Habitual consumption of Areca catechu may cause increased post prandial blood glucose levels in diabetics: a cross sectional study

MA Bari Siddiqui[1,*], Addanki Yottoshuka[2]

[1]Assistant Professor, [2]Professor, Dept. of Biochemistry, Bhaskar Medical College, Telangana

***Corresponding Author:**
Email: mabarisiddiqui@yahoo.com

Abstract

Diabetes has become a universal major health concern, personal habits form an integral part of its etiology and poor control of blood sugar is a major contributor of associated morbidity. Betel nut (Areca catechu) has become a personal habit of at least 10% of the world population. The alkaloids and nitrosated compounds inside betel nut are competitive inhibitors of GABA receptors affecting the body in various ways, including the brain, cardiovascular system, lungs, gut and pancreas. Betel nut usage is also associated with increased central obesity in man and effects of chronic usage in man are similar to those of smoking and increase the risks of ill health. In line with the above theory the present crossectional study was conducted in department of Biochemistry, Bhaskar Medical College, Yenkepally and Siddhartha Medical College, Vijayawada. 70 patients were enrolled in the study and the usage and effects of betel nut chewing in diabetic patients were documented. The majority of patients enrolled with diabetes were in age group of >45 years, many of them being overweight or obese. Those with the habit of betel nut chewing had poor glycemic control evidenced by the high mean of post prandial blood sugar of 160mg/dl ($p<0.001$) and HBA1C levels indicating poor control of > 7% ($p<0.001$) whereas the fasting blood sugar levels had no significant differences ($p>0.001$). Because most of the occasion's betel nut being taken after food and on the balance of evidence we can conclude that chronic consumption of betel nut in diabetic people is a major contributing factor for poor control of post prandial blood sugar levels and the explanation for the poor control being inhibition of GABA receptors on pancreas. Further work in the probable mechanism of poor control needs to be done to highlight the problem of this habit and necessary actions to be taken to prevent morbidity.

Introduction

Diabetes has become a universal major health concern, personal habits form an integral part of its etiology and poor control of blood sugar is a major contributor of associated morbidity. Since Betel leaf consumption with Betel nut (Areca catechu) which is a psychoactive and addictive substance and is relentlessly used by about 600 million people worldwide[1]. India tops the list of countries producing Betel nut followed by China and Myanmar. India tops the list of major betel nut consuming countries with most of the countries being from Asian continent[2]. Various mechanisms have been explained by which the specific ingredients like alkaloids and nitrosated compounds present in *Areca catechu* nuts, chewed alone or with traditional 'quids' made by wrapping chopped Betel-nut and slaked lime, and other ingredients, in a leaf of the Piper Betel vine produce both the physical and psychological effects[3]. Betel nut consumers have reported an increased sense of well-being and an enhanced effect on the digestion especially after a heavy meal, and some euphoria and hence used on many social occasions after food[4]. Hospitals have reported acute ill effects after high rates of consumption which include arrhythmias, exacerbation of COPD including asthma, psychosis and acute gastric upset.[5] The areca nut has four main active ingredients or alkaloids including arecoline, guvacine, arecaidine and guvacoline. These active alkaloids are anti-muscarinic on smooth muscle, arecoline being responsible for most of it. They bind to the GABA receptors present in the brain, leading to their pleasant psychoactive effects[6]. These GABA receptors are a type of chloride channels which have structural similarity with acetylcholine receptors and are widely distributed in the body, including the islets of pancreas, where the alkaloids have various physiological effects. Arecaidine is equally effective as GABA in stimulation of synthesis of collagen by buccal fibroblasts[7]. Arecoline acts as a GABA receptor blocker which prevents normal inhibition of neurotransmission by GABA[8]. Reports of severe extra pyramidal symptoms along with heavy betel quid and nut usage may be due to antagonism of the anti-cholinergic agent Procyclidine by the chief alkaloid Arecoline[9]. The acute toxic effects of Betel nut chewing can include palpitations, perspiration and flushing of the face with a feeling of heat below the skin. Studies have confirmed that skin temperatures in the face rapidly increase by 0.5 to 2^0C with increased Betel nut use[10]. Increase in the pulse rate, and increase in blood pressure are only seen in novices[11]. Betel nut has also been reported of producing higher basal secretion of catecholamine like adrenaline and nor adrenaline from adrenal chromaffin cells when compared to other paan ingredients[12].

