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RESEARCH ARTICLE

INVESTIGATION OF THE EFFECT OF MARAS POWDER (NICOTIANA RUSTICA LINN) USE ON INSULIN RESISTANCE

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ABSTRACT

Purpose: One of the common types of tobacco, which is widely used all over the world and has significant public health concerns, is smokeless tobacco. Maras powder (MP), a type of smokless tobacco, is consumed especially in the Southeastern and Eastern Anatolia regions of Turkiye, and it draws attention due to the lack of sufficient studies on its health effects. This study was conducted for the first time and aimed to determine the effect of MP use on insulin resistance.
Materials and Methods: A total of 58 male subjects (25 MP users and 33 control groups) between the ages of 20-49 years were included in the study. Demographic data, systolic pressure (SBP) and diastotic pressure (DBP) were recorded. For the study, 5 ml of blood was collected from the subjects and serum glucose (mg/dL), total cholesterol (mg/dL), triglycerides (mg/dL), and HDL (mg/dL) were measured via Cobas 6000 series c 501 clinical Biochemistry analyzer. Homeostasis Model Assesment-Insulin Resistance (HOMA-IR) method was used to evaluate insulin resistance.
Results: According to the statistical analysis, triglyceride, glucose, insulin and HOMA-IR levels were significantly higher in MP users compared to the control group ($p<0.05$). In addition, significant correlations were observed between insulin, HOMA-IR, glucose and triglyceride levels in MP users.
Conclusion: In this study, we obtained data indicating that the use of MP with limited information regarding its health effects, may be associated with insulin resistance. This study was conducted for the first time and we believe it will address the existing gap in the literature in this area of research and enhance the public awareness.

Keywords: Insulin resistance, Maras Powder, Tobacco

INTRODUCTION

More than one billion people worldwide are active tobacco users, mostly men in developing countries. Although Nicotiana tabacum (N. tabacum) of tobacco, which has many types, was previously used for actions such as religious rituals, it is now mostly used in the production of commercial cigarettes (1,2).

Smoking is the most common form of tobacco use, but the use of smokeless forms of tobacco is also increasing. Although various forms of smokeless tobacco are consumed in many parts of the world, Maras Powder (MP), a form of smokeless tobacco obtained from Nicotiana rustica Linn (N. rustica L.), is widely used in Turkiye (3). N. tabacum and N. rustica L. plants contain molecules such as nicotine, nornicotine and anatabine. Studies have shown that nicotine binds to nicotinic acetylcholine receptors (nAChR) in the brain and increases dopamine levels, which plays a key role in creating addiction. N. rustica L. contains about seven times more nicotine than N. tabacum and the use of this smokeless tobacco is known to have addictive effects like cigarettes (4).

Today, there are numerous studies proving the negative effects of smoking on health. Studies have shown that N. tabacum type tobacco induces the development of type 2 diabetes mellitus (T2DM) and has effects on the development of diabetes-related complications (5).

T2DM is a life-threatening metabolic disorder characterized by insulin resistance and pancreatic β-cell dysfunction in peripheral tissues (6). The global prevalence of diabetes has brought this disease to pandemic level (7). According to a study by Sun et al, there are more than 500 million diabetic patients in the world in 2021 and it is predicted that this number will exceed 780 million in 2045 (8). The major contributer to the high prevalence of diabetes is insulin resistance, which is frequently associated with dietary habbits, obesity and physical inactivity (6). Insulin resistance occurs approximately 10-15 years before the diagnosis of T2DM (9). Studies have shown that nicotine found in cigarettes is effective in the development of insulin resistance (10,11).

In the literature, over 20.000 articles on N. tabacum have been published in NCBI so far, while there are only 198 publications on N. rustica L. (12). N. rustica L. is consumed by sucking 1-2 g between the lips and gingiva. Due to its smokeless use, it does not contain CO gas in the content of cigarettes, but due to the high amount of nicotine, it has been reported to play a critical role in the development of oral, esophageal, pancreatic cancer, especially with its carcinogenic, genotoxic effects (13-15). In this study, which was conducted for the first time, we aimed to investigate the relationship between N. rustica L. smokeless tobacco (MP) and insulin resistance in males. Despite being published considerably less than N. Tabacum, the health implications of N. rustica L. remain insuffeciantly understood, especially due to its high nicotine content compared to N. Tabacum. We aimed that our study could contribute to address the literature gap in this topic.

MATERIALS AND METHODS

Study Design

This study was conducted in the Central Laboratory of Kahramanmaraş Necip Fazil City Hospital with the approval of the ethics committee of Kahramanmaras Sutcu Imam University Faculty of Medicine, Clinical Research Ethics Committee (Date: 14.06.2017; Decision No: 04). Between February and October 2017, 25 male volunteers who were non-smokers and used one-pack (approximately 16 g) of MP daily for at least five years were included in the study as the study group and 33 volunteers who were neither smokers nor MP users were enrolled as the control group. Demographic data and 5ml blood samples were collected from all the study participants.

