

# Impact of Khat (*Catha Edulis* Forsk), During Chewing Session, on Serum RBG Level in T2DM Patients Treated with Metformin

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## Abstract

**Background:** Despite its detrimental effects on health, chewing khat appears to be becoming more commonplace globally as a daily habit, particularly in the nations where it originated. As a result, it is very possible that khat users will take drugs while they chew the drug. That is high among them, increasing the likelihood of harmful khat-drug interactions. In these situations, it is critical to assess the impact of simultaneous khat and clinical medication delivery.

**Objective:** As a preliminary study to evaluate the effect of khat (*Catha edulis* Forsk) chewing on serum Random Blood Sugar (RBG) level in Type 2 Diabetic Mellitus (T2DM) patients treated with metformin.

**Material and Method:** Seventy-six male participants between the ages of 25 and 70 were included in the trial, 38 of them were already metformin-treated T2DM patients with a prior diagnosis. The remaining 38 people had no family history of diabetes, were healthy, and were not diabetic. Whether the individuals in the aforementioned two groups regularly chewed khat or not was used as a supplementary criterion for division. Using a drop of blood taken from each patient, a calibrated glucometer was used to take three readings of RBG levels.

**Results:** The findings showed that healthy persons (non-khat chewers) had RBG levels at 4 hours after lunch that were significantly different from their corresponding values at 2 hours earlier. Using an independent sample t-test to compare the RBG levels of healthy khat chewers to healthy non-khat chewers, it was discovered that khat chewers had significantly higher RBG levels 3 and 4 hours after lunch ( $P = 0.042$  and  $0.000$ , respectively). RBG levels at 4 h after lunch (2 h after khat chewing) were significantly lower by  $-54.36$  when compared to the level at 2 h after lunch of the same group of diabetic khat chewers taking metformin, whereas levels at 3 h after launch (1 h after khat chewing) were not statistically different.

**Conclusion:** When khat was consumed, healthy volunteers' serum RBG levels went up, whereas diabetic patients receiving metformin saw no change in their RBG levels.

**Keywords:** *Catha Edulis*, Effects, Khat, Metformin, T2DM.

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## INTRODUCTION

The native tree or large shrub *Catha edulis* Forsk, sometimes called as "khat," is found throughout the Arab Peninsula, particularly in Yemen, as well as in certain countries in Africa, including Ethiopia and Kenya, as well as western Asia (Al-Juhaishi *et al.*, 2012). Since ancient times, khat has been utilized for its psychostimulant, euphoric, and analgesic effects. To slowly release the active ingredients for salivary ingestion, the leaves are chewed. A chewing session could last anywhere from three to seven

hours. Around the world, an estimated 20 million people chew khat leaves every day (Alsalahi *et al.*, 2016). About 20 pharmacologically active substances are found in khat, but cathinone, an alkaloid that breaks down into nor-pseudoephedrine and nor-ephedrine quickly in the body and has effects similar to amphetamines, is the primary factor in almost all of them (Patel, 2000). Despite its detrimental consequences on health, khat chewing seems to be getting increasingly widespread globally, especially in the countries where it originated. Albaser and associates (2021). These individuals are at a high risk of co-administration of khat

and medications, which raises the possibility of harmful khat-drug interactions. It is crucial to determine how khat and prescription drugs interact in these situations. Nearly 4% of the world's population suffers from diabetes mellitus (DM), which is predicted to rise by 5.4% in 2025. (Thilagam *et al.*, 2021). Hyperglycemia caused by abnormalities in insulin secretion, insulin action, or both characterizes this group of metabolic disorders. The eyes, kidneys, nerves, heart, and blood arteries are particularly vulnerable to long-term damage, malfunction, and failure from diabetes (ADA. 2011).

