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A population-based study of the association between areca nut chewing and Type 2 diabetes mellitus in men (Keelung Community-based Integrated Screening programme No. 2)

T.-H. Tung[1] · **Y.-H. Chiu**[2] · **L.-S. Chen**[2] · **H.-M. Wu**[3] · **B. J. Boucher**[4] · **T. H.-H. Chen**[5]

[1] Department of Medicine Research and Education, Cheng Hsin Rehabilitation Center, Taipei, Taiwan
[2] Institute of Health Informatics and Decision Making, School of Medicine, National Yang-Ming University, Taipei, Taiwan
[3] Graduate Institute of Epidemiology, College of Public Health, National Taiwan University, Taipei, Taiwan
[4] Centre for Diabetes and Metabolic Medicine, St Bartholemew's and the Royal London School of Medicine and Dentistry, Queen Mary and Westfield College, London, UK
[5] Institute of Preventive Medicine, College of Public Health, National Taiwan University, Taipei, Taiwan

Abstract

Aims/hypothesis. The aim of this study was to assess whether the diabetogenicity of areca nut (*Areca catechu* or 'betel-nut'), which has previously been demonstrated experimentally in mice, independently contributes to the risk of hyperglycaemia or Type 2 diabetes in men in Taiwan, where the habit has become established relatively recently.
Methods. We used data from a population-based cross-sectional survey and a multiple-disease-screening programme that tested for hyperglycaemia, Type 2 diabetes and risk factors related to Type 2 diabetes. Data on habitual areca nut chewing were available for 14,816 men. Multiple logistic regression models were used to determine whether areca nut chewing was an independent risk factor for Type 2 diabetes.
Results. Compared with non-chewers, areca nut chewers had higher age-adjusted prevalence rates for hyperglycaemia (11.4% vs 8.7%) and Type 2 diabetes (10.3% vs 7.8%). Areca nut chewing independently increased the risk of hyperglycaemia (adjusted odds ratio [OR] 1.19, 95% CI 0.97–1.45) and Type 2 diabetes (adjusted OR 1.29, 95% CI 1.04–1.60). The independent effects of duration of chewing were dose-dependent for Type 2 diabetes (adjusted OR 1.32 for the duration of 10–19 years and 1.41 for the duration of ≥20 years), as were the effects of increased rates of areca nut chewing (adjusted OR 1.14 for <10 pieces/day, 1.30 for 10–19 pieces/day and 2.02 for ≥20 pieces/day); similar findings were noted for hyperglycaemia.
Conclusions/interpretation. The habit of chewing areca nut independently contributes to the risk of both hyperglycaemia and Type 2 diabetes in Taiwanese men. This association is dose-dependent with respect to the duration of areca nut use and the quantity of areca nut chewed per day.

Keywords Areca nut · Betel · Hyperglycaemia · Type 2 diabetes

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T. H.-H. Chen (✉)
Institute of Preventive Medicine, College of Public Health, National Taiwan University, No. 19, Hsu-Chow Rd, Taipei, Taiwan
E-mail: stony@episerv.cph.ntu.edu.tw
Tel.: +886-2-23587620
Fax: +886-2-23587707

Abbreviations: BUN, blood urea nitrogen · KCIS, Keelung Community-based Integrated Screening · LRT, likelihood ratio testing · OR, odds ratio

Introduction

In Taiwan, areca nut chewing has become one of the most popular lifestyle habits over the last 40 years. The habit of chewing the nut of the *Areca catechu* palm is commonly referred to in English as 'betel-chewing', a term arising from the use of leaves from the creeping vine *Piper betle* to wrap up chopped nuts to form quids. *Areca catechu* is currently used by about 2 million Taiwanese people (approximately 10% of the population), particularly the male 'blue collar' workers and those with low levels of education [1]. The main varieties of chews used in Taiwan are those prepared by combining unripe areca fruit with a

piece of the inflorescence (flower head) of the *Piper betle* vine and red lime paste, or by wrapping unripe areca fruit in leaves of the *Piper betle* vine with white lime paste [2]. It should be noted that no tobacco is added to the chews used in Taiwan.

