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ORIGINAL ARTICLE

Chewing areca nut as an independent risk factor for proteinuria in middle-aged men

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Abstract No previous large-scale research has reported the association of chewing areca nut (AN) with proteinuria. The aim of this study was to investigate such an association in men over a 7-year study. In this cross-sectional research, we retrospectively reviewed the records of health check-ups in a community hospital setting from 2003 to 2009. Laboratory tests, medical histories, and the status of smoking cigarettes, drinking alcohol, and chewing AN were obtained for each participant. Proteinuria was defined as having +/− or heavier protein response (including +/− to 4+) in a urine test performed by an automated chemical analyzer. We compared characteristics in participants with and without proteinuria, and analyzed the adjusted risk for proteinuria with chewing AN in middle-aged men. We also compared the changes in adjusted risk for proteinuria under a stricter definition of proteinuria (≥ 1+ proteinuria). There were 11,991 men with a mean age of 58.94 ± 12.06 years. The prevalence of proteinuria in AN chewers was 13.7%, and 11.2% for non-chewers ($p = 0.005$). Of the 1381 participants with proteinuria, the proportion chewing AN was 15.3%, and 12.6% for those without proteinuria ($p = 0.005$). In the multivariate logistic regression analysis with three different levels of adjustment models, with adjustment factors for age, drinking, smoking, hypertension, diabetes, hyperlipidemia, body mass index, chronic kidney disease, anemia, liver dysfunction, and hyperuricemia, the odds ratios of proteinuria for chewing AN were 1.61, 1.55 and 1.40 (all $p = 0.000$). With the stricter definition of proteinuria, the odds ratios

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became weaker (1.40, 1.36 and 1.19; $p = 0.009$, 0.029 and 0.24). We concluded that chewing AN was independently associated with risk of proteinuria in middle-aged Chinese men.

Introduction

Proteinuria is an important manifestation of chronic kidney disease (CKD). It has been accepted in many recent large cohort studies as an independent risk factor for end-stage renal disease, cardiovascular disease, ischemic stroke, and also as an important prognostic factor in cardiovascular and all-cause mortality [1–6]. Trace proteinuria is also a high-risk condition for all-cause and cardiovascular mortality, affecting 6–9% of the adult population [7], and can shorten life span by up to 7 years [4]. In a study by Wen et al., the magnitude of the increased risk due to trace proteinuria was approximately equivalent to the risk from smoking (1.70 vs. 1.55) [8].

Areca nut (AN) is the fourth most widely used addictive substance in the world; it is estimated that 10–20% of the world's population chews AN in some form [9]. The prevalence of AN use has gradually increased in Taiwan, especially in rural areas and in adolescence [9]. In addition to the associations with oral cancer [10], cardiovascular disorders [11], cerebrovascular deaths [12], hyperglycemia [13,14], obesity [15,16], metabolic syndrome [13], type 2 diabetes [14], liver cirrhosis [17], and CKD [18], AN chewing has previously been associated with increased urinary albumin excretion in patients with type 2 diabetes [19]. So far, there has been no large scale research investigating the association between chewing AN and proteinuria. In this study, we conducted a retrospective study to evaluate the association in middle-aged Chinese men.

Materials and methods

Participants

The National Health Insurance (NHI) Physical Check-up Program (PCP) is a formally designed physical check-up package for adults aged $\geq$ 40 years. It is issued by the Bureau of National Health Insurance, Taiwan. The methodology of the study is described in detail later [18]. A brief report is as below. From 2003 to 2009, there were a total of 15,836 men who attended the program in this hospital, with 16,844 records in total; 637 of them attended the program more than once in different years with a total of 1008 extra visits. All the participants were included in this retrospective record review study. For those participants who had more than one record, only the health records from the first visit were included. Participants with incomplete data ($n = 3845$) were excluded from the analysis, and a total of 11,991 participants were included. The project was approved by the Institutional Review Board of this hospital.

Methods

The NHI PCP contains a standard laboratory test package, a brief questionnaire for basic demographic data (age, sex, and address); health behaviors (status of smoking, drinking, and chewing AN); personal medical history (including diabetes, hypertension, and hyperlipidemia); and a physical examination (PE). The participants were asked to report the three aforementioned health behaviors in the last 6 months as a non-user, social user, or regular user. PE data include body height, body weight, systolic blood pressure (SBP), and diastolic blood pressure (DBP), and body mass index (BMI) was derived from the PE data. The standard laboratory studies include serum creatinine (Scr), total cholesterol (TC), triglyceride (TG), uric acid (UA), fasting blood sugar (FBS), alanine aminotransferase (ALT), hemoglobin (Hb), and urinalysis (including bio-chemical and sediment microscopic examinations), which were all measured with standard automated technology. In addition, we also calculated the estimated glomerular filtration rate (eGFR) for all included participants using the Modification of Diet in Renal Disease (MDRD) formula [20]. Participants fasted for 8 hours overnight before blood sampling in the morning.

Variable definition

CKD was defined as an eGFR $<$60 mL/min/1.73 m^2 as calculated by the MDRD formula [20]. Certain major medical diseases were defined according to domestic guidelines as below. Hypertension (HTN) was defined as a past personal history with or without medication or a blood pressure of at least 140/90 mmHg [21]. Diabetes mellitus (DM) was defined as a fasting plasma glucose level of $\geq$ 126 mg/dL or a history of DM with or without medication [22]. Hyperlipidemia was defined as a serum TC level $\geq$ 200 mg/dL, a TG level of $\geq$ 200 mg/dL, or a past personal history of high TC or TG with or without medication [23]. Hyperuricemia was defined as serum UA level $>$7.0 mg/dL according to domestic guidelines [24]. Participants were defined as non-smokers if they did not smoke and as smokers if they smoked socially or regularly, regardless of the amount they smoked. Participants were defined as non-chewers if they never chewed AN and as chewers if they chewed AN socially or regularly. Likewise, participants were defined as non-drinkers if they did not consume any alcohol and as drinkers if they consumed alcohol socially or regularly. Proteinuria was defined as having +/− or heavier protein response (including +/− to 4+) in a urine dipstick test. Liver dysfunction was defined as ALT $>$44 IU/L according to the upper limits of the automated technology in this hospital.