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The impact of smoking cessation on the control of diabetes mellitus and blood pressure in Saudi Arabia: A prospective randomized controlled clinical trial

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ABSTRACT

Diabetes mellitus is a major health problem that affects a wide range of populations worldwide. Recently, diabetes mellitus had become a growing public health concern in Saudi Arabia. The latest prevalence estimates indicate that there are about 4 million diabetic adults among Saudi population. The present study represents a prospective open labelled randomized controlled clinical trial with a two-group parallel design to detect the impact of smoking cessation on the control of diabetes mellitus and hypertension in Saudi populations. Assessment of smoking showed no difference in smoking duration between the two groups; whereas the intervention group had higher nicotine dependency level, greater amount of smoking and a higher level of expired carbon monoxide (CO). Indicators of diabetes control showed a minor, non-significant decrease in glycosylated hemoglobin (HbA1c) and a statistically significant increase in fasting blood glucose (FBG) (+18.34 ± 73.90 mg/dL versus -21.10 ± 46.20 mg/dL) in the intervention versus the control group respectively. In the present study, after one-year, smoking cessation intervention reduced systolic blood pressure (BP) by 7.8 mmHg and cigarette abstinence reduced it by 9.8 mmHg, by comparison to continued smoking where only a 2.8 mmHg decrease in systolic BP was observed. In conclusion, motivational smoking cessation interviews and telephone-calls follow-up along with the appropriate pharmacological interventions resulted in significant decline in the rate of smoking with significant reduction of systolic BP when compared versus those who continued smoking. However, smoking cessation, at least on the short-term run, didn't significantly affect the glycemic control.

Keywords: diabetes mellitus; smoking; cessation; primary care; body mass index; hypertension

1. INTRODUCTION

Diabetes mellitus is a complex metabolic illness characterised by chronic hyperglycaemia and associated with different abnormalities in carbohydrate, protein, and fat metabolism (Galicia-Garcia et al., 2020). This hyperglycaemic state leads to disturbances in insulin secretion and/or its action in the body leading in the mid- to long-term period to microvascular defects such as retinopathy, nephropathy, and neuropathy; in addition to macrovascular diseases such as coronary artery disease, peripheral arterial disease, and stroke (Negera et al., 2020). Type 2 diabetes mellitus (T2DM) is closely linked to obesity and occurs mostly in people with low physical activity (Chobot et al., 2018; Kabel et al., 2018). In addition, the prevalence of T2DM increases dramatically in high-income countries with westernisation of lifestyles. According to the International Diabetes Federation (IDF), the global estimates indicated that there were 425 million adult people aged between 20-79 years having diabetes of any type in 2017 (Cho et al., 2018).

Diabetes is a growing public health problem in Saudi Arabia. The latest Saudi prevalence estimates indicate that there are about 4 million diabetic adults aged between 18-99 years (Alshayban and Joseph, 2020). Saudi Arabia has the highest prevalence rate (18-22%) among Arabic countries, with one in five Saudis being diabetic. At the global level, two Arabic speaking countries (Saudi Arabia and Bahrain) are located among countries with the highest twenty prevalence rates (Alharbi and Alhazmi, 2020). Furthermore, Saudi Arabia reported the second highest number of individuals having T1DM in MENA region (35,000 cases) among children and adolescents less than 19 years old (Robert et al., 2018). This would possibly increase the burden on the local healthcare system as T1DM is involved in the development of a number of end-organ complications (Saberzadeh-Ardestani et al., 2018). For T2DM, there was a constant increase in reported diabetic cases in the last decade in both Saudi males and females (Alharbi and Alhazmi, 2020). This trend may be attributable to the increasing popularity of smoking, sedentary lifestyle and the change of food behaviour toward fast foods that are highly-calorific and sugary beverages (Gosadi, 2021).

Smoking can be referred to as the act of inhaling and exhaling the fumes of a burning plant, such as tobacco (Jha, 2020). Smoking is considered as one of the leading risk factors of several medical disorders worldwide. In addition, it has been reported that smoking is the second leading cause for early mortality at the global level with a significant contribution to overall disease burden, particularly in the developing world (Holipah et al., 2020). Globally, the age standardised prevalence of daily smoking was 25% in males and 5.4% in females in 2015 (GBD, 2015; Risk Factors Collaborators, 2016). Central and Eastern Europe and Southeast Asia constituted the highest places of smoking prevalence in males, whereas China, India, and Indonesia accounted for 51.4% of total world smokers. On the other hand, 27.3% of global female smokers were distributed in the United States, China, and India (Jafari et al., 2021). This study utilized a prospective open labelled randomized controlled clinical trial with a two-group parallel design to assess the impact of smoking cessation on the control of diabetes mellitus and blood pressure in Saudi Arabia.

2. METHODS

Design and target population

This study utilized a prospective open labelled randomized controlled clinical trial with a two-group parallel design. This study was conducted at the Endocrinology department, King Abdul-Aziz University hospital (KAUH), Jeddah, Saudi Arabia. The population targeted by this study consisted of adult patients with comorbid association of T2DM for duration of 5 years or longer, who smoked and lived in Jeddah, Saudi Arabia.

Inclusion criteria

This study was conducted on male and female individuals aged between 25 and 75 years, English or Arabic speaking who were diagnosed with type 2 diabetes mellitus since at least 5 years and who were cigarette smokers during at least 5 consecutive years, with more than ten cigarettes per day.

Exclusion criteria

These included absence of mental disorders, intellectual disability, or any history of skin sensitivity. Also, significant tobacco abstinence during the last 3 years; which is defined as ≥ 3 consecutive months or ≥ 6 cumulative months of total abstinence in the last 3 years should be absent. In addition, the patients should not have extreme obesity (class III) which is defined as body mass index (BMI) ≥ 40 Kg/m², as these patients are exposed to develop more severe obesity following smoking cessation. Any history of stroke or myocardial infarction (MI) was excluded, because of a reported, although controversial, vasoconstrictor action of nicotine. In addition, pregnancy or breastfeeding were excluded.

Ethical considerations

An application for the ethical clearance was made through local research ethics committees at the study site and endorsed by Strathclyde University ethics committees. Data was entered in an anonymous fashion, confidentially shared and processed, and accessed only by trustful persons contributing to data collection and analysis.

