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Original Article

Inflammatory parameters and insulin resistance and cigarette smoking intype 2 diabetes mellitus

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Abstract

Aim: Smoking remains a global problem and it is known as a cause of many diseases. Globally, tobacco use is the most important cause of preventable morbidity and mortality. The aim of this study is to evaluate the impact of smoking on insulin parameters and inflammatory markers, and the variation of these parameters according to the duration of smoking cessation in patients who quit smoking.

Material and Methods: 612 patients aged 18-70 years (n = 612) who were undergoing treatment and follow-up for type 2 diabetes mellitus were included in this study. The patients were categorized into 3 groups (i.e., smokers, ex-smokers, and nonsmokers). Test results ofof hemoglobin A1c (HbA1c), cholesterol, triglyceride, high density lipoprotein (HDL) levels, low density lipoprotein, leukocyte count, C-reactive protein, fibrinogen, and ferritin levels were obtained. Body mass indexes (BMI) and blood pressure were also measured.

Results: Smoking was significantly associated with the male gender, HbA1c, HDL level, BMI, waist circumference, the homeostatic model assessment-insulin resistance (HOMA-IR) core, and inflammatory markers. Current smokers who smoked ≥20 packs/year demonstrated poorer metabolic results compared to those who smoked 0-10 pack(s)/year. The metabolic parameters were worse in ex-smokers who quit smoking <1 year ago compared to ex-smokers who quit 1-5 years, 5-10 years, and >10 years ago.

Conclusion: We demonstrated that smoking increased insulin resistance, metabolic syndrome, and inflammation. Smoking was also observed to worsen glycemic control by further increasing insulin resistance in diabetic patients.

Keywords: Smoking; Diabetes Mellitus; Inflammation; Insulin Resistance.

INTRODUCTION

Smoking remains a global problem and it is known as a cause of many diseases such as atherosclerosis, lung disease, cancer, etc. Globally, tobacco use is the most important cause of preventable morbidity and mortality, and it is responsible for 1 in 10 deaths among adults (1). Smoking kills nearly 6 million people and causes billions of dollars in economic damage worldwide each year (2). Smokers consist of about 29% of the global population and thisproportion is higher among men (3).

Smoking increases insulin resistance, triggers the development of diabetes mellitus, and impairs glycemic control through several mechanisms, some of which are currently unknown (4). An association between smoking and metabolic syndrome has been demonstrated in a very large population-based cohort study; this relationship is stronger with increasing amount of smoking (5). In addition, smoking was shown to increase insulin resistance by potentiating inflammation and oxidative stress, inducing direct damage on β cells, and causing endothelial dysfunction (4).

Although there are many studies regarding the effects of smoking on insulin resistance, metabolic syndrome and inflammatory parameters, information regarding the change in these parameters following smoking cessation is limited (1,3,4).

The objective of the present study is to examine the impact of cigarette smoking on insulin parameters and inflammatory markers, and to investigate how these parameters are altered by the duration of smoking cessation in patients who quit smoking.

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MATERIAL and METHODS

Study subjects

The study included 612 patients aged between 18 and 70 years who were undergoing treatment and follow-up for type 2 diabetes mellitus (DM) at theInternal Medicine Department of Hospital.Patients included in the study were diagnosed with type 2 DM without microvascular (retinopathy, nephropathy, neuropathy) or macrovascular (cerebrovascular, cardiovascular diseases) complications of diabetes, had hemoglobin A1c (HbA1c) <8% and took an oral antidiabetic drug (OAD) without insulin injections. Patients with type 2 DM who had evident proteinuria, creatinine >1.5 mg/dL, HbA1c >8%, blood pressure >140/90 mmHg with or without medical treatment, and acute and/or chronic inflammatory disease and patients who were diagnosed type 1 DM were excluded. Patients with passive smoking exposure and those who are on diet and do exercises on a regular basis were excluded as these have no effect on study parameters. Obese patients and who were on anti-lipidemic medications were included in equal rates among the groups, as these factors mayaffect the inflammatory parameters. Patients who are on diet ≥3 days in a week under the supervision of a dietician were considered to be compliant with diet. Those who do exercised at least half an hour ≥3 days a week were considered compliant with excercise.

