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Betel nut chewing associated with increased risk of arterial stiffness

Yu-Ting Wei[a], Yu-Tsung Chou[a], Yi-Ching Yang[a,b], Chieh-Ying Chou[a], Feng-Hwa Lu[a,b], Chih-Jen Chang[a,b,**], Jin-Shang Wu[a,b,*]

[a] Department of Family Medicine, National Cheng Kung University Hospital, No.138, Sheng Li Road, Tainan, 70403, Taiwan
[b] Department of Family Medicine, College of Medicine, National Cheng Kung University, No. 1 University Road, Tainan, 70101, Taiwan

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ABSTRACT

Background: Betel nut chewing is associated with certain cardiovascular outcomes. Subclinical atherosclerosis may be one link between betel nut chewing and cardiovascular risk. Few studies have examined the association between chewing betel nut and arterial stiffness. The aim of this study was thus to determine the relationship between betel nut chewing and arterial stiffness in a Taiwanese population.

Methods: We enrolled 7540 eligible subjects in National Cheng Kung University Hospital from October 2006 to August 2009. The exclusion criteria included history of cerebrovascular events, coronary artery disease, and taking lipid-lowering drugs, antihypertensives, and hypoglycemic agents. Increased arterial stiffness was defined as brachial–ankle pulse wave velocity (baPWV) ≥1400 cm/s. According to their habit of betel nut use, the subjects were categorized into non-, ex-, and current chewers.

Results: The prevalence of increased arterial stiffness was 32.7, 43.3, and 43.2% in non-, ex- and current chewers, respectively (p = 0.011). Multiple logistic regression analysis revealed that ex-chewers (odds ratio [OR] 1.69, 95% confidence interval (CI) = 1.08–2.65) and current chewers (OR 2.29, 95% CI = 1.05–4.99) had elevated risks of increased arterial stiffness after adjustment for co-variables.

Conclusions: Both ex- and current betel nut chewing were associated with a higher risk of increased arterial stiffness. Stopping betel nut chewing may thus potentially be beneficial to reduce cardiovascular risk, based on the principals of preventive medicine.

1. Introduction

Betel nut (areca), grown from Areca palms, is the fourth most popular psychoactive substance in the world (Gupta and Ray, 2004). It is estimated that 10–20% of the world's population use betel nut, especially in South and Southeast Asia and the Asia Pacific region (Gupta and Ray, 2004; Gupta and Warnakulasuriya, 2002). In Taiwan, the prevalence of betel nut chewing is as high as 16.9% (31% in men and 2.4% in women) (Guh et al., 2007). Betel nut chewing has long been a tradition among the native Taiwanese population, and it is not only seen as a psychoactive agent but also a form of entertainment for blue-collar workers (Ko et al., 1992; Lin et al., 2017). What is sold as "betel nut" is commonly chewed with the *Piper betle* leaf. "Betel quid", the mixture of the betel nut, part of the betel pepper vine and slaked lime, may be wrapped in *P. betle* leaf or left unwrapped with the ingredients, such as cardamom, cloves, catechu, and tobacco (Humans, 2004; Organization, 2012; Zain et al., 1999). Although betel nut is neither illegal nor expensive (USD 0.2-0.7 per betel nut according to the quality and the growing season), the Taiwanese government discourages its cultivation, use and commerce given the negative health and environmental effects of its use and cultivation (Tham et al., 2017).

Epidemiological studies show that betel nut use is associated with the increased risk of hypertension (Heck et al., 2012; Tseng, 2008), metabolic disease (Chung et al., 2006; Guh et al., 2006; Yen et al., 2006), dyslipidemia (Guh et al., 2006; Hsu et al., 2010; Yen et al., 2006), type 2 diabetes (Tseng, 2010; Tung et al., 2004), cardiovascular disease (Gupta et al., 2005; Khan et al., 2014; Lan et al., 2007; Lin et al., 2008; Wen et al., 2005; Yen et al., 2008), and all-cause mortality (Gupta et al., 2005; Lan et al., 2007; Lin et al., 2008; Wen et al., 2005). Atherosclerosis plays an important role in the pathophysiology of developing coronary artery disease (Hansson, 2005). Moreover, arterial stiffness is strongly associated with atherosclerosis (van Popele et al., 2001), and is an independent predictor of coronary arterial disease (Liao and Farmer, 2014) and all-cause mortality (Vlachopoulos et al., 2010). In addition, subclinical atherosclerosis was recently shown to be a possible link between betel nut chewing and cardiovascular risk

* Corresponding authors at: Department of Family Medicine, National Cheng Kung University Hospital, No.138, Sheng Li Road, Tainan, 70403, Taiwan.
** Corresponding author.
E-mail address: jins@mail.ncku.edu.tw (J.-S. Wu).

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(McClintock et al., 2014).

To date, there has only been one study on the association between betel nut chewing and arterial stiffness, and this was carried out in a population of farmers and fishermen (Lin et al., 2014). The results showed an insignificant relationship between betel nut use and arterial stiffness without adjustment for potential confounders (such as lifestyle factors and lipid profile), and exclusion of certain underlying diseases (such as hypertension, diabetes mellitus, dyslipidemia, old stroke, and coronary artery disease). The aim of this study was thus to determine the association of betel nut chewing and arterial stiffness in a Taiwanese population, with careful consideration of the confounders and exclusion criteria.

2. Methods

2.1. Study population

We used secondary data analysis without personal identification information, and the research data was retrospectively retrieved from an existing dataset of self-motivated physical check-ups at the health examination center of National Cheng Kung University Hospital from October 2006 to August 2009. The informed consent of the participants was thus not required because the data were analyzed anonymously. The Institutional Review Board of National Cheng Kung University Hospital approved this study protocol (No. B-ER-105-130).

