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## Areca Nut Chewing Is Associated With Metabolic Syndrome

Role of tumor necrosis factor-leptin, and white blood cell count in betel nut chewing-related metabolic derangements

Areca nut (*Areca catechu*)/betel quid (BQ) is said to be the fourth most commonly used psychoactive substance in the world and is chewed regularly by at least 10% of the world's population (1). High prevalence's of BQ chewing were observed especially in South and Southeast Asia (1). High prevalence's of insulin resistance and metabolic syndrome were also observed in this area (2). Specific areca alkaloids act as competitive inhibitors of  $\gamma$ -aminobutyric acid receptors in the brain, cardiovascular system, and pancreas, which may promote one's appetite or altered insulin secretion (3). Moreover, BQ components have recently been shown to induce keratinocytes to secrete tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ) and interleukin-6, as well as induce reactive oxygen species and activate nuclear factor- $\kappa$ B expression (4), which may potentially provoke chronic inflammation. Recently, we confirmed that BQ chewing was associated with a higher risk of type 2 diabetes and central obesity in Taiwanese men (5). The detrimental effects of BQ chewing on selected components of the metabolic syndrome, and the induction of inflammatory cytokines and factors, raise the possibility that BQ chewing may increase the risk of metabolic syndrome.

In this study, a total of 1,466 aboriginal subjects of Southern Taiwan, 30–95 years of age, were enrolled. Metabolic syndrome was defined according to the National Cholesterol Education Program Adult Treatment Panel III definition. The age-adjusted prevalence of metabolic syndrome in the aborigines studied was 41.1% in men and 42.4% in women. BQ chewing subjects had significantly higher prevalence's of central obesity, hypertriglyceridemia, dysglycemia, and metabolic syndrome than those of nonchewers. Peripheral leukocyte count also significantly increased in chewers of both sexes, with plasma TNF- $\alpha$  level increased in men and plasma leptin level elevated in women. All were parallel to the number of components of the metabolic syndrome. Multiple logistic regression modelling adjusted for age, educational level, socioeconomic level, exercise, drinking, and smoking status showed that BQ chewing is an independent risk factor for the metabolic syndrome. The adjusted OR (95% CI) for male BQ chewers was 1.92 (1.15–3.27)

and that of female chewers was 1.60 (1.03–2.50). The study shows that chronic BQ chewing is an independent contributor of metabolic syndrome.

TNF- $\alpha$ , leptin, and leukocyte count are involved in BQ chewing-related metabolic derangements.

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FU-MEI CHUNG, MS <sup>1,2</sup>  
DAO-MING CHANG, MD<sup>1,5</sup>  
MIAO-PEI CHEN, MS<sup>1</sup>  
JACK C.-R. TSAI, MD, MPH<sup>1,3</sup>  
YI-HSIN YANG, PHD<sup>4</sup>  
TIEN-YU SHIEH, PHD<sup>4</sup>  
SHYI-JANG SHIN, MD, PHD<sup>3</sup>  
TONY HSIU-HSI CHEN, PHD<sup>5</sup>  
TONG-YUAN TAI, MD, PHD<sup>6</sup>  
YAU-JIUNN LEE, MD, PHD<sup>1</sup>

From the <sup>1</sup>Department of Clinical Research, Pingtung Christian Hospital, Pingtung, Taiwan; the <sup>2</sup>Graduate Institute of Dental Sciences, Kaohsiung Medical University, Kaohsiung, Taiwan; the <sup>3</sup>Graduate Institute of Medicine, Kaohsiung Medical University, Kaohsiung, Taiwan; the <sup>4</sup>Graduate Institute of Oral Health Sciences, Kaohsiung Medical University, Kaohsiung, Taiwan; the <sup>5</sup>Institute of Preventive Medicine and Public Health, National Taiwan University, Taipei, Taiwan; and the <sup>6</sup>Department of Internal Medicine, Ren-Ji Hospital, Taipei, Taiwan.

