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Research Article

Markers of gut barrier function and its associations with cardiometabolic indices among metabolically healthy obese Arab women

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ABSTRACT

The prevalence of obesity in Saudi Arabia is high, but a high percentage of the obese population is considered metabolically healthy. It is known that metabolically unhealthy obese individuals exhibit a dysfunctional gut barrier, but such dysregulation has not been demonstrated for other obesity phenotypes. The present cross-sectional study evaluated the associations between gut barrier function with cardiometabolic indices among metabolically healthy obese (MHO) Saudi women. A total of 100 Saudi women (mean age 31.0 ± 7.1 years; body mass index, Body Mass Index 35.1 ± 4.7 kg/m²) were screened for MHO [presence of 2 or fewer components of metabolic syndrome (obesity, dyslipidemia, hypertension, and elevated glucose)]. Demographic and clinical characteristics were measured, including anthropometrics. Fasting blood samples were taken to ascertain lipid and glycemic profiles using routine analysis. Circulating levels of cluster of differentiation 14 (CD14), fatty acid binding protein 2 (FABP2), and endotoxin were measured using commercially available assays. Bivariate associations showed that CD14 was inversely associated with C-peptide (R= -0.37, p=0.02). FABP2 was inversely associated with age (R= -0.21, p=0.04) and positively correlated with glycated hemoglobin (R= 0.24, p=0.02). Stepwise linear regression analyses using gut barrier function markers as dependent variables revealed that CD14 explains 15% of the variance perceived in insulin sensitivity, as measured using homeostasis model assessment for β function (HOMA-β) (adjusted R^2 = 0.15; p=0.02). On the other hand, FABP2 predicted 17% of the variance perceived in triglyceride levels (adjusted R^2 = 0.17; p=0.02). No significant predictors were seen in endotoxins. In conclusion, the findings suggest that gut barrier function markers like CD14 and FABP2 may serve as early indicators of metabolic risk among women with MHO. Prospective studies are needed to explore the mechanisms behind these associations, especially in populations like Arab women, where genetic, dietary, and lifestyle factors may play a unique role.

1. Introduction

It has been recently acknowledged that the gut barrier function plays a crucial role in intestinal homeostasis, regulation of nutrient absorption, and protection against harmful pathogens, essential components that dictate overall health and disease (Assimakopoulos *et al.*, 2018; Alodaini, 2023). Disruptions to the gut barrier, especially to the gut microbiota ecosystem, lead to gut dysbiosis, which has been directly and strongly linked to various metabolic and inflammatory disorders (Das and Nair, 2019; Chong *et al.*, 2025), including obesity (Almalki *et al.*, 2024; Shemtov *et al.*, 2023), and aging (Xu *et al.*, 2024), highlighting the complex interactions between the gut microbiota, intestinal permeability, and metabolic health (Koutoukidis *et al.*, 2022; Hairul Hisham *et al.*, 2025).

Recently, several endogenous markers of gut barrier function have been observed to be altered among individuals with low-grade chronic inflammation, a hallmark of abdominal obesity and insulin resistance-related diseases linked to mortality (Kajikawa and Higashi, 2022; Zhang *et al.*, 2024). Some of these gut dysbiosis markers include lipopolysaccharides (LPS) or endotoxin, cluster of differentiation 14 (CD14), and fatty acid binding protein 2 (FABP2). Endotoxins are bacterial fragments/components found within the gut microbiota that are is harmful when released in the circulation, contributing to low-grade chronic inflammation among obese individuals (Wang *et al.*, 2024). CD14 is a glycoprotein on myelomonocyte lineage cells, involved in cell differentiation, immune response, and binding endotoxins (Roberts *et al.*, 2024). FABP2 is an intestinal damage biomarker, which is released into the circulation when intestinal epithelial cells die, serving as a biomarker of intestinal damage (Efremova *et al.*, 2024).

In Saudi Arabia, altered gut microbiota composition has been observed to be linked with adiposity markers, particularly in obese women (Aljazairy *et al.*, 2022). Consequently, a recent epidemiologic study identified that 3 out of 10 obese Saudi Arabian adults are considered metabolically healthy obese (MHO), a distinct phenotype of obesity that is more common in women, that has no inherent cardiometabolic abnormalities or cardiovascular risk factors commonly

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associated with obese individuals (Wani *et al.*, 2024). Consequently, among MHO individuals, the relationship between adiposity indices and gut barrier function markers remains poorly understood. To fill this gap, the present study sought to examine the associations of cardiometabolic indices and gut barrier function markers among MHO Saudi women. Understanding these relationships could open new avenues for targeted therapeutic strategies in managing obesity-related disorders, particularly in under-investigated homogenous populations such as the Arab ethnic group with distinct genetic, dietary, and lifestyle factors.