Preparation of Samples

After an overnight fasting, venous blood of all individuals participating in the study was collected in gel tubes. After waiting for 30 minutes for clotting, serum was separated by centrifugation (Hettich Zentrifugen Rotanta 460R, Germany) at 3000 rpm for 10 minutes. Serum samples were stored at -20°C until analyzed.

Measurement of Biochemical Parameters

Serum glucose, triglyceride, total cholesterol and HDL cholesterol levels were measured spectrophotometrically using Cobas 6000 series c 501 clinical biochemistry analyzer (Roche Diagnostics, Germany) and LDL cholesterol levels were calculated by Friedewald formula. Homeostasis Model Assesment-Insulin Resistance (HOMA-IR) method was used to evaluate insulin resistance. HOMA-IR was calculated as [fasting blood glucose (mmol/L/18) x fasting insulin (mU/ml)] divided by 22.5.

Statistical Analysis

IBM SPSS version 22 package program was used for data analysis. In the statistical evaluation, the compatibility of the variables with normal distribution was examined by Shapiro-Wilk test. Independent samples “T test” was used to compare variables with normal distribution between the study groups. Mann-Whitney U test was used to compare variables that did not show normal distribution between the study groups. The relationship between variables was analyzed by Pearson and Spearman correlation tests. Correlation coefficients r >0.89 were considered very strong correlation, as strong correlation r=0.70-0.89, moderate correlation r=0.40-0.69, and weak correlation r=0.10-0.39. Results were expressed as median (min-max). Statistical significance was accepted as $p<0.05$.

RESULTS

A total of 58 male volunteers aged 20-49 years, including MP users (43.1%) and control group (56.9%), participated in the study. Demographic findings, systolic pressure (SBP), diastolic pressure (DBP) and biochemical data are presented in Table

1. According to the statistical analysis, triglyceride, glucose, insulin and HOMA-IR levels were significantly higher in MP users compared to the control group ($p<0.05$). In addition, significant correlations were observed between insulin, HOMA-IR, glucose and triglyceride levels in MP users (Tables 2 and 3).Whereas, a very strong correlation was observed between insulin and HOMA-IR($r=0.973$; Table 2); moderate correlations were observed between insulin and glucose ($r=0.439$) (Table 2) and HOMA-IR with glucose ($r=0.692$) and triglyceride ($r=0.592$) (Table 3).

DISCUSSION

According to studies, tobacco, which is associated with many diseases such as cancer, heart disease, stroke, and diabetes, has approximately 1.5 billion users, with more than one billion cigarette tobacco and over 350 million smokeless tobacco (16). MP, which is a type of smokeless tobacco widely used in Kahramanmaras and surrounding provinces of Turkiye as well as all over the world, is a significant public health issue. Local people prefer MP because it is cheap, easily accessible, has a higher drug effect than cigarettes, and is an alternative substance to quit smoking. However, it has been shown that MP has mutagenic, carcinogenic, genotoxic, and teratogenic effects on cardiovascular system, nervous system, oral health, and gastrointestinal system disorders in addition to creating physiological and psychological addiction (17). These effects are shown by the fact that trace elements such as lead, zinc, copper, manganese and aluminium are high enough to be harmful to health and toxic substances such as nicotine, nornicotine, arsenic which are found in cigarettes, are found much more in MP content (4, 17). In addition, the fact that urinary cotinine level is up to three times higher in MP is one of the evidences showing the negative effects on health (18).

Although it has been reported that more than 650.000 people have lost their lives worldwide due to smokeless tobacco consumption, studies on MP are quite insufficient (17). In a limited number of studies, it has been found that MP has negative effects on the cardiovascular system by decreasing nitric oxide (NO) levels (19). In another study, lesions in the lower lip mucosa of MP users were examined and moderate dysplasia was commonly observed. It was found that the risk of oral cancer was correlated with the duration of MP use and this risk increased significantly in those who used MP for more than 15 years (20). Kurtul et al. demonstrated that MDA level was higher in MP than in control groups and MP increased serum lipid peroxidation level (21). When the effects of MP use on haematological parameters were examined, it was determined that iron and leukocyte levels were higher in MP users compared to the control group, while monocyte and platelet levels were lower. It has been reported that nicotine and tobacco-specific nitrosamine levels found in MP lead to chronic inflammatory changes in systemic circulation, various cells, and organs (22).

Smoking is at higher risk factor for atherosclerosis and cardiovascular disease (23). Some studies comparing non-smokers with smokers have revealed that smokers developed hyperinsulinaemic and insulin resistance and that these changes lead to dyslipidaemia and endothelial dysfunction (24,25). Faccihini et al. showed that smokers developed hyperinsulinaemic and insulin resistance (26). Li et al. showed that nicotine exposure suppresses nuclear

Table 1. Demographic and laboratory data of MP users and non-users (Results are given as Median (Min-Max))