I*n vitro*, chewing juices can inhibit the secretion and release of catecholamine in response to high potassium concentrations and Carbachol, suggesting Betel quid components may affect the entry of Calcium into cells entering through high-voltage channels[13]. Glutamate decarboxylase (GAD) is a GABA shunt enzyme also found in islet cells and acys as an antigen which is associated with the appearance of GAD antibodies in serum at the onset of type I diabetes in

man[14]. As active Areca alkaloids are GABA receptor inhibitors, by blocking the inhibitory effects of GABA on hormonal secretion of glucagon and somatotrophin, they could increase their release. A rise in glucagon with hyperglucagonemia is an immediate effect seen, a mechanism, that might be responsible for hyperglycemia, or Diabetes eventually, over a period of time. Expression of GAD is reduced by GABA inhibition and this in turn reduces autoimmune responses to GAD in islets of pancreas and brain[15]. A character common to all diabetogenic nitroso compounds, including STZ, is that they contain a moiety with a `ring' structure which has similar structure to the chair-shaped `pyranose ring' of glucose. It is this similar part of the alkaloid, by binding to glucose receptors on beta cells, account for the diabetogenicity of these compounds[16]. Studies have also confirmed that an increase in maternal intake of areca alkaloids is associated with an increased incidence in childhood type I diabetes in man[17].

The effect of alkaloid on glucose tolerance and on the beta cells of pancreatic islets has been investigated[18]. Study revealed that 8.3% of adults developed hyperglycaemia, central obesity and enlargement of pancreatic islets with changes in beta cells similar to human type II diabetes in contrast to 0.5% incidence of diabetes in the colony as a whole and in control animals. Areca nut consumption increases the risk of the development of diabetes was established by a study showing hyperglycemia in relation to betel leaf usage and other risk factors for type II diabetes in East London Bangladeshi adults living in Tower Hamlets, between the years 1991 and 1993[19]. Hence a theoretical basis exists for suspecting that Areca nut might be a diabetogenic item in the diet. In view of the theory above, the present study was conducted in Department of Biochemistry Bhaskar Medical College, Yenkepally Siddhartha Medical College, Vijayawada. A total of 70 patients were enrolled in the present cross sectional study with an aim to document the usage and effects of Betel nut chewing in Diabetic patients attending the hospital.

Materials and Methods

This cross-sectional study was conducted in Department of Biochemistry, Bhaskar Medical College, Yenkepally and Siddhartha Medical College, Vijayawada from May 2013 to June 2015. About 70 patients with documented Diabetes Type II and who were on treatment were enrolled after taking their due consent. Interview and the medical history were taken from all the enrolled patients and was estimated that half of the enrolled diabetic patients were betel nut chewers with a 95% confidence interval of 44%-56%. Exclusions of the study included Patients on treatment with Insulin or with other co-morbid conditions. The study enrollments were divided into two groups, those who are Betel nut chewers and those who are non-chewers. Blood investigations were done once at the time of diagnosis and once after three months of follow up in both the study groups. Samples were drawn in Oxalate-NaF for blood glucose estimation and in plain tubes or HbA1C. Both fasting and post prandial blood glucose two hours after food was estimated along with HBA1c[20]. Blood glucose was estimated using GOD POD method[21] and HBA1C using Ion Exchange Resin Method.