Clinical and laboratory measurements

Demographic information (i.e., age and gender) were documented for all patients. Height (meters) and weight (kg) measurements were obtained to calculate the body mass index (BMI). Waist circumference (cm) was measured midway between the lower rib margin and the iliac crest. Patients whose BMI is <25 kg/m2 were considered to have normal body weight, 25-29 kg/m2as overweight and ≥30 kg/m2 as obese (6). Systolic and diastolic blood pressures were measured using an automatic sphygmomanometer with an appropriate cuff size on the right arm after a resting period of 10 min.

Patients fasted overnight and blood samples were drawn in the morning of the next day from an antecubital vein into vacuum tubes for laboratory tests, which were sent to the central laboratory. Levels of HbA1c, cholesterol, triglyceride, high density lipoprotein (HDL), low density lipoprotein (LDL), leukocyte count, C-reactive protein (CRP), fibrinogen, and ferritin were measured for each patient and homeostatic model assessment-insulin resistance (HOMA-IR) score were calculated. The leukocyte count was determined with automated cell counter. Blood glucose and lipid profile were measured by enzymatic methods. CRP and HbA1c were measured by immunoturbidimetric method and high performance chromatography respectively. Serum ferritin levels were also measured by direct chemiluminescent immunoassay method and fibrinogen was measured by a photometric light-scattering method. Serum insulin was measured by an immunoradiometric assay. HOMA-IR was calculated using the formula: Fasting insulin (μU/mL) × fasting blood glucose (mg/dl) concentrations, divided by 405.

Smoking assessment

The participants' smoking habits were questioned in detail. Participants were categorized into three groups: smokers, ex-smokers, and nonsmokers. The amount of cigarettes smoked was expressed as pack(s)/year (each package containing 20 cigarettes). Smoking history of patients was calculated in pack(s)/year, determined from the number of pack(s) smoked per day multiplied by number of years smoked. The year of smoking cessation for ex-smokers was recorder. Patients with passive smoking exposure were excluded.

Ethics statement

All participants provided written consent for participation in the study. Ethics approval for conducting this study was received from the Ethical Committee of the Hospital. All procedures were in accordance with the ethical standards of the committee on human experimentation of our institution and with the Declaration of Helsinki.

Data analysis

The IBM SPSS 22 (IBM SPSS, Turkey) programme was used for statistical analyses of data. The relationship of smoking with demographic parameters, glycemic control, and insulin resistance and inflammatory parameters was analyzed using chi-square, Mann-Whitney U test, and independent samples t-tests. Quantitative data were reported as percentages and mean ± standard deviation; normally distributed parameters were compared using Student's t-tests and non-normally distributed parameters were compared using Mann Whitney U tests. Qualitative data were compared using the chi-square test.A p value <0.05 was considered statistically significant.

RESULTS

A total of 612 type 2 DM patients (369 females and 243 males) were enrolled in the study. Their age ranged between 32 and 65 years with a mean age of 52±9.6 years. 70.5% (n=432) of the subjects were non-smokers, 15.1% (n=93) were ex-smokers, and 14.4% (n=87) were current smokers. Obesity and anti-lipidemic drug intake was not significantly different between the study groups. 253 (58.5%) out of 432 non-smoker patients were obese, while 66 (70%) out of 93 ex-smoker patients and 57 (65%) out of 87 current smoker patients were obese. Anti-lipidemic medicationswere used by 210 (48.6%) non-smoker patients, 48 (51.6%) ex-smokers and 45 (51.7%) current smokers.

