Comparative cross-sectional study between conventional and IQOS smoking and impact on fatty acid-binding protein 4

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Abstract. Smoking tobacco remains a leading global health threat, particularly in Jordan, where a notable portion of the population, including children, are smokers. Despite health campaigns, traditional smoking persists, prompting interest in the health impacts of alternatives such as heat-not-burn (HNB) devices such as 'I quit ordinary smoking' (IQOS). Examining biomarkers such as fatty acid-binding protein 4 (FABP4), a marker of early vascular and metabolic damage, may provide insight into the health outcomes of these smoking methods. The present study aimed to compare the effects of both traditional cigarette smoking and IQOS use on FABP4 levels. Venous blood samples from 204 participants (65 IQOS users, 75 conventional smokers and 64 non-smokers) were analyzed for complete blood count, alanine transaminase (ALT), C-reactive protein, superoxide dismutase (SOD) and FABP4 levels. Male cigarette smokers exhibited significantly elevated mean corpuscular volume compared with non-smokers (P=0.003), and IQOS smokers compared with non-smokers showed similar trends (P=0.035). ALT levels were significantly higher in IQOS smokers compared with both non-smokers (P<0.0001) and cigarette smokers (P=0.001). FABP4 levels were also highest in IQOS smokers, significantly surpassing both non-smokers (P<0.0001) and cigarette smokers (P=0.001). ALT and FABP4 were positively correlated (ρ=0.234, P=0.001). In the IQOS group, weight was positively correlated with hemoglobin, red blood cell count and FABP4 levels. Moreover, IQOS users who exercised had lower FABP4 levels compared with non-exercisers (P=0.001), indicating notable health marker differences associated with smoking habits, particularly among IQOS users. Smoking, whether through conventional cigarettes or alternative options such as IQOS, significantly affects blood composition, liver function indicated by high ALT and markers of oxidative stress, such as SOD. IQOS smoking significantly increases FABP4 levels, a marker of inflammation and tissue damage. To the best of our knowledge, the present study is the first to assess the impact of IQOS and smoking on FABP4.

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Introduction

Smoking tobacco is a major global health hazard, accounting for a large portion of morbidity and mortality rates accounting for ~7 million deaths in 2020, worldwide (1,2). Increasing interest has been paid to other tobacco products as a potential to replace traditional combustible cigarettes (TCCs) (3-5). There are thousands of harmful chemicals in TCCs, the majority of are listed as toxicants and carcinogens by health authorities, such as the Centers for Disease Control and Prevention and American Cancer Society (6). These include formaldehyde, hydrogen cyanide and benzene among others, as well as radioactive materials. Heating tobacco instead of burning it has been claimed to be less harmful (7), however new toxicity data mainly in the pulmonary and cardiovascular systems confirm that heated tobacco products release fewer toxic chemicals compared with traditional cigarettes, but still carry health risks due to the presence of harmful substances (8). A non-combustible alternative to TCC, including heat not burn (HNB) devices, such as 'I Quit Ordinary Smoking (IQOS™), a tobacco-heating product developed by Philip Morris International (9) and Glo manufactured by Lorillard Tobacco Company have become available, However, research is ongoing to determine the relative health advantages of these products compared with TCCs (10).

Understanding the potential effects of both traditional and new HNB devices is key. According to 2023 statistics from the Health Ministry in Jordan, 66% of males and 16% of females smoke (11), despite the numerous public health campaigns and restrictions on smoking (12). However, a 26% of smokers have switched from using TCCs to non-combustible alternatives as a healthier replacement (13). IQOS was the only HNB device available in Jordan for a number of years. This electrically heated device warms sticks filled with processed tobacco, producing a nicotine-containing aerosol that contains fewer harmful chemicals than cigarette smoke, thus rendering IQOS less harmful for consuming nicotine (13,14).

However, there is ongoing debate in the scientific community about whether IQOS is healthier than TCCs (15,16). The results of studies investigating the different effects of these two modes of smoking are inconclusive (10,11). Certain studies have shown potential detrimental effects with long-term use of HNB (10,17), while others have shown decreased exposure to harmful substances compared to conventional smoking (9). It has been indicated in previous studies that reactive carbonyls and superoxide radicals, two highly toxic substances found in mainstream smoke, but not in vapor from HNB products such as IQOS, may have potential health benefits among individuals who wish to quit or cut down on their cigarette intake due to safety concerns (18-20).

Comparative assessments on health test claims for safety improvement over risk reduction associated with IQOS. The aim of the present study was to compare traditional smoking with IQOS to determine whether the use of IQOS is less harmful health compared with traditional cigarettes. The findings may provide useful information for regulatory authorities concerned with global health care systems and development strategies, as regards the advantages and disadvantages of HNB cigarettes.

The present study aimed to compare the hematological and biochemical parameters between non-smokers and TCC and HNB smokers. These parameters are critical in clarifying the effects of smoking on health, such as complete blood count (CBC), hemoglobin (Hb) levels, hematocrit, mean corpuscular volume (MCV). In addition, the present study examined the levels of alanine transaminase (ALT), an indicator of liver health, superoxide dismutase (SOD), a key antioxidant enzyme that protects against oxidative tissue damage (20), and fatty acid-binding protein 4 (FABP4), a marker of inflammation and oxidative stress in numerous types of tissue, including lung tissue, and their association with cardiovascular risk factors, including insulin resistance and atherosclerosis (21).

