Iran J Public Health, Vol. 54, No.12, Dec 2025, pp.2701-2711

Original Article

Effect of I Quit Ordinary Smoking (IQOS) Use on Hepcidin and Iron Parameters in Comparison with Conventional Smoking

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(Received 16 Jul 2025; accepted 03 Oct 2025)

Abstract

Background: IQOS (I Quit Ordinary Smoking) has been introduced as a "safer" alternative to traditional tobacco smoking. We aimed to determine how heated tobacco products influence iron metabolism by examining the impact of IQOS use and conventional cigarette smoking on hepcidin and iron-related parameters.

Methods: In this cross-sectional study, an iron panel and hepcidin levels were measured in participants who were using IQOS for at least six months and compared with those of conventional smokers or non-smokers.

Results: A total of 185 adults (18-40 years) of both sexes participated in the study, including 80 IQOS users, 49 cigarette smokers and 56 non-smokers. No significant differences were found in hemoglobin level, red blood cell count, mean corpuscular volume, white blood cell count, platelet count or total iron level between IQOS users and non-smokers in both sexes. However, ferritin levels were significantly higher in male IQOS users compared to non-smokers (P=0.022). Hepcidin levels were markedly higher in IQOS users (375.77 ± 98.59 pg/mL) compared with cigarette smokers (26.35 ± 8.81 pg/mL; P = 0.0001) and non-smokers (31.27 ± 7.78 pg/mL; P = 0.0001). No significant difference in unsaturated iron-binding capacity, total iron-binding capacity or transferrin saturation was found between IQOS users compared to non-smokers.

Conclusion: IQOS use was associated with significantly elevated hepcidin levels and higher ferritin in males, suggesting a potential disruption of iron regulation compared to conventional smokers and non-smokers.

Keywords: Ferritin; Heated tobacco products; Hepcidin; Smoking

Introduction

Tobacco smoking is one of the most significant public health problems worldwide, leading to an estimated 7.3 million deaths in 2021 (1). Smoking has long been recognized as a leading cause of chronic diseases, including cardiovascular disease, chronic obstructive pulmonary disease (COPD), and various cancers such as those of the lung, mouth, and esophagus (2-5). Moreover, smoking adversely affects non-smokers through exposure to second-hand smoke, further exacerbating its impact on public health (6).

Heated tobacco products such as IQOS (I Quit Ordinary Smoking) have been introduced as a "safer" alternative to traditional tobacco smoking. IQOS, launched by Philip Morris International in 2014, employs a battery-powered heating blade that warms processed tobacco sticks (HEETS) to approximately 350 °C, producing

DOI: https://doi.org/10.18502/ijph.v54i12.20822

aerosols containing nicotine and other chemicals while avoiding combustion (7). In recent years, the use of heated tobacco devices has increased because there is no side smoke emission, in addition to the belief that they are less harmful than traditional smoking (8). While IQOS may reduce exposure to certain toxicants compared to cigarettes, it also increases exposure to other toxicants with unknown health effects (9). Independent studies have indicated that heated tobacco products are less toxic and have fewer health risks than conventional smoking (10). Paradoxically, other studies have suggested that heated tobacco products have similar health consequences to conventional smoking cigarettes, prominently an increased risk of respiratory and cardiovascular disease and hepatotoxicity (11-13).

Iron is an essential trace element involved in critical biological functions such as oxygen transport, DNA synthesis, and enzymatic reactions (14). Its dysregulation can lead to the production of reactive oxygen species (ROS) through the Fenton reaction, further exacerbating oxidative damage (15). Hepcidin, a liver-derived hormone, is the central regulator of iron metabolism, controlling dietary absorption and release from stores. Altered hepcidin levels have been reported in smokers, likely driven by inflammation, hypoxia, and oxidative stress, leading to iron imbalance (16).

Conventional smoking has been shown to lower serum hepcidin through hypoxia-induced erythropoiesis while simultaneously promoting tissue iron accumulation and oxidative stress (16, 17). In contrast, IQOS use may activate distinct inflammatory and oxidative pathways (18), potentially exerting unique effects on hepcidin regulation. Because hepcidin integrates signals from inflammation, iron status, and erythropoiesis, evaluating its regulation in IQOS users compared with smokers is critical to understanding differential effects on iron balance and clinical outcomes.