Chewing areca nut has been found to significantly contribute to the development of oral cancer [3, 4], primary hepatocellular cancer [5, 6] and oesophageal carcinoma [7]. In addition, the arecal nitrosamines formed from the specific arecal alkaloids [8, 9] have been shown to be carcinogenic experimentally. Many nitrosamines are diabetogenic, and it has been suggested that arecal nitrosamines may be diabetogenic in man [10]. However, no population-based studies investigating the direct relationship between areca nut chewing and Type 2 diabetes have been performed to date. The habit of areca nut chewing is now common among Taiwanese men but, like Type 2 diabetes, this has only occurred over the last 20+ years. This reduces the risk of confounding due to the possible inheritability of the diabetogenic effects of areca nut (as previously reported in experimental animals [9]) or of parental diabetes [11] in this population. This is of particular importance since the habit has been common for 2000 years or more in virtually all other countries where areca nut is used. Based on this fact, the aim of the present study was to investigate the dose-dependent effects of areca nut on the development of Type 2 diabetes in the Taiwanese population.

Subjects and methods

Study subjects. All data were derived from the Keelung Community-based Integrated Screening (KCIS) programme. This was a multiple-disease-screening programme that was carried out in Keelung, the northernmost county of Taiwan, between 1 January 1999 and 31 December 2001. Details of the study design and some preliminary results have been described elsewhere [12]. Briefly, a total of 42 387 subjects (including 15,097 men and 27,290 women) were enrolled in the KCIS programme and attended a screening for Type 2 diabetes. Subjects with hyperglycaemia or Type 2 diabetes were diagnosed according to the criteria of the American Diabetic Association (ADA) as defined in 1999 [13]. Subjects with fasting plasma glucose levels of ≥6.1 mmol/l were defined as having hyperglycaemia and those with fasting plasma glucose levels of ≥7.0 mmol/l were defined as having Type 2 diabetes. Patients with previously diagnosed Type 2 diabetes were identified by questionnaire. As only 231 women either reported the use of areca nut or were ex-chewers, the present study focused on males alone. After the exclusion of a further 281 male subjects with incomplete data for areca nut use, the final study population on which the present analyses were based consisted of 14,816 subjects. This project was approved by the local health committee, which is run by the Taiwan Community-based Integrating Group [12]. Subjects gave their consent to participate in the on-site KCIS screening after being fully informed about the survey by public health nurses with formal documentation in Chinese.

Data collection. Data on behavioural risk factors (smoking, alcohol intake and areca nut chewing) were collected at one-to-one interviews using a structured questionnaire. The main type of areca nut chews used in Keelung city are the so-called 'Lao-Hwa', which are prepared by combining portions of unripe areca nut with a piece of the inflorescence (flower head) of the *Piper betle* vine and red lime paste [2]. Subjects were divided into three categories according to areca nut use: (i) current chewers; (ii) non-chewers (never); and (iii) ex-chewers. The duration of areca nut use and the number of portions of areca nut chewed each day were also recorded.

To investigate whether demographic and socio-economic factors (occupation and education) differed between the areca nut chewers and the non-chewers, these data were also collected. Occupation was classified as in the study by Hashibe et al. [14]. Data on biological factors associated with the risk of Type 2 diabetes were also collected, including systolic blood pressure, diastolic blood pressure, BMI, total cholesterol, triglyceride, blood urea nitrogen, serum creatinine, uric acid and central obesity (as waist circumference). The univariate distribution of these factors is summarised in Table 1.

Statistical analysis. The prevalences of hyperglycaemia and Type 2 diabetes in chewers and non-chewers were compared using the chi square test. Subjects were classified into five groups according to age (<40, 40–49, 50–59, 60–69 and ≥70 years). Multiple logistic regression modelling was then used to investigate whether areca nut chewing had an independent effect on the risk of hyperglycaemia or of Type 2 diabetes after adjustment for age, risk factors associated with Type 2 diabetes and socio-economic status. The models used were chosen to minimise residual confounding [15, 16]. Continuous confounders were adjusted either as linear terms or by quintile distribution. The choice of which adjustment to use for each continuous variable was determined by testing for departure from linearity between two models, one including dummy variables and the other assuming linearity for the variables of interest using likelihood ratio testing (LRT). When the result of the LRT was significant, the confounder in question was included after stratification into quintiles, otherwise the linear data for the confounder was used. Trend analysis, based on LRT, was also used to define the models for the assessment of dose–response relationships of areca nut use with respect to the duration and the quantity or intensity (duration × quantity) of areca nut chewed [17]. A p value of less than 0.05 was considered significant.

