

Effect of Khat Chewing on the Level of Testosterone Hormone in Blood among Adult Males in Rada'a Town -Yemen

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Abstract

This study relied on case-control method, and included 50 healthy people who were randomly selected out of people chewing khat with age ranged between 18-30 years old and had a body mass index (BMI) of less than 30. All people with any diseases, factors and treatments that interfere or affect the results of this study have been excluded. The sample was divided into two groups, i.e. experimental and control. The experimental group was further divided into two groups. The first consisted of 20 chewing khat daily, while the second consisted of 10 chewing khat only once a week. The control group included 20 people who do not chew khat. Venous blood was collected from every group and subjected directly to measure of testosterone hormone level in Al-Saeeda Specialized Laboratories in Rada'a city.

Also, this study showed that the mean level of testosterone in people who chew khat daily was significantly higher ($p = 0.026$) in comparison with those who do not chew it (control group), the average increase in the level of testosterone hormone in daily khat chewer group by 1ng/ml of serum. Also the results showed no significant difference observed in testosterone level between one time per week khat chewers and non-chewing but the level of testosterone increased gradually from zero day (non-chewing) and reached the maximum with seven days per week chewing group. The study also showed that there was no statistically significant effect of the variables of age, body mass, time period of chewing khat and the number of hours of chewing khat per day on the level of testosterone in the blood.

We conclude that the effect of khat on testosterone was very low when compared to other studies, may be because khat contains some chemicals such as pesticides and agricultural fertilizers that directly or indirectly affect the level of testosterone in the blood of khat chewer.

Keywords: Testosterone Hormone; Khat; Rada'a Town

تأثير تعاطي القات على مستويات هرمون التستوستيرون في الدم لدى البالغين الذين يمضغون القات في مدينة رداع محافظة البيضاء

الملخص

هدفت الدراسة إلى معرفة تأثير تعاطي القات على مستويات هرمون التستوستيرون في الدم لدى البالغين الذين يمضغون القات في مدينة رداع محافظة البيضاء، ومعرفة علاقة ذلك بالعمر ومؤشر كتلة الجسم. واعتمدت هذه الدراسة على طريقة case control، وشملت 50 شخصاً سليماً تم اختيارهم عشوائياً بناءً على المقابلة الشخصية والاستبيان، حيث تراوحت أعمارهم بين 18 و 30 عاماً وكان مؤشر كتلة الجسم لديهم أقل من 30.

تم تقسيمهم إلى مجموعتين، ضمت مجموعة الحالات (المجموعة التجريبية) 30 شخصاً يتعاطون القات، من بينهم 20 شخصاً يتعاطون القات بشكل يومي، بينما يستخدم 10 أشخاص القات يوماً واحداً فقط في الأسبوع، والمجموعة الضابطة ضمت 20 شخصاً لا يتعاطون القات. مع العلم أنه تم استبعاد جميع الأمراض والعوامل والعلاجات التي قد تتدخل أو تؤثر على نتائج هذه الدراسة. تم سحب 3 مل من الدم الوريدي من كل حالة ووضعها مباشرة في أنابيب لا تحتوي على مضادات التخثر، وبعد أن تجلط الدم بشكل كامل، تم فصل المصل واستخدامه لقياس مستوى هرمون التستوستيرون في مختبرات السعيدة التخصصية بمدينة رداع.

وأظهرت هذه الدراسة أن متوسط مستوى هرمون التستوستيرون لدى الأشخاص الذين يمضغون القات يومياً كان أعلى بكثير $p = 0.026$ بالمقارنة مع أولئك الذين لا يمضغونه (المجموعة الضابطة). وتشير النتائج إلى زيادة متوسطة في مستوى هرمون التستوستيرون في مجموعة مضغ القات اليومية بمقدار 1 نانوجرام / مل من مصل الدم، ولا يزال هذا التغيير ضمن النطاق الطبيعي لهرمون التستوستيرون لدى الذكور البالغين، كما لم تظهر النتائج فروقاً معنوية ملحوظة في مستوى هرمون التستوستيرون بين مضغين القات ليوم واحد فقط في الأسبوع وغير المضغين، ولكن مستوى هرمون التستوستيرون زاد تدريجياً من صفر يوم (غير مضغ) ووصل إلى الحد الأقصى مع مضغ مجموعة سبعة أيام في الأسبوع، كما أوضحت الدراسة عدم وجود تأثير ذي دلالة إحصائية لمتغيرات العمر وكتلة الجسم والفترة الزمنية لمضغ القات وعدد ساعات مضغ القات في اليوم على مستوى هرمون التستوستيرون في الدم.