This study addressed the lack of scientific data on how heated tobacco products influence iron metabolism by examining the impact of IQOS use and conventional cigarette smoking on hepcidin and iron-related parameters. By filling this knowledge gap, it provides essential insights into whether IQOS poses unique risks for iron regulation and associated health outcomes. Parallel assessment of iron parameters further clarifies the extent of dysregulation, with potential implications for anemia risk, systemic oxidative injury, harm-reduction strategies, and clinical monitoring.

Materials and Methods

Study design and participants

This cross-sectional study was conducted between June and September 2024. Participants included healthy individuals aged 18–40 years, stratified into three groups: IQOS users, conventional cigarette smokers, and non-smokers (control group). Inclusion criteria for smokers required consistent use of either IQOS or conventional cigarettes for a minimum of six months. Exclusion criteria included the presence of immunological or hematological disorders, recent iron supplementation or blood transfusion (within the past three months), and the simultaneous use of more than one type of smoking. For women, pregnancy, lactation, or menorrhagia led to exclusion. Additionally, all shisha smokers were excluded.

Ethical approval was obtained from the Al-Ahliyya Amman University Ethics Committee (Decision No. AAU/3/20/2023-2024). Written informed consent was secured from all participants. Demographic and lifestyle information, including age, sex, presence of diseases, iron supplementation, blood transfusion, dietary habits and smoking patterns were collected through a questionnaire.

Sample collection and biochemical analysis

Venous blood samples were drawn under sterile conditions. Two milliliters of blood were collected in EDTA tubes and analyzed immediately using the Sysmex XP-300 analyzer (Germany) for measuring hemoglobin, platelet count, WBC count and RBC count. For serum, clot activator tubes were centrifuged at 3500 rpm for 10

minutes, and serum aliquots were stored at –80 °C for further analysis.

Biochemical tests

Hepcidin levels were measured using a sandwich ELISA kit (R&D Systems, USA). The assay involved incubation of standards and samples with biotin-conjugated antibodies and detection using a horseradish peroxidase-streptavidin system. Optical density was read at 450 nm.

Serum iron, ferritin, and unsaturated iron-binding capacity (UIBC) were assessed using an automated analyzer (Mindray BS-200, China). Total iron-binding capacity (TIBC) was calculated as serum iron + UIBC. Transferrin saturation was calculated according to the formula: Transferrin saturation = (serum iron/TIBC) × 100.

Statistical analysis

Data were analyzed using SPSS version 26.0 (IBM Corp., Armonk, NY, USA) and presented as mean ± standard deviation. The Kolmogorov-Smirnov test assessed data normality. Kruskal-Wallis tests compared mean values across groups followed by Bonferroni adjustment for multiple testing. Spearman correlation coefficients evaluated relationships between variables. Statistical significance was set at $P<0.05$.

Results

This study involved 185 participants who belonged to one of three groups. The first group consisted of 80 IQOS users (53 males and 27 females); the second group consisted of 49 (36 males and 13 females) conventional cigarette smokers and the third group consisted of 56 non-smokers (30 males and 26 females) as a control group.

Effect of smoking type on Hb, RBC and MCV

In males, no significant difference in the distribution of red blood cells (RBC) or mean corpuscular volume (MCV) was observed across smoking groups (Table 1, Fig. 1). On the other hand, cigarette smokers had significantly higher hemoglobin (Hb) levels compared to non-smokers ($P=0.036$) while there was no significant difference between non-smokers and IQOS users or between IQOS users and cigarette smokers in Hb levels ($p>0.05$) (Fig. 1). In females, no significant difference in Hb, RBC and MCV was found between the three groups (Table 1, Fig. 1).