Material and methods

Samples. Of 204 participants (age, 18 to 35 years, the blood samples was collected at golden hands lab in Amman, Jordan the study included 65 individuals who used IQOS, 75 who smoked TCC and 64 non-smokers. Blood samples were obtained from participants (148 male and 65 female) between November 2023 and January 2024. Inclusion criteria were no history of chronic disease, not using medications that may affect the studied parameters and not using other forms of nicotine delivery system, such as pipes, hookahs and vaping. Individuals under the age of 18 or above 35, with chronic diseases and having medication or mixing other smoking types were excluded. All participants signed a consent form. Under aseptic conditions, venous blood samples (5 ml) were collected using plain and EDTA (Greiner Bio-One) tubes. Tubes were centrifuged for 10 min at 4400 (rpm) 3,000 x g at 4˚C to obtain serum to perform FABP4, ALT and SOD assay. Serum aliquots were stored at -20˚C. Ethical approval was obtained from Al-Ahliyya Amman University (approval no. AAU/6/11/2023-2024; Amman, Jordan).

CBC. CBC was performed on the Sysmex XP-300 (Sysmex Corporation). CBC test included white blood cell (WBC) and red blood cell (RBC) counts, Hb and platelet count. In addition to measuring MCV, CBC test was performed for after running high, low and normal controls, and standards on the Sysmex analyzer to ensure the accuracy.

ALT assay. ALT levels were measured using an assay kit ALT4511 (Shenzhen Mindray Bio-Medical Electronics Co., Ltd.) and spectrophotometer (colorimetric and turbidity methods) according to the manufacturer's instructions.

FABP4 assay. FABP4 levels were assessed using a Human FABP4/A-FABP DuoSet ELISA kit DY3150-05 (Bio-Techne). A total of 100 μl/well samples or standards was covered with an adhesive strip and incubated for 2 h at room temperature (RT). Liquid was removed and 100 μl detection Ab/Ag solution was added to each well for another 2 h at RT. The plate was covered with a new adhesive strip and incubated for 2 h at RT, followed by the removal of the liquid. A total of 100 μl working dilution of Streptavidin-HRP was added to each well for 20 min at RT, followed by removing the liquid and adding 100 μl substrate solution to each well for 20 min at RT. Lastly, the reaction was stopped using 50 μl stop solution and the absorbance was read immediately at 450 nm by the microplate reader (BioTek Instruments, Inc.). Concentration of FABP4 in each sample was calculated according to the manufacturer's instructions.

SOD assay. SOD levels were determined using an Activity assay kit (cat. no. NBP3-24484 (Bio-Techne), according to the manufacturer's instructions. SOD standard curve was prepared by serially diluting the SOD standard in triplicate using 1X SOD buffer, with concentrations ranging from 0.1 to 10.0 units/25 μl. Similarly, triplicate wells containing 1X SOD buffer were prepared as activity controls. Serum was diluted in 1X SOD buffer and added to triplicate wells. A master mix was added to all wells to a total volume of 175 μl. Reactions were initiated by adding 1X xanthine solution to all wells, and absorbance readings at 450 nm were taken every minute for 10 min at RT using a plate reader. The rate of change in absorbance was determined by calculating the slope of absorbance curves against time. Finally, the percentage inhibition of the rate of increase in absorbance at 450 nm was calculated as follows: % Inhibition=(slope of 1X SOD buffer control-slope of sample)/slope of 1X SOD buffer control) x100.

Statistical analysis. Categorical variables are presented as frequency and percentage, whereas numerical variables are presented as mean ± SD or median (interquartile range) of two independent experiments. Differences in categorical variable frequencies between groups were tested using the χ^2 or Fisher's exact test depending on the expected values in each cell of the contingency table. The differences between numerical variables were tested with unpaired t-test for independent samples or Wilcoxon rank sum test after checking the normality of the distribution. One-way ANOVA or Kruskal-Wallis rank sum test followed by Holm's or Dunn's post hoc test was used to test the differences between >2 groups after checking the distribution of the values. Correlation between numerical variables was measured with Spearman correlation. All analyses and figures were produced in R version 4.3.3 R Foundation for Statistical

Table I. Demographic characteristics of the study groups.

Characteristic	Non-smoker (n=64)	Cigarettes (n=75)	IQOS™ (n=65)	Overall (n=204)	P-value
Sex (%)					
Female	39.0 (70.0)	5.0 (9.0)	12.0 (21.0)	56.0 (27.5)	<0.0001[a]
Male	25.0 (17.0)	70.0 (47.0)	53.0 (36.0)	148.0 (72.5)	
Mean age, years	23.6±4.7	25.3±5.2	25.2±3.7	24.7±4.6	0.0170[b]
Median age (IQR), years	22.5 (20.0-25.0)	24.0 (21.0-30.0)	25.0 (22.0-27.0)	24.0 (21.0-27.0)	
Age range, years (%)					
18-25	50 (38.0)	48 (36.0)	34 (26.0)	132 (65.0)	
26-35	14 (19.0)	27 (38.0)	31 (43.0)	72 (35.0)	

[a]Pearson's χ^2 test; [b]Kruskal-Wallis rank sum test. IQOS, I Quit Ordinary Smoking.