ونستنتج أن القات بما يحتويه من مواد كيميائية ومبيدات وأسمدة زراعية قد يؤثر بشكل مباشر أو غير مباشر على مستوى هرمون التستوستيرون في دم متعاطي القات، ولذلك يوصي الباحثون بضرورة الإقلاع عن ظاهرة مضغ القات لما له من آثار سلبية على الصحة العامة وصحة الجهاز التناسلي بشكل خاص.

الكلمات المفتاحية: هرمون التستوستيرون؛ قات؛ مدينة رداع

1- Introduction:

There is a spread of a group of negative phenomena and habits in some societies of the Arab world, including those related to the use of some plants or their extracts, whose effects are negatively reflected on human life and vital functions. One of the health, social and economic damages, the danger of which increases with the danger of the pesticides and fertilizers used for it is khat. Therefore, khat is still a deadly epidemic and the major problem that afflicts people in Yemen (**Manghi et al., 2009**). Khat (*Catha edulis*) is a wild tree or perennial tree evergreen with many branches, fruitless, with a height of 70 cm to 8 meters, its leaves are oval in shape with serrated edges with a short neck, light green and shiny color and tinged with red, and the middle vein of the leaf is prominent from bottom and used by chewing in the mouth (**Kennedy, Teague and Fairbank, 1980**). Khat was moved to Yemen from Abyssinia which is considered as the original home of khat in the world. The scientific name of Khat is *Spelasternum* or *Ulex* of the *Leguminosae* family (**Lamina, 2010**). This plant is widely grown in Yemen and it may live for nearly 100 years and grows in hot and temperate regions and the most appropriate areas for its growth are mountainous areas. This tree is characterized by the ability to adapt to the environment, and is resistant to drought, pests and weather conditions compared to other crops and has many types and varieties (**Ali et al., 2004**). Khat is widespread in East Africa, especially in Abyssinia, Ethiopia, Somalia, Djibouti, Eritrea, Kenya, Tanzania, Uganda, South Africa, Yemen, Afghanistan, Turkmenistan, Malawi, Tanzania, Congo, Mozambique, Zimbabwe, Britain, the Netherlands, the United States, and Italy. Yemen is one of the most consuming countries for khat and it is one of the most income crops in it. Khat contains a number of important chemical components such as Cathinone which is considered as the main material that activate the central nervous system

and highly concentrated in leaves. Cathine or Norephedrine is available in leaves and trunks. Cathine and cathinone are responsible for sympathetic symptoms that occur during chewing khat such as increased heartbeat, pupil dilatation and increased blood pressure. Norephedrine is a material concentrated in the more durable parts of khat. Methcathinone, Cathidinols are found in a small percentage in khat (**Pennings, Opperhuizen, Amsterdam JGC, 2008; Getahun, Gedif and Tesfaye, 2010**).

In addition to that, Amino acids are found in khat by 5% and the most important of which are Asparagine, Threonine, Valine, Serine, and Proline. Vitamins are also found in khat in very small proportions like Carotene which is the precursor of vitamin A, vitamin B¹ (Thiamine), vitamin B² (Riboflavin), vitamin B³ (niacin), calcium, iron and magnesium (**Manghi, et al., 2009**). The absorption of khat may go through two stages, the first is through the oral mucosa and the second through the small intestine and then transferred into bloodstream (**Ahmed and Hamoud, 2015**). The concentration of cathinone in blood depends on the dose and time of ingestion of khat. A small amount of less than 7% is excreted without change in urine (**Bárbara, 2022**). Cathinone is rapidly metabolized when passing through the liver by liver microsomal enzymes through the β -keto group reducing to alcohol resulting in cathine and norephedrine. These materials reach their maximum effects within 15-35 minutes (**Glenice and Hagen, 2018 ; Bárbara, 2022**). Chewing Khat has many different effects on the digestive and nervous system such as constipation, urinary retention, a sense of alertness, and psychological symptoms such as anxiety, insomnia and others (**Alem and Shibre, 1997; Wabe and Nasir, 2011**). Khat can interact with some drugs either synergy or inhibition, and many studies have found that there are interactions of khat with anesthetic drugs and also affects the bioavailability of some antibiotics

(Bárbara, 2022). Khat is one of the influences on the human body, as it affects the functions of the central nervous system because it contains a substance called (cathine), which is a narcotic substance and a stimulant to the central nervous system (Berihu and Asfeha, 2015) and gives some symptoms such as wakefulness, insomnia, anxiety, depression, and neurological and psychological disorders (Dalu, 2000).