The clinical and laboratory parameters were compared between the three groups. When non-smokers were taken as reference, ex-smokers showed significantly higher BMI, waist circumference, total cholesterol, CRP, HOMA-IR, HbA1c, ferritin, and fibrinogen levels and significantly lower level of HDL cholesterol;and no significant difference was found in age, triglyceride, LDL cholesterol and leukocyte levels. When non-smokers were taken as reference, current smoker patients showed significantly higher BMI, waist circumference, triglycerides, HOMA-IR, leukocytes, ferritin, fibrinogen, CRP and HbA1c levels and

significantly lower levels of HDL cholesterol while there was no significant difference in age, total cholesterol and LDL cholesterol levels (Table 1).

The total number of cigarettes was used to sub-categorize current smokers into the following 3 groups: 0-10 pack(s)/year (n:21), 10-20 packs/year (n:39), and ≥20 packs/year (n:27). Compared to patients who smoke 0-10 pack(s)/year, patients who smoke 10-20 packs/year showed significantly higher HbA1c, BMI, waist circumference and significantly lower levels of HDL cholesterol and ferritin; no significant difference was found in theremaining parameters. Compared to patients who smoke 0-10 pack(s)/year, patients who smoke ≥20 packs/year had significantly higher HbA1c, BMI, waist circumference, total cholesterol, LDL cholesterol, HOMA-IR, leukocytes, fibrinogen and CRP levels and significantly lower levels of HDL cholesterol; no significant relationship was found in the remaining parameters (Table 2).

Ex-smokers were divided into 4 groups according to the duration since smoking cessation;<1 year, 1-5 years, 5-10 years, and >10 years. Compared to non-smokers, those who quit smoking within 1 year showed significantly higher waist circumference, HOMA-IR, leukocytes and CRP levels (p<0.001), significantly lower level of HDL cholesterol (p<0.001), significantly higher BMI and HbA1c (p:0.005, p:0.003, respectively); no significant difference was found in total cholesterol (p:0.55), triglycerides (p:0.06), LDL cholesterol (p:0.31), ferritin (p:0.40) and fibrinogen (p:0.06). Compared to non-smokers, those who quit smoking 1-5 years ago had significantly lower levels of total cholesterol and HDL cholesterol (p:0.02, p:0.02, respectively) and significantly higher HbA1c (p:0.04), HOMA-IR (p:0.02) and ferritin levels (p:0.004); no significant difference was found in BMI (p:0.83), waist circumference (p:0.57), triglycerides (p:0.64), LDL cholesterol (p:0.21), leukocytes (p:0.31), fibrinogen (p:0.38), and CRP (p:0.11). Compared to non-smokers, those who quit smoking 5 to 10 years ago had no significant difference in BMI (p:0.18), waist circumference (p:0.80), total cholesterol (p:0.25), triglycerides (p:0.21) LDL cholesterol (p:0.76), HDL cholesterol (p:0.10), HbA1c (p:0.98), HOMA-IR (p:0.17), leukocytes (p:0.95), ferritin (p:0.72), fibrinogen (p:0.53) and CRP (p:0.14).

Compared to non-smokers, those who quit smoking >10 years ago had no significant differencein BMI (p:0.26), waist circumference (p:0.15), total cholesterol (p:0.17), triglycerides (p:0.97), LDL cholesterol (p:0.11) HDL cholesterol (p:0.49), HbA1c (p:0.53), HOMA-IR (p:0.77), leukocytes (p:0.28), ferritin (p:0.06), and CRP (p:0.67) but had significantly higher fibrinogen levels (p:0.01) (Table 3).