	MP users (n=25)	Control group (n=33)	P value
Age[a]	36.00 (25.00-49.00)	38.00 (20.00-48.00)	0.659
Body Mass Index (BMI)[b]	21.10 (16.30-29.90)	21.10 (12.40-37.00)	0.715
Systolic Pressure (mmHg)[a]	120.00 (100.00-140.00)	120.00 (100.00-140.00)	0.386
Diastolic Pressure (mmHg)[a]	80.00 (60.00-100.00)	80.00 (60.00-90.00)	0.182
Triglyceride (mg/dL)[a]	120.00 (40.00-292.00)	70.00(45.00-290.00)	0.015*
Glucose (mg/dL)[a]	98.00 (72.00-141.00)	91.00 (74.00-143.00)	0.014*
Cholesterol (mg/dL)[a]	161.00 (76.00-270.00)	130.00 (65.00-249.00)	0.101
HDL (mg/dL)[a]	57.00 (29.00-88.00)	67.00 (32.00-81.00)	0.315
LDL (mg/dL)[a]	78.00 (43.00-161.00)	76.00 (11.00-184.00)	0.379
Insulin (µU/L)[a]	15.10 (4.98-40.20)	10.10 (4.40-50.30)	0.047*
HOMA-IR[a]	4.18 (1.15-8.93)	2.34 (0.92-14.28)	0.032*

*[a]Mann-Whitney U test; [b]Independent samples t test; α:0.05; *Statistically significant.*

factor erythroid 2 (NRF2) and causes glucose intolerance and thus insulin resistance (27). In a study conducted in Turkiye it was found that smoking did not affect HOMA-IR in women but decreased it in men (28).

Increased insulin resistance may lead to disorders in carbohydrate body metabolism, hypertension and dyslipidaemia. In our study, the fact that glucose levels in MP users were higher than non-users may be due to the fact that MP use affects blood glucose balance. Elevated triglycerides, decreased HDL and increased LDL levels, also called atherogenic dyslipidaemia, may be associated with insulin resistance. It is known that smokers have high plasma triglyceride and decreased HDL levels29. Since smokers have both insulin resistance and dyslipidaemia, the risk of cardiovascular disease is increased among these individuals (30). In our study, LDL cholesterol was found to be high and HDL cholesterol was found to be low in MP smokers, but the difference between the two groups was not statistically significant. This suggests that increased insulin resistance may cause dyslipidaemia in MP users. Moreover, triglyceride levels were significantly higher in MP users in our study. While triglyceride levels were found to be elevated in smokers in some studies, other studies reported low triglyceride levels among smokers (26). Changes in triglyceride levels in both smokers and MP users may be associated with lifestyle, genetic predisposition, and dietary habits.

The correlation analysis of insulin among MP users revealed a statistically significant very strong positive correlation with HOMA-IR (r=0.973; p<0.001) and a positive moderate correlation with glucose (r=0.439; p<0.011) (Table 2). In addition to our results, moderate correlations of HOMA-IR with glucose (r=0.692; p<0.001) and triglyceride (r=0.592; p<0.001) were observed in MP users (Table 3).

Study Limitations

In our study, urinary cotinine level and the amount of nicotine in the blood were not measured in the study groups in order to objectively determine MP use, the duration of weed use in the MP-using group (5 years/ 1 pack per day) was low, relatively few cases were included, and our data need to be supported by larger-scale studies. In addition, this study was conducted only in male individuals for homogenous distribution and no research was conducted in females.

Table 2. Correlations of insulin and measurement parameters in MP users.

	Insulin	
	r	**p value***
Age	0.031	0.865
Glucose (mg/dL)	0.439	0.011*
Triglyceride (mg/dL)	0.362	0.039*
Cholesterol (mg/dL)	0.065	0.721
HDL (mg/dL)	-0.065	0.718
LDL (mg/dL)	0.029	0.874
HOMA-IR	0.973	0.001*

*Pearson correlation test; α: 0.05; *Statistically significant.*

Table 3. Correlations of HOMA-IR with other parameters in MP users.

	HOMA-IR	
	r	**p value***
Age	0.212	0.237
Glucose (mg/dL)	0.692	<0.001*
Triglyceride (mg/dL)	0.592	<0.001*
Cholesterol (mg/dL)	0.199	0.266
HDL (mg/dL)	-0.166	0.355
LDL (mg/dL)	0.015	0.403

*Pearson correlation test; α: 0.05; *Statistically significant*

CONCLUSION

MP, a smokeless tobacco, is a type of tobacco that is very harmful to health, contrary to what is known. The presence of toxic components such as nicotine, nornicotine, arsenic as well as trace elements that may threaten health in cigarettes causes carcinogenic, mutagenic and genotoxic effects. This study was conducted for the first time, and it revealed that MP may support insulin resistance. We believe that the nicotine substance in MP may affect insulin resistance either through the NRF2 pathway or by increasing catecholamine synthesis as in cigarettes. Studies on MP are very limited, and we anticipate that further research on this tobacco, which may threaten public health, will be highly beneficial.

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Conflict of Interests: The authors state no conflict of interest with respect to the research, authorship, and/or publication of this article.

Ethical Approval: Before the initiation of the study, all participants received an explanation of the procedure and the risks that would later be faced in their participation, and they provided informed

consent to participate in this study. The study was approved by the ethics committee of the Kahramanmaras Sutcu Imam University Faculty of Medicine, Clinical Research Ethics Committee (Date: 14.06.2017; Decision No: 04), and all procedures were in accordance with the Declaration of Helsinki.

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