Impact of Khat Chewing on Serum Uric Acid and Albuminuria Levels in Yemeni Type II Diabetes Mellitus Patients

Abstract:

Background: Diabetes mellitus is the major cause of end-stage renal disease and is a common endocrine illness defined by chronic hyperglycemia. In addition to diabetes, substance addiction is considered to be a cause of renal issues. The World Health Organization has classed khat (Catha edulis) as an illicit substance. Khat interferes with regular physiological activities, which may have negative health impacts on organs and systems. **Objectives:** To determine the effect of khat and uric acid on nephropathy intype II diabetes mellitus. **Material and methods:** This is an analytical, cross-sectional study that was conducted on 215 males aged 35 to 55 years who had previously been diagnosed with type II diabetes mellitus and were visiting AL- Thawra General Hospital in Ibb City. The diabetic person was corresponded in age and BMI by the control participant. The subjects were divided into two groups. There were 105 people with type II diabetes mellitus(59% chewing Khat and 46% not chewing Khat), 110 people were healthy and did not have type II diabetes (44 % of them chewed Khat and 66% did not chew Khat). **Results:** A significant increase in albuminuria and proteinuria within the normal range in the diabetes mellitus Khat Chewer group compared to the diabetes mellitus Non-Khat Chewer group ($p<0.001$). However, no significant differences were seen in the healthy control group. **Conclusion:**Khat chewing has a strong effect on those with type II diabetes and increases the progression of kidney nephropathy. There was an association between khat chewing and higher uric acid levels in both diabetic and non-diabetic patients.

Keywords:Type II diabetes mellitus, Catha edulis, Khat chewing.

Introduction:

People in Yemen and East African countries chew the leaves of the Khat (Catha edulis) plant between 4 and 6 hours each day; however, this habit has extended to certain other countries where Yemeni and other East African groups live **[1,2].** In Yemen, general health and socioeconomic consequences of Khat chewing have been reported **[3].** Khat includes amphetamine-like compounds, primarily cathinone and, to a lesser extent, cathine **[4].** Cathinone is the most important active component in Khat, and it is responsible for the majority of the pharmacological actions **[5].** Furthermore, Khat leaves are high in phenolic substances such as flavonoid glycosides and condensed tannins **[6].** Despite the presence of various antioxidants as chemical components of Khat **[7,8],** free radicals and oxidants are now seriously implicated in Khat toxicity, despite the fact that decreased activity of antioxidant enzymes due to reactive oxygen species (ROS) and oxidative stress has been reported in rats **[7,9]** and humans **[10,11].** ROS have the ability to cause significant cell damage by oxidizing important cellular elements such as proteins, lipids, and DNA **[12].** The biological effects of oxidative stress are proportional to the extent of these alterations, with a cell capable of overcoming minor perturbations and returning to its former state. More extreme oxidative stress, on the other hand, can cause cell death, and even moderate oxidation can produce apoptosis, whilst strong stresses can cause necrosis **[13].** These ROS effects may cause liver and kidney cells to be destroyed, resulting in excessive levels of their contents in the blood **[14].** Besides its stimulant properties, the plant's processed leaves and roots are used to cure a variety of diseases such as influenza, cough, asthma, gonorrhea, vomiting, and headache **[15].** Furthermore, certain native East Africans and the Meru tribe of Kenya utilize khat to cure malaria **[15-17].** Similarly, some Yemenis utilize khat to manage obesity, reduce hunger, and alleviate migraines by inhaling the vapors of burning khat leaves **[18].** Alkaloids, terpenoids, flavonoids, sterols, glycosides, tannins, amino acids, vitamins, and minerals are all found in khat **[19].** The stimulating action of khat, on the other hand, is mostly due to its alkaloid component, cathinone, and a lesser amount of cathine and norephedrine **[20].** Cathinone is an intermediary metabolite in the production of cathine that is mostly present in young fresh leaves of the khat plant **[20].** Khat is rapidly absorbed after oral ingestion and reaches maximal plasma levels 1.5-3.5 hours from the start of chewing **[21,22].** Cathinone is relatively fragile and decomposes after a few days of being picked, or it converts into cathine and norephedrine if the leaf is dried **[23].**Diabetes mellitus is a metabolic condition characterized by chronically elevated blood glucose levels