Computing, Vienna, Austria. P<0.05 was considered to indicate a statistically significant difference.

Results

Participant characteristics. The mean age of the participants was 24.7±4.6 years, ranging from 18 to 35 years (Table I). Male participants comprised 72.5% of all the subjects. Most subjects were aged between 18 and 25 years (65%). The majority of females (70%) were non-smokers, 21% were IQOS smokers or and 9% were conventional cigarette smokers. Most males were conventional cigarette smokers (47%), followed by IQOS smokers (36%). These differences in the distributions of males and females among the three groups were significant.

A total of 60.9% of the non-smokers were female, 93.3% of the conventional cigarette smokers were male and 81.5% of the IQOS smokers were male.

In addition, there was a significant difference in the mean age of subjects in the three groups. The mean age of the non-smoker group was the youngest (23.6±4.7 years vs. 25.3±5.2 years for the cigarette smokers and 25.2±3.7 for the IQOS smokers).

For the age group of 18-25 years, the highest proportions of the subjects were almost equally split between non-smokers (38%) and cigarette smokers (36%). On the other hand, the largest proportion (43%) of those aged between 26 and 35 years were IQOS smokers. The majority (78%) of the non-smoker group consisted of subjects aged between 18 and 25 years. Cigarette smokers were also mostly (64%) aged between 18 and 25 years. IQOS smokers were divided almost equally between the two age groups (18-25, 52% and 26-35 years, 48%; Table I). As the study groups significantly differed in their sex distribution and normal hematological ranges vary by sex, the hematological parameters were studied for males and females separately (22).

Hematological parameters. There were no significant differences in Hb concentration and WBC, RBC or platelet count between the study groups for males. Mean WBC count was elevated in both traditional cigarette (8.2±2.1x10^9/l) and IQOS smokers (8.2±2.4x10^9/l) compared with non-smokers (7.7±2.0x10^9/l; Table II).

Differences in MCV (mean size of RBC) between the three groups were significant for males. Male cigarette smokers had a significantly higher MCV compared with non-smokers (86.8±3.7 vs. 84.3±2.5 fl, respectively). The differences in MCV between the male cigarette and IQOS smokers were not significant. However, the difference in MCV between the male IQOS smokers (mean, 84.2±11.7; median, 85.8 fl) and non-smokers (mean, 84.3±2.5; median, 85 fl) was significant (Table II; Fig. 1A).

There were no significant differences in mean Hb concentration, mean WBC, RBC or platelet count or MCV between the study groups for females (Fig. 1B). IQOS group had the highest mean WBC count (8.6±2.6x10^9/l) compared with cigarette smokers (7.7±1.3x10^9/l) and non-smokers (8.2±2.1x10^9/l; Table III).

A total of ~20% of female non-smokers and cigarette smokers had Hb values ≥14 g/dl which is the upper limit of normal range. On the other hand, 25% of female IQOS smokers had Hb levels ≥14. However, the differences between the three groups were not significant (Table IV). Most male cigarette smokers had Hb values ≥16 (47%). A total of ~40% of non-smoker and IQOS smoking males had Hb levels ≥16. The differences in these frequencies were not significant (Table IV).

ALT. ALT levels were significantly different among the three study groups regardless of sex. IQOS smokers had the highest mean (22.6±16.6 U/l) and median ALT levels (16.6 U/l). This was significantly higher than in the non-smoker group (mean, 10.6±9.1; median, 7.7 U/l). Moreover, there was a significant difference in ALT between non-smokers and cigarette smokers (mean, 17.9±13.7; median, 16.4 U/l). There was no significant difference in ALT between cigarette and IQOS™ smokers (Table V; Fig. 2A).

SOD. There was no significant difference between the three study groups in the levels of SOD. The overall mean SOD value was 138.2±59.2 U/ml (Table V; Fig. 2B).

FABP4. The three smoking status groups differed significantly in the levels of FABP4. The IQOS group had the highest mean (421.8±356 ng/ml) and median (376 ng/ml) levels.

Table II. Hematological parameters for the males in the study groups.

Parameter	Non-smoker (n=25)	Cigarettes (n=70)	IQOS™ (n=53)	Overall (n=148)	Normal range	P-value
Mean Hb, g/l	155.2±10.1	158.9±9.4	157.5±10.1	157.8±9.8	140.0-	0.341[a]
Median Hb (IQR), g/l	156.0 (145.0-166)	159.0 (153.0-162.0)	155 (150-164)	157.0 (152.0-163.0)	180.0	
Mean WBC, $x10^9$/l	7.7±2.0	8.2±2.1	8.2±2.4	8.1±2.2	4.5-11.0	0.598[b]
WBC (IQR), $x10^9$/l	7.9 (6.4-9.1)	8.0 (6.7-10.0)	8.3 (6.4-9.7)	8.1 (6.4-9.8)	4.7-6.1	0.778[a]
Mean RBC, $x10^6/\mu$l	5.3±0.5	5.3±0.4	5.4±0.4	5.3±0.4		
Median RBC (IQR), $x10^6/\mu$l	5.4 (4.9-5.6)	5.4 (5.1-5.6)	5.4 (5.1-5.6)	5.4 (5.1-5.6)		
Mean MCV, fl	84.3±2.5	86.8±3.7	85.7±5.5	85.4±7.6	80.0-96.0	0.004[a]
Median MCV (IQR), fl	85.0 (82.8-85.3)	86.9 (85.1-88.9)	86.0 (83.7-89.4)	86.0 (83.7-88.8)		
Mean platelet count, cells/μl	271.8±56.6	268.0±67.4	264.1±67.6	267.3±65.4	150.0-	0.807[a]
Median platelet count (IQR), cells/μl	274.0 (218.0-318.0)	259.0 (223.0-299.0)	265.0 (205.0-320.0)	262.0 (214.0-312.0)	400.0	

