we did not observe a significant difference between group 1 and group 5 in mortality risk. After further adjusting for race/ethnicity, survey cycle, BMI, serum albumin, Hb, eGFR, diabetes, hypertension, CVD, previous stroke, history of HCV infection, smoking status, educational attainment, marital status, and family income to poverty ratio, we showed that group 2 (HR: 0.82, 95% CI 0.70-0.97, $p<0.05$), group 3 (HR: 0.79, 95% CI 0.67-0.93, $p<0.01$), and group 4 (HR: 0.82, 95% CI 0.69-0.97, $p<0.05$) had lower all-cause mortality risk compared with group 1, but there was no significant difference between group 1 and group 5. Furthermore, when compared with group 3, we observed that group 5 was associated with higher mortality risk (HR: 1.20, 95% CI 1.01-1.44, $p<0.05$) after adjusting for potential confounders.

To explore the differences in characteristics of each group, we conducted a multinomial logistic regression analysis. We found that, when compared with group 3, group 1 was associated with lower Hb, lower eGFR, being males, and being more likely to be current smokers. There was no significant difference in BMI, age, race/ethnicity, serum albumin, diabetes, hypertension, CVD, previous stroke, history of HCV infection, marital status, educational attainment, and family income to poverty ratio between group 1 and group 3. Additionally, group 5 tended to be females, younger in age, lower BMI, lower serum albumin, higher Hb, having a history of diabetes or HCV infection, more likely to be never or former smokers, and less likely to be non-Hispanic Whites when compared with group 3. There was no significant difference in eGFR, hypertension, CVD, previous stroke, marital status, educational attainment, and family income to poverty ratio between group 3 and group 5.

Conclusion

Among middle-aged and older U.S. adults, we observed a U-shaped association between serum Klotho levels and long-term mortality risk. While lower serum Klotho levels were a predictor of mortality risk, higher levels also correlated to increased mortality risk. Future studies are needed to be conducted to see if our findings can be replicated and to explore the underlying mechanisms.