Cathinone and norpseudoephedrine in khat have been found to increase blood pressure and heart rate; these effects may be due to the sympathetic activity of cathinone. In comparison with non-khat users, khat users have a higher risk of death through ischemia, myocardial hypertrophy, cardiogenic shock, arrhythmias, and stroke (Menyar et al., 2015 ; Al-Motarreb, 2004). Khat affects the urinary system, which leads to slight retention or difficulty when urinating, and because of its stimulating effect on the sympathetic system. This leads to a narrowing of the bladder wall and the smooth muscles of the urinary system, which leads to a large number of urination (Nasher et al., 1995; Alem, and Shibre, 1997). Chewing khat also leads to damage of the liver and kidneys as it increases the activity of kidney bilirubin and alkaline phosphatase and leads to a high concentration of creatinine, urea and uric acid in the blood, which may lead to liver and renal poisoning (Malasevskaja, Al-Awadhi and Mohammed, 2020). At the beginning of chewing khat, it leads to sexual arousal and then gradually decreases, leading to the inability to have sex in general. Khat causes gonorrhea in the stores, and has a negative effect on the testicle and this effect leads to cell atrophy and reduces the secretions of sex hormones, which leads to poor sex in males in the future. Khat is the main cause of most sexual disorders that occur in married couples, and it has been found to increase the number of abnormal sperm (Dalu, 2000).

There are some effects of khat on respiratory system

such as coughing, phlegm, shortness of breath, chest pain and wheezing. Some studies have also shown a decrease in lung function and a decrease in oxygen saturation levels among khat chewers compared to non-topical chewers. Chronic use of khat may increase the risk of pulmonary edema and bronchitis (Garedew and Geta, 2014; Glenice and Hagen, 2018; Ayana and Alemeshet, (2013). Khat affects the digestive system and leads to :1. Acute and chronic stomatitis, including the gums, tongue and pharynx, and these infections may lead to ulcers of the oral mucosa, bleeding and receding gums, and an increased risk of oral cancer; 2. Inflammation of the esophagus and stomach, accompanied by severe acidity and may reach the occurrence of peptic ulcers such as stomach and duodenal ulcers;

3. Loss of appetite as a result of norciclovophedrine and this affects the general health. In addition to that, khat prevents the absorption of many useful substances due to the presence of tannin that hinders the absorption of some substances such as iron and zinc and leads to general wasting and anemia diseases (Nigussie, Gobena and Mossie, 2013; Alshoabi et al., 2022). Khat negatively affects the functions of the endocrine glands, leading to a disturbance in the functioning of the hypothalamus gland, which leads to a feeling of loss of appetite and high body temperature. It also affects the function of other glands, resulting in the rise levels of the prolactin hormone, thyroid-stimulating hormone TSH, thyroid hormones FT³, FT⁴, and also affects the gonads, leading to a slight increase in the hormones testosterone and estradiol in men. In addition to that, khat affects the adrenal gland, which leads to a decrease in cortisol levels in the blood (Al-Ghamdi, 2012). It causes imbalances in some substances in the blood such as sugar (Al-Motarreb, 2004). Testosterone is the sex hormone responsible for the appearance of traits

in males and is present in men more than women. This hormone is made from cholesterol (**Elazeem, Modawe and Abdelrahman, 2015 ; Oswal and Yeo, 2010**). It is produced primarily in the testicles. Testosterone is available in three types in the body : **a-** Free testosterone, It is called free hormone because there are no proteins or molecules attached to it, this type accounts only; **b-** 3% of the total testosterone inside our bodies. **b-** Testosterone hormone associated with globulin, this type is linked to globulin SHBG and it is available in 40-50% of total testosterone in the body ; **c-** Albumin-bound testosterone. This type binds to albumin and it is available in 47 -68% (**Elazeem, Modawe and Abdelrahman, 2015 ; Mandal, 2019**).