[a]Kruskal-Wallis rank sum test; [b]one-way analysis of variance. IQOS, I Quit Ordinary Smoking; Hb, hemoglobin; WBC, White blood cell; RBC, Red blood cell; MCV, Mean corpuscular volume.

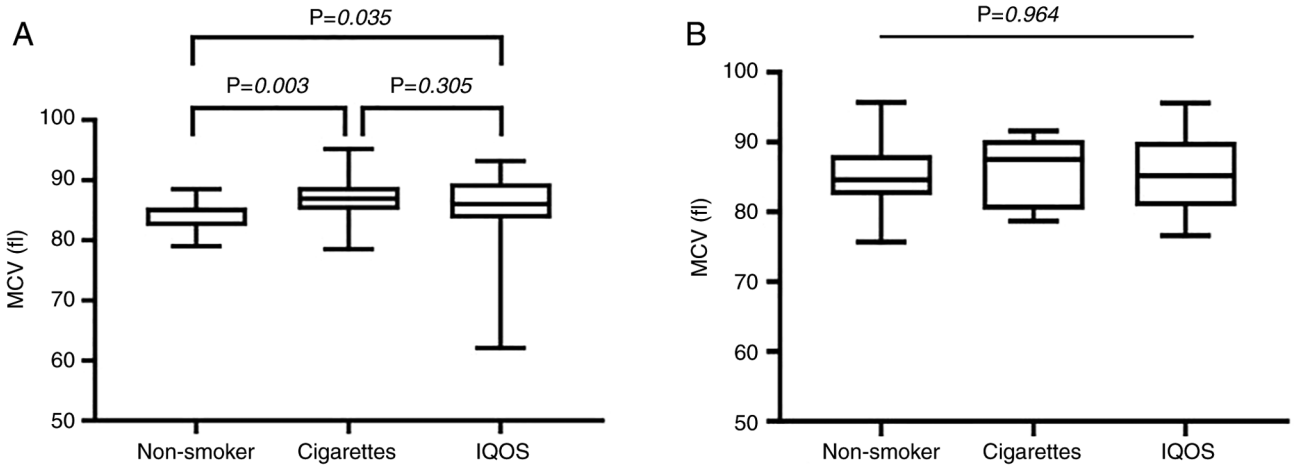

Figure 1. MCV levels. MCV for (A) male and (B). MCV for the Females. P-values are from post hoc Dunn's pairwise tests. fl, femtoliter; MCV, Mean corpuscular volume; IQOS, I Quit Ordinary Smoking.

This was significantly higher than in the non-smoker group (mean, 269.5±119; median, 234 ng/ml). Moreover, cigarette smokers also had significantly higher levels of FABP4 (mean, 348.0±135.0; median, 321 ng/ml) than non-smokers (Table V; Fig. 2C).

There was a positive association between ALT and FABP4 for the entire study population. Levels of FABP4 increased with increasing ALT. The correlation was moderate (ρ=0.234) and significant (Fig. 3A). There was no correlation between levels of FABP4 and SOD for the study population (ρ=0.005; Fig. 3B).

The mean weight in the IQOS smoking group was 77.3±19.0 kg. The members of this group had been smoking on average for 2.9±1.1 years. The majority of the IQOS smokers (66.2%) smoked ≥1 packs/day. Moreover, 52.3% of the group reported that they engage in some form of exercise (Table VI).

Hb was positively correlated with the weight of the male IQOS group (ρ=0.318). FABP4 increased with increasing weight of the IQOS group (ρ=0.415; Table VII). On the other hand, SOD was strongly correlated with the weight of the female IQOS smokers (ρ=0.606; Table VIII).

IQOS smokers with higher daily consumption had been smoking for longer periods of time. Daily consumption was not significantly associated with hematological parameters or ALT, SOD or FABP4 levels (Table IX).

No significant differences were found between the IQOS smokers who reported exercising and those who reported no exercising except for FABP4 (P=0.001). The mean FABP4 levels in the group who exercise was lower (342.2±148.3 vs.

Table III. Hematological parameters for the females in the study groups.