Results

Table 1 shows the distribution of demographic and biochemical data according to areca nut use. Table 2 shows the prevalence of areca nut use according to age. The average overall usage rate was 14.4%. Table 3 shows that the unadjusted prevalence rate for hyperglycaemia was 9.3% in chewers and 10.7% in non-chewers (p=0.046). However, when divided into five groups according to age (see Subjects and methods section), chewers aged 50–69 years had statistically higher prevalence rates for hyperglycaemia than non-chewers (age 50–59 years p=0.032, age 60–69 years p=0.002). As regards subjects aged less than 50 years, the prevalence rates for hyperglycaemia in chewers were still higher than those in non-chewers. This difference was not statistically significant for the group

Table 1. Univariate distribution of demographic and biochemical variables categorized by areca nut chewing in men (KCIS programme, 1999–2001)

Variable	Areca nut chewing		
	Current or ex-chewers (n=2120)	Non-chewers (n=12,696)	Total (n=14,816)
Demographic variables			
Age (years)	45.1±10.3	55.6±13.9[a]	54.1±14.0
Physical activity (% yes)	82.3	86.9[b]	86.2
Education (%)			
College or above	9.8	20.2[b]	18.7
Senior high school	41.4	26.8	28.9
Junior high school or below	48.8	53.0	52.4
Occupation (%)			
None	21.8	37.6[b]	35.3
Retired	1.7	6.1	5.5
Manual	35.3	19.5	21.8
Teacher, office holder, military	11.2	12.4	12.2
Business, professional	19.6	17.2	17.5
Service trade, others	10.4	7.3	7.7
Biochemical variables			
BMI (kg/m^2)	25.5±3.6	24.9±3.5[a]	25.0±3.5
Waist circumference (cm)	85.7±9.6	85.4±9.3	85.4±9.4
Systolic BP (mm Hg)	128.2±20.0	131.4±20.9[a]	131.0±20.8
Diastolic BP (mm Hg)	83.0±11.9	82.5±11.6	82.6±11.6
Total cholesterol (mmol/l)	5.02±1.03	5.05±1.09	5.05±1.08
Triglyceride (mmol/l)	1.99±2.13	1.50±1.21[a]	1.57±1.39
BUN (mmol/l)	0.54±0.16	0.59±0.20[a]	0.58±0.19
Creatinine (μmol/l)	95.28±28.35	99.06±37.30[a]	98.52±36.17
Uric acid (mmol/l)	0.38±0.10	0.38±0.10	0.38±0.10

Data are means ± SD or percentages. [a] A p value of less than 0.05 for the two sample independent t tests was considered significant for continuous variables; [b] a p value of less than 0.05 for the chi square tests was considered significant for categorical variables

Table 2. Prevalence of areca nut chewing with age in men (KCIS programme, 1999–2001)

Age (years)	n[a]	Areca nut chewing						
		Current chewers		Ex-chewers		Non-chewers		p value for χ^2 test
		n	%	n	%	n	%	
<40	2707	398	14.7	331	12.2	1978	73.1	<0.0001
40–49	3737	421	11.3	365	9.8	2951	78.9	
50–59	2522	205	8.1	161	6.4	2156	85.5	
60–69	3031	105	3.5	91	3.0	2835	93.5	
≥70	2819	19	0.7	24	0.9	2776	98.4	
Total	14816	1148	7.8	972	6.6	12696	85.6	

[a] See Subjects and methods section for details of population screened

aged 40–49 years (p=0.18) and of borderline statistical significance in subjects younger than 40 years of age (p=0.09). In subjects aged 70 years or older, non-chewers had only a marginally higher prevalence rate than chewers. These findings suggested that age was a confounding factor and should be adjusted for. The overall age-adjusted prevalence of hyperglycaemia was 11.4% in chewers and 8.7% in non-chewers (p<0.0001). The age at which the prevalence of hyperglycaemia rose above 15% was younger in chewers than in non-chewers. Similar findings were noted for Type 2 diabetes (Table 3).

