Respiratory Function, Physical Capacity, and Metabolic Syndrome Components in Combustible Cigarettes and Heated Tobacco Products Users: A Four-Year Follow-Up Cohort Study

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Abstract: *Purpose:* Chronic obstructive pulmonary disease (COPD) is one of the leading causes of death worldwide and is the fourth leading cause of death in Kazakhstan. Cigarette smoking is a prevalent risk factor for COPD. While quitting smoking is the preferred way to reduce COPD risk, literature suggests that heated tobacco products (HTP) might be a better option for people who cannot quit smoking. The aim of this paper was to analyze the long-term effects of shifting to HTP use in long-term smokers compared to continued combustible cigarettes (CC) use.

Patients and methods: A cohort of 1200 participants (400 HTP and 800 CC) aged 40-59 years with a minimum of 10 pack-year smoking history were recruited and followed for four years. The functional outcomes compared between HTP and CC users included: (1) COPD Assessment Test (CAT); (2) post-bronchodilator lung function; (3) 6-minute walking distance (6MWD) test; and (4) metabolic syndrome components. One way ANOVA was used to compare functional outcomes between visits, while multivariable linear mixed models were used to test associations between health outcomes and smoking type (HTP vs. CC) over time.

Results: Out of 1200 participants 893 (609 CC users and 284 HTP users) remained in the study by the fourth year of follow up. Comparison between functional outcomes showed that most of them have improved between visits, while lung function and fasting blood glucose levels got worse. Linear mixed models showed HTP use was associated with better functional outcomes over time compared to CC users. Lung function decrease was significantly less in HTP users, while improvements in CAT scores, waist circumference, and systolic blood pressure were significantly better compared to CC users.

Conclusion: This study demonstrated that HTP users experienced it to a significantly lesser decrease in lung function compared to CC users, while demonstrating better improvements in other functional outcomes. The results of this study suggest that HTP might be a less deleterious alternative compared to CC in people with long history of CC use and who cannot quit smoking.

Keywords: Heated tobacco products, Combustible cigarettes, Cohort study, Health outcomes, smoking, COPD self-reported score.

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is the third leading cause of death with 3.2 million deaths worldwide in 2019 [1]. In Kazakhstan, COPD is the fourth leading cause of death and affects approximately 1.4 million people [2]. COPD is a major healthcare burden as it negatively affects the quality of life and is the third leading cause of hospital readmission within 30 days [3, 4].

Cigarette smoking is the most common risk factor for COPD [5]. The results of a recent cross-sectional study of COPD among three groups of men and women aged 40-59 who currently smoke cigarettes, do not smoke, and stopped smoking 1-5 years ago demonstrated that smoking significantly reduced functional exercise capacity such as ability to walk 450 meters within 6 minutes in the 6-minute walking distance (6MWD) test [6]. Compared to never-smokers, current and former smokers had higher values in all components of the COPD Assessment Test (CAT) score: cough, phlegm, chest tightness, breathlessness going up hills/stairs, activity limitation at home, confidence leaving home, sleep, and energy. At the same time, these parameters were lower among those who stopped smoking 1-5 years ago compared to those who continued to smoke. However, smoking cessation is a challenge for long-term smokers [7-9]. A recent study of 100 COPD patients showed that almost half of the patients continued smoking even after being diagnosed with COPD [10]. As a result, it is important to study less deleterious alternatives to CC use for those who cannot quit smoking.

Heated tobacco products (HTP) emerged on the global market as an alternative to combustible cigarettes (CC). HTP are presented as "modified risk" tobacco products because switching to HTP can

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potentially reduce deleterious health effects associated with CC use. In a recent study, changes in a daily cigarette smoking, annualized disease exacerbations, lung function indices, patient-reported CAT scores, and 6-Minute Walk Test were measured in 19 COPD patients using HTP at 12-, 24-, and 36-months and compared with a group of age- and sex-matched COPD patients who continued using CC [11]. Subjects using HTP had a substantial decrease in annualized COPD exacerbations within the group mean at baseline and three year follow-up. In addition, substantial and clinically significant improvements in CAT scores and 6MWD were identified at all three time points in the HTP cohort. No significant changes were observed in COPD patients who continued smoking.