Table 1. Demographics, anthropometric, and laboratory parameters in smokers and non-smokers

Variables	Non-smokers	Ex-smokers	P-value	Smokers	P-value
Female/Male	288/144	33/60	<0.001	48/39	<0.001
Age (yr)	55.7±12	55.3±9.2	0.79	53.8±9.4	0.16
HbA1C (%)	6.9±0.7	7.0±0.8	0.05	7.3±0.7	<0.001
BMI (kg/m2)	29.8±4.9	31.2±4.2	0,01	32.2±4.4	<0.001
WC (cm)	92.9±10.8	96.7±7.9	0,001	101±9.7	<0.001
Cholesterol (mg/dl)	206±44.7	195±41.6	0.02	210±33.8	0.34
Triglyceride (mg/dl)	154±93.6	152±54.1	0.83	195±125	<0.001
LDL (mg/dl)	125±38.3	120±38.6	0.24	121±33.2	0.41
HDL (mg/dl)	51±13.6	45.6±9.5	<0.001	41.8±14.6	<0.001
HOMA	4.4±5.4	6.3±4.3	0,001	7.9±6.4	<0.001
Leukocyte (×109/L)	6.7±1.6	7.0±1.8	0.09	8.2±2.7	<0.001
CRP (mg/dl)	4.2±2.7	5.1±4.3	0.003	6.6±4.4	<0,001
Ferritin (mg/dl)	60±64.6	77.4±73.1	0.01	131±98.4	<0.001
Fibrinogen (mg/dl)	298±85.6	323±91.5	0.005	370±94.8	<0.001

NS, non-significant; HbA1C, hemoglobin A1C; BMI, body mass index; LDL, low density lipoprotein; HDL, high density lipoprotein; HOMA,homeostatic model assessment;CRP, C-reactiveprotein, WC, Waist circumference.

Table 2. Demographics, anthropometric and laboratory parameters relationship between the amounts of cigarettes smoked

VARIABLES	0-10 pack/year	10-20 pack/year	P value	20 pack/year	P value
Female/Male	9/12	27/12	0.59	12/15	0.52
Age (yr)	51±13.5	53.8±8.6	0.32	56±6.06	0.90
HbA1C (%)	7.2±0.7	7.3±0.7	<0.001	7.5±0.8	<0.001
BMI (kg/m2)	30.8±5.6	32.3±4.2	<0.001	33.4±4.3	<0.001
WC (cm)	97.6±12.2	101.2±11.3	<0.001	103.6±5.7	<0.001
Cholesterol (mg/dl)	194±32	207±28	0.11	228±39	0.002
Triglyceride (mg/dl)	196±100	199±159	0.93	189±104	0.80
LDL (mg/dl)	113±35.5	118±37.9	0.58	132±25.2	0.02
HDL (mg/dl)	46.2±13.4	42.9±8.3	<0.001	48.1±19	<0.001
HOMA	5.1±2.3	5.6±3.9	0.57	13.6±8.2	<0.001
Leukocyte (×109/L)	6.6±2.1	7.7±2.5	0.07	9.7±2.5	<0.001
CRP (mg/dl)	4.04±1.4	4.56±3.2	0.48	11.8±3.3	<0.001
Ferritin (mg/dl)	154±100	78±92	0.003	190±73	0.13
Fibrinogen (mg/dl)	354±94	327±94	0.26	446±48	<0.001

NS, non-significant; HbA1C, hemoglobin A1C; BMI, body mass index; LDL, low density lipoprotein; HDL, high density lipoprotein; HOMA,homeostatic model assessment;CRP, C-reactiveprotein, WC, Waist circumference.