Sample size

Sample size was calculated to detect a 0.5 point of difference in one-year HbA1c levels (primary outcome) between the two groups; using a 1:1 intervention to control group ratio. The hypotheses tested were: H0 (null hypothesis); tobacco cessation induces no change in HbA1c i.e., no difference between the two groups: HbA1c (intervention) = HbA1c (control), and H1 (alternative hypothesis); tobacco cessation induces a significant (positive or negative) change in HbA1c, resulting in a statistically significant difference between the two groups: HbA1c (intervention) ≠ HbA1c (control) with ≥ 0.5 of difference. The level of significance was fixed for a 0.05 two-sided p-value (type 1 error = 5%) to reject the null hypothesis, and an 80% statistical power (type II error = 0.20).

The formula used for sample size calculation for difference in means:

$$n = \frac{2\sigma^2 (Z_\beta + Z_{\alpha/2})^2}{\text{difference}^2}$$

Where:

σ^2 = variance of HbA1c = 1.04^2 (Ohkuma, 2015)

Difference = clinically significant change in HbA1c after intervention = 0.5% (Centre for Clinical Practice at NICE (UK), 2009;Nathan et al., 2009; Little et al., 2011)

$Z\beta = 0.84$ (80% statistical power)

$Z\alpha/2 = 1.96$ (0.05 type I error)

Sample size N = 67.8 = 68 in each group

Anticipating a 30% success rate in smoking cessation using combined NRT and telephone counselling, the intervention group was increased to (68 x 100/30) = 227 patients in group 1. Total sample size = 227+68 = 295 patients.

Study procedure

Ethical clearance, invitations, and Consent

An application for ethical clearance was made through local research ethics committees in the study site. Patients were invited to participate in the study using posters that were advertised in the wards of the Endocrinology department. The pre-selected participants received a PIS to understand the protocol and were allowed time (minimum of one week) to consult healthcare staff or their families about participation. The eligibility questionnaire was administered to volunteers by a trained nurse, to check their eligibility according to the fore-mentioned inclusion and exclusion criteria. During the first interview, the participant's general practitioner (GP) explained the study protocol to each patient, answered his/her questions and obtained their signed written consent. During the same visit, the principal investigator (PI) completed the patient's case report form (CRF) with a patient's unique identifier, name of the GP and date of the consent. Recruitment was initiated on 1st October 2020 with recruitment concluded on 30th November 2020. Afterwards, the included participants were scheduled for a baseline visit and randomization to treatment. The expired carbon monoxide (CO) levels were measured using a Smokerlyzer® (Bedfont Scientific Ltd, UK). Medical records of T2DM patients were checked for diagnosis confirmation, and relevant clinical biochemistry was collected.

Baseline visit

All participants underwent an initial consultation with the GP, prior to randomisation and intervention, to collect baseline data and classify the patient in the appropriate stratum. Baseline clinical examination and laboratory tests include socio-demographic characteristics such as age, gender, marital status, nationality, family income, educational level, and lifestyle parameters. Also, the anthropomorphic measures including body weight and height were assessed using a digital scale (HY RGT, Shenzhen Hanyu Electronic Technology Co., Ltd, China) on which BMI was calculated. History of diabetes or any other medical condition that could interfere with glucose metabolism (e.g. thyroid dysfunction, chronic corticosteroids) was recorded. In addition, the baseline

diabetes and metabolism characteristics were assessed. These included HbA1c (DCA Vantage® Analyser, Siemens, USA), FBG (Accutrend Plus®, Roche, Swaziland), lipid profile such as TG (Accutrend Plus®, Roche, Swaziland) and TC (Accutrend Plus®, Roche, Swaziland), blood pressure (BP) (SM-300, KBM, Japan) and physician's assessment of diabetic management (satisfactory, moderately satisfactory or unsatisfactory). Smoking-related clinical features such as smoking duration, amount of smoking, nicotine dependency level (using the Fagerström score), and the expired CO level were determined. Moreover, depression, anxiety and stress were assessed using DASS questionnaire, at both baseline and endpoint; to investigate their association with smoking status, as well as their correlation with glycaemic outcomes. Also, the cardiac risk was determined using the QRISK scale.

Grouping

A stratified randomised technique was used to control for two major confounders: BMI (normal weight = BMI < 25, versus overweight and obesity = BMI ≥ 25 kg/m2) and years of smoking (< 20 years, versus ≥20 years). Participants were knowledgeable of the probability of being allocated to one or the other group: group 1; intervention (smoking cessation) and group 2; controls. However, participants were advised that, at the end of the study, an opportunity was available for participants from group 2 to benefit from free smoking cessation treatment if so desired. All this information was detailed in the informed consent.

Intervention

Nicotine replacement therapy

Nicotine transdermal patches (Nicotinell®, Roche, Swaziland) were prescribed for 8 weeks, starting with a dose of 21mg/24 hours for 4 weeks for all patients in the intervention group. Afterward, the dose was decreased to 14mg/24hr for 2 weeks, then 7mg/24hr for 2 weeks. The first patch was administered during the smoking cessation consultation, during which the physician explained the therapeutic procedure and terms of follow-up. At the end of that consultation, participants were provided with a one-month free supply of 21mg/24 hours nicotine transdermal patches and follow-up appointments were made by the hospital-clinic appointment system.

Telephone counselling

Behavioural intervention was organized as six telephone counselling sessions; which were scheduled at 1, 2, 3, 5, 6 and 7 weeks following the baseline visit and the start of NRT. Counselling sessions were performed by a trained GP, using a proactive approach and including intensive behavioural, cognitive and motivational interviewing. In order to maintain a standard of care between the patients, a range of items from intensive behavioural support was included in the questionnaire to guide the counsellor. Call sessions lasted approximately 10 to 15 minutes. In addition to this proactive approach, reactive counselling was optionally provided through a helpline number, where the patients could contact a counsellor for further information or support.

Clinic visits

Patients were invited to attend two clinic visits, 4 and 8 weeks after the start of the smoking cessation programme. During these visits, patients were assessed for treatment compliance, their new smoking status (e.g. abstinence, reduction, relapse), as well as their weight, BP and expired CO level. The outcomes of the clinic visits were compared to behaviors self-reported during telephone counselling. Another focus of the clinic visits was to reinforce behavioural therapy. Furthermore, NRT supply for the upcoming month was delivered at the one-month clinic visit. Patients from the control group (group 2) were also invited to attend these two clinic visits to reduce the gap in follow-up between the two groups. Control group patients underwent weighing and expired CO level measurement. In telephone counselling and clinic visit, patients were assessed for nicotine withdrawal symptoms which were classified into two categories: affective and somatic symptoms; and adapted solutions were proposed to help the patients fight these symptoms.