(hyperglycemia) caused by insulin insufficiency, resistance, or both **[24].** Diabetes can cause major consequences, increasing mortality and morbidity **[25].** Cathinone, the primary active component of khat, stimulates dopamine release from central dopaminergic nerve terminals, enhancing the activity of dopaminergic pathways. These catecholamines would raise blood glucose levels by activating glycogenolysis in the skeletal muscles and liver; an adrenoceptor-mediated reaction. Insulin release from pancreatic -cells is also inhibited by -adrenoceptor stimulation, which raises blood glucose levels **[26,27].** the khat chewing causes hypoglycemic potential due to the presence of flavonoids, flavones, flavonols, saponins, and trace elements such as magnesium, chromium, manganese, zinc, iron, vanadium, copper, nickel, lead, and strontium.Hyperuricemia is widespread in metabolic syndrome, and various epidemiological studies have shown the link between hyperuricemia and metabolic syndrome **[28,29].** In T2DM patients, serum UA and microalbuminuria levels were significantly positively linked with renal disease **[30].** Patients with higher SUA levels have lower renal function, regardless of HbA1c or diabetes duration **[31].** Higher blood UA has an independent and substantial positive connection with an increased risk of impaired glomerular filtration rate in T2DM **[32].** The National Institute of Drug Abuse estimates that 10 million individuals worldwide chew khat. Although the World Health Organization's Expert Committee on Drug Dependence (ECDD) classified khat as a class III drug in its 1971 convention, it wasn't until 2002 that the WHO judged there was enough evidence to reclassify khat as a class I drug. Khat use is now outlawed in only 27 states in the United States. Increased immigration from Ethiopia, Yemen, and Somalia has resulted in an increase in hospitalizations for seizures, insanity, and severe hepatitis caused by khat chewing. Khat chewing is a prevalent social behavior in Yemen that has been performed for decades by both men and women, and sometimes even children, for a few hours per day, and is often a lifetime habit

Materials and methods:

Study design:

This is an analytical, cross-sectional study.

Study Area:

From 2017 to 2018, the research was conducted at Ibb City AL-Thawra Public Hospital Alfa Medical Laboratories.

Sample Size and Subject:

The sample size was 215, calculated using the Open Epi software with a 95% confidence level, Subject males aged 35 to 55 years who have previously been diagnosed with type II diabetes mellitusand attend AL-

AL-Thawra general hospital in Ibb City were chosen for this study. In terms of age and BMI, the selected control subject matched the diabetic patient. The subjects will be divided into two categories. 105 subjects withtype II diabetes mellitus(Case group), 59% of whom chewed Khat and 46% of whom did not chew Khat. (Control group), 110 people were healthy and did not have type II diabetes mellitus. 44% of them chewed Khat and 66% did not chew Khat.

Sample collection:

Blood sample:

According to the Ethical Consideration of Sanaa University, the consent was told that participation is voluntary. Fasting blood samples of 5 mL were obtained from an antecubital vein and placed in two pre-labeled vacuum tubes. The first tube contains a full EDTA blood sample for HbA1c testing. The second sample was centrifuged after it had clotted. The serum supernatant was used for the biochemical examination of creatinine, uric acid, FBS, cholesterol, triglyceride, and HDL. Following sample collection, laboratory analysis begins.

Urine sample:

Spot Morning urine was collected and examined as soon as possible in a clean urine container. Urine Dipstick for biochemistry straight from a urine sample and urine sample centrifugation were conducted. The supernatant was utilized to quantify urine creatinine, albumin, and protein.

Included Criteria

Male subjects fasting 12 hours healthy control and type II diabetes mellitusbetween the ages of 35 and 55 with no advanced DM complications. khat chewing greater than one year and Diabetic age >5 years. Patients who have not engaged in strenuous exercise over the previous 24 hours will be enrolled in the investigation.