Initially, a total of 7540 participants were enrolled. The exclusion criteria included subjects with a past history of hypertension, diabetes mellitus, coronary artery disease, and old stroke, taking medications for hypertension, diabetes mellitus and dyslipidemia, age < 18 years, and incomplete data. A cross-sectional sample of 6504 consecutive subjects (59.3% male, 40.7% female) who met these criteria was recruited for the final analysis.

2.2. Clinical variables

The baseline data included demographic information, medical and medication history, and lifestyle factors such as smoking, alcohol consumption, betel nut chewing and exercise habits. Smoking habit was classified as non-, ex- and current smokers. A current smoker was defined as smoking at least once per week for at least the previous six months. An ex-smoker was defined as a person who had smoked at least one pack per month for at least six months but stopped smoking at least six months previously. Alcohol drinking habit was classified as non-, ex- and current drinker. A current drinker was defined as drinking at least once per week for at least the previous six months. An ex-drinker was defined as a person who had drunk at least once per week for at least six months but ceased at least six months previously. Betel nut chewers were classified as non-, ex- and current chewers. A current chewer was defined as a person who had chewed betel nut at least once per week for at least the previous six months. An ex-chewer was defined as a person who had chewed betel nut at least once per week for at least six months but ceased at least six months previously. Exercise habit was classified as none to less than three times of vigorous exercise per week, and three times or more per week.

Body mass index (BMI) was defined as body weight (kilogram) divided by the square of body height (meter). Right brachial systolic and diastolic blood pressures (SBP, DBP) were taken in a supine position after at least 15 min of rest using a DINAMAP TM vital signs monitor (Model 1846SX, Critikon Inc, Irvine, California, U.S.A.). The laboratory data included fasting plasma glucose (FPG), creatinine, total cholesterol (TC), triglyceride, and high-density lipoprotein cholesterol (HDL-C) concentrations.

The brachial–ankle pulse wave velocity (baPWV) value was measured using a noninvasive vascular screening device (BP-203RPE II; Colin Medical Technology, Komaki, Japan) with four pneumatic pressure cuffs, wrapped on both upper arms and ankles, simultaneously measuring blood pressure and pulse waves in the bilateral brachial and tibial arteries after at least five minutes of bed rest. The baPWV value was calculated as the distance traveled by the pulse wave divided by the time taken to travel the distance. The right-sided baPWV values were used for the analysis. The reference value of baPWV with a cut-off of 1400 cm/s or more was considered to be an indicator of atherosclerotic cardiovascular risk (Yamashina et al., 2003); increased arterial stiffness was thus defined as baPWV ≥1400 cm/s.

2.3. Statistical analyses

We performed the statistical analyses using the 17th version of the SPSS software (Chicago, Illinois, USA: SPSS Inc). Continuous variables were expressed as the means ± standard deviations, and categorical variables were presented as numbers (percentages). Comparisons between subjects with and without increased arterial stiffness were performed by Pearson's chi-square test for categorical variables, and the Student's *t*-test for continuous variables. Using multiple logistic regression, the adjusted odds ratio (OR) and 95% confidence interval (CI) were calculated after adjustments for age, gender, BMI, systolic blood pressure, fasting plasma glucose level, estimated glomerular filtration rate (eGFR), TC/HDL-C ≥5, habits of smoking, drinking, and betel nut use, and exercise. Statistical significance was set at $p < 0.05$.

3. Results

3.1. Description of study population

A total of 6504 subjects were recruited for the final analysis. The prevalence of ex- and current betel nut chewers was 2.2 and 0.7% respectively. The baseline characteristics of the group with and without increased arterial stiffness are shown in Table 1. The prevalence of increased arterial stiffness was 32.7, 43.3, and 43.2% in non-, ex- and current chewers, respectively ($p = 0.011$), with a significant trend ($p < 0.001$). There were significant differences in age, gender, BMI, systolic and diagnostic blood pressures, eGFR, fasting plasma glucose, total cholesterol, triglyceride, HDL-C, and the prevalence of smoking, alcohol drinking, habitual exercise, and betel nut use, as well as the length of betel nut chewing (years), the daily chewing amount and the cumulative exposure of betel nut use, measured by quantity per day in pieces multiplied by duration in years, between subjects with and without increased arterial stiffness.

3.2. Association of betel nut chewing and arterial stiffness

The results of multiple logistic regression analysis on the relationship between betel nut chewing and increased arterial stiffness are summarized in Table 2. Ex-chewers (odds ratio [OR] 1.69, 95% confidence interval (CI) = 1.08–2.65) and current chewers (OR 2.29, 95% CI = 1.05–4.99) had elevated risks of increased arterial stiffness after adjustment for co-variables in model 1. In comparison to non-chewers, the associated risk of increased arterial stiffness was significantly elevated in subjects with chewing betel nut ≥10 years (OR 2.04, 95% CI = 1.14-3.64, $p = 0.009$), but not significant in subjects with chewing betel nut < 10 years in model 2. As for the quantity of daily chewing, the associated risk was 1.76 (95% CI = 1.16–2.68, $p = 0.008$) in subjects with betel nut use ≥5 pieces per day, but insignificant in subjects who chewed < 5 pieces per day in model 3. Finally, both ≥100 piece-year (OR 1.99, 95% CI = 1.09-3.61, $p = 0.025$) and < 100 piece-year (OR 1.70, 95% CI = 1.03–2.81, $p = 0.038$) of the cumulative exposure to betel nut use were positively associated with increased arterial stiffness in model 4. In addition, other independently associated factors of increased arterial stiffness were age, gender, BMI, systolic blood pressure, TC/HDL-C ≥5, fasting plasma glucose level, and habitual exercise. We also performed multiple logistic regression analysis for groups with age < 60 years and age