Results

Age, sex, weight and BMI: Out of the enrolled 70 diabetic patients, 44 were males and 26 were females, their ages ranging from 25 years to 78 years at the time of their enrollment. 60% of the patients were aged 45 years and above and their mean age, median age and interquartile range were respectively 47, 49 and 40 - 55 years for males and 44.9, 45.0 and 38-54 years for females. There were more male than female patients in each group. 11% were under 35 years old while 40% of the cases were in the 45-54 years age group and those aged 55 years and above constituted 22%. The maximum weight was 92kg and minimum weight recorded at diagnosis was 38 kg. The overall mean, median and interquartile range for weight was 69, 71 and 63-78 kg. The overall mean weight and interquartile range for males and females were 73, 64-82 and 69, 60-74 kg respectively (Table 1, Fig. 1).

The highest BMI was 40 kg/ m2 and lowest BMI 17 kg/m2 with the overall mean and interquartile range of 26 kg/m2 and 23-28 kg/ m2 respectively. For males the mean and interquartile range were respectively 27.6 kg/ m2 and 25-30 kg/m2, and for females the mean and interquartile range were respectively 24.7 kg/m2 and 23-31 kg/m2 as shown in Table 1 and Fig. 1. Out of the 70 diabetic patients, the family history revealed, 25 (35.7%) had a history of diabetes in their families. One parent was affected in 7 of the 25 (28%) and 12 (48%) had an affected brother or sister, and the others had a parent in addition to a sibling with diabetes. Out of the cases 35% of men and 36% of women had a family history of diabetes mellitus.74% of the diabetic patients were chewing Areca nut before their diagnosis and continued the habit even after their diagnosis. Betel nut chewing was more common with female patients who constituted 79% while males constituted only 67%. The majority (57%) of patients used less than 5 betel nuts per day; only 23% chewed 5-9 nuts per day and 19% of them had heavy consumption of 10 or more nuts per day.

Table 1: Comparison of age, sex, weight and BMI

	Number	Age		Weight		BMI	
		Mean	Interquartile range	Mean	Interquartile range	Mean	Interquartile range
Males	44	47	40-55	73	64-82	27.6	25-30
Females	26	45	38-54	69	60-74	24.7	23-31

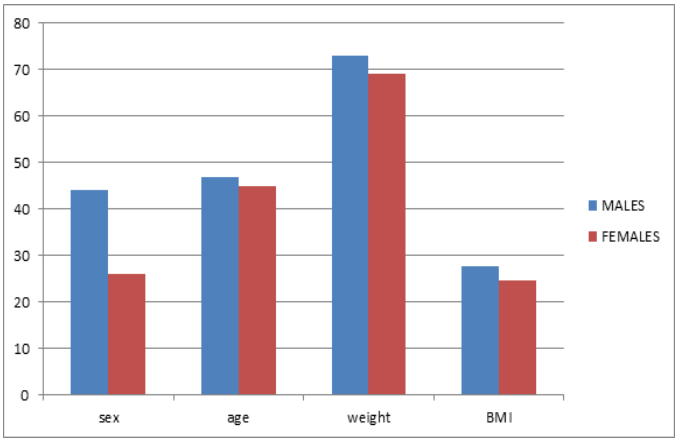

Fig. 1

Blood glucose level: At time of diagnosis both fasting and post prandial blood sugar levels were estimated and most recent i.e. 3 months post diagnosis again the levels of both fasting and post prandial blood sugar levels were estimated. In Areca nut chewers initially at the time of diagnosis the estimated overall mean of fasting blood glucose level was 156.2 mg/dl with an interquartile range of 119-202 mg/dl. The mean fasting glucose was 148.3 mg/dl for males and 166 mg/dl for females. The interquartile range among males was 112-211.3 mg/dl and for females 108-224.7 mg/dl. The most recent fasting blood glucose level overall means were 89.7mg/dl with the recent interquartile range of 117.7-182.1 mg/dl. The mean and interquartile range in males and females were 87 and 92 mg/dl respectively and the interquartile ranges were 72.2-140.4 mg/dl for males and 69 to 154.2 mg/dl in females. In non-chewers group the overall mean at the time of diagnosis for fasting glucose was 150.2 with an inter quartile range of 117.5-198.2 mg/dl. The mean and interquartile ranges of fasting blood glucose for males were 152.4 mg/dl, 110.4 – 216.2 mg/dl and in females were 148.6 mg/dl, 109.1–232 mg/dl. After 3 months the overall mean and interquartile ranges of fasting blood glucose were 92.6 mg/dl and 112–176.5 mg/dl. Males had a mean and interquartile range of 78.1 mg/dl, 68.6 – 139.9 mg/dl and in females' mean and interquartile range were 90.7 mg/dl, 71.6 – 149.9 mg/dl. the difference in fasting levels between betel nut chewers and non-chewers after 3 months was statistically not significant with P >0.001.