The first-line treatment for type 2 diabetes is metformin, an oral hypoglycemic medication from the biguanide class. It is the anti-diabetic drug that is most frequently prescribed worldwide and the only one that has been shown to lower cardiovascular and overall mortality (Chika *et al.*, 2019). Its mode of action includes lowering plasma glucose levels by preventing gluconeogenesis in the liver, reducing gastrointestinal glucose absorption, and enhancing insulin sensitivity by enhancing peripheral glucose uptake and utilization. It is used clinically to treat diabetes. Metformin also improves lipid and cholesterol metabolism, reduces inflammation, and inhibits cell development, among other pleiotropic effects (Hattori *et al.*, 2015). A member of the incretin family of peptide hormones, glucagon-like peptide-1 (GLP-1) increases plasma levels of incretin, which is released from the stomach in response to ingested glucose. It causes pancreatic beta cells to release insulin, delays gastric emptying, prevents beta cell glucagon release, and creates a sensation of satiety (Nasri & Rafieian-Kopaei, 2014). There are few studies about the effects of khat chewing on clinical drugs (Albaser *et al.*, 2021). For our knowledge, this is first study about effect of khat chewing on metformin, which was a preliminary study to evaluate the effect of khat (*Catha edulis* Forsk) chewing on serum Random Blood Sugar (RBG) level in Type 2 Diabetic Mellitus (T2DM) patients treated with metformin.

## MATERIALS AND METHODS

### Ethical Consideration

The study was initiated after the ethical approval of the Institutional Ethics Committee of Al-Razi University Medical College (REF: Al-RMC/IEC/20/1). Subjects had to sign an informed consent and assent form in both English and Arabic before they could participate in the study.

### Study Design

This study was conducted among individuals, previously diagnosed as having T2DM treated with metformin and who came to medical clinic (the diabetic clinic) in AL-Gumhory Teaching Hospital in Sana'a city.

### Study population

Thirty eight of the 76 male participants in the trial, who

were all between the ages of 25 and 70 year, had previously been diagnosed as T2DM patients receiving metformin treatment. The remaining 38 people had no family history of diabetes, were healthy. Whether the individuals in the aforementioned two categories regularly chewed khat or not was used to further classify them into the two groups. 16 healthy non-khat chewers made up Group I; 22 healthy khat chewers made up Group II; 16 T2DM patients receiving metformin who were also non-khat chewers made up Group III; and 22 T2DM patients receiving metformin who were also khat chewers made up Group IV. A drop of blood was collected from each patient, and three readings of RBG levels were taken using a calibrated glucometer (ACCUCHEK active apparatus, Germany). The initial reading was taken 0 hour before to the khat chewing session (approximately 2hours after lunch). After lunch, three and four hours later, the RBG level's second and third readings were collected (i.e. 1 and 2 hours after starting khat chewing in case of groups II and IV). Following lunch and prior to the first RBG reading, participants were advised to abstain from eating and drinking for the next three hours, with the exception of water. To each individual in groups II and IV, the same quantity of khat (about 100 g of fresh khat leaves) was administered (Saif-Ali *et al.*, 2003).

### Inclusion and Exclusion Criteria

Patients with T2DB who were older than 25 years of age and treated only with metformin drug were included. Patients with T1DM and T2DM treated with other drugs were excluded.

### Samples and Data Collection

The subjects` data were collected in two steps: the first was a clinical information obtained from the patients. Information included the name, sex, age, body mass index (BMI), duration of diabetic, chronic disease associated, and used drugs by (questionnaire) and the second was blood glucose testing.

### Statistical analysis

The data were analyzed using the IBM SPSS software in its version 25.0 and the findings were presented as means with standard deviations. The significance of the data was determined using paired sample t-tests within each group and independent sample t-tests across groups. When  $P < 0.05$ , differences were considered significant.

## RESULTS

### Subjects

The background information on the 76 samples in the all groups is summarized in (Table 1).

Table 1: Subjects Characteristics

Parameter	Healthy non-khat chewers (n =16)	Healthy khat chwers group (n = 22)	Metformin treated non-khat chewers (n =16)	Metformin treated khat chewers (n = 22)
Age	25 – 70 Year	25 – 70 Year	25 – 70 Year	25 – 70 Year
Sex	Males	Males	Males	Males
BMI (kg/m <sup>2</sup> )	26.31± 3.78	28.71 ± 2.52	28.38 ± 2.74 76.8 ± 9.40	30.32 ± 3.06 80.27 ± 10.96
Weight	78.3 ± 11.99	79.73 ± 8.67	164.33 ± 6.37	163.32 ± 5.84
Length	172.5 ± 6.43	166.5 ± 4.48		
RBG reading before lunch (mg/dl)	113 ± 22.85	108.27 ± 18.17	163 ± 55.67	212.77 ± 60.38