Parameter	Non-smoker (n=39)	Cigarettes (n=5)	IQOS™ (n=12)	Overall (n=56)	Normal range	P-value
Mean Hb, g/l	133.0±8.7	131.4±8.6	130.8±12.1	132.4±9.4	120.0-	0.987[a]
(IQR), g/l	132.0 (127-138)	131.0 (130.0-138.0)	133.0 (129.0-138.0)	132.0 (127.0-138.0)	160.1	
Mean WBC, x10^9/l	8.2±2.1	7.7±1.3	8.6±2.6	8.2±2.1	4.5-11.0	0.710[b]
Median WBC (IQR), x10^9/l	8.2 (7.0-9.4)	7.7 (6.9-8.5)	8.2 (7.3-9.9)	8.1 (7.1-9.5)		
Mean RBC, x10^6/μl	4.7±0.3	4.6±0.2	4.7±0.3	4.7±0.3	4.7-6.1	0.848[a]
Median RBC (IQR), x10^6/μl	4.7 (4.5-5.0)	4.6 (4.5-4.6)	4.7 (4.5-5.0)	4.6 (4.5-5.0)		
Mean MCV	85.3±4.3	85.8±5.3	85.1±5.8	85.3±4.7	80.0-96.0	0.964[b]
Median MCV (IQR), fl	84.6 (82.5-88.0)	87.5 (82.0-89.0)	85.2 (81.0-88.9)	84.9 (82.0-88.4)		
Mean platelet count, cells/μl	315.9±67.8	302.8±23.8	304.3±41.9	312.3±60.0	150.0-	0.833[a]
Median platelet count (IQR), cells/μl	317.0 (268.0-356.0)	300.0 (298.0-316.0)	313.0 (286.0-329.0)	317.0 (276.0-353.0)	400.0	

[a]Kruskal-Wallis rank sum test; [b]one-way analysis of variance. IQOS, I Quit Ordinary Smoking; Hb, hemoglobin; WBC, White blood cell; RBC, Red blood cell; MCV, Mean corpuscular volume.

Table IV. Participants with high and low Hb values.

Group	Non-smoker	Cigarettes	IQOS™	P-value
Female (%)				
Hb <14 g/dl	31 (79)	4 (80)	9 (75)	0.875[a]
Hb ≥14 g/dl	8 (21)	1 (20)	3 (25)	
Male (%)				
Hb <16 g/dl	15 (60)	37 (53)	31 (58)	0.750[b]
Hb ≥16 g/dl	10 (40)	33 (47)	22 (42)	

[a]Fisher's exact test; [b]Pearson's χ^2 test. Hb, hemoglobin; IQOS, I Quit Ordinary Smoking.

509.0±227.5 ng/ml) than in the group who do not exercise (Table X).

Discussion

Despite the well-established health hazards associated with smoking, numerous individuals, particularly young people, have switched to alternatives, such as IQOS, considering it to be a safer option as IQOS provides nicotine without the harmful effects of combustion typically associated with traditional cigarettes (21,23). However, the safety of IQOS remains a contentious issue, as increasing research (23,24) suggests that its use may still be associated with substantial health risks. To the best of our knowledge, the effects of the use of IQOS compared with traditional cigarette smoking have not yet been comprehensively studied. The present study included younger individuals because they are less likely to have transitioned from conventional cigarettes to IQOS. Since individuals who mostly switch from conventional cigarettes to IQOS may experience persistent effects from long-term traditional smoking, potentially mask the effects associated with IQOS use. Thus, by selecting participants at earlier stages of smoking behavior, we aimed to isolate the specific impact of IQOS on the measured health indicators (25).

Smoking alters hematological parameters, including RBC count, Hb, hematocrit, MCV and MCHC (26). Hematocrit levels are typically elevated in smokers due to increased RBC production in response to hypoxia, which may increase blood viscosity and cardiovascular risks (27). In the present study, while smokers exhibited higher levels of these hematological markers mainly Hb, no significant differences were found between cigarette smokers, IQOS users and non-smokers, potentially due to the young age and short duration of smoking status of the participants.