This paper reports the results of the previously described cohort study at two years of follow-up [12]. The aim of this paper was to analyze the functional outcomes of CAT, post-bronchodilator spirometry results, 6MWD test, and components of metabolic syndrome (MetS) over two-year follow-up time in long-term smokers who cannot quit. Another aim was to compare these functional outcomes between CC users and those who shifted to HTP use.

MATERIAL AND METHODS

Sample

This prospective cohort study was conducted in accordance with the principles and criteria set by the Declaration of Helsinki "On Ethical Principles for Medical Research Involving Human Subjects" and was approved by the Ethical Review Committee of the Academy of Preventive Medicine (protocol #4). Signed informed consent was obtained from all study participants before enrolment to the study. The design of the study was described in detail in the previously published protocol [13]. Briefly, this study is a cohort study which matched one HTP user to two CC users by gender (men and women), age, education, and baseline exposure level (number of pack-years). HTP users were defined as participants who switched from CC to HTP use and predominantly use HTP during the day (≥ 70% of time). We recruited 1200 participants (400 HTP and 800 CC users) aged 40-59 years with a minimum of 10 pack-year smoking history. Study personnel provided participants information on health hazards associated with smoking and advised them on how to quit CC or HTP use. The participants were followed up for 48 months with functional outcomes and smoking status (HTP/CC/Quit smoking) measured at baseline, 12-, 24-, 36-, and 48-month period.

Functional Outcome Measures

The clinical and functional outcomes were compared between HTP and CC users and included continuous: (1) patient-reported CAT scores; (2) post-bronchodilator lung function parameters, including forced expiratory flow in 1s – FEV1 and forced vital capacity – FVC; (3) exercise tolerance using 6MWD test; and (4) MetS components, including waist circumference, fasting glucose, blood lipids, and blood pressure.

Study Procedures

Computer-Assisted Personal Interviewing. KAPM was developed an electronic data capture system in the form of its proprietary computer-assisted personal interviewing platform called ClouDoc. The questionnaire was designed to collect data on possible COPD risk factors including history of smoking, current smoking (HTP/CC/Quit smoking), level of smoking exposure (in pack-years), passive smoking, history of lung disease, etc. The questionnaire contains covariates: age, gender, ethnicity, and self-reported morbidity.

Spirometry. Spirometry data was collected by a trained specialist using the combined spirometry system, BTL-08 SPIRO. All spirometry studies are reviewed centrally to ensure quality control. Bronchodilator responsiveness is considered positive if the subject had a ≥12% change in FEV1 or FVC above pre-bronchodilator measurements [14].

COPD self-reported score. The CAT is a validated, short (8-item) questionnaire to be completed by study participants. Despite the fact that CAT was designed for patients with COPD, it can be used to measure respiratory symptoms among all participants including those who have preserved pulmonary function.

Anthropometry. Anthropometric measurements include height, weight, waist circumference, heart rate, and blood pressure.

Exercise tolerance. The 6MWD test is a simple and effective test that measures the distance that a patient can quickly walk on a flat, hard surface in a period of 6 minutes.

Laboratory Data. Blood donated by the study participants is processed at the KAPM COPD Center for shipment, biochemical analysis, intermittent (at -20°C) and long-term (at -80°C) storage in accordance with biobanking standards.