After adjusting for age, socio-economic status, and other biological factors, the adjusted odds ratios [ORs] for the association between areca nut use and the risk of hyperglycaemia and Type 2 diabetes were 1.19

Table 3. Prevalence of hyperglycaemia and Type 2 diabetes in men stratified by age (KCIS programme, 1999–2001)

Age	Total		Hyperglycaemia					Type 2 diabetes				
	Current or ex-chewers	Non-chewers	Current or ex-chewers		Non-chewers			Current or ex-chewers		Non-chewers		
	n	*n*	*n*	Prevalence (%)	*n*	Prevalence (%)	*p* value for χ^2 test	*n*	Prevalence (%)	*n*	Prevalence (%)	*p* value for χ^2 test
<40	729	1978	26	3.6	47	2.4	0.090	20	2.7	33	1.7	0.073
40–49	786	2951	58	7.4	179	6.1	0.179	43	5.5	146	4.9	0.552
50–59	366	2156	62	16.9	276	12.8	0.032	56	15.3	235	10.9	0.015
60–69	196	2835	45	23.0	421	14.9	0.002	45	23.0	402	14.2	0.001
≥70	43	2776	6	14.0	439	15.8	0.740	6	14.0	469	16.9	0.609
Total	2120	12696	197	9.3	1362	10.7	0.046	170	8.0	1285	10.1	0.003
Age-adjusted prevalence[a]				11.4		8.7	<0.0001		10.3		7.8	0.003

Hyperglycaemia was defined as a fasting plasma glucose concentration ≥6.1 mmol/l. [a] Standardised to the world population (Segi's standard [22])

Table 4. Adjusted odds ratios for significant factors of hyperglycaemia or Type 2 diabetes in areca-nut-chewing men using multiple logistic regression models (KCIS programme, 1999–2001)

Model	Hyperglycaemia		Type 2 diabetes	
	OR	95% CI	OR	95% CI
Adjusted for age[a]	1.39	1.17–1.64	1.41	1.18–1.68
Adjusted for age and other confounders	1.19[b]	0.97–1.45	1.29[c]	1.04–1.60

Areca nut chewers (*n*=2120) vs non-chewers (*n*=12,696). Hyperglycaemia was defined as a fasting plasma glucose concentration ≥6.1 mmol/l. [a] Age was divided into five groups: <40, 40–49, 50–59, 60–69 and ≥70 years; [b] other confounders included obesity (yes/no), hypertension (yes/no), physical activity (high/low), education and occupation categorised as in Table 1, total cholesterol (quintiles), triglyceride (quintiles), creatinine (quintiles), uric acid (quintiles), BMI (quintiles), and log-transformed BUN (linear term); [c] confounders and their characteristics were similar to those in footnote b except total cholesterol was adjusted as a linear term after log-transformation of values

(95% CI 0.97–1.45) and 1.29 (95% CI 1.04–1.60) respectively (Table 4).

After controlling for relevant factors, significant dose–response relationships were noted with respect to the duration of chewing and quantity of nuts chewed (Table 5). All trend tests were statistically significant ($p<0.05$). Compared with non-chewers, the risk of Type 2 diabetes was 1.41 times higher (95% CI 1.08–1.86) in those who had chewed areca nut for more than 20 years and 2.02 times higher (95% CI 1.31–3.09) in those who had chewed more than 20 pieces of areca nut per day. Similar findings, though of smaller magnitude, were noted for hyperglycaemia. Table 5 also shows the combined effect of usage rates and duration of use expressed as intensity (duration × quantity). Trend tests for the intensity values divided into quartiles were statistically significant for hyperglycaemia ($p=0.01$) and Type 2 diabetes ($p<0.01$).

Discussion

The present study used a population-based design to investigate the association between the use of areca nut chews (the type prepared by combining areca nut, *Piper betle* vine leaf and lime paste) and hyperglycaemia and Type 2 diabetes. Three major findings of this study are in agreement with previous experimental work showing that feeding areca nut to young adult mice can induce permanent glucose intolerance in a significant proportion of animals [9].