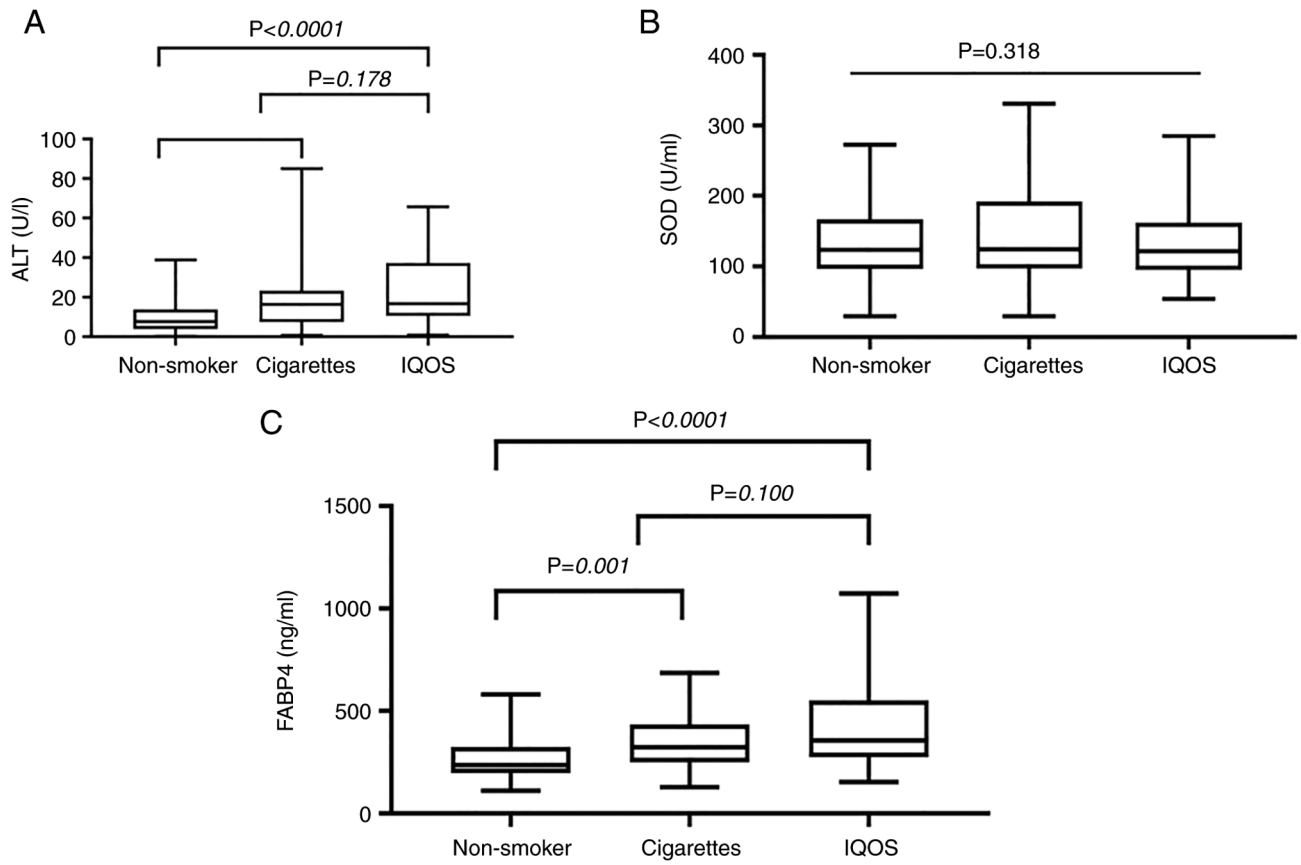

Figure 2. Marker levels in the smoking status groups. Levels of (A) ALT, (B) SOD and (C) FABP4. P-values are from post hoc Dunn's pairwise test. ALT, alanine transaminase; SOD, superoxide dismutase; FABP4, fatty acid-binding protein 4.

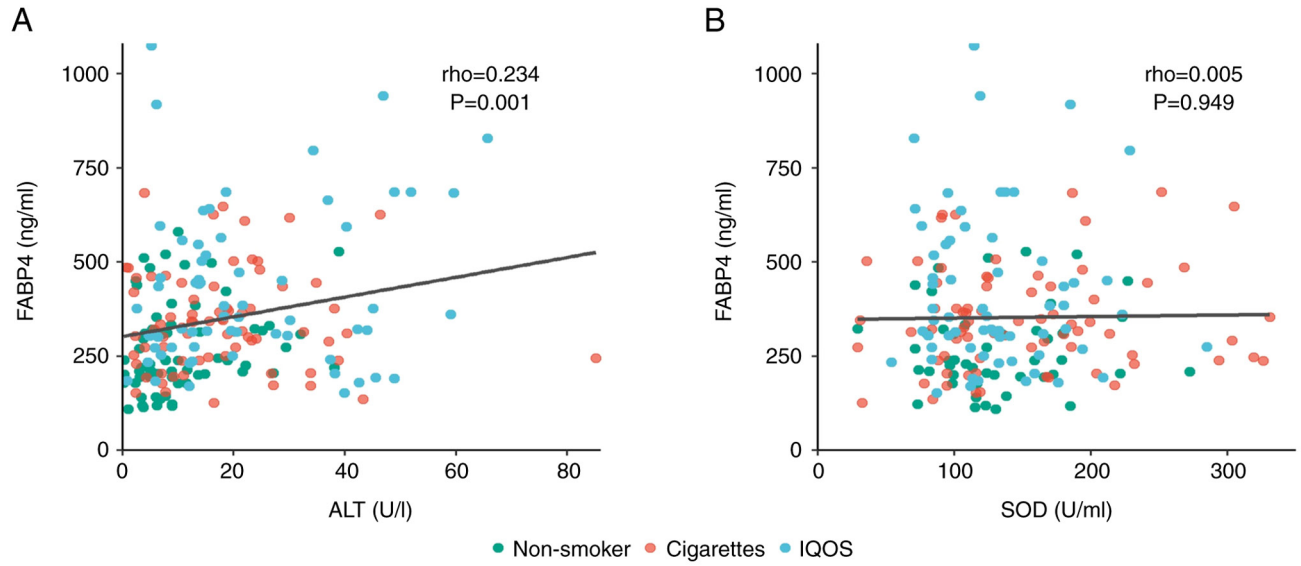

Figure 3. Scatterplots for FABP4. Correlation between FABP4 and (A) ALT (ρ=0.234) and (B) SOD (ρ=0.005). P-values are from Spearman correlation tests. FABP4, fatty acid-binding protein 4; ALT, alanine transaminase; IQOS, I Quit Ordinary Smoking; SOD, superoxide dismutase.

