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ARECA-NUT CHEWING HABIT IS A SIGNIFICANT RISK FACTOR FOR METABOLIC SYNDROME: A SYSTEMATIC REVIEW

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Abstract: *Background:* Areca-nut (AN) chewing habit has been associated with oral diseases including oral cancer, oral submucous fibrosis and periodontal disease; however, some authors have reported that the AN-chewing abuse may also jeopardize the systemic health among its users. *Objectives:* The objective was to review any reported association between AN-chewing and the metabolic syndrome (MetS). *Methods:* To address the research question "Is there an association between areca-nut chewing habit and the MetS?" the MEDLINE and PubMed databases were searched from 1991 up to and including April 2010. The search criteria included: human studies, metabolic syndrome, diabetes, areca nut (AN). Only articles published in English were included. *Results:* Eight cohort studies were included in the review. The sample size of the selected studies ranged from 210 to 56,116 individuals (age range 15-83 years). The daily frequencies of AN-chewing reported by the users ranged between once a day to 76 times daily. The duration of use ranged from 6 years to ≥ 20 years. Two studies associated AN-chewing habit with hyperglycemia and type 2 diabetes while five studies studies reported an association between AN-chewing and metabolic syndrome. Four studies related AN-chewing with obesity and an increased body mass index. Higher triacylglycerol levels were reported in one study among AN-chewers compared to non-chewers. Though the numbers of publications on this subject are limited, the available studies indicate that AN-chewing could be associated with the metabolic syndrome, and individually with two of the recognized components of the syndrome i.e. diabetes mellitus and central obesity.

Key words: Areca-nut, betel quid, body mass index, diabetes mellitus, metabolic syndrome.

Introduction

Areca-nut (AN) (synonym betel-nut) is the endosperm of the fruit of the Areca catechu tree. It is also the major constituent in betel-quid (BQ) (a mixture of AN, slaked lime, artificial sweeteners and sometimes added tobacco, wrapped in Piper-betel leaf) (1). Instead of mixing with other constituents of betel quid some populations chew AN alone. Regular AN-chewing habit is very prevalent in South, South East and East Asian populations (2); however, chewing of this substance is not restricted to Asia as it is also enjoyed by migrant communities settled in Australia, Canada, Europe and the United States of America (3, 4). Though the actual global prevalence of AN-chewing habit is yet to be documented, it has been reported that approximately 600 million individuals worldwide chew AN on a daily basis (1). In a seminal paper by Strickland et al. (5) that reported patterns and reasons for use. AN-chewers cited the chewing habit to be "beneficial" as it helped them to suppress hunger, dispel nausea, aid digestion, aid cognitive performance and to act as an antidepressant to achieve euphoria. Deleterious effects of areca nut on oral soft tissues are published extensively in the dental literature. These include oral cancer (1), oral submucous fibrosis (1, 6), lichenoid reactions (7) and inflammatory conditions of the periodontium (8).

The MetS (previously termed Syndrome X) is a group of disorders associated with abdominal obesity; hyperglycemia (diabetes mellitus), dyslipidemia and hypertension. Exact clinical definition of MetS varies depending on the criteria published by several organizations (9-12): WHO Consultation, 1988; European Group for the Study of Insulin Resistance (EGIR), the National Cholesterol Education Program's Adult Treatment Panel III report (ATP-lll) and International Diabetes Federation (IDF). Clinical identification of MetS is based on several factors including: 1) central obesity (waist size), (ATP-lll) > 102 cm and >88 cm in males and females respectively, IDF waist >94 cm in European men and 90 cm and >80 cm in Asian men and women correspondingly; 2) triglycerides ≥ 1.7; 3) fasting serum glucose ≥ 6.1 (WHO, EGIR, ATP lll) or > 5.6 (IDF) and 4) blood pressure ≥130/≥ 85 mmHg (13, 14). Individuals with MetS are nearly three times as likely to have cardiovascular disorders and five times as likely to develop type 2 diabetes compared with individuals without MetS (12). With an increase in the global prevalence of obesity, the numbers of individuals with diabetes mellitus are also increasing globally (15). In the year 2000, there were nearly 177 million individuals worldwide with diabetes; however this number is expected to rise to nearly 370 million by the year 2030 (15).