Firstly, the associations between areca nut use and the risk of hyperglycaemia or Type 2 diabetes remained after adjustment for age, socio-economic status and potentially confounding lifestyle and biologi-

Table 5. Multiple logistic regression models on the risk factors for the development of hyperglycaemia and Type 2 diabetes in men (KCIS programme, 1999–2001)

Variables	Hyperglycaemia			Type 2 diabetes		
	OR	95% CI	Test for trend	OR	95% CI	Test for trend
Duration of chewing areca nuts						
No chewing	1.00	–	$\chi_{(1)}^2$=5.62	1.00	–	$\chi_{(1)}^2$=6.63
<10 years	0.74	0.39–1.40	p=0.018	0.75	0.37–1.50	p=0.010
10–19 years	1.26	0.87–1.81		1.32	0.89–1.94	
≥20 years	1.35	1.05–1.75		1.41	1.08–1.86	
Quantity of areca nuts chewed (per day)						
No chewing	1.00	–	$\chi_{(1)}^2$=4.05	1.00	–	$\chi_{(1)}^2$=9.56
<10 pieces	1.18	0.89–1.58	p=0.044	1.14	0.83–1.56	p=0.002
10–19 pieces	1.20	0.80–1.78		1.30	0.85–1.98	
≥20 pieces	1.47	0.95–2.27		2.02	1.31–3.09	
Intensity of chewing (quantity × duration)[b]						
No chewing	1.00	–	$\chi_{(1)}^2$= 6.46	1.00	–	$\chi_{(1)}^2$= 9.47
<1.3	1.01	0.62–1.66	p=0.010	1.08	0.64–1.80	p=0.002
1.3–3.5	1.04	0.67–1.62		1.13	0.71–1.80	
3.5–9.3	1.25	0.84–1.85		1.16	0.75–1.80	
≥9.3	1.62	1.14–2.31		1.93	1.35–2.77	

Hyperglycaemia was defined as a fasting plasma glucose level ≥6.1 mmol/l. The results for 14 816 subjects were analysed. [a] The confounders adjusted for in this model are identical to those listed in Table 4; [b] values are expressed as $\times 10^4$ piece-days

cal factors. This suggests an independent effect of this particular habit. Our findings, together with more recent population survey data from Papua New Guinea, strengthen the argument for the diabetogenicity of areca nut use [18].

In the present study, the younger age of onset of Type 2 diabetes in chewers compared with non-chewers is consistent with the fact that a study conducted in Coventry (UK) revealed that South Asian subjects developed Type 2 diabetes at an earlier age than the European subjects [19]. Furthermore, these individuals required supplemental hypoglycaemic medication more frequently and at a younger age than the Europeans [19]. The younger age of onset observed in our study also paralleled the increased prevalence of the areca nut habit in younger people, reflecting the comparatively recent uptake of the habit over the last 40 years.

The finding of significant dose–response relationships between areca nut use (both in terms of quantity and duration) and hyperglycaemia and Type 2 diabetes suggests that an active arecal agent is directly toxic to beta cells. It is possible that the diabetogenicity of arecal chews might be due to the lime paste used rather than the areca nut. However, there have been no reports to date to suggest that lime paste is either diabetogenic or carcinogenic, though it appears to have a local inflammatory effect in the mouth [20]. In addition, the hyperglycaemia reported experimentally in mice followed the feeding of areca nut without other chew components [9].

In contrast with a previous study conducted in the UK [21], significant direct associations were observed between areca nut use and clinically damaging increases in glycaemia. This discrepancy may reflect the much larger population examined in the present study. Alternatively, it may be due to the fact that the Bangladeshi Asians who took part in the UK study were from communities that have chewed betel-quids (areca nut) for thousands of years [21], whereas the current levels of areca nut use in Taiwanese men have only been reached over the last 40 years. In view of the degree of inheritability of increased glycaemia (with islet damage) that has been demonstrated experimentally in mice fed with areca nuts, the authors of the UK study speculated that the failure to find direct associations in areca-using communities where the habit was long standing may reflect confounding by the similar inheritability of diabetogenic effects in man. Furthermore, it was postulated that any association of environmental exposure to diabetogenic nitroso-compounds with diabetes would be more easily detected in populations where this particular risk factor had only recently been introduced [21]. Thus, the relationships found between Type 2 diabetes and arecal use in the present study are particularly pertinent, since the recent uptake of areca nut chewing by this population has provided a unique opportunity to test the postulated diabetogetogenicity of this habit in man.

In conclusion, we have demonstrated an association between areca nut chewing and Type 2 diabetes using a population-based study in a community in which the habit is of recent origin.

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