Table 1: Comparison of hemoglobin, red blood cells, and mean corpuscular volume in males and females across the three study groups: Non-smokers, IQOS users, and cigarette smokers. Data are presented as mean ± standard deviation. HB: Hemoglobin (g/dL); RBC: Red Blood Cells ($\times 10^{12}$/L); MCV: Mean Corpuscular Volume (fL)

Variable	Males				Females			
	IQOS (n =53)	Cigarette (n =36)	Non-smokers (n =30)	*P*	IQOS (n = 27)	Cigarette (n = 13)	Non-smokers (n = 26)	*P*
Hb (g/L)	15.60 ± 0.97	16.15 ± 1.10	15.54 ± 1.16	0.022	12.96 ± 0.96	13.48 ± 1.21	13.47 ± 0.82	0.134
RBCs ($\times 10^{12}$/L)	5.43 ± 0.48	5.52 ± 0.50	5.57 ± 0.48	0.388	4.62 ± 0.34	4.61 ± 0.35	4.76 ± 0.27	0.157
MCV (femtoliters)	84.82 ± 6.79	84.99 ± 7.44	82.72 ± 7.04	0.334	86.93 ± 6.95	86.56 ± 5.84	84.23 ± 4.94	0.320

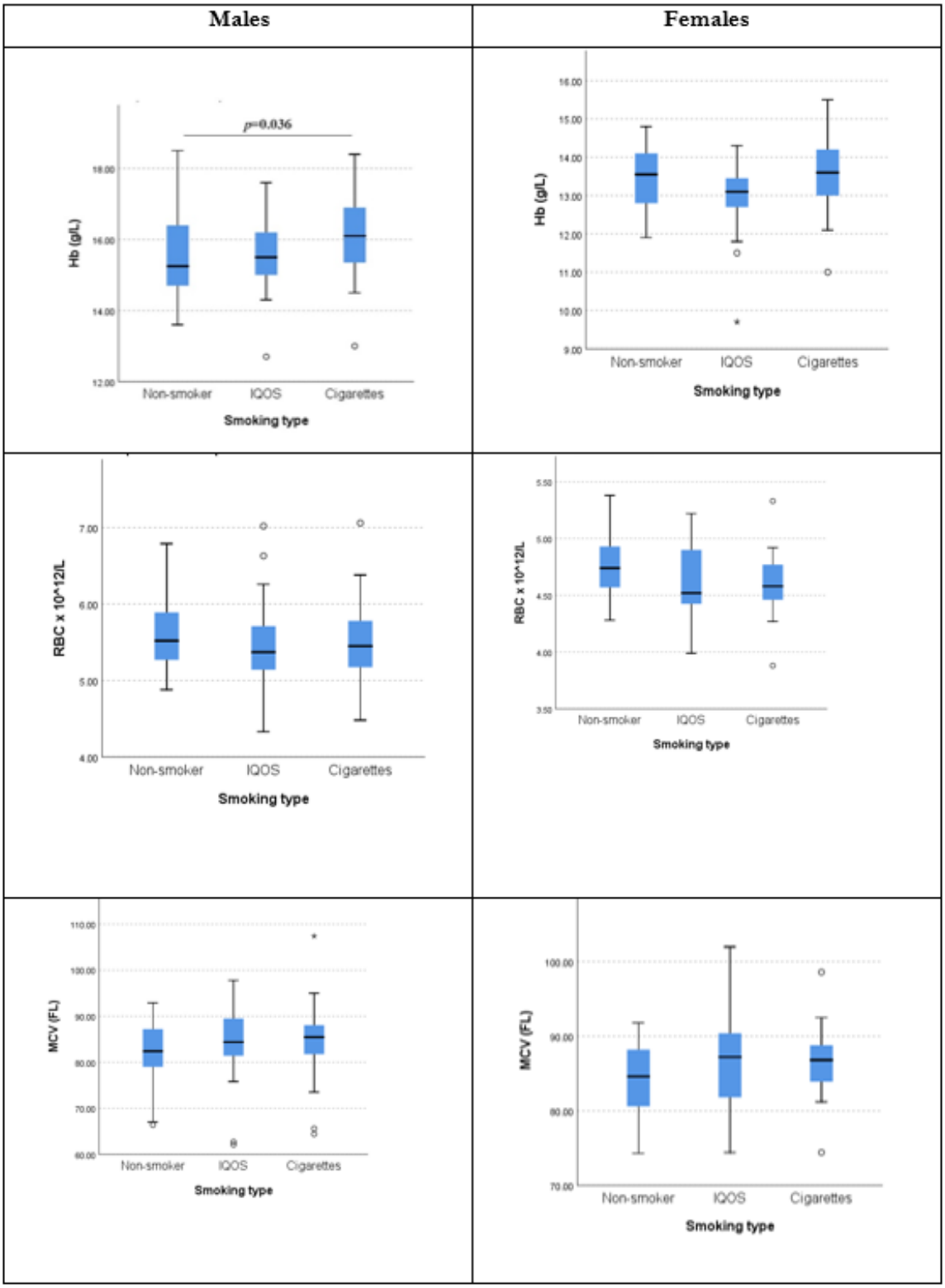

Fig. 1: Comparison of hemoglobin, red blood cells, and mean corpuscular volume in males and females across the three study groups: Non-smokers, IQOS users, and cigarette smokers. Data are presented as mean ± standard deviation. Hb: Hemoglobin (g/dL); RBC: Red Blood Cells ($\times 10^{12}$/L); MCV: Mean Corpuscular Volume (fL)

Effect of smoking type on WBC and platelets

Our analysis showed no significant differences in white blood cells (WBC) counts for both sexes between the three groups (P = 0.371). On the other hand, a significant difference in platelet count among the three groups was found (P = 0.039). Platelet levels were significantly lower in cigarette smokers than non-smokers (P = 0.016). However, no significant difference was observed between IQOS users and non-smokers (P = 0.061) or IQOS users and cigarette smokers (P = 1.000).

Effect of smoking type on iron parameters

In males, no significant difference was found in iron level across smoking types (P = 0.362). On the other hand, significantly higher ferritin levels in IQOS users were observed compared to non-smokers (P = 0.022). Despite that cigarette smokers had higher ferritin levels than non-smokers, this difference was not significant (P = 0.193). Also, ferritin level was not significantly different between IQOS users and cigarette smokers (Table 2, Fig. 2). In females, no significant differences were observed in serum iron or ferritin levels between different groups (Table 2, Fig. 2).