Address correspondence to Dr. Yau-Jiunn Lee, Department of Clinical Research, Pingtung Christian Hospital, No. 60 Da-Lien Rd., Pingtung, 90000, Taiwan.

E-mail: t3275@ms25.hinet.net.

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## An Epidemiologic Study on the Prevalence of Diabetes, Glucose Intolerance, and Metabolic Syndrome in the Adult Population of the Republic of Cyprus

The study was conducted in Cyprus (November 2003 through January 2005). Stratified random sampling was used to select 1,200 individuals aged 20–80 years (from a total population of 477,000). In all subjects, anthropometrical measurements were taken, fasting lipids were measured, eating habits were evaluated according to a standardized questionnaire, and an oral glucose tolerance test (OGTT) was performed (except in known diabetic patients).

In the absence of OGTT-diagnosed diabetes or impaired glucose tolerance (IGT), impaired fasting glucose (IFG) was defined by fasting plasma glucose  $\geq 110$  mg/dl and  $<126$  mg/dl, whereas “new” IFG was defined by fasting plasma glucose  $\geq 100$  and  $<126$  mg/dl. Metabolic syndrome was defined according to the National Cholesterol Education Program Adult Treatment Panel III criteria.

Of the 1,200 subjects, 78 (6.5%) had known diabetes and 45 (3.8%) were newly diagnosed by the OGTT, which brought the total prevalence of diabetes to 123 (10.3%). Another 78 (6.5%) subjects had IGT, 36 (3.0%) had IFG, and 171 (14.2%) had “new” IFG. Logistic regression showed that significant risk factors for diabetes were age, male sex, family history of diabetes ( $P < 0.001$ ), hypertension ( $P = 0.004$ ), and obesity ( $P = 0.003$ ). Risk factors for IGT were age and family history of diabetes ( $P < 0.01$ ). Risk factors for IFG and “new” IFG were age and obesity ( $P < 0.01$ ).

The prevalence of metabolic syndrome was 22.2% overall, 68.5% among subjects with diabetes, 43.6% among those with IGT, 86.1% among subjects with IFG, 35.7% with “new” IFG, and 12.3% among subjects with normal glucose tolerance. The prevalence of metabolic syndrome increases with age, is higher in men than in women (26.5 vs. 18.3%, respectively,  $P = 0.001$ ), and is higher in rural than in urban areas (26.0 vs. 20.6%, respectively,  $P = 0.037$ ).

The average daily energy intake was 2,509 kcal, to which carbohydrates contributed 53.3%, fats contributed 31.8%, and proteins contributed 14.9%. Comparing the OGTT ( - ) group with the three groups of various degrees of glucose intolerance, after age and sex adjustment, no differences were found regarding energy intake (range 2,551–2,231 kcal) or the qualitative composition of the diet (carbohydrates 53.1–54.9%, proteins 14.4–15.4%, and fats 30.7–32.1%). Moreover, the above parameters did not differ between subjects with or without metabolic syndrome.

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In conclusion, the study revealed a very high prevalence of diabetes and IGT in Cyprus, among the highest in Europe, compared with five centers of the DECODE (Diabetes Epidemiology: Collaborative Analysis of Diagnostic Criteria in Europe) study (1) and higher than in the U.S. (2), while the prevalence of metabolic syndrome is comparable with that of other Western countries (3). Dietary habits, evaluated by cross-sectional analysis, do not seem to contribute to the development of glucose intolerance. Interventions aimed at IGT and the components of metabolic syndrome are urgently needed in order to reduce the incidence of diabetes.

**THEODOROS LOIZOU, MD<sup>1</sup>**  
**STAVROS POULOUKAS, PHD<sup>2</sup>**  
**CHARALAMBOS TOUNTAS, MD<sup>3</sup>**  
**ANASTASIA THANOPOULOU, MD<sup>3</sup>**  
**VASILIOS KARAMANOS, MD<sup>3</sup>**

From the <sup>1</sup>Nicosia Diabetes Centre, Nicosia, Cyprus; the <sup>2</sup>Department of Computer Science, Intercollege, Nicosia, Cyprus; and the <sup>3</sup>Diabetes Centre, Department of Internal Medicine, National University of Athens, Athens, Greece. Address correspondence to Theodoros Loizou, MD, Griva Digeni 48, Nicosia 1080, Cyprus. E-mail: dorosloizou@yahoo.com.