The testosterone produced mainly from the testicles (Leydig cells) and usually controlled by the hypothalamus gland and the pituitary gland secretion, where the hypothalamus gland sends a signal to the pituitary gland to secrete stimulating hormones (FSH) and (LH). When the percentage of testosterone is high, the hypothalamus sends a signal to the pituitary gland to reduce the secretion of stimulating hormones and subsequently reduce testosterone secretion from testicles (**Hejazian, Dashti and Rafati, 2007**).

Testosterone performs several functions in the body including fat production and distribution, muscle strength, sperm production, body hair growth, red blood cell production, pallor of voice, development of testicles and penis and bone growth and strength. It also helps in improving psychological mood, ovarian function, natural sexual desire and sexual behavior (**My clevelandclinic, 2022**).

There are a number of factors that affect testosterone including genetic abnormalities (Klein-Flutter syndrome), Health conditions (exp. pituitary and hypothalamus glands disease and diabetes, especially type II), obesity is associated with low testosterone, age: As men age, there is a slight gradual decrease in the level of testosterone in the blood and Steroids drug abuse may negatively affect testosterone and may lead to infertility (**Oswal and Yeo , 2010; Healthy male org, 2021**).

The percentage of testosterone in males is often from 265_923 Nano-grams per deciliter in the blood, while females have a much lower percentage than males, where testosterone levels differ between people or individuals significantly according to the factors affecting them (**Claire Sissons, 2023**).

The age	Male (ng/dL)	Female (ng/dL)
7-10 years	5,68_1,80	10,29_2,69
13-17 years	496,58_208,08	31,55_16,72
19 years and over	923_265	70_15

Table (1): shows the normal percentage of testosterone in the blood in males and females by age group (**Claire Sissons, 2023**).

In this study, We intend to show the effect of khat abuse on testosterone levels in the blood among adult khat chewers in the city of Rada'a Al-Baydha Governorate, and to know its relationship to age and body mass index .

2-Materials and Methods

2.1-Data collection:

The data was collected by personal interview by means of a questionnaire, designed specifically to

include personal information, general information about chewing khat, as well as information about diseases and medications that can affect testosterone levels in the blood. The data collection process took from three weeks to one month. The study sample consisted of a group of healthy adult males in the Rada'a town whose ages range between 18-30 years, and the body mass index BMI has less than 30. The number of the selected study sample was 50 people after the screening and exclusion

process and they were randomly selected. The study sample was divided into two groups:

The first group included 20 people who do not chew khat as a control group.

The second group included 30 people using khat as an experimental group. This group was further divided into two groups: 1- A group of 20 people who use khat on a daily basis. 2- A group of 10 people who use khat only once a week.

2.2- Blood collection

By 5ml syringes, 3 ml of venous blood was withdrawn from each case into non-anticoagulant tubes (Gel clot Activator tubes), and incubated in ice. After the blood clotted completely, the serum was collected and used for measuring the level of testosterone (Hormone test).

2.3- Data Sorting

Approximately 54 samples were collected but after sorting 4 samples were excluded due to their conformity with the exclusion criteria represented in the following: diabetes, blood pressure, heart disease, kidney disease, liver disease, high blood lipids, endocrine problems (such as pituitary or thyroid disorder), problems in the testicles (such as tumors, inflammation) and psychological problems (such as anxiety and depression). In addition to that, people using the following medicines: cytochrome B450 inhibitors, 5alpha reductase inhibitors (such as finasteride and dutasteride), aromatase inhibitors (such as anastrozole), antiandrogen drugs (such as

cyproterone acetate, spironolactone, picalutamide) and synthetic testosterone drugs. Smoking and alcohol drinking people were avoided. People over the age of 30 and whose body mass index is more than or equal to 30 were also excluded.

2.4- Hormonal Assay:

Immediately after collecting blood samples, tubes were transferred to Al-Saeeda Specialized Laboratories in Rada'a Town, for hormonal assay. Serum was separated from blood samples using centrifuge and then serum hormone was tested by Elisa device (from Snibe company, China)

2.5 -Statistical analysis:

The data were analyzed statistically using SPSS and Bython programs for performing regression test, t-test, correlation test, and frequency. All these tests were used to analyse the significant relationship between the independent variables and testosterone levels in the blood and to identify the factors that affect this variable.