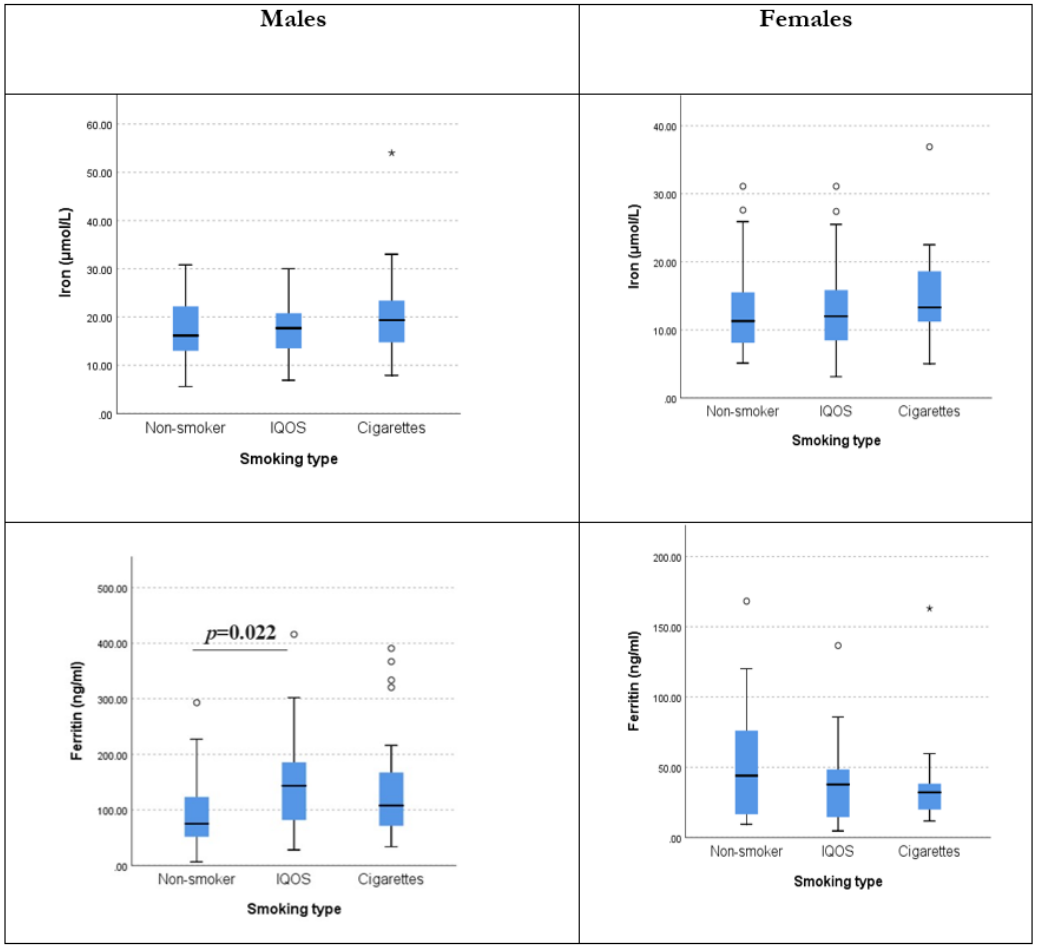

Fig. 2: Comparison of iron and ferritin levels in males and females across the three study groups: Non-smokers, IQOS users, and cigarette smokers. Data are presented as mean ± standard deviation.

Table 2: Comparison of iron and ferritin levels in males and females across the three study groups: Non-smokers, IQOS users, and cigarette smokers. Data are presented as mean ± standard deviation

Variable	Males				Females			
	IQOS (n =53)	Cigarette (n =36)	Non-smokers (n =30)	*P*	IQOS (n = 27)	Ciga-rette (n = 13)	Non-smokers (n = 26)	*P*
Iron (µmol/L)	17.78 ± 5.13	20.09 ± 8.53	17.34 ± 6.50	0.362	13.68 ± 7.23	15.48 ± 7.86	13.38 ± 7.17	0.520
Ferritin (ng/ml)	142.80 ± 80.73	135.87 ± 91.96	98.32 ± 69.31	0.026	38.72 ± 29.81	40.29 ± 39.34	52.85 ± 40.90	0.366

IQOS users had significantly lower UIBC compared to cigarette smokers (P = 0.001) while no significant difference was found between cigarette smokers and non-smokers or IQOS users and non-smokers in UIBC levels (Fig. 3). Similarly, a significantly lower TIBC in IQOS users compared to cigarette smokers (P = 0.0001) while no significant difference was found between cigarette smokers and non-smokers or IQOS users and non-smokers in TIBC level (Fig. 3).

Hepcidin levels revealed highly significant differences between cigarette smokers and IQOS users (P = 0.0001) and between non-smokers and IQOS users (P= 0.0001) (Fig. 3). UIBC levels revealed significantly higher UIBC level in cigarette smokers compared to IQOS users (P = 0.001) while no significant difference between non-smokers and IQOS users or non-smokers and cigarette smokers was found. TIBC levels revealed significantly higher values in cigarette smokers compared to IQOS users (P = 0.0001) while no significant difference between non-smokers and IQOS users or non-smokers and cigarette smokers was found (Fig. 3). On the other hand, no significant difference in transferrin saturation percent was found between the three groups (Table 3).

Table 3: Comparison of total iron-binding capacity (TIBC), unsaturated iron-binding capacity (UIBC), Transferrin saturation percentage and hepcidin in males and females across the three study groups: Non-smokers, IQOS users, and cigarette smokers. Data are presented as mean ± standard deviation

Variable	IQOS (n =80)	Cigarette (n =49)	Non-smokers (n =56)	*P*
TIBC (µmol/L)	80.31±22.24	94.08±34.70	89.90±22.89	0.0001
UIBC (µmol/L)	63.86±22.85	75.08±36.54	74.05±24.27	0.001
Transferrin saturation %	21.79±9.85	25.18±16.42	18.73±10.18	0.150
Hepcidin (pg/ml)	375.77±98.59	29.56±7.50	31.27±7.78	0.0001