Smoking cessation strategy

The strategy used in this study for smoking cessation was abrupt quitting. The choice of this method was based on the reportedly high efficacy (30% success rate) and the cost-effectiveness in comparison with the "cut-down-to-quit" strategy. At the end of the study (12 months), each participant was asked to give their experience on nicotine patches and the trial by scoring (from 0 to 10) the usefulness, difficulty, and satisfactory of the trial.

Treatment interruption

Treatment was interrupted if any significant NRT side effect was detected or reported or if any severe symptoms of nicotine withdrawal such as depression with suicidal ideas were suspected at any time of the follow-up. Any other expected or unexpected adverse drug reactions were reported in the patient's file and serious reactions were reported within 24 hours to the regulatory bodies.

Compliance with the study medications (NRT)

To assess compliance of the patients with the study medications, the patients were allowed to self-report on their medication use in the month prior to the interview and their regular attendance at the clinic. Patients were also asked if they had missed any doses of medication on a day-to-day basis over a one-week period. In addition, breath CO expired level measured at all follow-up visits were used to confirm self-reporting of continuous abstinence; and CO value of more than 6 ppm was used to categorize individuals as a smoker.

Follow-up visits

After the end of the intervention, patients from both groups were invited for a clinic visit at 3, 6, 9, and 12 months, after observing an 8-hour fasting period. During these visits, HbA1c, FBG, and lipid metabolism including TC and TG were assessed for all patients (intervention and control). Additionally, post-cessation parameters including smoking status (abstinence, decreased, or relapse), CO expired level, weight, residual cigarettes number, BP, and affective and somatic behaviors were assessed for patients from intervention group.

Assessment of the cardiac risk

Assessment of the cardiac risk was performed for all patients at baseline and 12 months later, using the QRISK® tool. This tool predicts the probability of cardiac events as calculated based on a multi-risk factors model including age, sex, ethnicity, BMI, type of diabetes, smoking status, and number of cigarettes smoked daily, BP treatment, systolic BP and TC level.

Measurement of the expired CO

Expired CO was measured using Smokerlyzer®, (Bedfont Scientific Ltd, UK), a breath carbon monoxide monitor that defines a non-smoker as 0-6ppm, a low-dependence smoker as 7-15ppm and strongly addicted smokers as over 15ppm. In this study, the CO-oximeter was used to measure the CO level and to monitor smoking cessation, enhance motivation to quit and as a cofactor for effect of smoking cessation on the glycemic control.

Determination of nicotine dependence

Nicotine dependence was assessed using the Fagerström test for nicotine dependence which consists of a revision of the Fagerström Tolerance questionnaire integrating two supplemental items including the time to first cigarettes of the day and the number of daily cigarettes smoked, which enhanced psychometric properties as well as the correlation between the total scoring and the biochemical assessments of the heaviness of smoking. Furthermore, the Fagerström test for nicotine dependence was strongly correlated with withdrawal, indicating the level difficulty maintaining abstinence. The questionnaire contains 4 other questions (total 6 questions) for a score up to 10 categorized as low (score=1-2), low to moderate (3-4), moderate (5-7) and high (8+) nicotine dependence.

Psychological tests

The 21-item version of the Depression, Anxiety and Stress Scale (DASS), was used to assess the psychological impact of smoking cessation. It is a validated tool to measure the presence and intensity of symptoms related to depressive, anxious or stress disorders. It is widely used in clinical studies as a screening tool for anxio-depressive disorders.

Statistical analysis

Data obtained from the present study was subjected to statistical analysis using IBM Statistical Package for Social Sciences (SPSS) programme, version 22.0. Descriptive analysis was presented as mean ± standard deviation (SD) for continuous and discrete variables, and frequency (percentage) for qualitative variables. Quantitative outcome variables including HbA1c, FBG, TC and TG and QRISK were analysed with the assumption of normal distribution in the general T2DM population.

3. RESULTS

Demographic data

Baseline demographic data showed male predominance in both groups (97.2% versus 92.9%; p=0.275) and relatively older age (mean ± SD age = 54.17 ± 9.26 versus 50.23 ± 9.24; p=0.013) among the intervention group versus the control group respectively. Differences were also observed in monthly income and education, as the intervention group had lower monthly income (p<0.0001) and educational level (p=0.026) (Table 1). Lifestyle and clinical factors showed that the intervention group was characterised by lower physical exercise, higher systolic BP, lower diastolic BP, higher prevalence of diabetes complications except for neuropathy, less prevalence of thyroid dysfunction, and worse quality of diabetes control according to the physician's assessment. However, no differences were observed in BMI and diabetes treatment regimens between both groups (Table 1).

Assessment of smoking showed no difference in smoking duration between the two groups (p=0.537); whereas the intervention group had higher nicotine dependency level (p=0.00001), greater amount of smoking (p=0.001) and a higher level of expired CO (p=0.002) (Table 1). Psychological assessment using DASS score showed a low prevalence of depression, anxiety and stress in both groups without statistically significant differences between the two groups. Glucose metabolism showed higher levels of HbA1c (mean ± SD = 8.95 ± 2.48 versus 7.74 ± 1.64%; p=0.001) and FBG (mean ± SD = 167.56 ± 61.90 versus 142.89 ± 47.76 mg/dL; p=0.009) in the intervention versus the control group respectively. Similarly, the intervention group had higher levels of TG and lower levels of HDL; while no differences were observed in TC and LDL (Table 1).