RBG: random blood glucose; BMI: body mass index

The results displayed that the level of RBG at 3h after lunch of healthy individuals (non-khat chewers) was not significantly different from its respective value at 2 hours after lunch. In contrast, the level of RBG at 4h after lunch was significantly different for the same group. Similarly, the

RBG levels at 3h and 4h after lunch (1h and 2h after khat chewing) of healthy and khat chewers individuals were not affected. Comparing RBG level of healthy individuals who were khat chewers with those of healthy non-khat chewers using independent sample t-test, showed that the RBG level at 3h and 4h after lunch were significantly higher in khat chewers (P = 0.042 and 0.000 respectively). In contrast, the RBG level at 2h after lunch was not significantly different. The serum RBG levels at 3 and 4 h after lunch of metformin-treated diabetic and non-khat chewers did not differ significantly. They were affected by values -4.67 and 4.00 respectively when compared to their levels at 2 h after lunch of the same group. In contrast, the RBG level at 4 h after lunch (2 h after khat chewing) of metformin treated diabetic khat chewers was significantly decreased by -54.36 when compared with the level at 2 h after lunch of the same group, while the levels at 3h after launch was not-significantly different. In comparing serum RBG levels of metformin diabetic khat chewers with their respective control group (metformin-treated diabetic non-khat chewers) via independent sample t-test, there was significant difference of RBG level at 2h ( P = 0.003) and no significant differences at 3h and 4 h after lunch (Table 2 & Figure 1).

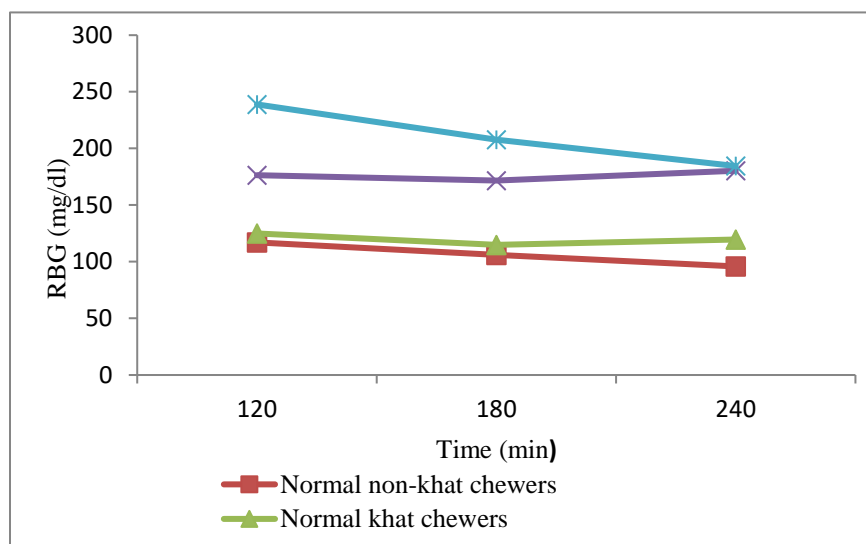


Figure 1: Effect of Khat, during chewing session, on serum RBG level in T2DM patients treated with metformin

Table 2: Effect of khat, during chewing session, on serum RBG level in T2DM patients treated with metformin

Parameters	Normal		Type 2 diabetic patients	
	Non-khat chewers(n = 16)	Khat chewers (n = 22)	Metformin-non-khat chewers (n = 16)	Metformin-khat chewers (n = 22)
RBG 2 hours after lunch	116.93 ± 23.01	124.95± 23.93	177.19± 51.36	238.86 ± 64.65 <sup>+</sup>
RBG 3 hrs after lunch (1 hrs after Khat chewing)	105.69 ± 12.34	114.91 ± 12.04 <sup>+</sup>	173.44 ± 61.03	207.82 ± 65.59
RBG 4 hrs after lunch (2 hrs after Khat chewing)	95.50 ± 6.25 <sup>*</sup>	119.55 ± 15.22 <sup>+</sup>	182.19 ± 64.28	184.50 ± 59.62 <sup>*</sup>

RBG: random blood glucose

(\*): Significant comparing the same group with those of 2 hours using paired sample t-test. (+): Significant comparing the two tested groups using independent t-test. P value < 0.05.