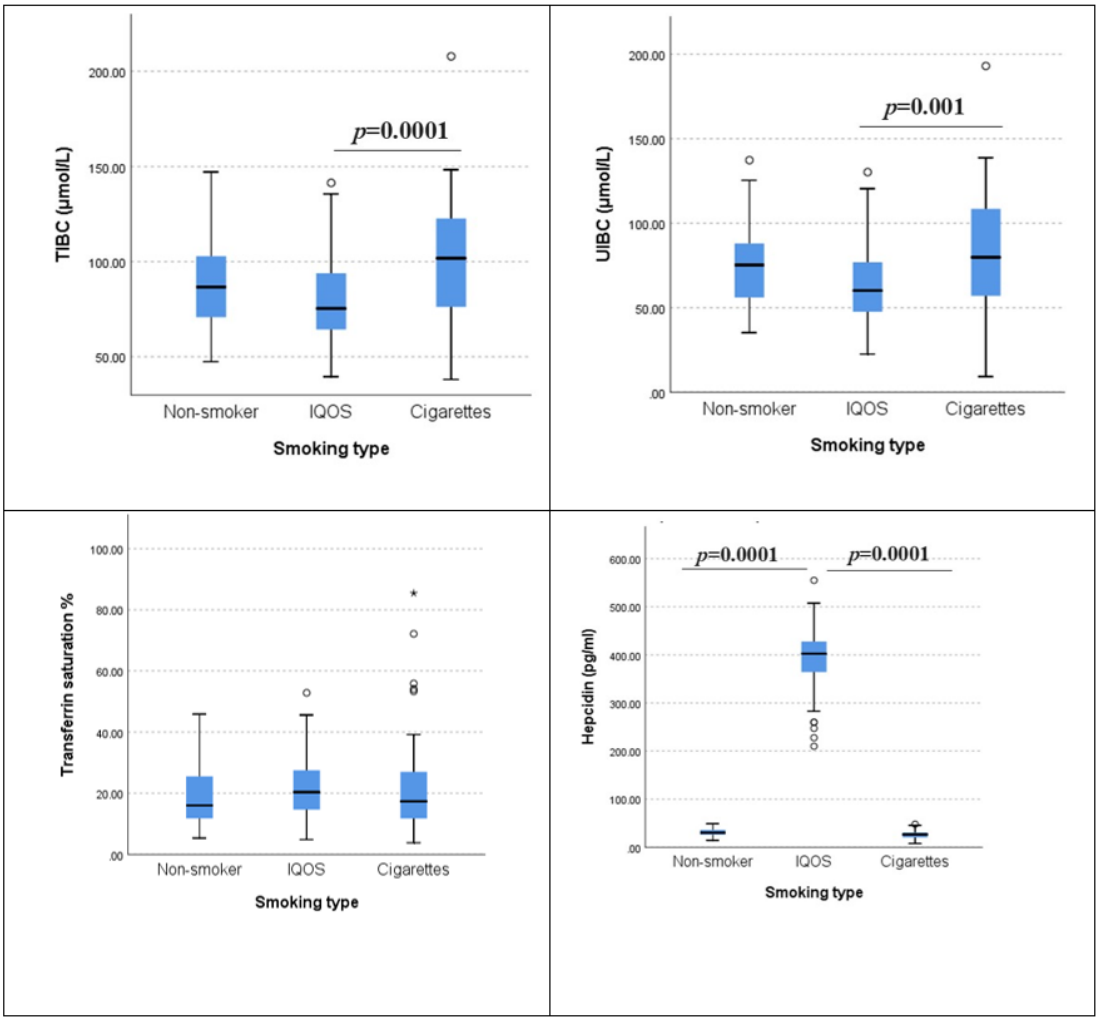

Fig. 3: Comparison of total iron-binding capacity (TIBC), unsaturated iron-binding capacity (UIBC), Transferrin saturation percentage and hepcidin in males and females across the three study groups: Non-smokers, IQOS users, and cigarette smokers. Data are presented as mean ± standard deviation

Correlation analysis between the amount of IQOS use with hematological and iron parameters

Correlation analysis was performed to study the association between the amount of IQOS use and various hematological and biochemical parameters. In males, both Hb levels and RBC count showed weak negative correlations with the amount of IQOS used (r = -0.323, P = 0.018 and r = -0.304, P = 0.027, respectively). In contrast, TIBC demonstrated a weak positive correlation with the amount of IQOS used (r = 0.291, P = 0.034). No significant correlations were observed with WBC count, platelet count, MCV, ferritin, serum iron, UIBC, or hepcidin levels, as indicated by their respective P-values ($P > 0.05$).

In females, a significant weak negative correlation between the amount of IQOS use and RBC count (r = -0.477, P = 0.012) was found. Conversely, a significant positive correlation was observed with MCV (r = 0.475, P = 0.012) and ferritin levels (r = 0.518, P = 0.006). No significant correlations were found between the amount of IQOS use and Hb, WBC count, platelet count, serum iron, UIBC, TIBC, or hepcidin, as their P-values exceeded 0.05.