Table 1 Baseline demographic, clinical and biological data of participants

Parameter	Category	Intervention (N=71)		Control (N=70)		p-value
		Freq./M	%/SD	Freq./M	%/SD	
Demographic data						
Gender	Male	69	97.2	65	92.9	.275[F]
	Female	2	2.8	5	7.1	
Age (year)	Mean, SD	54.17	9.26	50.23	9.24	.013*
Marital status	Single	3	4.2	0	0.0	.112
	Married	67	94.9	66	94.3	
	Divorced	0	0	3	4.3	
	Widowed	1	1.4	1	1.4	
Occupation	Employed	46	64.8	47	67.1	.208
	Unemployed	17	23.9	10	14.3	
	Housewife	1	1.4	5	7.1	
	Retired	7	9.9	8	11.4	
Monthly income (SAR)	Up to 5k	63	88.7	32	45.7	.000001*
	5k – 10k	5	7.0	25	35.7	
	10k-15k	1	1.4	8	11.4	
	>15k	2	2.8	5	7.1	
Education	Illiterate	7	9.9	6	8.6	.026*
	Primary	34	47.9	21	30.0	
	Secondary	19	26.8	15	21.4	
	University	9	12.7	23	32.9	
	Post-grad.	2	2.8	5	7.1	
Lifestyle and clinical factors						
Physical exercise	Regular	3	4.2	12	17.1	.000096*
	Irregular	11	15.5	26	37.1	
	None	57	80.3	32	45.7	
BMI (kg/m^2)	<25	31	43.7	31	44.3	.941
	≥25	40	56.3	39	55.7	
BMI	Mean, SD	26.54	4.97	27.47	4.26	.235
Weight (kg)	Mean, SD	75.18	17.67	81.48	12.57	.016*

Height (cm)	Mean, SD	167.75	8.70	172.07	9.01	.004*
Diabetes treatment	Oral AD	60	84.5	65	92.9	.183[F]
	Insulin	22	31.0	23	32.9	.812
	Other	30	42.3	41	58.6	.053
Anti-cholesterol		22	31.0	56	80.0	.000000*
Blood pressure	Systolic	137.08	20.53	129.73	19.03	.029*
	Diastolic	78.49	9.99	82.44	8.33	.012*
Diabetes complications	Atherosclerosis	31	43.7	9	12.9	.000000*
	Neuropathy	45	63.4	31	44.3	.028*
	Retinopathy	26	36.6	12	17.1	.025*
	Nephropathy	1	1.4	7	10.0	.011*
Thyroid dysfunction	Yes	6	8.5	23	32.9	.001*
	Unknown	19	26.8	10	14.3	
Physicians' assessment of diabetic control	Satisfactory	1	1.4	6	8.6	.020*
	Fair	19	26.8	28	40.0	
	Unsatisfactory	51	71.8	36	51.4	
Smoking assessment						
Smoking duration	< 20 years	18	25.4	21	30.0	.537
	≥20 years	53	74.6	49	70.0	
Nicotine dependency level	Low (0-3)	21	29.6	49	70.0	.000010*
	Moderate (4-5)	20	28.2	8	11.4	
	High (6-10)	30	42.3	13	18.6	
Smoking duration (years)	Mean, SD	26.77	11.80	22.40	10.37	.021*
Amount of smoking (cig./day)	Mean, SD	23.28	15.36	16.37	8.09	.001*
Expired CO (ppm)	Mean, SD	24.99	14.14	18.54	9.73	.002*
Psychological assessment						
Depression	Normal	69	97.2	65	92.9	.646
	Mild	2	2.8	2	2.9	
	Moderate	4	5.6	2	2.9	
	Severe	0	0.0	0	0.0	
	Extremely severe	0	0.0	1	1.4	
Anxiety	Normal	49	69.0	54	77.1	.121
	Mild	6	8.5	8	11.4	
	Moderate	13	18.3	3	4.3	
	Severe	1	1.4	2	2.9	
	Extremely severe	2	2.8	3	4.3	
Stress	Normal	55	77.5	63	90.0	.328
	Mild	6	8.5	3	4.3	
	Moderate	5	7.0	2	2.9	
	Severe	4	5.6	1	1.4	
	Extremely severe	1	1.4	1	1.4	
Laboratory data						
Hb_{A1C} (%)	Mean, SD	8.95	2.48	7.74	1.64	.001*
FBG (mg/dL)	Mean, SD	167.56	61.90	142.89	47.76	.009*
Total C. (mg/dL)	Mean, SD	192.55	62.03	180.07	51.66	.197
LDL C. (mg/dL)[‡]	Mean, SD	77.33	59.08	116.71	36.40	.062
HDL C. (mg/dL)[‡]	Mean, SD	24.81	16.06	35.65	6.61	.012*

TG (mg/dL)	Mean, SD	212.28	108.21	164.35	90.51	.005*
Cardiac risk assessment						
Q-Risk	Mean, SD	25.80	11.29	20.31	11.71	.006*

Freq.: Frequency; M: mean; %: percentage; SD: standard deviation; * statistically significant result ($p<0.05$); [F] significance level calculated using Fisher's exact test; AD: antidiabetic; [‡] results were available for a limited number of patients (4 from intervention and 35 from controls).

The primary outcome

Intention to treat (ITT) analysis

By reference to the baseline, 12-month ITT results showed no significant difference between the intervention and the control groups regarding change in weight and diastolic BP; whereas the intervention group exhibited a greater mean decrease in systolic BP (mean ± SD change = -7.81 ± 19.24 mmHg versus -2.83 ± 14.42 mmHg) versus control group, but the difference was not statistically significant (p=0.336) (Table 2).

Indicators of diabetic control showed a minor, non-significant decrease in HbA1c (p=0.276) and a statistically significant increase in FBG (+18.34 ± 73.90 mg/dL versus -21.10 ± 46.20 mg/dL; p<0.001) in intervention versus control group, respectively. The effect of 12-month smoking cessation on lipid metabolism showed decreasing trends in both total cholesterol (mean ± SD change = -20.41 ± 52.62) and TG (mean ± SD change = -36.94 ± 76.15), which was not significantly different from the control group. Assessment of cardiac risk showed a significant decrease in Q-Risk score in the intervention group (-2.96 ± 5.40%), while no significant change was observed in the control group (-0.03 ± 2.86%) and the difference between the two groups was statistically significant (p<0.001) (Table 2).

Per protocol (PP) analysis

In PP analysis, the intervention group showed significant decrease in weight (-1.38±6.39 Kg), which was greater than that in control group (-0.48 ± 3.35 Kg) and the difference between the two groups was statistically significant (p<0.001). Similarly, the decrease in systolic BP was greater in the intervention group (-9.80 ± 26.22 mmHg) versus control group (-2.83 ± 14.41 mmHg) and the difference was statistically significant (p=0.002) (Table 2). Conversely, a non-significant decreasing trend in diastolic BP was observed in the intervention group, which was smaller than that observed in the control group without statistically significant difference between the two groups (p=0.398).