Excluded Criteria:

Patients receiving uric acid lowering therapy or suffering from severe sickness, fever, or urinary tract infection. Patients other than diabetics under the age of 35, as well as those suffering from heart failure, liver failure, or renal failure. A patient having a serum creatinine level greater than 2 mg/dl and a glomerular filtration rate (GFR) less than 60 mL/min. Thyroid dysfunction is seen in this patient.

Ethical Consideration

Each participant will provide written informed consent (labeled at the end of the proposal), and we will be notified that participation is voluntary and that the Committee for Research Ethics of Sanaa University, Faculty of Medicine and Health Sciences, Yemen, has approved this study.

Results and discussion:

Demographical characters and clinical data of diabetes mellitus and control groups have been shown in table 1.There were no association between age, weight, BMI, waist circumference, and hip circumference in Diabetes (Kat and Non-Kat Chewers) and non-diabetic (Kat and Non-Kat Chewers) groups (Table 1).According to some experts, the overall effect of khat on diabetic patients is negative since the user is less likely to follow dietary guidance, and the intake of sweetened beverages with khat aggravates hyperglycemia **[6].** Over 20 years ago, a clinical investigation on diabetes patients was undertaken in Yemen. **[33].** It was discovered that when the khat extract was mixed with the glucose used in the glucose tolerance test, there was a significant reduction in blood glucose levels as compared to the non-khat (control) arm of the trial. This effect was linked to the delayed glucose absorption from the stomach caused by the action of khat tannins and inorganic ions, particularly magnesium, which has a significant inhibitory influence on gastrointestinal function. It appears that khat-induced delayed gastric emptying may also have a role in lowering postprandial hyperglycemia in type II diabetic patients **[34].** A systemic review and meta-analysis study that comprised 25 studies from 1976 to 2016 found that khat is a risk factor for the development of T2DM**[36].** Furthermore, an experimental study in Malaysia revealed that khat-induced diabetes mellitus has a cytotoxic effect by destroying pancreatic -cells and modifying the architecture of the islets of Langerhans**[35].**In the current study, FBGin Diabetes groups (Kat and Non-Kat Chewers) was non-significant increasedthan non-diabetic (Kat and Non-Kat Chewers) groups(p0.060)(Table 2).This conclusion was validated by additional research that found comparable results**.[35,37,38]** A systemic review and meta-analysis study that comprised 25 studies found that khat had no effect in lowering blood glucose levels**.[38]** Another study conducted in Malaysia found no link between khat chewing and glycemic management**.[35]** Similarly, a Somali investigation found that khat had no effect on blood glucose levels**.[37]** However, two investigations conducted in Yemen discovered that khat chewing elevated blood glucose levels in T2DM patients**[39,40].**There was no significant difference in glycated hemoglobin HbA1c levels between NDNKC and NDKC, indicating that chronic khat chewing has no effect on the basal line of plasma glucose in normal,

but there were significant increases in the HbA1c level DKC group as compared to DNKC (p0.060)(Table 2). This discovery was made by Al-Sharafi and Gunaid, **[54].** This is consistent with our findings that khat chewing in type II diabetes mellitus is related to poor glycemic control and a higher HbA1c. An HbA1c of less than 9% (75 mmol/mol) was found in approximately 57.6% of Non-Khat Chewer patients and 45.6% of Khat Chewer patients. This could be because khat chewing has a negative effect on glucose utilization and insulin activity. It contradicts the widely held idea among patients that khat chewing is beneficial to diabetes. There was no significant difference in random blood sugar levels between DM non-khat chewers and DM khat chewers**[55].** This study agrees with our result in that there was no significant difference in blood glucose levels between diabetic subjects chewing and non-chewing khat, (p0.096)(Table 2). This could be due to cathinone's short half-life, and it is simply the acute effect of khat chewing and my sample was taken after a 10- to 12-hour fast.