Discussion

In this study, the distributions of various hematological and iron-related parameters were tested across categories of smoking type (non-smoker, IQOS users, and cigarette smoker). Hemoglobin levels were significantly higher in male cigarette smokers compared to non-smokers. This aligns with previous studies that reported that smoking cigarettes increases hemoglobin levels (2). In contrast, no significant difference in hemoglobin levels was observed between IQOS users and non-smokers in males. This suggests that IQOS use may not affect hemoglobin levels in the same way as traditional cigarette smoking. It was reported that IQOS produces significantly lower levels of carbon monoxide compared to cigarette smoking (19). Switching from traditional cigarette smoking to IQOS led to an improvement in carboxyhemoglobin levels after six months (20). These findings suggest that IQOS may reduce the risk of smoking-related secondary polycythemia.

No significant differences in RBC count were observed between cigarette smokers and non-smokers of either sex. This finding aligns with previous research showing no notable variation in RBC count between these groups (21). However, studies have reported higher RBC levels in cigarette smokers compared to non-smokers (2). A possible explanation for this increase in RBC count among smokers is the hypoxia induced by carbon monoxide exposure and reduced oxygen levels, which trigger erythropoietin production and, consequently, enhance RBC production (22). Concerning MCV, no significant changes were observed between cigarette smokers compared to non-smokers in both males and females. Previous studies reported higher MCV levels in smokers (21) while other studies reported lower MCV levels (23). The current study found no significant difference between cigarette smokers and non-smokers as well as between IQOS users and non-smokers in RBC or MCV levels.

Total WBC counts in IQOS users showed no significant differences compared with the other groups. This aligns with previous reports that no elevation in WBC counts accompany IQOS use (24). Similarly, total WBC counts showed no significant differences between cigarette smokers and the non-smokers. Previous studies have reported increased WBC counts in smokers (23). This discrepancy may reflect the influence of smoking intensity and duration on hematological changes. Our findings could be attributed to the underrepresentation of heavy smokers.

Platelet counts were significantly lower in cigarette smokers compared to non-smokers (P= 0.015). On the other hand, no significant differences in platelet counts were observed between IQOS users and non-smokers or between IQOS users and cigarette smokers. Previous studies have reported conflicting results: some found that smoking increased platelet counts (25) while others reported lower platelet counts in cigarette smokers (23). These discrepancies may be influenced by factors such as age, smoking duration, frequency and cigarette brand.

The study measured three key iron parameters: iron, ferritin, and UIBC. Additionally, TIBC and transferrin saturation were calculated. Hepcidin, the hormone responsible for regulating iron metabolism, was also measured. Laboratory analysis revealed no significant difference in iron levels across smoking categories in both males and females, suggesting that smoking type may not have a direct influence on total serum iron. However, iron levels alone may not fully capture the nuances of iron metabolism, as evidenced by other biomarkers, including ferritin and TIBC. A study reported no difference in plasma total iron between tobacco smokers and non-smokers (26).

Serum ferritin is widely regarded as a reliable marker of iron status, frequently used to diagnose iron deficiency and to detect iron overload. As such, it is considered one of the most essential tools for assessing iron balance. In females no differences in ferritin levels between the three groups were noted. In women of childbearing age, menstrual bleeding is a significant source of iron loss leading to a decrease in iron stores. This may explain the lower mean ferritin in females in the control group compared to males (52.85 ± 40.90 vs. 98.32 ± 69.31, respectively).

Ferritin levels were significantly higher in male IQOS users compared to non-smokers, likely reflecting IQOS-induced inflammation (18), as ferritin is an acute-phase reactant that rises with inflammatory states (27). To our knowledge, this study is the first to report the effect of IQOS on ferritin and other iron parameters in humans. Ferritin has been extensively studied in relation to cigarette smoking, with consistent reports of elevated levels among smokers (28). However, increased ferritin does not always indicate iron overload or adequate iron stores; it can also reflect inflammation, liver injury, or increased iron storage. In liver diseases such as nonalcoholic fatty liver disease (NAFLD), high ferritin often signals hepatic iron accumulation and hepatocellular damage, correlating with disease severity and fibrosis progression, independent of systemic inflammation (29). This multifaceted role underscores ferritin's value as a biomarker, but also its non-specificity, requiring careful interpretation in the clinical context.