Statistical Analyses

Basic descriptive statistics used to characterize the study populations are presented as mean (SD) and frequency (%). Demographic and personal characteristics were compared between HTP and CC users using the Student's t-test for continuous variables and Chi-Square test for categorical variables. One-way ANOVA was used to compare outcome measures at baseline, 12-. 24-, 36-, and 48- months for HTP and CC users separately. Outcomes which were significantly different between follow-up periods were further investigated using linear mixed models. Linear mixed models including repeated measures were performed to compare the effects of smoking status on: (1) patient-reported CAT scores; (2) post-bronchodilator lung function parameters, including FEV1 and FVC as separate outcomes; (3) exercise tolerance using 6-minute walking distance (6MWD) test; and (4) metabolic syndrome components, including waist circumference, fasting glucose, blood lipids, and blood pressure. These models included time (at baseline, 12-, 24-, 36, and 48- months) and smoking status, and were further adjusted for participant's age, sex, years of smoking, ethnicity, history of lung disease, marital status, and interaction between time of follow-up and smoking status. Participants who quit smoking were excluded from repeated measures analyses. All statistical analyses were done with SAS (SAS Institute Inc., Cary, NC). A two-tailed *p* value of less than 0.05 was considered of statistical significance.

RESULTS

Recruited participants (N=1200) were followed-up for 48-months during which 26% of participants were lost to follow-up. The mean duration of HTP use was 7 months (SD 4). The demographic and clinical characteristics of the participants by baseline smoking status are presented in Table **1**. There were no significant differences between CC and HTP users at baseline, except for CAT score, which was significantly lower for HTP group.

The dynamic of the main outcomes between baseline, 12-, 24-, 36, and 48- months follow-up are presented in Figure **1**. Overall, both CC and HTP users experienced improvements in all health outcomes, except for measures post-bronchodilator lung function parameters. Both CC and HTP users experienced decline in lung function, but HTP users had better scores after 24-months of follow-up.

The differences between the main outcomes' values between baseline, 12-, 24-, 36, and 48- months follow-up are presented in Tables **2** and **3** separately for CC and HTP users. The analyses show that CAT score, FEV1, FVC, 6MWD, waist, HDL cholesterol, and systolic blood pressure (SBP) were significantly different between follow-up for CC and HTP users. In particular, CAT scores significantly decreased for both CC and HTP users, from 12.83 (SD 3.17) to 9.87 (SD 2.21) for CC users and from 11.89 (SD 2.89) to 9.59 (SD 1.88) for HTP users. Otherwise, the health parameters of the participants have improved over the observed period. The 6MWD increased from 520.79 (SD 52.54) to 544.14 (SD 44.62) for CC users and from 519.61 (SD 55.69) to 549.30 (SD 43.01) for HTP users (both P<.0001). Metabolic syndrome components including waist circumference, and HDL cholesterol significantly improved over time, while HTP users also experienced decrease in systolic blood pressure (Table **3**).

The results of repeated measures analyses of main outcomes with smoking status (HTP vs CC) as main predictor are presented in Tables **4** and **5**. Smoking type significantly was significantly associated CAT scores, post-bronchodilator FVC, waist circumference for both CC and HTP users, while smoking type follow-up time interaction was associated with CAT score, FEV1, FVC, 6MWD, waist, and SBP.

The CAT scores have improved over time for both CC and HTP users (p<0.0001), though HTP smoking was significantly associated with lower CAT scores for 48-month follow-up compared to CC smokers (p<0.0001). Having larger number of pack years, not being married, and having previous history of lung disease increased the CAT score.

Post-bronchodilator FEV1 and FVC have decreased over time for both CC and HTP users. FVC for HTP users was significantly lower compared to CC users (p<0.0001) while over time their lung function improved and became significantly better compared to CC users. Factors negatively affecting FVC were age and history of lung disease, while being female and Caucasian ethnicity increased post-bronchodilator FVC.

Among the MetS components, waist circumference decreased over time in the observed participants. It was significantly higher for HTP users compared to CC users (p<.0001). However, over time HTP users show significant decreases in waist circumference compared to CC users.