MCV tends to be higher in smokers, potentially due to smoking-related toxins affecting bone marrow function, resulting in larger red blood cells (28). In the present study, male smokers exhibited a significantly higher MCV than non-smokers; however, no significant difference was found between cigarette smokers and IQOS users. This suggested that while the effect of smoking on MCV is evident in traditional smokers, the impact of IQOS on this parameter may be less pronounced; however, further investigations are required. Female participants exhibited no significant differences in hematological parameters, which may be due to small number of participants in the conventional cigarette group, although

Table V. Marker levels.

Parameter	Non-smoker (n=25)	Cigarettes (n=70)	IQOS™ (n=53)	Overall (n=148)	Normal range	P-value[a]
Median ALT (IQR), U/l	10.6±9.1 7.7 (4.0-13.7)	17.9±13.7 16.4 (7.6-23.2)	22.6±16.6 16.6 (10.7-37.0)	17.1±14.3 13.2 (6.5-22.8)	<45.0	<0.0001
Mean SOD, U/ml	130.7±49.1	149.9±72.5	130.1±45.9	138.2±59.2	110-215	0.3180
Median SOD (IQR), U/ml	123.0 (97.0-164.0)	125.0 (101.0-190.0)	121.0 (96.0-160.0)	123.0 (96.0-171.0)		
Median FABP4 (IQR), ng/ml	269.5±119 234.0 (196.0-322.0)	348±135 321.0 (249.0-435.0)	421.8±206.5 356.0 (273.0-547.0)	346.9±167.8 313.0 (224.0-442.0)	Not applicable	<0.0001

[a]Kruskal-Wallis rank sum test. IQOS, I Quit Ordinary Smoking; ALT, alanine transaminase; SOD, superoxide dismutase; FABP4, fatty acid-binding protein 4.

Table VI. Weight and smoking habits of the I Quit Ordinary Smoking group.

Variable	Value (n=65)
Mean weight, kg	
Male	81.6±17.6
Female	58.6±12.7
Mean duration of smoking, years	2.9±1.1
Daily consumption, packs (%)	
<1	22.0 (33.8)
≥1	35.0 (66.2)
Exercise (%)	
Yes	34.0 (52.3)
No	31.0 (47.7)

Table VII. Correlation between body weight of male I Quit Ordinary Smoking users with hematological parameters and markers.

Variable	Correlation coefficient	P-value
Hb	0.318	0.020
WBC	0.011	0.936
RBC	0.270	0.051
MCV	-0.142	0.312
Platelet count	0.095	0.498
ALT	0.088	0.534
SOD	0.055	0.700
FABP4	0.415	0.002

Hb, hemoglobin; WBC, White blood cell; RBC, Red blood cell; MCV, Mean corpuscular volume; ALT, alanine transferase; SOD, superoxide dismutase; FABP4, fatty acid-binding protein 4.

Table VIII. Correlation between body weight of female I Quit Ordinary Smoking users with hematological parameters and markers.

Variable	Correlation coefficient	P-value
Hb	0.228	0.475
WBC	0.368	0.239
RBC	-0.116	0.719
MCV	0.481	0.114
Platelet count	0.263	0.409
ALT	-0.007	0.983
SOD	0.606	0.048
FABP4	-0.039	0.905

Hb, hemoglobin; WBC, White blood cell; RBC, Red blood cell; MCV, Mean corpuscular volume; ALT, alanine transaminase; SOD, superoxide dismutase; FABP4, fatty acid-binding protein 4.

there was a notable difference in MCV between IQOS users and non-smokers.

Smoking triggers systemic inflammation, typically reflected in elevated WBC counts and changes in leukocyte subtype, which can indicate generalized infection or inflammation (29). While the present study found an increased WBC count in smokers, no significant difference was observed compared with non-smokers, which may be attributed to the relatively short smoking duration of the participants. Previous research has demonstrated that smokers with longer duration of smoking tend to have significantly higher WBC count (30).

The present study demonstrated significant differences in serum ALT levels among the three groups. IQOS users exhibited the highest mean serum ALT levels, followed by cigarette smokers, with non-smokers exhibiting the lowest levels. This suggested that smoking, including the use of alternative devices, such as IQOS, may affect liver function. Similar findings have been reported in previous studies, which

Table IX. Hematological parameters and markers for the I Quit Ordinary Smoking group by daily consumption.

Variable	Daily consumption, packs		P-value
	<1 (n=22)	≥1 (n=43)	
Mean duration of smoking, years	2.4±1.1	3.2±1.0	0.005[a]
Mean Hb, g/l	150.7±18.3	153.5±12.6	0.527[b]
Mean WBC count, x10^9/l	8.0±2.3	8.5±2.5	0.432[c]
Mean RBC count, x10^6/μl	5.3±0.4	5.3±0.5	0.889[c]
Mean MCV, fl	85.1±4.2	85.8±6.1	0.292[a]
Mean platelet count, cells/μl	261.5±64.0	276.6±66	0.308[a]
Mean ALT levels, U/l	24.0±15.7	21.9±17.1	0.621[a]
Mean SOD levels, U/ml	122.1±43.0	133.8±47.2	0.392[a]
Mean FABP4 levels, ng/ml	349.6±136.6	458.7±227.0	0.076[a]

[a]Wilcoxon rank sum test; [b]Welch two sample t-test; [c]two sample t-test. Hb, Hemoglobin; WBC, White blood cell; RBC, Red blood cell; MCV, Mean corpuscular volume; ALT, alanine transaminase; SOD, superoxide dismutase; FABP4, fatty acid-binding protein 4.