The TIBC and UIBC, which reflects the body's ability to bind iron, showed no significant difference between IQOS users and non-smokers. On the other hand, cigarette smokers exhibited significantly higher levels of both TIBC and UIBC compared to IQOS users. However, these levels in cigarette smokers did not differ significantly from those in non-smokers. A previous study reported elevated TIBC levels in cigarette smokers compared to non-smokers (30).

Transferrin saturation, which represents the percentage of transferrin bound to iron, showed no significant difference between cigarette smokers and the control group. This finding is consistent with a previous study (30), including comparisons among mild, moderate, and heavy smokers (31). Similarly, no significant difference in transferrin saturation was observed between IQOS users and non-smokers.

Hepcidin, a key regulator of iron homeostasis, showed the most striking differences across smoking groups. Significantly higher values were observed in IQOS users compared to cigarette smokers and non-smokers. These findings suggest that IQOS use has a particularly strong effect on hepcidin levels, potentially reflecting a unique impact on iron regulation in the body. Hepcidin is regulated through feedback by iron level. Moreover, inflammation induces elevation in hepcidin levels (16). Since previous studies reported that IQOS use is accompanied by an inflammatory response and ROS production (11, 13), a probable cause of the high hepcidin levels in IQOS users is inflammation.

In males, the weak positive correlation between IQOS use and TIBC may reflect subtle alterations in iron metabolism. Potential mechanisms include IL-6–mediated hepcidin induction (32), oxidative stress, or low-grade inflammation, which can modulate iron absorption and distribution and cause mild iron sequestration or shifts in erythropoiesis, explaining slight decreases in Hb and RBC counts. In females, IQOS use was negatively associated with RBC and positively with MCV and ferritin. Most other parameters, including WBC, platelets, serum iron, UIBC, and hepcidin, showed no notable correlations, suggesting that IQOS use may induce modest changes in certain hematological and iron-related markers.

The notably higher mean hepcidin levels observed in IQOS users are striking. Samples were analyzed using a standardized, validated ELISA under consistent pre-analytical conditions, making assay variability unlikely to fully explain the difference. Biologically, elevated hepcidin may reflect alterations in iron homeostasis or low-grade inflammatory responses induced by IQOS, consistent with prior studies on smoking-related hepcidin regulation. These findings highlight a potential link between heated tobacco product use and iron metabolism, warranting further investigation to clarify underlying mechanisms and causal relationships.

The correlation analysis showed weak associations between IQOS use and certain hematological and iron-related parameters ($r \approx 0.3–0.5$). In males, Hb and RBC showed slight negative correlations, while TIBC was weakly positive. In females, IQOS use was negatively associated with RBC and positively with MCV and ferritin. These statistically significant correlations indicate mod-

est correlations, suggesting that IQOS use may be associated with small but measurable changes in some hematological and iron-related markers, while other parameters, including WBC, platelets, serum iron, UIBC, and hepcidin, were not notably related.

This study has some inherent limitations. The cross-sectional design allows for the identification of associations but does not establish causality. Certain factors, such as inflammatory markers (e.g., CRP, IL-6), body mass index (BMI), dietary iron intake, alcohol use, and physical activity, were not included in the analysis. Additionally, although results are reported separately for males and females, the study was not primarily designed to evaluate statistical power within these subgroups.

Conclusion

To our knowledge, this is the first study investigating associations between IQOS use and iron metabolism in humans, emphasizing its novelty. The results show that IQOS use is linked to modest variations in certain hematological and iron-related biomarkers, particularly hepcidin, ferritin, and TIBC, which may reflect subtle effects on iron homeostasis and low-grade inflammation. While based on a cross-sectional design, these findings highlight meaningful associations. Future longitudinal studies are warranted to better understand the underlying mechanisms, the durability of these changes, and their potential implications for public health, including iron-related and inflammatory outcomes.

Journalism Ethics considerations

Ethical issues (Including plagiarism, informed consent, misconduct, data fabrication and/or falsification, double publication and/or submission, redundancy, etc.) have been completely observed by the authors.

Funding

No funding was received.

Conflict of interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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