Table 1: Baseline Demographics of the Subjects on the Study Compared using Descriptive Statistics

	CC (n=800)	HTP (n=400)	P
Age (mean, SD)	49.16 (5.21)	48.95 (5.18)	0.5044[a]
Ethnicity (n, %)			
Asian	592 (74.00%)	276 (69.00%)	0.0680[b]
Caucasian	208 (26.00%)	124 (31.00%)	
Sex (n, %)			
Male	396 (49.50%)	196 (49.00%)	0.8703[b]
Female	404 (50.50%)	204 (51.00%)	
Married (n, %)			
No	208 (26.00%)	111 (27.75%)	0.4878[b]
Yes	592 (74.00%)	289 (72.25%)	
History of lung disease (n, %)			
No	749 (93.63%)	375 (93.75%)	0.9332[b]
Yes	51 (6.38%)	25 (6.25%)	
Pack years (mean, SD)	22.83 (10.52)	22.76 (10.60)	0.9232[a]
CAT score (mean, SD)	12.83 (3.17)	11.89 (2.89)	<.0001[a]
FEV (mean, SD)	3.11 (0.74)	3.17 (0.71)	0.1616[a]
FVC (mean, SD)	3.74 (0.88)	3.70 (0.83)	0.4392[a]
6-minute walking distance (mean, SD)	520.80 (52.55)	520.00 (55.46)	0.8061[a]

[a]Student's t test; [b]Chi Square test.

Table 2: One-Way ANOVA Comparison of CC and HTP Users at Baseline, 12-, and 24-Month Follow-Up Visits for CC Users

	Baseline	12-Month Follow-up	24-Month Follow-up	36-Month Follow-up	48-Month Follow-up	P[a]
FEV (mean, SD)	3.11 (0.73)	3.03 (0.72)	3.00 (0.72)	2.94 (0.73)	2.86 (0.71)	<.0001
FVC (mean, SD)	3.74 (0.88)	3.64 (0.85)	3.52 (0.84)	3.43 (0.83)	3.36 (0.86)	<.0001
6-minute walking distance (mean, SD)	520.80 (52.55)	531.98 (49.08)	532.99 (48.10)	540.15 (48.10)	544.26 (44.56)	<.0001
Waist circumference (mean, SD)	90.89 (12.47)	88.93 (12.21)	88.41 (11.88)	89.26 (11.99)	89.24 (12.08)	0.0014
Fasting blood glucose (mean, SD)	5.33 (1.32)	5.45 (1.39)	5.36 (1.20)	5.56 (1.36)	5.70 (1.42)	<.0001
Triglycerides (mean, SD)	1.67 (1.15)	1.73 (1.38)	1.62 (1.20)	1.65 (1.23)	1.64 (1.12)	0.5362
HDL cholesterol (mean, SD)	1.35 (0.40)	1.37 (0.39)	1.30 (0.45)	1.34 (0.39)	1.37 (0.40)	0.0068
Systolic blood pressure (mean, SD)	119.19 (13.95)	118.91 (13.68)	118.15 (12.91)	119.16 (12.54)	119.19 (11.99)	0.5279
Diastolic blood pressure (mean, SD)	75.72 (10.42)	75.12 (10.25)	75.36 (9.01)	76.64 (8.15)	77.25 (7.82)	<.0001

[a]One-way ANOVA test.

Table 3: One-Way ANOVA Comparison of CC and HTP Users at Baseline, 12-, and 24-Month Follow-Up Visits for HTP Users

	Baseline	12-Month Follow-up	24-Month Follow-up	36-Month Follow-up	48-Month Follow-up	P[a]
CAT score (mean, SD)	11.89 (2.89)	10.61 (2.25)	10.80 (2.39)	10.06 (1.76)	9.51 (1.88)	<.0001
FEV (mean, SD)	3.17 (0.71)	3.10 (0.67)	3.11 (0.67)	3.06 (0.65)	3.01 (0.69)	0.0284
FVC (mean, SD)	3.70 (0.83)	3.73 (0.81)	3.65 (0.80)	3.54 (0.77)	3.49 (0.80)	0.0006
6-minute walking distance (mean, SD)	519.99 (55.46)	537.12 (44.87)	539.00 (51.14)	544.87 (48.68)	549.32 (43.09)	<.0001