The detrimental effects of AN chewing habit on the metabolic system were first reported by Boucher and Mannan (16). The suppression of hunger reported by chewers may induce a state of malnutrition among the users of AN. Ogunkolade et al. (17) reported that AN-chewing aggravates the effects of vitamin-D deficiency. Vitamin D deficiency has

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been identified as a risk factor for systemic conditions including metabolic syndrome (MetS) (18) and diabetes mellitus in AN consuming Asian residents in East London (19). It has been reported that AN-chewing is also a risk factor for abdominal obesity and increased body mass index (BMI) among a Thai population as well as Bangladeshi migrants living in London (20, 21); however, this subject needs further appraisal in different population groups and deserves more extensive research. The exact mechanism of AN-induced abdominal obesity and hyperglycemia is debatable; however, three potential etiological categories: obesity and disorders of adipose tissue; insulin resistance; and a constellation of independent factors (such as molecules of hepatic, immunologic and vascular origin) that mediate specific components of MetS (13) have been discussed in relation to areca abusers (16). Various theories have been proposed regarding the association between AN-chewing abuse and diabetes. Arecoline (a major AN alkaloid) suppressed the appetite while increasing postprandial carbohydrate use (21). On the other hand it was reported that arecoline can promote appetite by inhibiting the gamma-aminobutyric acid receptors (22). In their experimental study, Boucher et al. (23) demonstrated an increased incidence of impaired glucose tolerance in mice fed with AN compared to control mice.

To date, the relationship between AN-chewing abuse and MetS remains speculative probably due the limited number of publications on this topic. In this context, the aim of this study was to conduct a systematic review of the published literature examining any association between AN-chewing habit and MetS.

Methods

Focused question

The addressed focused question was "Is there an association between areca-nut chewing habit and MetS?"

Inclusion and exclusion criteria

Since AN is an essential component and the main ingredient in the BQ (1), human studies on individuals consuming AN as well as BQ were included in the present study. The following eligibility criteria were applied: 1) human studies; 2) individuals with diabetes mellitus, obesity and or MetS ; 3) individuals consuming AN- or BQ-chewers (at least once a day since the past 12-months) were categorized as “AN-chewers”; 4) control group: individuals without a diagnosis of diabetes, obesity, MetS and not using AN and tobacco in any form; and 5) articles published in English.

Studies on animal models, abstracts in the form of unpublished articles, letters to the editor and historic reviews were excluded.

Search protocol (Data source and search strategy)

As a first step, the authors searched the MEDLINE–PubMed (National Library of Medicine, National Institutes of Health, Bethesda, Maryland) and the Google-Scholar databases for appropriate articles addressing the focused question. Databases were searched from 1991 up to and including April 2010 using different combinations of the following keywords: “areca”, “betel”, “body mass index”, “diabetes mellitus”, “disorder”, “disease”, “metabolic syndrome”, “nut”, “obesity” and “quid”.

The next step was to hand-search the reference lists of pertinent original and review articles that were found to be relevant in the first search. Titles and abstracts of articles obtained using the above described search protocol were screened by each author and checked for agreement. Any disagreements between the authors were resolved via discussion. The initial search yielded 21 articles. Thirteen studies which did not abide by the inclusion criteria were excluded (see Appendix). Due to the limited number of original research studies addressing our focused question on MetS, the present review was expanded to also include the main individual components of the syndrome.

Odds ratios with 95% confidence intervals were extracted as given by the authors from the included studies to evaluate any association between AN-chewing habit, MetS, obesity and diabetes.

Results

Characteristics of publications included in the present review

Eight studies (20, 24-30) that fulfilled the eligibility criteria were included in the review and were used for data extraction. These studies are listed in Table 1. All of the included studies (20, 24-30) were cohort studies and were either conducted at universities or at healthcare centers. The sample sizes of the individual reports ranged from 210 to 56,116 individuals. The ages of the participants ranged between 15 years to 83 years. In four studies (24-27), all participants were male; whereas in three studies (20, 28, 30), there was no significant difference in gender among the male and female participants. In one study (29), gender of the study subjects was not reported. Six studies (24-28, 30) were performed in Taiwan, one study was carried out in Papua New Guinea (29) and one study was conducted in the United Kingdom (20).

Six studies (20, 24, 25, 27, 28, 30) reported the frequency of AN-chewing habit which ranged from at least once daily to 76 times daily. The duration of AN-chewing habit was reported by four studies (26, 28-30) which ranged between 6 years and ≥ 20 years.

Five studies (24-28) showed a positive association between AN-chewing habit and the MetS. Two studies (29, 30) associated AN-chewing with hyperglycemia and type 2 diabetes. Obesity and increased BMI were associated with AN-chewing in four of the studies (20, 24-26). In one study (25), higher serum triacylglycerol levels were reported among AN-chewers compared to non-chewers.