In the group including Areca nut chewers the overall mean post prandial blood glucose level at the time of diagnosis was 245.7 mg/dl and the interquartile range around 179-287 mg/dl. At the time of diagnosis the mean post prandial blood glucose levels for males were 271 mg/dl and for females 244.8 mg/dl. The interquartile range for males was 203.4 -298.8 mg/dl and for females 180-293.4 mg/dl. Three months later the mean and interquartile range was 188.8mg/dl, 141-248.2 mg/dl respectively. The post prandial blood glucose mean levels in males and females were 184 and 192 mg/dl respectively and the interquartile ranges were 142.2-240.4 mg/dl for males and 139 to 254.3 mg/dl in females. (Table 2, Fig. 2).

In the group including non-chewers, the overall mean and interquartile range at the time of diagnosis was 224.4 mg/dl, 168-261.2 mg/dl respectively. In males and females the means were 236mg/dl and 218.1 mg/dl with the respective interquartile ranges of 172.2-262.4 mg/dl for males and 164.4-251.3 mg/dl for females. After three months the levels in post prandial blood sugar were slightly lower than in betel nut chewers with overall mean and interquartile range of 151.7 mg/dl, 114 – 172.9 mg/dl respectively. Mean and interquartile ranges for males were 142.3 mg/dl, 106.4 – 182.1 mg/dl and in females were 158.6 mg/dl, 114 – 172.9 mg/dl. The difference in post prandial blood glucose levels at three months between betel nut chewers and non-chewers was statistically significant with p<0.001. (Table 3, Fig. 2).

Table 2: Blood glucose in betel nut chewers

Category	Betel nut chewers (all values are in mg/dl)							
Time	At diagnosis				After 3 months			
Type	Fasting		Post prandial		Fasting		Post prandial	
Sex	Male	Female	Male	Female	Male	Female	Male	Female
Mean	148.3	166	270	244.8	87	92	185	191
Interquartile range	112-211.3	108-224.7	203.4-298.8	180-293.4	72.2-140.4	69-154.2	142.2-240.4	139-254.3

Table 3: blood glucose in non-chewers

Category	Non chewers (all values are in mg/dl)							
Time	At diagnosis				After 3 months			
Type	Fasting		Post prandial		Fasting		Post prandial	
Sex	Male	Female	Male	Female	Male	Female	Male	Female
Mean	152.4	148.6	236	218	78.1	90.7	142.3	158.6
Interquartile range	110.4-216.2	109.1-232	172.2-262.4	164.4-251.3	68.6-139.9	71.6-149.9	106.4-182.1	104.9-176.4