Waist circumference (mean, SD)	91.72 (14.55)	88.06 (13.72)	87.54 (14.16)	88.70 (14.53)	88.43 (14.17)	0.0005
Fasting blood glucose (mean, SD)	5.33 (1.09)	5.42 (1.36)	5.41 (1.14)	5.56 (1.00)	5.62 (1.10)	0.0084
Triglycerides (mean, SD)	1.89 (1.72)	1.69 (1.18)	1.74 (1.24)	1.75 (1.34)	1.70 (1.49)	0.2764
HDL cholesterol (mean, SD)	1.41 (0.49)	1.45 (0.46)	1.34 (0.47)	1.36 (0.38)	1.44 (0.44)	0.0044
Systolic blood pressure (mean, SD)	119.09 (13.58)	117.40 (13.23)	116.69 (12.86)	117.53 (12.75)	118.66 (12.28)	0.0947
Diastolic blood pressure (mean, SD)	75.47 (10.23)	74.07 (10.04)	74.75 (8.80)	75.71 (8.00)	76.79 (8.43)	0.0035

[a]One-way ANOVA test.

Table 4: Multivariable Repeated Measures Analyses of Functional Outcomes Over Time

	CAT Score	FEV	FVC	6-Minute Walking Distance
Follow-up 12-months	-1.5615***	-0.0711***	-0.0811***	11.7157***
Follow-up 24-months	-1.7816***	-0.0873***	-0.1912***	11.6988***
Follow-up 36-months	-2.3222***	-0.1402***	-0.2729***	18.1590***
Follow-up 48-months	-2.9514***	-0.2097***	-0.3304***	21.7401***
HTP use (ref. CC)	-0.9697***	-0.0162	-0.1227***	-3.6545
Age	0.0145	-0.0424***	-0.0409***	-1.8876***
Female sex (ref. Male)	-0.3258*	0.9968***	1.2085***	27.2952***
Pack years	0.0290***	-0.0034*	-0.0028	-0.4583**
Caucasian ethnicity (ref. Asian)	0.3642**	0.1546***	0.2660***	4.7017
Previous history of lung disease (ref. No)	2.1652***	-0.2238**	-0.2214**	-5.3785
Not married (ref. Yes)	0.1810	0.0676*	0.0655	-3.2234
12-months * HTP use (ref. CC)	0.3139	0.0227	0.1294***	4.6970
24-months * HTP use (ref. CC)	0.6535**	0.0493*	0.1714***	7.4267*
36-months * HTP use (ref. CC)	0.4907*	0.0468*	0.1431***	6.5685*
48-months * HTP use (ref. CC)	0.6376*	0.0716*	0.1557***	7.9134*

*Significant at ≤.05; **Significant at ≤.01; ***Significant at ≤.0001.

Table 5: Multivariable Repeated Measures Analyses of Metabolic Syndrome Components Over Time

	Waist Circumference	Fasting Blood Glucose	HDL Cholesterol	Systolic Blood Pressure
Follow-up 12-months	-1.8917***	0.1277**	0.0259	-0.3450
Follow-up 24-months	-2.2572***	0.0633	-0.0564**	0.1053
Follow-up 36-months	-1.2926***	0.2364***	-0.0239*	1.2343**
Follow-up 48-months	-1.1029**	0.3891***	0.0018	1.8762***
HTP use (ref. CC)	1.6485**	0.0510	0.0498*	0.4880
Age	0.2539*	0.0161*	0.0051**	0.1573**
Female sex (ref. Male)	10.9240***	0.3259***	-0.3020***	4.4811***
Pack years	0.1020*	0.0095*	-0.0020*	0.0558*
Caucasian ethnicity (ref. Asian)	0.8405	-0.2303***	-0.0211	1.4732**
Previous history of lung disease (ref. No)	2.2823	-0.1808	0.0857	-1.7862
Not married (ref. Yes)	-0.3053	0.0620	0.0438	-0.7506
12-months * HTP use (ref. CC)	-1.5314***	-0.0021	0.0015	-0.9322
24-months * HTP use (ref. CC)	-1.3139**	0.0116	-0.0265	-1.0572
36-months * HTP use (ref. CC)	-1.0617*	0.0005	-0.0303	-0.9176

48-months * HTP use (ref. CC)	-1.1118*	-0.0608	0.0012	-0.1546

*Significant at ≤.05; **Significant at ≤.01; ***Significant at ≤.0001.