Regarding indicators for diabetic control, mean ± SD change in HbA1c was comparable between the two groups. On the other hand, the intervention group showed an increase in FBG (mean ± SD change = +13.07 ± 82.93 mg/dL), contrasting with a decrease (-21.10 ± 46.20 mg/dL) observed in the control group (p=0.007). Similar to ITT results, PP analysis showed a decreasing trend in both total cholesterol and TG without statistically significant differences between the intervention and control groups. Cardiac risk assessment showed a clinically and statistically significant decrease in Q-Risk score in the intervention group (mean ± SD change = -7.58 ± 6.11%) compared with little change in the control group (-0.03 ± 2.86%), (p<0.001) (Table 2).

Table 2 Effect of 12-month smoking cessation on glycaemic control and metabolism in Saudi diabetic patients (intention to treat analysis) [independent t-test; Chi-square]

Parameter	Category	Intervention				Control (N=70)		p-value	
		ITT (N=68)		PP (N=15)				ITT-C	PP-C
		Freq./M	%/SD	Freq./M	%/SD	Freq./M	%/SD		
Clinical data									
Weight (kg)	Mean, SD	75.27	18.15	83.11	24.11	81.00	12.44	.032*	<.001*
Δ Weight	Mean, SD	-0.55	4.82	-1.38	6.39	-0.48	3.35	.918	<.001*
Diabetes treatment	Unchanged	57	83.8	9	81.8	66	94.3	.122	1.000[F]
	Increased	10	14.7	2	18.2	4	5.7		
	Reduced	1	1.5	0	0.0	0	0.0		
Blood pressure	Systolic	129.87	15.89	126.67	11.95	126.90	14.53	.254	.443
	Diastolic	79.00	8.61	76.87	11.10	81.00	5.24	.101	<.001*
Δ BP	Δ Systolic	-7.81	19.24	-9.80	26.22	-2.83	14.42	.087	.002*

	Δ Diastolic	-0.76	10.34	-1.53	9.40	-2.27	7.85	.336	.398
Smoking assessment									
Amount of smoking (cig./day)	Mean, SD	12.50	10.64	0	0.00	16.39	7.64	.015*	<.001*
Δ Amount of smoking (cig./day)	Mean, SD	-11.04	14.78	-15.80	6.12	0.01	1.92	<.001*	<.001*
Expired CO (ppm)	Mean, SD	16.07	10.43	7.00	6.26	17.41	7.11	.378	.213
Δ Expired CO (ppm)	Mean, SD	-8.81	13.91	-11.07	8.37	-1.13	5.70	<.001*	.066
Laboratory data									
Hb_{A1C} (%)	Mean, SD	8.48	2.03	7.40	1.29	7.04	1.48	<.001*	.597
Δ Hb_{A1C} (%)	Mean, SD	-0.42	1.69	-0.92	1.91	-0.70	1.27	.276	.096
FBG (mg/dL)	Mean, SD	184.82	79.43	173.53	70.95	121.79	38.47	<.001*	<.001*
Δ FBG (mg/dL)	Mean, SD	18.34	73.90	13.07	82.93	-21.10	46.20	<.001*	.007*
TC (mg/dL)	Mean, SD	168.28	54.92	157.53	65.77	145.10	45.73	.008*	.019*
Δ TC (mg/dL)	Mean, SD	-20.41	52.62	-11.02	58.19	-28.49	37.42	.300	.059
TG (mg/dL)	Mean, SD	171.01	74.10	158.33	82.49	133.11	73.94	.003*	.291
Δ TG (mg/dL)	Mean, SD	-36.94	76.15	-41.93	85.36	-31.24	82.50	.672	.227
Q-Risk	Mean, SD	22.84	10.35	15.81	8.10	20.28	11.01	.612	.228
Δ Q-Risk	Mean, SD	-2.96	5.40	-7.58	6.11	-0.03	2.86	<.001*	<.001*

ITT: Intention-to-treat; PP: per-protocol; ITT-C: comparison between ITT and control groups; PP-C: comparison between PP and control groups; Freq.: frequency; M: mean; %: percentage; SD: standard deviation; * statistically significant result ($p<0.05$); [F] significance level calculated using Fisher's exact test; AD: antidiabetic; [‡] results were available for a limited number of patients (4 from intervention & 35 from controls); Δ baseline-to-6-month change.

Correlation of main outcomes with the pattern of smoking cessation

Analysis of the pattern of smoking cessation at 12 months showed 15 patients with complete abstinence, 9 with ≥66.6% reduction in smoking, 20 with ≥33.3% reduction in smoking, 7 with <33.3% reduction, and 17 with continued or increased daily number of cigarettes smoked. Comparison between the 5 subgroups showed that the change in the Q-Risk score was greater (mean ± SD change= -7.58 ± 6.11%) in completely abstinent patients followed by those with ≥66.6% reduction (-4.88 ± 2.61%), whereas patients with continued or increased smoking had an increase in their Q-Risk (+1.17 ± 4.76). The difference between the groups was statistically significant in both parametric (One-way ANOVA, $p<0.001$) and nonparametric (Kruskal-Wallis test, $p<0.001$) tests (Table 3). A decreasing trend in HbA1c was observed in completely abstinent patients (mean ± SD change = -0.92 ± 1.91%), which was higher than in other subgroups; however, differences between the subgroups were not statistically significant. No statistically significant difference between the 5 subgroups was observed in the other parameters including Δ FBG, Δ systolic or diastolic BP, Δ weight, Δ CO, Δ TC and Δ TG, using both parametric and nonparametric tests (Table 3).

Table 3 Smoking cessation pattern sub-group analysis at 12 months (One-Way ANOVA)

Parameter	Pattern of smoking cessation										p-value
	Complete abstinence (N=15)		≥66.7% reduction (N=9)		≥33.3% reduction (N=20)		<33.3% decrease (N=7)		Continued or increased (N=17)		
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	
Δ Hb_{A1C} (%)	-0.92	1.91	0.04	2.55	-0.53	1.41	-0.29	1.48	-0.16	1.40	.253 (.385 [K])
Δ FBG (mg/dL)	13.07	82.93	48.33	72.78	3.25	91.88	19.00	41.18	24.59	51.81	.654 (.579 [K])

Δ Systolic BP	-5.73	23.51	-13.22	20.81	-5.25	13.98	-12.43	23.37	-3.12	19.00	.785 (.693 [K])
Δ Diastolic BP	-1.53	9.40	-0.78	18.38	0.65	10.99	0.71	4.23	-2.35	6.66	.915 (.914 [K])
Δ Weight (kg)	-1.38	6.39	-0.17	5.47	-0.41	2.69	-0.45	3.14	-0.25	5.80	.968 (.331[K])
Δ CO (ppm)	-9.27	10.11	-8.33	5.75	-7.30	16.70	-14.29	25.34	-6.76	10.50	.915 (.829 [K])
Δ TC (mg/dL)	-11.02	58.19	-11.11	46.35	-18.04	54.19	-16.57	38.08	-38.00	55.26	.615 (.520 [K])
Δ TG (mg/dL)	-41.93	85.36	-23.33	71.35	-48.59	89.32	-17.29	28.76	-34.12	71.42	.868 (.749 [K])
Q-Risk	-7.58	6.11	-4.88	2.61	-2.14	3.17	-2.99	5.32	1.17	4.76	<.001* (<.001* [K])

Test used One-way ANOVA and [k] Kruskal-Wallis test; * statistically significant result (p<0.05).