## DISCUSSION

The effects of khat were evaluated, during chewing session, on serum RBG level in T2DM metformin-treated patients. The study revealed that khat chewing increased serum RBG level in healthy subjects while in diabetic patients who are taking metformin, it had no effect on RBG levels during khat session. Results were in agreement with those demonstrated by an updated systematic review and meta-analysis is justified to incorporate data brought to light since 1976. The outcome showed inconsistent results and the glycemic effect of khat remains conflictin (Alsalahi *et al.*, 2016). Variations might be attributed to unadjusted experimental factors or related to other factors such as the differences in phytochemical composition of khat itself. Therefore, identification and quantification of the phytochemical content of the khat cultivar used in this study must be determined in further studies as to provide a meaningful assessment of its glycemic properties. Moreover, well-controlled clinical studies should also be conducted to confirm whether or not chewing khat is associated with the development of T2DM, since this would be a source of concern bearing in mind that the plant is widely consumed in certain populations (Alsalahi *et al.*, 2016). According to El-sayed & Amin, (2012) there is a strong correlation between chronic khat administration and T2DM development. In a recent meta-analysis the association of khat with a significant increase in BGL in human diabetic patients has been reported (Alsalahi *et al.*, 2016).

The above-mentioned hyperglycemic action of khat may be due to the fact that chewing khat increased serum cortisol and resistin levels while lowering insulin levels. Since the primary active ingredient, cathinone, shares structural and functional similarities with amphetamine, it stimulates catecholamine release, activates  $\alpha$ -adrenergic receptors, and raises the levels of serum cortisol and adrenocorticotrophic hormone, which contribute to the inhibition of insulin release (Brenneisen *et al.*, 1990). Additionally, the increase in catecholamines increases the breakdown of glycogen in skeletal muscles (Al-Motarreb *et al.*, 2002). The primary reason for the khat-associated increase in serum resistin concentration, which mediates insulin resistance and results in problems of glucose metabolism, is the rise in norepinephrine levels together with raised calcium and copper levels (Atlabachew *et al.*, 2010; Overbeck *et al.*, 2008). Khat also lowers zinc levels, which can have an impact on DM in a number of different ways because it is necessary for the production of insulin hexamers and for the preservation of proteins' and enzymes' sulfhydryl groups (Meyer & Spence, 2009). It worsens hyperglycemic symptoms, causing glucose urea and increased osmotic diuresis, which increases Zn excretion, increasing insulin resistance due to impaired insulin synthesis, increased oxidative stress, and the formation of advanced glycation end products (AGEs), according to Dilina do Nascimento

Marreiro *et al.*, (2007). Copper and other excessive metal ions have been linked to peripheral neuropathy (Zheng *et al.*, 2008).

Despite the fact that the earlier research by Saif-Ali *et al.*, (2003) did not find a statistically significant difference between the BGL of khat-chewing and non-khat-chewing non-diabetic patients. According to Al-Sharafi & Gunaid, (2015) khat can control high blood glucose levels. According to Taleb & Bechynne, (2009) healthy non-diabetic patients who chew khat had a slight drop in BGL. According to Heymann *et al.*, (1995), khat delayed stomach emptying time, supporting and possibly explaining the earlier findings.

Because norepinephrine is only 10% as effective at lowering blood sugar levels in healthy individuals as adrenaline, the hypoglycemic effect of khat can be explained (Cryer, 1987). This can be resisted by the pancreas cells' strong reactivity, which secretes insulin that quickly lowers blood sugar by increasing hepatic glucose production. According to normal circumstances, an increase in peripheral insulin levels of 60–100% and a complete inhibition of hepatic glucose output without any stimulation of peripheral glucose utilization occur in healthy non-diabetic subjects with a serum glucose concentration increase of 10-15 mg/dl (Röder *et al.*, 2016). Within the first 30 minutes, this impact may develop spontaneously.

## LIMITATIONS

The drawback of the study is that the number of participants who were involved in it was comparatively small, due to financial constraints as a consequence of war and siege in Yemen. The variations in the demographic characteristics of the participants such as uncontrolled diabetes. Thus, further investigations are required to evaluate the impact of khat (*Catha edulis* Forsk) chewing on diabetic parameters level in T2DM patients treated with metformin and other antidiabetic drugs.

## CONCLUSION

In conclusion, khat use seems to raise serum RBG levels in healthy people while having a khat session had no effect on RBG levels in people with diabetes using metformin.

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