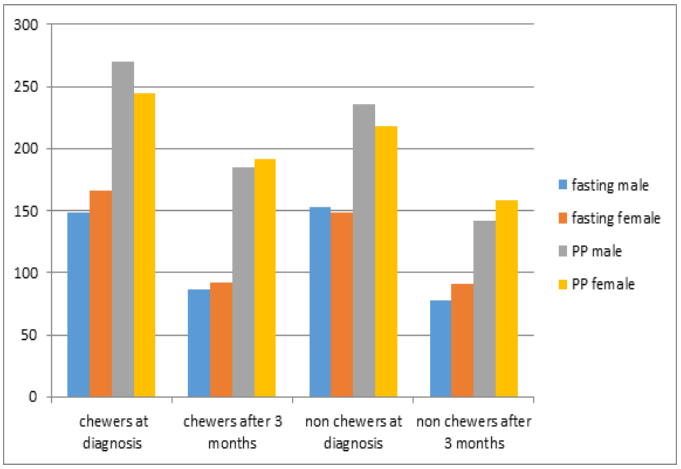

Fig. 2: Mean of blood glucose levels in diabetic betel nut chewers and non-chewers

In betel nut chewers the mean HbA1c after three months was 8.1 with interquartile range 7.1 - 9.8, and a minimum and maximum level of 5.8 and 12.2 respectively. Males had better control with mean HbA1c levels of 7.9 with interquartile range of 5.7 to 9.2 whereas females had mean HbA1c levels of 8.3 and interquartile ranges of 6.3 – 11.0. In non-chewers the mean and interquartile ranges were 7.6, 5.6 – 8.8 with no significant difference between male and female with their respective means and interquartile range being 7.2 and 7.4, 5.3-8.3 and 5.2 – 8.5, P>0.001. The difference in HbA1c levels in betel nut chewers and non-chewers was statistically significant with P <0.001. Only 17% of men and 23% of women in the study had fairly good control of their blood glucose (<180mg/dl). 80% of patients had poor control of their blood glucose level (>180 mg/dl). Of the 56 diabetic patients with poor control of their blood glucose level, 41 (73.2%) were betel nut chewers. (Table 4, Fig. 3).

Table 4: HbA1c levels

	Betel nut chewers		Non chewers	
Sex	Male	Female	Male	Female
Mean	7.9	8.3	7.2	7.4
Interquartile range	5.7-9.2	6.3-11	5.3-8.3	5.2-8.5

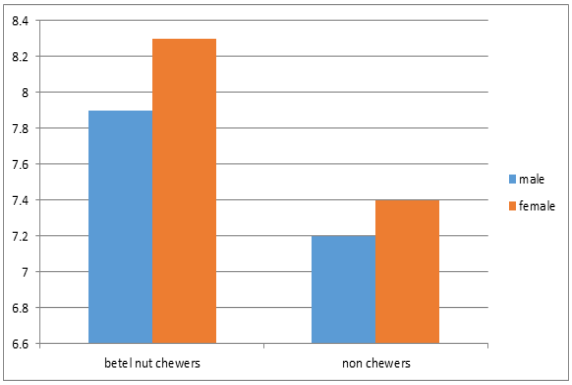

Fig. 3: HbA1c comparison

Discussion

The majority of the patients was from either Hyderabad or Vijayawada city and had adapted an urban lifestyle. We have observed that Diabetes mellitus is more common in the older age group and in those who have lived in urban centers for a long time and have adopted a more western lifestyle. Many of the enrolled patients prefer to eat western-type food including Burgers, Pizza and a local delicacy like Biryani and kebab was common among all. History also revealed that most of them could not eat on time either due to work or some other delay. Most of them had habit of chewing paan or having plain betel nut after taking a meal and few had habit of eating flavored betel nut throughout the day and some had them at social events, majority (57%) using less than 5 betel nuts per day. Betel nut chewing was more common among females than in males. All of the enrolled patients had picked up this habit of chewing betel nut from their elders. Over 70% of the diabetic patients in the study were betel nut chewers before their diagnosis, and have continued the habit while undergoing treatment for diabetes of whom the majority (80%) of the patients had poor control of their post prandial blood glucose level which suggests a possible relation between chewing of betel nut after food and poor blood glucose control. A study in the UK concluded an association between weight gain and hyperglycemia with betel nut chewing among Asians who have been living in eastern parts of London[22], and similar studies in other places like Taiwan and Port Moresby showed the prevalence of high fasting blood glucose was found to be greater than 30% among betel nut chewers compared to 10% in those who didn't have the habit[23] and concluded that betel nut chewing is a risk factor for type II diabetes mellitus[24]. Adapted to a sedentary lifestyle most of their work included working from an office chair and involved less than 30 minutes of workout. History also revealed that only 20% of the enrolled members were smokers and many of them only smoked socially. 35% of them had family history of diabetes with males and females having almost equal distribution.