Baseline-to-twelve-month changes in the main study parameters were compared between intervention subgroups and control group using One-way ANOVA test, and results are presented in figure 1. The most remarkable statistically significant results include completely abstinent subgroup being associated with the second lowest increase in FBG (p=0.005) and greatest reduction in cardiac risk (p<0.001), by comparison to other subgroups and control group. Other notable, non-statistically significant results include: greatest decrease in HbA1c (p=0.494), greatest weight loss (p=0.978), and second greatest decrease in TG (p=0.927) in completely abstinent subgroup by comparison to other subgroups and control group.

4. DISCUSSION

In the present study, the early phase of cigarette abstinence (first 3 months) was associated with approximately 10 mmHg increase in both systolic and diastolic BP. This change may be attributable to the use of NRT in the smoking cessation intervention. It has been reported that nicotine nasal spray and nicotine chewing gums can cause an increase of heart rate by 10-15 beats/minute and is associated with an elevation of plasma epinephrine, due to binding to the nicotinic receptors in the adrenal medulla, which would ultimately lead to elevation of systolic BP up to 5-10 mmHg (Mündel et al., 2017; Najem et al., 2006). Yugar-Toledo and co-authors (2005) found that the acute effects of nicotine patches led to a slight increase in morning BP and it was associated with a weaker reduction of the nocturnal BP after 48 hours of starting the therapy when compared with placebo. In addition to epinephrine stimulation, another potential explanation of increased BP exerted by nicotine is the stimulation of the sympathetic nervous system and subsequent peripheral vasoconstriction (Carney et al., 2020).

The latter mechanism is ascribed to binding of nicotine in NRT to the nicotinic receptors of the autonomic ganglia and brain (Onor et al., 2017). Although the NRT-associated increase of heart rate and BP over a short-term period seems to pose a relative risk, particularly for diabetic patients with a concomitant cardiovascular disease, NRT does not alter oxygen carrying capacity, mediate coagulation, or results in the development of arterial diseases (McRobbie and Hajek, 2001; Wadgave and Nagesh, 2016). Therefore, when NRT is used as recommended, the comparative risk to smoking favours the use of NRT since the latter is less harmful or even harmless in regards to its impact on BP and cardiovascular performance (McRobbie and Hajek, 2001). Regarding other pharmacological interventions for smoking cessation, it has been reported that bupropion causes an increase in BP regardless of the pre-established hypertension due to its effects on the reuptake of norepinephrine (Sobieraj et al., 2013). However, clinical data hadshown that the use of bupropion for smoking cessation did not significantly affect BP levels after treatment for 12 weeks (Cinciripini et al., 2013) or 52 weeks (Tonstad et al., 2003). On the other hand, varenicline did not impact BP in healthy smokers when compared to placebo (Benowitz et al., 2018). Nonetheless, varenicline was associated with a small increase in systolic BP (by 0.5 mmHg) and no change in diastolic BP in patients with cardiovascular disease (Rigotti et al., 2010). The latter finding is of important implication for diabetic patients since a considerable proportion of diabetic smokers are at a great risk of developing cardiovascular disorders (Campagna et al., 2019).