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## The Metabolic Syndrome and Glucose Tolerance Status Deterioration Over 23-Year Follow-Up

Individuals with impaired glucose tolerance or impaired fasting glucose are at high risk of developing type 2 diabetes and cardiovascular diseases (1). Identifying those individuals whose glucose tolerance status (GTS) will deteriorate over the years would be of public health importance, due to its preventive implications.

We assessed the metabolic syndrome and lifestyle habits as predictors of 23-year GTS deterioration among survivors of a nationwide longitudinal study (the Israeli Glucose Intolerance, Obesity and Hypertension Study) subsample (2). The study was approved by the institutional review board, and all subjects gave written informed consent. Among the 562 nondiabetic subjects at baseline to whom either oral glucose tolerance test or fasting glucose were available at follow-up (298 male and 264 female subjects, mean age  $70.4 \pm 6.8$  years), 54.6% deteriorated (i.e., they were normoglycemic at baseline and became impaired or diabetic at follow-up or were impaired and became diabetic). Male subjects experienced higher deterioration rates (59.4%) than female subjects (49.2%) ( $P = 0.02$ ). Among the ethnic groups, North African-born subjects had the highest rates of deterioration and European/American-born subjects the lowest (67.4 and 47.1%, respectively;  $P = 0.01$ ). Those who have ever smoked cigarettes and sedentary individuals exhibited higher deterioration rates than those who have never smoked and those currently physically active (58.6 vs. 50.9%,  $P = 0.06$  for smoking and 59.7 vs. 50.6%,  $P = 0.03$  for physical activity, respectively). All metabolic syndrome components other than HDL cholesterol were found to be significantly associated to deterioration. In multiple logistic regression analysis, subjects with the metabolic syndrome had a sex-, age-, ethnic origin-, smoking-, and physical activity-adjusted 3.09 increased risk for GTS deterioration (95% CI 1.67–5.72; C index = 0.65).

In the study, an increasing number of metabolic syndrome components were significantly associated with increasing rates of deterioration in GTS from 43.2% among those who had none of the components to almost 90% in those who had four or five components ( $P < 0.001$ ).

Presence of the metabolic syndrome at baseline was found to predict both the deterioration in GTS, a smoldering process on the axis of time, and diabetes incidence. When evaluating its predictive value in detecting type 2 diabetes or GTS deterioration, one must relate to the paradigm of fasting blood glucose being a component of both the outcome and the metabolic syndrome. Our study exhibited similar results, with metabolic syndrome not including fasting blood glucose (odds ratio for deterioration of those positive for metabolic syndrome 2.22 [95% CI 1.19–4.11]). Assuming that those who did not survive were subjects with the less-favorable health status, these results are

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most likely underestimated. Modifiable lifestyle characteristics were found to predict 23-year GTS deterioration in order to facilitate the prevention or delay of type 2 diabetes.

**RACHEL S. DANKNER, MD, MPH<sup>1,2</sup>**

**ANGELA CHETRIT, MA<sup>1</sup>**

**URI GOLDBOURT, PHD<sup>2,3</sup>**

From the <sup>1</sup>Cardiovascular Epidemiology Unit, Gertner Institute for Epidemiology and Health Policy Research, Tel-Hashomer, Israel; the <sup>2</sup>Department of Epidemiology and Preventive Medicine, Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel; and the <sup>3</sup>Neufeld Cardiac Research Institute, Sheba Medical Center, Tel Hashomer, Israel.

Address correspondence to Rachel Dankner, MD, MPH, Cardiovascular Epidemiology Unit, Gertner Institute for Epidemiology and Health Policy Research, Tel-Hashomer, 52621. Israel.

E-mail: racheld@gertner.health.gov.il.

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