Table 3. Demographics, anthropometric and laboratory parameters relationship between the time to cessation smoking

	Non-smokers	<1 year ex-smokers	1≤5 years ex-smokers	5≤10years ex-smokers	>10 years ex-smokers
Female/Male	288/144	9/6	0/27	12/18	12/9
Age (yr)	55.7±12	55.2±5.8	53.1±8.0	57.9±12.7	54.8±8.0
HbA1C (%)	6.9±0.7	7.5±0.2	7.2±0.6	6.9±0.6	6.8±0.9
BMI (kg/m2)	29.8±4.9	33.6±3.2	30.2±4.1	31.2±4.5	31.2±3.3
WC (cm)	92.9±10.8	102.6±6.5	94.1±8.0	96.4±7.5	96.3±7.4
Cholester-ol(mg/dl)	206±44.7	213±56.1	190±45.5	196±36.9	193±40.3
Triglyceride (mg/dl)	154±93.6	199±81	146±39.5	133±42.2	155±57.5
LDL (mg/dl)	125±38.3	135±53	116±39	123±36	112±37.6
HDL (mg/dl)	51±13.6	39±6.8	44±11.4	47±7.0	49±11
HOMA	4.4±5.4	9.5±1.0	6.8±4.2	5.8±4.3	4.1±2.1
Leukocyte (×109/L)	6.7±1.6	8.6±0.9	6.4±0.9	6.7±2.1	7.1±2.2
CRP (mg/dl)	4.2±2.7	9.4±6.3	5.1±2.8	3.5±1.3	4.5±2.2
Ferritin (mg/dl)	60±64	74±40	96±72	56±67	90±68
Fibrinogen (mg/dl)	298±85	397±56	284±116	308±77	346±94

NS, non-significant; HbA1C, hemoglobin A1C; BMI, body mass index; LDL, low density lipoprotein; HDL, high density lipoprotein; HOMA,homeostatic model assessment;CRP, C-reactiveprotein, WC, Waist circumference.

DISCUSSION

In this study, we demonstrated increased insulin resistance and poor glycemic control in diabetic smokers; these changes were proportional to the amount of smoking. We also observed that the adverse consequences on insulin resistance and glycemic control were reversed in ex-smokers who quit >5 years ago. In large studies, it has been shown that an increased risk of developing diabetes is associated with smoking. Smoking has been associated with the development of diabetes and increased risk of developing diabetes with increasing amounts of daily smoking according to a study that included 21,068 subjects (7), and a meta-analysis of 25 studies conducted by Willi et al (8).

Smoking potentiates insulin resistance and worsens glycemic control in patients with DM (9). Morimoto et al.reported that insulin secretion was twice as impaired in smokers as individuals who have never smoked.This relationship was directly proportional to the pack/year value of smokers (10). In a previous study that involved 5047 patients with DM, the mean HbA1c level was

significantly higher in smokers compared to non-smokers (7.9±1.3% and 7.3±1.1%, respectively) (11). In our study, insulin resistance and HbA1c were significantly higher in ex-smokers who quit ≤5 years ago than that in those who have never smoked; however, no significant differences were observed between ex-smokers who quit >5 years and those who have never smoked. Wannamethee et al. demonstrated that ex-smokers were at a higher risk of developing diabetes over the first years but this risk decreased after 5 years (12). Will et al. have also shown that the risk of developing diabetes for ex-smokers (i.e., women and men who did not smoke for >5 and >10 years, respectively) was the same as individuals who have never smoked (13). Additionally, a significant decrease in the mean HbA1c level, from 7.7±2.2% to 7.0±1.6%, was observed 1 year after smoking cessation in a previous prospective study (14).

The underlying mechanism of cigarette smoking-induced insulin resistance increase needs to be further evaluated. In our opinion, several mechanisms could explain this observation. Firstly, insulin resistance may be owing to the direct effects of nicotine, carbon monoxide, or other agent in the tobacco smoke, resulting in the release of counter-regulatory hormones (i.e., growth hormone, noradrenaline, and adrenal androgens). Secondly, smoking induces oxidative stress and impairs endothelial cell function. Therefore, insulin mediated reduction in glucose uptake may be explained by smoking-induced oxidative stress associated with a decreased peripheral endothelial function (15). Even though the exact mechanism by which smoking increases the risk of metabolic syndrome development is not clear, some mechanisms have been suggested. Smoking can lead to dyslipidemia by reducing lipoprotein lipase activity, increasing 3-hidroxy-3-methylglutaryl-CoA reductase and glucose 6 phosphate dehydrogenase activities, and potentiating central obesity (16). It has been shown that smokers have higher cortisol levels, which stimulate the sympathetic nerve system. It has also been reported that there is an initial period of weight gain following smoking cessation due to slower metabolism and increased appetite, which later equilibrates (16).