3- Results

The mean level of testosterone in people who daily chew khat was significantly higher ($p = 0.026$) in comparison with those who do not chew it (control group). The results indicate an average increase in the level of testosterone hormone in daily khat chewer group by 1ng/ml of serum (fig1)

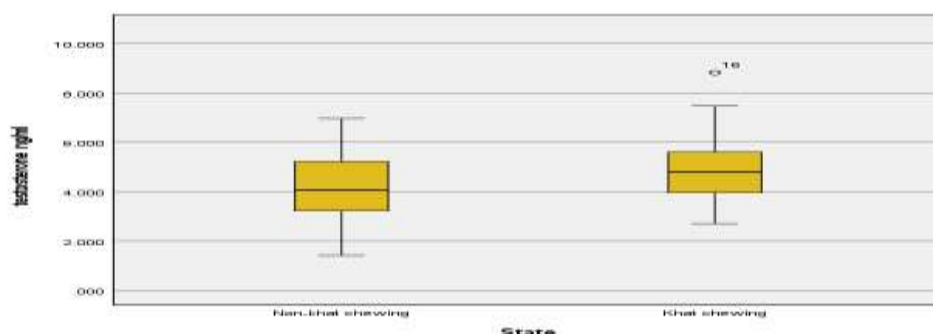


Figure 1 : Effect of khat on level of serum testosterone of daily chewing khat in

However, the effect of frequency of khat chewing per week on testosterone level was

evaluated. The result show no significant difference observed in testosterone level between one day per week khat chewer and non-chewing but the level of testosterone increased gradually from zero day (non chewing) and reaches the maximum with seven days per week chewing group.(fig2).

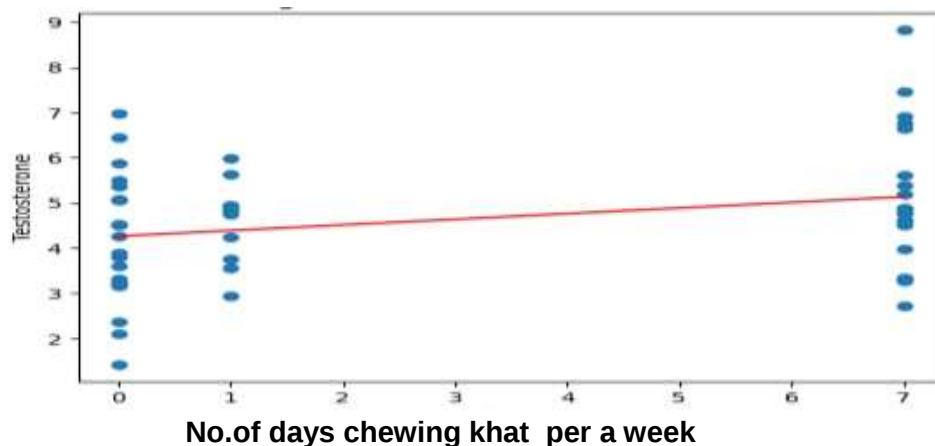
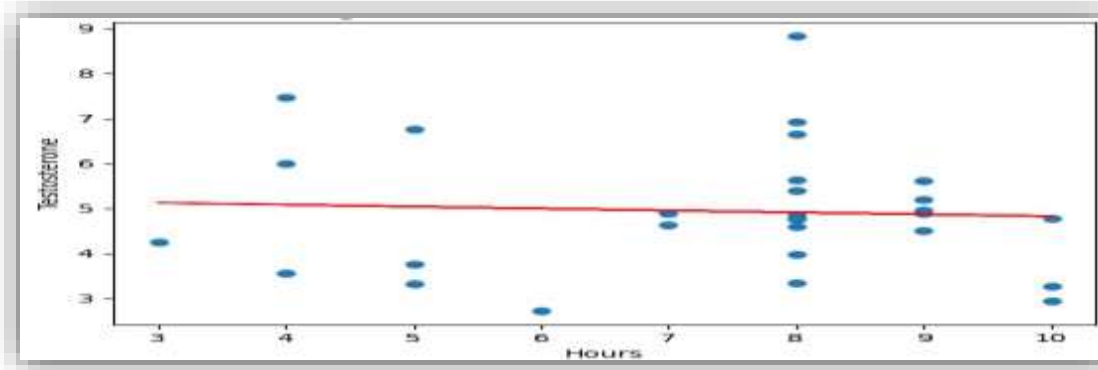