Table X. Hematological parameters and markers for the I Quit Ordinary Smoking group by exercise habit.

Variable	Exercise (n=34)	No exercise (n=31)	P-value
Mean duration of smoking, years	2.7±1.1	3.1±1.1	0.126[a]
Mean Hb, g/l	152.4±16.2	152.7±13.1	0.875[a]
Mean WBC count, x10^9/l	8.6±2.8	8.0±1.9	0.336[b]
Mean RBC count, x10^6/μl	5.3±0.6	5.3±0.4	0.906[c]
Mean MCV, fl	85.0±6.6	86.2±4.1	0.604[a]
Mean platelet count, cells/μl	262.7±58.8	281.1±71.3	0.237[a]
Mean ALT levels, U/l	24.2±15.7	20.9±17.6	0.236[a]
Mean SOD levels, U/ml	128.3±42.8	132.2±50.0	0.918[a]
Mean FABP4 levels, ng/ml	342.2±148.3	509.0±227.5	0.001[a]

[a]Wilcoxon rank sum test; [b]Welch two sample t-test; [c]two sample t-test. Hb, hemoglobin; WBC, White blood cell; RBC, Red blood cell; MCV, Mean corpuscular volume; ALT, alanine transaminase; SOD, superoxide dismutase; FABP4, fatty acid-binding protein 4.

emphasize ALT as a valuable marker for liver damage (31,32). Although ALT levels alone cannot diagnose liver disease, they offer high specificity and sensitivity for detecting liver injury, particularly in the context of smoking (33).

SOD is a key antioxidant enzyme that protect cells from oxidative damage. While certain studies have reported significantly elevated SOD levels in smokers due to the adaptive response of the body to increased levels of oxidative stress (33,34). The present study did not reveal significant differences in SOD levels between the smoking and non-smoking groups. This inconsistency may be due to varying methods of measurement, smoking duration or the adaptive mechanisms of the body in response to chronic smoking (35,36).

FABP4 is a key protein involved in lipid metabolism and inflammation. Elevated levels of FABP4 are associated with metabolic abnormality, including insulin resistance, obesity and cardiovascular disease (37,38). The present study found that both cigarette smokers and IQOS users had higher levels of FABP4 compared with non-smokers, with a positive correlation between FABP4 and ALT levels, suggesting a potential association between increased FABP4 levels and liver damage. This is supported by research indicating that cigarette smoke elevates FABP4 levels, which may contribute to tissue inflammation and damage (39,40). Further studies are required to assess the role of FABP4 as a potential biomarker for smoking-associated disease, particularly liver damage. On the other hand, certain biomarkers, including carboxyhemoglobin and certain urinary metabolites like 3-hydroxypropyl mercapturic acid and S-phenylmercapturic acid, have been reported at lower levels in users of heated tobacco products (HNB) compared with conventional cigarette smokers, suggesting a relative reduction in exposure to specific toxicants (41,42).

The present study also revealed notable associations among IQOS smokers. The positive correlation between ALT and FABP4 levels suggested that the use of IQOS may lead to liver damage, similar to traditional cigarette smoking. Additionally, the daily consumption of IQOS was positively associated with both weight and smoking duration, highlighting the cumulative effects of smoking intensity over time. Of note, a number of IQOS smokers also engaged in physical activity showed significant decrease in FABP4 levels, suggesting a potential mitigating factor in decreasing smoking-associated health risks.

Furthermore, the association between Hb, RBC count and weight suggests that certain physiological adaptations may occur in response to smoking, potentially to compensate for the negative effects of smoking on the cardiovascular system. These findings underscore the need for a holistic approach when assessing the health impacts of smoking alternatives, considering both smoking behavior and lifestyle choices.

While the present study provided insight into the impact of IQOS and conventional smoking on FABP4 levels, there were limitations. The study included 204 participants, which may be suitable for preliminary findings, but still limits the

generalizability of the results to broader populations. Future studies should use larger and more diverse cohorts to confirm these findings. Additionally, FABP4 levels are influenced by various metabolic conditions, which need to be controlled in the study. Incorporating additional biomarkers such as C reactive protein, TNF-α, and IL-6 in future studies may offer a more comprehensive assessment of inflammation and metabolic impact.

The present study highlighted the complex and multifaceted effects of smoking, including the use of alternatives, such as IQOS, on health markers. While IQOS may be perceived as a safer alternative to traditional cigarettes, it may affect liver function, specifically the positive correlation between ALT and FABP4 levels, which may indicate its risk to liver health, hematological parameters and metabolic health. Further research is warranted to explore the long-term effects of IQOS and other smoking alternatives on health, particularly among young users, and to develop strategies for mitigating the health risks associated with smoking in all forms.

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Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

LEM and MMA confirm the authenticity of all the raw data. LEM designed the study, analyzed data and wrote the manuscript. MMA conceived and designed the study, analyzed data and wrote, reviewed and edited the manuscript. SZ analyzed data and reviewed and edited the manuscript. BAAM performed the experiments and reviewed and edited the manuscript. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

The present study was approved by Al-Ahliyya Amman University (approval no. AAU/6/11/2023-2024; Amman, Jordan). All participants gave written informed consent before participation.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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