DISCUSSION

To our knowledge, this is one of the few studies which compares the two-year effect of shifting to HTP use in a large population of long-term CC users who were unable to quit smoking. This study has shown that both HTP and CC use are associated with decline in lung function over time, HTP use was associated with a lesser decline compared to CC users during the follow-up period. This study has also demonstrated that HTP users have experienced significant over time improvements in functional health outcomes compared to CC users. The results of the study suggest that shifting to HTP use might be less deleterious compared to continuation of CC use for experienced smokers (>10 pack years) who are not able to quit the habit.

This study demonstrates that lung function decreases significantly less for participants who shifted to HTP compared to CC users over time despite that it was significantly worse for HTP users at the baseline. While improvements in the health in this cohort can be attributed to a regular access to qualified physicians running this study, HTP users showed significantly better functional outcomes, including self-reported COPD scores, exercise tolerance, and MetS, components compared to CC users. These findings are supported by the existing literature with a systematic review of 15 studies demonstrating reduced health risks associated with HTP use when compared to CC use, especially considering the potential indirect effects of CC use on the chronic diseases [15].

A meta-analysis of ten nonblinded randomized clinical trials involving a total of 1766 participants demonstrated that the levels of 12 biomarkers of exposure were significantly lower for participants assigned to HTP compared to CC use. Moreover, out of 12 biomarkers of exposure eight were statistically equivalent and four significantly elevated when HTP use was compared to smoking abstinence [16]. In another randomized study participants who shifted to HTP use (n=488) demonstrated favorable changes after six months of follow-up compared to those continued smoking their preferred cigarette brand (n=496). There were statistically significant improvements in five out of eight biomarkers for smokers who switched to HTP when compared with those who continued to smoke CC [17].

In our previous study we compared 627 CC smokers and 308 IQOS users, men and women aged between 40 and 59 residing in Almaty, Kazakhstan matched by gender, age, education, and smoking history [12]. We compared spirometry measurements, the 6MWD, components of metabolic syndrome and anthropometric measurements as a part of the baseline and one-year assessments. We observed significantly better outcomes for HTP users in most of CAT scores, spirometry outcomes, and in some metabolic syndrome components. The changes in CAT score and in spirometry FEV1 over FVC ratios were worsening at higher pace for CC smokers compared to HTP users after one year of observation.

This study has several strengths, including large sample size (n=1200), low attrition rate (25%), and measurement of the study outcomes by experienced staff. There are several limitations to this study. The major limitation is that four years follow-up is not sufficient to study the effect of shifting to HTP use on chronic conditions. The other major limitation is that the cohort participants were recruited and followed up in healthcare centers which led to significant improvements in health outcomes for both CC and HTP users. This limits generalizability of the results of this study as not everyone has access to quality healthcare. Additionally, over time decline in FEV1 and FVC observed in CC users falls within normal clinical variability and should be interpreted with caution. There might be some potential residual confounding that might explain associations reported in this study. However, the models were adjusted for important factors and the chance of significant residual confounding is low.

CONCLUSION

The results of this study demonstrate that shifting to HTP use can potentially be less deleterious that continued CC for long-term smokers. Future research should concentrate on further follow-up of this cohort to identify effects of shifting to HTP on existing and emerging chronic conditions, as well as health related measures and outcomes. While this study has shown shifting to HTP use to be less deleterious compared to CC use, the results of study should be interpreted with caution, and quitting smoking is more advisable that continuous use of CC or HTP.

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DISCLOSURE

The authors report no conflicts of interest in this work.

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