Figure 2: Regression analyses between level of testosterone and number of days chewing khat per a week

In addition to that, the regression analysis was performed to determine the relationship between level of testosterone and the number of hours of khat chewing in people who chew khat. This result indicates no statistically significant differences (fig.3)



Similarly, linear regression analyses also used to demonstrate the level of testosterone based on other various related factors such as age, body mass index (BMI), years of chewing, The results show that there was a decrease of 0.24ng/ml in testosterone hormone percentage for every one-unit increase in BMI .fig4

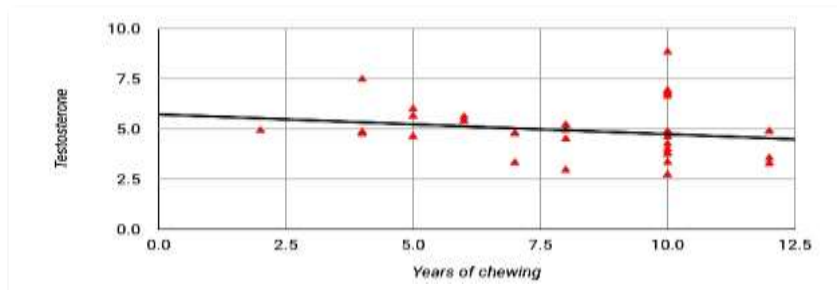
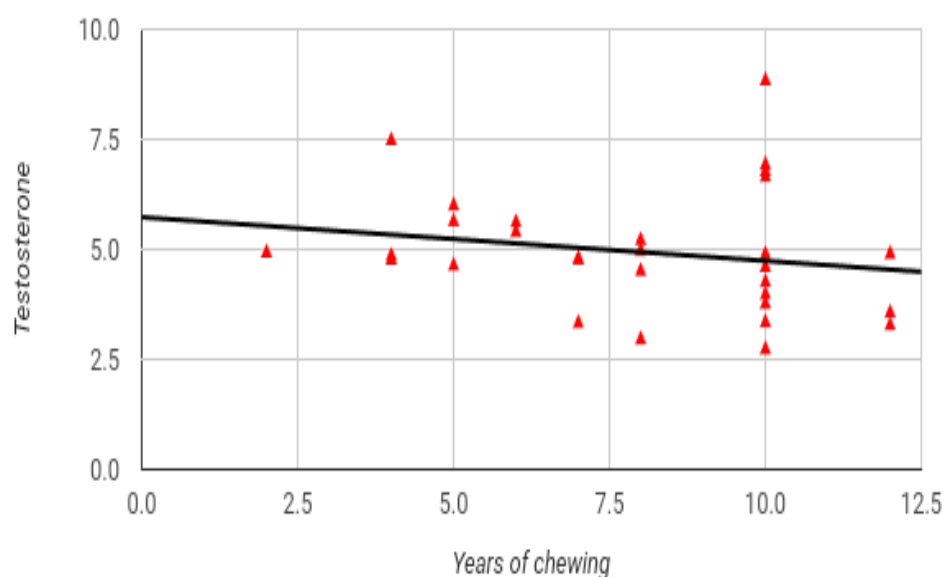


Figure 6: Correlation of hormone parameters with years chewing.

On the other hand, the correlation analysis shows a non significant very small negative relationship between age and testosterone ($p = 0.77$). There is a decrease of 0.135 in testosterone hormone percentage for every one-year increase fig5.

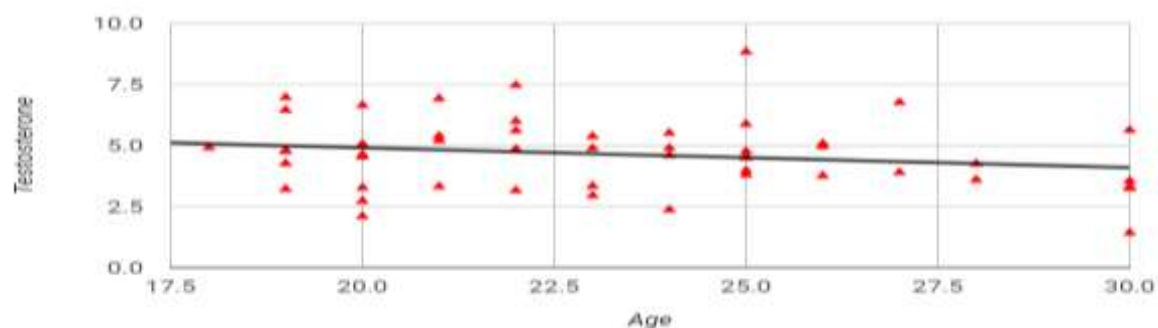
Variables	Correlation coefficient	p Value
Age	-0.262	0.077
BMI	0.012	0.927
Hours spent in chewing khat	0.261	0.080

To study the effect of period of chewing khat, correlation analysis was done and the result indicates that there is a non significant very small negative relationship between years of chewing and testosterone. (fig.6).