In the study by Guh et al (27), a significant difference was noted in the prevalence of MetS among male and female AN-

Table 1
Summary of studies included

Author/s, Year	Study design	Study subject/s (Male:Female)	Age range (years)	Daily frequency of AN use	Duration of AN use (years)	OR (95%CI)	Metabolic conditions associated with AN usage
Mannan et al. 2000 (20)	Cohort	993 (1:1.1)	15 to 83	1-22 times	NA	1.17 (1.1-1.2)	Increased waist and weight
Lin et al. 2009 (24)	Cohort	1049 males	≥ 40	76 times	NA	2.01 (1.2-3.4)	General and central obesity.
Lin et al. 2008 (25)	Cohort	56,116 males	≥ 20	Once a day	NA	1.30 (1.1-1.7)	Higher BMI, waist circumference and triacylglycerol level.
Chang et al. 2006 (26)	Cohort	6126 males	20 to 59	NA	13.4	1.40 (1.2-1.8)	Obesity.
Guh et al. 2006 (27)	Cohort	3,910 (1:1.2)	20 to 64	3.5 times	NA	1.3 (1.1-1.5)	Metabolic syndrome.
Yen et al. 2006 (28)	Cohort	19,839 males	30 to 79	≥20nuts/day	< 10 to ≥ 20	1.3 (1.1-1.6)	Metabolic syndrome.
Benjamin and Margis 2005 (29)	Cohort	210 (NA)	≥ 45	NA	At least six years	1.30 (1.1-1.7)	Hyperglycemia and T2D.
Tung et al. 2004 (30)	Cohort	14,816 (1:2)	50 to 69	1-20 times	10-20	1.30 (1.04-1.7)	Hyperglycemia and T2D.

BMI: Body mass index; CI: Confidence interval; NA: Not available; OR: Odds ratio; T2D: Type 2 diabetes mellitus

chewers. A daily AN consumption rate of 10 times per day was associated with the development of MetS, hypertriacylglycerolemia and hypertension. Likewise, Yen et al. (28) reported the prevalence of MetS to be highest among current chewers (25.13%), followed by ex-chewers (22.04%), compared to non-chewers (15.73%). In these two studies, after adjusting for other significant correlates such as a family history of hypertension and diabetes, the Odds ratios (95% Confidence Intervals (CI)) for MetS among ex- and current AN-chewers were 1.38 (CI: 1.19, 1.60) and 1.78 (CI: 1.53, 2.08) respectively (28), thus providing evidence to our focused question.

Discussion

AN-chewing by itself has been regarded as a major risk factor for insulin resistance and metabolic syndrome (13). The exact mechanism that may trigger metabolic distress in AN-chewers remains unclear; however, various mechanisms have been proposed. It has been reported that AN- derived nitrosamines may be diabetogenic, in a way similar to Streptozotocin that targets and damages islet beta-cell glucose receptors (10). According to Mannan et al. (20), arecoline induces sympathetic activation which is positively associated with insulin resistance and the metabolic syndrome. Also, arecoline has been shown to lead to the blockage of the gamma-aminobutyric acid receptor which in turn has been suggested to induce insulin resistance (21-23).

From the literature reviewed, it seems exigent to assess the relationship between the frequency of AN consumption and MetS. For example, in the study by Guh et al. (27), AN-chewers were exposed to the abuse approximately three times daily; however, in another study (13), individuals with abdominal obesity were chewing areca-nut up to 76 times daily. Likewise, due to a huge variation in AN-chewing frequency in patients with diabetes mellitus, it was difficult to predict a threshold for the frequency of AN-chewing that could probably expose its consumers to the endocrine disorder. Simultaneously, the role of confounding parameters such as a low socioeconomic status and poor education that might also trigger areca-nut chewing habit as well as diabetes cannot be disregarded (1, 2, 24, 25). In the study by Javed et al. (2) AN-chewers cited the chewing habit to be "beneficial" as it helped them to control hunger and attain a state of mind which they termed as "mental peace". Simultaneously, a meager education level may also persuade AN-chewers to continue with the chewing habit regardless of being aware of their impaired health status (31).

Gender has been shown to influence the oral as well as systemic inflammatory conditions (25, 32); however, the role of gender in relation to AN-chewing and prevalence of MetS remains debatable. From the studies that fulfilled our eligibility criteria, it seems that MetS seems to be more prevalent among male AN-chewers compared to female chewers; however, it is noteworthy that four out of the eight studies included in the current review had only male participants; while the remaining studies did not show any significant difference in the male:female ratios. In this context the question "Does gender influence the connection between AN-chewing and diabetes?" is yet to be answered and further studies are required to explore this relationship.

Conclusion

While oral health effects of AN had been known for over a century, information on systemic effects of regular AN use is just emerging. In addition to diabetes and abdominal obesity, MetS appears to have a significant association with AN use. Clinicians should inquire on AN-chewing habit among undiagnosed individuals suspected to have physical and biochemical abnormalities of MetS. Awareness on this risk-factor and likely complications of MetS should be promoted through public health programs to encourage cessation that may offer a foundation for an improved quality of life for Asian subjects who are at risk of multiple systemic diseases due to regular AN use.

Conflict of interest: None of the authors had a conflict of interest in relation to this manuscript.

Appendix
List of excluded studies

a. Owen PL, Martineau LC, Caves D, Haddad PS, Matainaho T, Johns T. Consumption of guava (Psidium guajava L) and noni (Morinda citrifolia L) may protect betel quid-chewing Papua New Guineans against diabetes. Asia Pac J Clin Nutr. 2008; 17: 635-643.
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