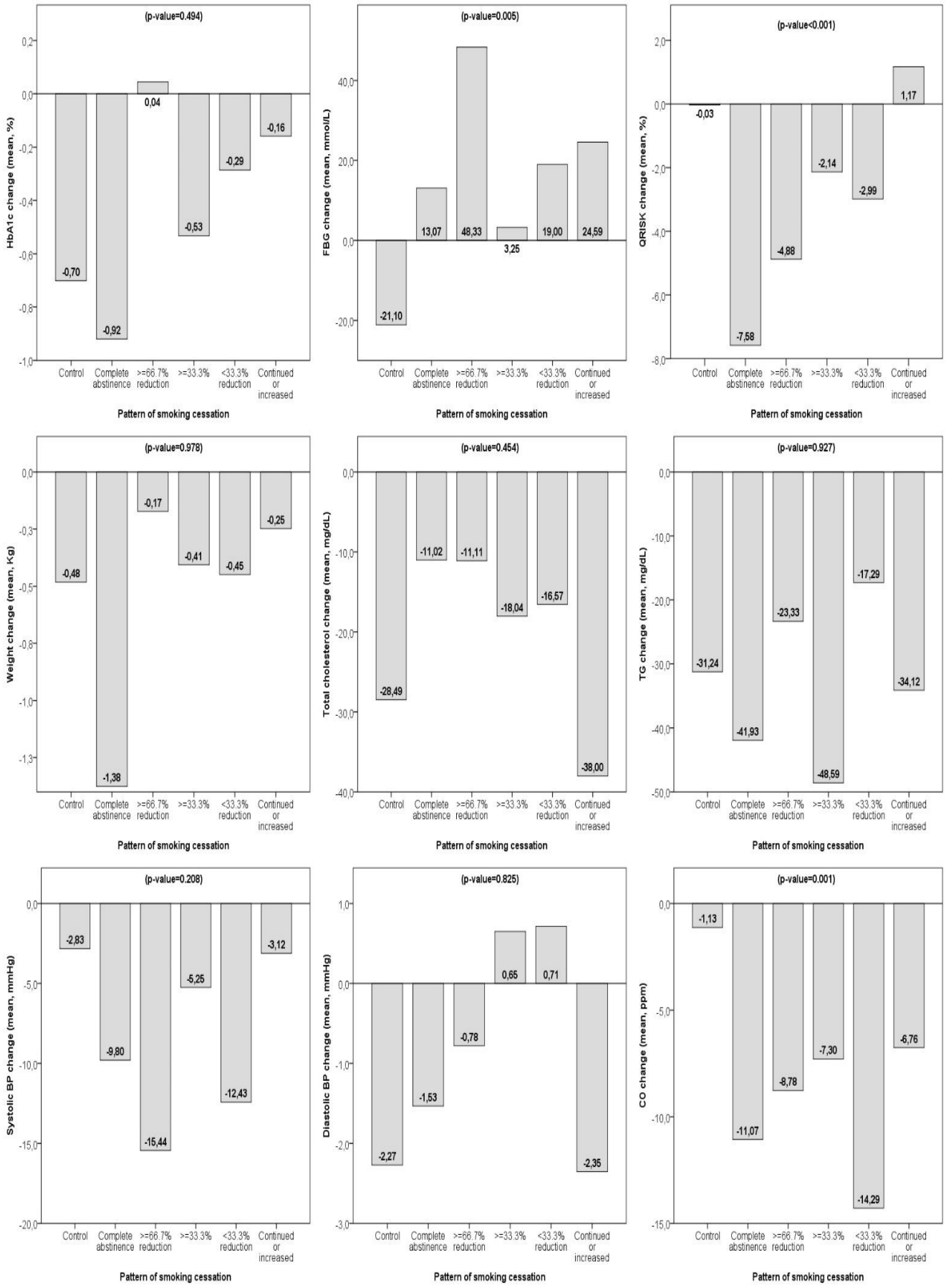

Figure 1 Baseline-to-twelve-month changes in main study outcomes: intervention subgroups by percentage reduction versus control.

In the present study, after one-year, smoking cessation intervention reduced systolic BP by 7.8 mmHg and cigarette abstinence reduced it by 9.8 mmHg, by comparison to continued smoking where only a 2.8 mmHg decrease in systolic BP was observed. This finding is typically consistent with that of other studies, where motivational smoking cessation interviews and telephone follow-up along with the appropriate glycaemic pharmacological interventions resulted in significant reduction of systolic BP by 26.8 mmHg when compared to continuing smoking (Tsai et al., 2021). In addition, the newly diagnosed diabetic patients had decreased BP by 13.6 mmHg after one year of motivational smoking cessation (Voulgari et al., 2011). Additionally, diastolic BP improved significantly in ex-smokers compared to current smokers (decreased by 9.9 and 6.2 mmHg, respectively). Unfortunately, the authors did not reveal BP data at regular intervals during the study period (Voulgari et al., 2011). It is possible that quitting smoking is associated with an overall improvement in health behaviour and healthy diet, which can contribute to reducing BP (Tsai et al., 2021). Furthermore, the lack of using NRT for smoking cessation might contribute to lowering BP over a long period of follow-up (Voulgari et al., 2011).

5. CONCLUSION

The current study showed that with the intervention protocols, the rate of smoking can be reduced to a more manageable level. This by extension would act to reduce the type II diabetic prevalence in the nation that is directly attributed to smoking. It is of particular note that the intervention is not only based on the follow up program but in combination with NRT within the protocol. In addition, smoking cessation might significantly reduce the systolic BP to acceptable levels.

Authors' contributions

Conceptualization: Ali M. Alshahrani and Ahmed M. Ashour; Methodology, Investigation, Formal analysis, Writing- Original draft preparation: Ali M. Alshahrani, Ahmed M. Kabel, Mohammed A. Alsuwat, and Ahmed M. Ashour; Writing- Reviewing and Editing: Ali M. Alshahrani and Ahmed M. Ashour.

Institutional Review Board Statement

This study was conducted according tothe guidelines of the Declaration of Helsinki, and approved by the Research Ethics Committee of King AbdulazizUniversity, Saudi Arabia (Approval code 77-16).

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Conflicts of interest

The authors declare that there are no conflicts of interests.

Data and materials availability

All data associated with this study are present in the paper.

REFERENCES AND NOTES

1. Alharbi AMD, Alhazmi AMS. Prevalence, Risk Factors, and Patient Awareness of Diabetic Retinopathy in Saudi Arabia: A Review of the Literature. Cureus 2020; 12(12):e11991. doi: 10.7759/cureus.11991
2. Alshayban D, Joseph R. Health-related quality of life among patients with type 2 diabetes mellitus in Eastern Province, Saudi Arabia: A cross-sectional study. PLoS One 2020; 15(1):e0227573. doi: 10.1371/journal.pone.0227573
3. Benowitz NL, Pipe A, West R, Hays JT, Tonstad S, McRae T, Lawrence D, St Aubin L, Anthenelli RM. Cardiovascular Safety of Varenicline, Bupropion, and Nicotine Patch in Smokers: A Randomized Clinical Trial. JAMA Intern Med 2018; 178(5):622-631. doi: 10.1001/jamainternmed.2018.0397
4. Campagna D, Alamo A, Di Pino A, Russo C, Calogero AE, Purrello F, Polosa R. Smoking and diabetes: dangerous liaisons and confusing relationships. Diabetol Metab Syndr 2019; 11:85. doi: 10.1186/s13098-019-0482-2
5. Carney G, Bassett K, Maclure M, Taylor S, Dormuth CR. Cardiovascular and neuropsychiatric safety of smoking cessation pharmacotherapies in non-depressed adults: a retrospective cohort study. Addiction 2020; 115(8):1534-1546. doi: 10.1111/add.14951
6. Cho NH, Shaw JE, Karuranga S, Huang Y, da Rocha Fernandes JD, Ohlrogge AW, Malanda B. IDF Diabetes Atlas: Global estimates of diabetes prevalence for 2017 and

projections for 2045. Diabetes Res Clin Pract 2018; 138:271-281. doi: 10.1016/j.diabres.2018.02.023.