Many of the diabetic patients were overweight or obese at the time of their diagnosis with males being more obese and Andhra Pradesh ranks 5th in the obesity ranking[25]. The association between obesity, physical inactivity and type II diabetes is common among populations in Indians who are obese and physically less active and live in metropolitan cities[26]. Obesity is considered as an important risk factor as it develops resistance to insulin in type II Diabetes mellitus[27]. The number of insulin receptors on the target cells and/or decreasing glucose transport through post receptor changes may occur in obesity[28]. Considering these findings, the habit of chewing betel nut by the diabetic patients helps to explain the fact that the majority of them have very poor control of their blood glucose level. This is indicated by the observations that mean post prandial blood glucose levels at the time of diagnosis were slightly lower in non-chewers (236,218.1mg/dl) than that of betel nut chewers (270,244.8 mg/dl) in both males and females respectively. There was no significant difference ($p>0.001$) in the fasting values at the time of diagnosis and values in both males and females showed similar distribution. Post prandial blood glucose levels at three months in non-chewers (142.3, 158.6 mg/dl) were significantly lower ($P<0.001$) than that of betel nut chewers (185, 191 mg/dl) in both males and females respectively. Females showed a better control of post prandial blood glucose than males at 3 months ($P< 0.01$). The statistical difference was not significant ($P>0.001$) when fasting blood glucose was compared at 3 months intervals and both males and females had similar distribution of values ($P>0.001$). HbA1c levels in non-chewers (7.2, 7.4) were significantly lower ($P<0.001$) than betel nut chewers (7.9, 8.3) in both males and females respectively. Female non chewers showed better control with lower mean blood glucose levels ($P<0.001$). The above results clearly indicate that chewing betel nut has a significant effect on post prandial blood glucose levels and the effect appears to be more prominent in females. It is imperative that patients are involved in their own self-care management. Counseling programs on physical activity improve blood glucose control in diabetes[29]. There is evidence that adequate patient education improves control of blood glucose level and reduces complications[30]. The patients also need to be informed about the likely harmful effects of betel nut chewing on their diabetes mellitus. In this study, there are possible confounders (that have not been controlled for) such as non-compliance with treatment, change of oral hypoglycemic and choice of oral hypoglycemic drugs and the patients' inappropriate diet including alcohol that would contribute to poor glycemic control. However, in view of the findings in the present study and other studies, betel nut chewing is likely to be a contributing factor to the poor glycemic control mostly affecting the post prandial blood glucose levels.

Conclusion

Betel nut chewing may be a contributing factor to the poor glycemic control in diabetic patients affecting the post prandial blood glucose levels. As the majority of diabetic patients have poor control of their blood glucose, this observation concerning the effect of betel nut chewing on blood glucose control and its predilection towards females should be made known to the patients, their families and the community because many people chew betel nut but do not know the risks involved in this habit. They should be specifically advised to avoid betel nut chewing after food as this practice may be helpful in better control of post prandial blood glucose and avoidance of large doses of oral hypoglycemic drugs. Diabetes patients' education

and training is one of the most important activities in the overall management of diabetes mellitus. It is important for the patients and their families to increase their knowledge, skill and self-management abilities in order for them to make changes in their lifestyle, and enable them to cope with the disease. Good diabetes knowledge with a positive emotional outlook, and understanding of the problems that may occur in the course of the disease, may help the patient to maintain good health. Further investigations' involving other GABA receptor inhibitors is necessary to test the link between betel nut chewing and poor glycemic control.

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