These results can be used to clarify the real relationships between the independent variables and testosterone levels in the blood and to identify the factors that affect this variable.(Table 1)

Table 1: Correlation coefficients between testosterone levels and independent variables.



Discussion

The results of our study show that there was a significant increase in plasma

testosterone levels in khat chewers compared to the control group (they do not chew khat), however, these changes are still within

normal ranges. This result is consistent with the Mwenda et al. study on the olive baboon (**Mwenda, 2006**) and with the study of Saeed Al-Ghamdi on humans (**Al-Ghamdi, 2012**), which showed an increase in testosterone in plasma. However, this result is contradictory to previous observations in humans (**Kalix, 1988**), mouse (**Islam et al., 1990**) and rabbits (**Nyongesa et al., 2008**) as well as on contrary to the results of Meseret Yibrah et al conducted on humans (**Yibrah et al., 2019**) which showed a decrease in testosterone in the blood. First, this result may depend on the amount of dose used of khat (**Hu et al., 2018**) where it was found that the use of low concentrations of khat extract led to a slight increase in testosterone, while the use of high concentrations of khat inhibited testosterone production. This means that high testosterone levels may be due to low-dose khat consumption, and it is noticeable that most of the participants in our study were consuming low to moderate doses of khat. Second, it may be due to environmental, physiological and nutritional factors (**Naomi, and Timothy, (2000)**. or perhaps due to the quality of khat itself, which may need to be scientifically proven. Third, the use of pesticides and agricultural fertilizers by khat farmers may compound the effects of khat (**Atieq, Ghewahi and El-Sebae, (2009)**, and affect male sex hormones (**AYED, 2018**). However, this increase in testosterone does not mean that chewing khat may improve sexual functions, but rather that this increase becomes useless in the presence of chemical compounds khat, especially cathene, which has many negative effects on the functions of the reproductive system (**Balint, Ghebrekidan and Balint, 1991; Mwenda et al., 2003**).

The results of our study also show that the increase in the number of days of chewing

khat per week had a significant effect on the level of testosterone compared to khat users for only one day a week, and this may indicate that the effect is actually on khat and its chemical compounds, toxins or fertilizers.

The results of our study also show that other factors such as age, body mass, past time period of chewing khat and the number of hours of khat chewing per day have no statistically significant effect and this may be due to the survey criteria taken when collecting samples and the size of the sample of the study itself.

Conclusion

From the results of our study, it can be concluded that khat, with its chemicals, pesticides and agricultural fertilizers, may directly or indirectly affect the level of testosterone in the blood of khat users. Where it was found that there was a significant increase (significant difference) in the level of testosterone in the blood of khat chewers compared to the control group (do not chew khat). Moreover, it was noted that there is a direct relationship between the level of testosterone in the blood and the number of days spent by a person to chew khat per week.

Recommendations

1. Researchers recommend the need to quit the use of khat because of its harmful effects on various body systems, including the male reproductive system, and to raise public awareness of the health risks resulting from this.
2. Supporting scientific research on khat in various institutions and universities to explore the different effects of khat on public health.
3. Integrating health education about the dangers of khat in the curricula of the primary, secondary and university levels.
4. Future studies on the effect of khat

abuse on the level of testosterone in the blood, so that it includes a large number of samples and covers several Yemeni governorates, in order to control environmental factors and special factors.

5. Future studies on the effect of khat abuse on the level of testosterone, LH, and FSH in the blood in adult males.

6. Future studies on the effect of khat on the level of testosterone and prolactin in adult males.

7. Future studies on the relationship between the level of testosterone and the number and motility of sperm in Yemeni khat chewers.

8. Future studies on the effect of khat on female sex hormones and testosterone in Yemeni women chewing khat.

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