7. Chobot A, Górowska-Kowolik K, Sokołowska M, Jarosz-Chobot P. Obesity and diabetes-Not only a simple link between two epidemics. Diabetes Metab Res Rev 2018; 34(7):e3042. doi: 10.1002/dmrr.3042
8. Cinciripini PM, Robinson JD, Karam-Hage M, Minnix JA, Lam C, Versace F, Brown VL, Engelmann JM, Wetter DW. Effects of varenicline and bupropion sustained-release use plus intensive smoking cessation counseling on prolonged abstinence from smoking and on depression, negative affect, and other symptoms of nicotine withdrawal. JAMA Psychiatry 2013; 70(5):522-533. doi: 10.1001/jamapsychiatry.2013.678
9. Galicia-Garcia U, Benito-Vicente A, Jebari S, Larrea-Sebal A, Siddiqi H, Uribe KB, Ostolaza H, Martín C. Pathophysiology of Type 2 Diabetes Mellitus. Int J Mol Sci 2020; 21(17):6275. doi: 10.3390/ijms21176275
10. GBD 2015 Risk Factors Collaborators. Global, regional, and national comparative risk assessment of 79 behavioural, environmental and occupational, and metabolic risks or clusters of risks, 1990-2015: a systematic analysis for the Global Burden of Disease Study 2015. Lancet 2016; 388(10053):1659-1724. doi: 10.1016/S0140-6736(16)31679-8
11. Gosadi IM. Lifestyle Counseling for Patients with Type 2 Diabetes in the Southwest of Saudi Arabia: An Example of Healthcare Delivery Inequality between Different Healthcare Settings. J Multidiscip Healthc 2021; 14:1977-1986. doi: 10.2147/JMDH.S320996
12. Holipah H, Sulistomo HW, Maharani A. Tobacco smoking and risk of all-cause mortality in Indonesia. PLoS One 2020; 15(12): e0242558. doi: 10.1371/journal.pone.0242558
13. Jafari A, Rajabi A, Gholian-Aval M, Peyman N, Mahdizadeh M, Tehrani H. National, regional, and global prevalence of cigarette smoking among women/females in the general population: a systematic review and meta-analysis. Environ Health Prev Med 2021; 26(1):5. doi: 10.1186/s12199-020-00924-y
14. Jha P. The hazards of smoking and the benefits of cessation: a critical summation of the epidemiological evidence in high-income countries. Elife 2020; 9:e49979. doi: 10.7554/eLife.49979
15. Kabel AM, Al Thumali AM, Aldowiala KA, Habib RD, Aljuaid SS. Sleep disorders in a sample of students in Taif University, Saudi Arabia: The role of obesity, insulin resistance, anemia and high altitude. Diabetes Metab Syndr 2018; 12(4):549-554. doi: 10.1016/j.dsx.2018.03.024
16. McRobbie H, Hajek P. Nicotine replacement therapy in patients with cardiovascular disease: guidelines for health professionals. Addiction 2001; 96(11):1547-1551. doi: 10.1046/j.1360-0443.2001.961115472.x
17. Mündel T, Machal M, Cochrane DJ, Barnes MJ. A Randomised, Placebo-Controlled, Crossover Study Investigating the Effects of Nicotine Gum on Strength, Power and Anaerobic Performance in Nicotine-Naïve, Active Males. Sports Med Open 2017; 3(1):5. doi: 10.1186/s40798-016-0074-8
18. Najem B, Houssière A, Pathak A, Janssen C, Lemogoum D, Xhaët O, Cuylits N, van de Borne P. Acute cardiovascular and sympathetic effects of nicotine replacement therapy. Hypertension 2006; 47(6):1162-1167. doi: 10.1161/01.HYP.0000219284.47970.34
19. Negera GZ, Weldegebriel B, Fekadu G. Acute Complications of Diabetes and its Predictors among Adult Diabetic Patients at Jimma Medical Center, Southwest Ethiopia. Diabetes Metab Syndr Obes 2020; 13:1237-1242. doi: 10.2147/DMSO.S249163
20. Onor IO, Stirling DL, Williams SR, Bediako D, Borghol A, Harris MB, Darensburg TB, Clay SD, Okpechi SC, Sarpong DF. Clinical Effects of Cigarette Smoking: Epidemiologic Impact and Review of Pharmacotherapy Options. Int J Environ Res Public Health 2017; 14(10):1147. doi: 10.3390/ijerph14101147
21. Rigotti NA, Pipe AL, Benowitz NL, Arteaga C, Garza D, Tonstad S. Efficacy and safety of varenicline for smoking cessation in patients with cardiovascular disease: a randomized trial. Circulation 2010; 121(2):221-9. doi: 10.1161/CIRCULATIONAHA.109.869008.
22. Robert AA, Al-Dawish A, Mujammami M, Dawish MAA. Type 1 Diabetes Mellitus in Saudi Arabia: A Soaring Epidemic. Int J Pediatr 2018; 2018:9408370. doi: 10.1155/2018/9408370
23. Saberzadeh-Ardestani B, Karamzadeh R, Basiri M, Hajizadeh-Saffar E, Farhadi A, Shapiro AMJ, Tahamtani Y, Baharvand H. Type 1 Diabetes Mellitus: Cellular and Molecular Pathophysiology at A Glance. Cell J 2018; 20(3):294-301. doi: 10.22074/cellj.2018.5513.
24. Sobieraj DM, White WB, Baker WL. Cardiovascular effects of pharmacologic therapies for smoking cessation. J Am Soc Hypertens 2013; 7(1):61-67. doi: 10.1016/j.jash.2012.11.003
25. Tonstad S, Farsang C, Klaene G, Lewis K, Manolis A, Perruchoud AP, Silagy C, van Spiegel PI, Astbury C, Hider A, Sweet R. Bupropion SR for smoking cessation in smokers with cardiovascular disease: a multicentre, randomised study. Eur Heart J 2003; 24(10):946-955. doi: 10.1016/s0195-668x(03)00003-4
26. Tsai SY, Huang WH, Chan HL, Hwang LC. The role of smoking cessation programs in lowering blood pressure: A retrospective cohort study. Tob Induc Dis 2021; 19:82. doi: 10.18332/tid/142664
27. Voulgari C, Katsilambros N, Tentolouris N. Smoking cessation predicts amelioration of microalbuminuria in

newly diagnosed type 2 diabetes mellitus: a 1-year prospective study. Metabolism 2011; 60(10):1456-1464. doi: 10.1016/j.metabol.2011.02.014

28. Wadgave U, Nagesh L. Nicotine Replacement Therapy: An Overview. Int J Health Sci (Qassim) 2016; 10(3):425-435.
29. Yugar-Toledo JC, Ferreira-Melo SE, Sabha M, Nogueira EA, Coelho OR, Consolin Colombo FM, Irigoyen MC, Moreno H Jr. Blood pressure circadian rhythm and endothelial function in heavy smokers: acute effects of transdermal nicotine. J Clin Hypertens (Greenwich) 2005; 7(12):721-728. doi: 10.1111/j.1524-6175.2005.04597.x