In our study, inflammatory parameters were significantly higher in smokers and this was directly proportional to the amount of smoking. Inflammation in ex-smokers who quit >1 year ago was similar to those who have never smoked. A higher incidence of inflammation in smokers and a direct proportional relationship between the inflammation and amount of smoking have also been reported in other previous studies. Inflammation parameters were reported to regress to normal ranges within weeks to months following smoking cessation (17,18).

There are several possible mechanisms by which smoking may be associated with systemic markers of inflammation. Firstly, acute phase proteins may be surrogates for smoking-induced chronic inflammatory processes, such as periodontitis, airway inflammation, and atherosclerosis itself. Secondly, certain compounds of smoke (i.e., free radicals and phenol-rich glycoproteins) directly exert an inflammatory stimulus on macrophages, which may trigger the production of inflammatory cytokines (i.e., Tumor necrosis factor-α, Interleukin (IL)-1, and IL-6). Thirdly, an indirect effect of nicotine-induced catecholamine release on the modulation of systemic and local cytokine balance is possible (16,18).

Many studies demonstrated that smoking increased microvascular and macrovascular complications in patients with type 2 DM (4,19,20). A study conducted byUnited Kingdom Prospective Diabetes Study group demonstrated that smoking is an independent and important risk factor for coronary artery disease in patients with type 2 DM (21). As shown by multi-regression analyses, smokers die 8 to 10 years earlier than non-smokers (4). Smoking is known to increase diabetic incidence, aggravate glucose homeostasis and increase diabetic complications (22,23,24). In a study by Chow et al. on the patient awareness in patients with ischemic heart disease, it was stated that smokers had significantly lower drug compliance and did less dieting and exercising (26). In Turkey, increased inflammation and oxidative stress, direct damage to β cell, increased endothelial dysfunction and insulin resistance caused by smoking along with inability to comply with life style changes and medication schedule, which are very important in diabetes regulation, increase poor glycemic control rate and complications, as a result diabetes management becomes difficult.

Our study has strengths as well as limitations. Its strengths lie in the multicenter large design consisting of patients from both sexes representing a wide range of ages. Furthermore, investigating the relationship between the amounts of cigarette smoked, duration of smoking cessation and insulin resistance and inflammation in addition to the relationship between smoking and insulin resistance and inflammation in patients with type 2 DM is very important. The importance of the study increases as there are a limited number of studies conducted in developing countries and due to the fact that this is the first large epidemiological study performed in Turkey (3). On the other hand, limitations are patients'subjective verbal responses to questions about smoking and smoking cessation. As this is not objective data such as plasma concentration measurement, verbal responses has the possibility to be erroneous. Also, there is a possibility of error margin as diet and exercise compliance was evaluated based on patients' verbal statements.

CONCLUSION

In conclusion, we demonstrated that smoking increased insulin resistance, MS, and inflammation; these parameters returned to normal ranges within weeks, months, or years in ex-smokers. We also showed that smoking worsened glycemic control by further increasing insulin resistance in diabetic patients. Diabetes involves a complex pathogenesis and is strongly associated

with polygenic inheritance and environmental factors. Therefore, eliminating environmental factors, such as cigarette smoking, is crucial for both the prevention of new diabetes cases and managing existing diabetic patients.

Competing interests: The authors declare that they have no competing interest.

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Ethical approval: Ethics approval for conducting this study was received from the Ethical Committee of the Hospital. All procedures were in accordance with the ethical standards of the committee on human experimentation of our institution and with the Declaration of Helsinki.

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