Uric acid (UA) is the final product of purine nucleotide catabolism in the human system **[41],** and its levels in blood and urine are useful indications of certain clinical disorders. Abnormal UA levels have been linked to a variety of illnesses, including renal disease **[42].** UA is found in all bodily fluids and tissues, and its concentration in plasma is higher than that of most endogenous antioxidants **[43].** According to reports, UA protects erythrocytes against singlet oxygen damage, reduces lipid peroxidation, and protects against free radical-induced DNA damage in vitro. **[44].** ROS and oxidative stress have been shown to reduce antioxidant enzyme activity in rats fed Khat **[45,46]** and in the plasma of female Khat chewers **[47].** in this study, Uric acid in Kat Chewers significantly increased within the normal range than Non-Kat Chewers in case and control groups ($p<0.05$)(Table 3), due to a natural reaction to Khat's generation of oxidants and indicates a high frequency of arthritis in (DKC). The chemical components of Khat also have an effect on the constituents of the lipid profile. Cathinone is more similar to amphetamine, so these substances have similar pharmacodynamic properties. AlRajhi et al. **[48]** found decreases in total cholesterol, HDL, LDL, and glucose levels in the serum of rabbits fed Khat leaves, as well as histological abnormalities in the liver, confirming Khat's toxicity. ROS have the ability to cause significant cell damage by oxidizing important cellular elements such as proteins, lipids, and DNA **[49].** This study revealed that Albuminuria among Diabetes (Kat and Non-Kat Chewers) was significantly increased than non-diabetic (Kat and Non-Kat Chewers) groups($p<0.001$)(Table 3). due to an increase in ROS produced by Khat; these findings are consistent with those of Al-Hashem et al., **[50],** who found a significant decrease in serum total protein and

albumin of Khat extract-treated rats compared to control rats. This suggests compromised liver function and decreased protein synthesis, either as a result of direct liver cell injury or as a result of decreased protein intake and amino acid absorption. Serum creatinine elevation has been connected to renal disease **[50].** Khat extract significantly increased serum creatinine in rats, indicating decreased renal function due to a reduced ability to eliminate these products. These effects could be caused by alterations in the tubular re-absorption threshold, renal blood flow, and glomerular filtration rate **[51,52].**Alsalahi et al. found a higher amount of creatinine in the serum of male and female rats fed Khat. **[53].** in this study, Diabetes (Kat and Non-Kat Chewers) and non-diabetic (Kat and Non-Kat Chewers) groups showed a significant increase in Creatinine concentration but within the normal range($p<0.001$)(Table 3). Albuminuria, urine protein, serum creatinine, UACR, and eGFR were all substantially higher in T2DM compared to normal healthy controls, with($p<0.001$)(Table 3). In T2DM this discovery explains the involvement of diabetes in renal degeneration. Renal disease progression mechanisms include renal hemodynamic alterations, oxidative stress, inflammation, hypoxia, and an overactive renin-angiotensin-aldosterone system (RAAS) all play a part in the etiology of DKD, with renal fibrosis playing a critical role **[56].** This study is limited by the fact that the study sample was not randomly selected. It does, however, provide information on the effect of khat chewing on type II diabetes among Yemenis.

Table 1. Demographical Characters and clinical data of diabetes mellitus and control groups.

Parameters	***Non-Diabetes Mellitus***		***Type II Diabetes Mellitus***	
	Non-Khat Chewer No= 66	Khat Chewer No= 44	Non-Khat Chewer No= 46	Khat Chewer No= 59
Age (years)	43±5.4	44.4±7.3	45.5±6.3	44.9±5.0
	P value 0.547		*P value0*.960	
Weight (Kg)	73.7±6.7	71.2±7.6	76.9±8.6	74.2±11.1
	P value 0.561		*P value* 0.390	
Length (Meter)	1.69±0.06	1.68±0.5	1.67±0.05	1.68±0.07
	P value 0.808		*P value* 0.901	
Body Mass Index	25.6±2.1	25.2±3.3	27.3±3.3	26.1±2.9
	P value 0.876		*P value* 0.71	
Waist Circumference	89.3±7.8	89.31±7.3	94.32±8.9	92.3±9.1
	P value 1.0		*P value* 0.623	
Waist Hip Ratio	0.90±0.06	0.89±0.18	0.94±0.06	0.94±0.12
	P value 0.030		*P value* 0.851	

Table 2. Comparison of FBS, HbA1c, Uric acid, and SerumCreatinine among Type II Diabetes Mellitus and Non-DiabetesMellitus khat and non-khat chewer

Parameters	**Non Diabetes Mellitus**		**Type II Diabetes Mellitus**	
	Non Khat Chewer N=66	Khat Chewer N=44	Non Khat Chewer N= 46	Khat Chewer N=59
*Fasting Blood Sugar mg/dl	96.2 93.2 –99.8	90.5 87.8 – 93.6	146.8 134.7 –163.4	164.9 151.9 –183.4
	p. value *0.605*		p. value ***0.096***	
Glycated HbA1c %	5.4±0.40	5.2±0.37	8.20±1.8	9.6±2.1
	p. value *0.963*		p. value $\boldsymbol{2.7\times10^{-6}}$	
Uric acid mg/dl	4.59±0.72	5.31±0.85	4.71±0.75	5.29±0.91
	p. value $2.4\times\mathbf{10^{-5}}$		p. value **0.023**	
Serum Creatinine mg/dl	1.0±0.14	0.93±0.12	1.09±0.13	1.2±0.10
	p. value 0.107		p. value $2.3\times\boldsymbol{10^{-4}}$	

The results are presented as means and Standard deviation except Fasting Blood Sugar expressed as Geometrics mean with 95% Confidence interval of mean evaluated by ANOVA, Bold values are significant.

Table 3. Comparison of renal biomarker between Type II Diabetes Mellitus and Non Diabetes Mellitus groups khat and non khat chewer.

Parameters	**Non Diabetes Mellitus**		**Type II Diabetes Mellitus**	
	Non Khat Chewer N=66	Khat Chewer N=44	Non Khat Chewer N= 46	Khat Chewer N=59
*Albuminuria mg/dl	12.7 (11.9 – 14.7)	15.0 (14.0 –17.0(	23.2 (21.3 –26.4)	35.6 (33.3 –39.0)
	p. value 0.128		*p. value* $\boldsymbol{8.2\times10^{-8}}$	
Urine protein	29.9±8.5	29.6±6.4	44.5±16.7	73.4±21.3
	p. value ***0.****983*		*p. value* $\boldsymbol{4.3\times10^{-13}}$	
*UACR *mg/g*	7.90 (7.5 –9.7)	8.74 (8.05 –10.0)	16.5 (15– 20.)	22.3 (20.6 –25.3)
	p. value 0.937		*p. value* ***0.013***	
*UPCR	2.10 (1.9 – 2.3)	1.97 (1.8– 2.1)	3.51 (3.0 – 4.0)	4.89 (4.43 – 5.41)
	p. value 0.812		*p. value* $\boldsymbol{8.2\times10^{-8}}$	
eGFR ml/min	99.80±20	101.74±18	92.49±20.3	81.06±13.4
	p. value 0.963		*p. value* $\boldsymbol{3.4\times10^{-4}}$	
MDRD	88.78±15.19	95.15±16.42	81.20±18.8	69.66±8.99

	p. value 0.160	*p. value* $\boldsymbol{6.8\times10^{-4}}$

The results presented as means and Standard deviation except *Albuminuria, Urinary Albumin-Creatinine Ratio and*Fasting Blood Sugar expressed as Geometrics mean with 95% Confidence interval of mean evaluated by ANOVA, , Bold values are significant. .eGFR: estimated Glomerular Filtration Rate, UACR:Urinary Albumin-Creatinine Ratio, UPCR: Urinary Protein Creatinine Ratio. MDRD: Modified Diet Renal Disease.

Conclusion

Khat chewing has a strong effect on those with type II diabetes and increases the progression of kidney nephropathy. There was an association between khat chewing and higher uric acid levels in both diabetic and non-diabetic patients.

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