2. Material and Methods

2.1 Study design and participants

In this cross-sectional study, a total of 100 apparently healthy adult Saudi women with obesity (BMI) ≥ 30 kg/m^2, aged 18 to 40 years) were recruited to participate at the College of Applied Medical Science Clinical Nutrition Clinic, King Saud University (KSU), Riyadh, SA. A general questionnaire, including demographic data assessment, was given. The exclusion criteria included individuals under 18 or over 40 years of age, those who were overweight or not obese, individuals with chronic diseases (such as renal, hepatic disease, or malignancy), those taking oral hypoglycemics, anti-hypertensives, or statin medications, and pregnant or postmenopausal women. Additionally, individuals with chronic inflammatory conditions such as rheumatoid arthritis or a history of long-term steroid or immunomodulator use were excluded. For the purpose of this study, MHO was operationally defined as having 2 or fewer of the 5 metabolic syndrome (MetS) components described from the previous local epidemiologic study (Wani *et al.*, 2024). The original MetS definition involved a cluster of cardiometabolic components which include obesity, hypertension (or not on anti-hypertensive medications), dyslipidemia (elevated triglycerides >1.7 mmol/L and low high-density lipoprotein-cholesterol specific for women <1.29 mmol/L, or not on statins), and elevated glucose >5.6mmol/L (or no intake of anti-diabetes drugs) (Grundy *et al.*, 2005). This study was carried out in full adherence to the ethical standards set in the Declaration of Helsinki. Written informed consent was obtained prior to inclusion. Ethical approval was obtained from the Institutional Review Board of the College of Medicine, KSU Medical City (KSUMC) (Approval# 21/0049/IRB, 24/12/2020), and all laboratory analyses were performed at the Chair for Biomarkers of Chronic Diseases (CBCD), KSU.

2.2 Anthropometrics

Body measurements were assessed using internationally approved procedures for measuring clinical obesity indicators, including height (cm), weight (kg), waist (WC), and hip circumference (HC) (cm) by certified nurses. Waist-hip ratio (WHR) was calculated. Weight was measured to the nearest 0.5 kg, without shoes or socks, and while the participant wore light clothing. Measurements were taken using an internationally recognized standard scale, the BC-418 (MA TANITA) body composition analyzer (TANITA, Tokyo, Japan). The same body composition analyzer was used to automatically calculate basal metabolic rate (BMR) and body mass index (BMI).

2.3 Blood sample collection

All participants were requested to submit overnight fasting blood samples (≥ 10 hours), which were extracted by a trained technician into vacutainers (10 mL). The blood samples were centrifuged and stored at -80°C immediately at the biobank facility of CBCD, KSU, Kingdom of Saudi Arabia for further analysis.

2.4 Lipid and glycemic profile

Routine blood analyses for triglycerides, total, , high density-lipoprotein (HDL) and low density lipoprotein (LDL) cholesterol, and fasting glucose were performed using routine bioassay kits and an automated bioanalyzer (Konelab 20i, Thermo Scientific, Espoo, Finland, catalogue numbers 981812, 981823, 981301, and 981379, respectively). Glycated hemoglobin (HbA1c) was measured using the Bio-Rad D-10 Hemoglobin testing system (Bio-Rad Laboratories, California, USA, catalogue# 220-0201). Levels of serum insulin and C-peptide were assessed with Luminex Multiplex assay kits (Luminexcorp, Austin, TX, USA, catalogue# HBNMAG-51 K), which had intra- and inter-assay variations of 1.4-7.9% and <21%, respectively. Additional glycemic measures, including the Homeostatic Model Assessment for Insulin Resistance (HOMA-IR) and insulin sensitivity (Homeostasis Model Assessment of β-cell function, HOMA-β), were calculated as previously described (Aldisi *et al.*, 2024a).

2.5 Gut barrier function markers

To evaluate changes in markers of gut barrier function, levels of endotoxin, intestinal FABP2, and soluble CD14 were measured using commercially available enzyme-linked immunosorbent assays (ELISA) kits (Quantikine kits, Bio-techne, Minneapolis, MN, catalogue numbers QCL 1000, DC140, and DFBP20, respectively). These assay kits had an inter- and intra-assay variability of <5% CV. The assay ranges were 78-5000 pg/mL (endotoxin), 15.6-1000 pg/mL (FABP2), and 250-16000 pg/mL (CD14), according to the manufacturer (Aldisi *et al.*, 2024b).

2.6 Statistical analysis

Power calculation was performed using G*Power (version 22.0) and was taken from previous literature showing the association between endotoxin and markers of healthy aging in Arab adults without diabetes (Al-Daghri *et al.*, 2021). With an obtained coefficient (R) of 0.29, effect size of 0.53, and α=0.05, a sample size of N=34 has an actual power of 95% to detect significant associations. The present study included n=100. Statistics were performed using Statistical Package for Social Sciences v.22. (IBM, Chicago, IL, USA). Non-normal variables were log-transformed prior to performing association analyses. Descriptive statistics were presented as mean ± standard deviation (SD) for continuous variables with a normal distribution, and as median (interquartile range) for variables with a non-normal distribution. Pearson correlation coefficients (R) were calculated to determine associations between variables of interest (endotoxin, CD14, and FABP2) and all parameters (anthropometrics, lipids, and glycemic markers). Stepwise linear regression models were used to identify predictors of CD14, FABP2, and endotoxin levels, with all parameters measured used as independent variables. Significance was considered if $p<0.05$.

3. Results

More than half of the participants were single (52%), and 82% had at least a college or post-graduate degree. None of the participants were smokers, and none had existing comorbidities or any type of medications (not shown in Table 1). Table 1 shows the descriptive clinical and metabolic characteristics of all 100 participants. The participants had a mean age of 31.0 ± 7.1 years, with an average weight of 88.4 ± 12.5 kg and a BMI of 35.1 ± 4.7 kg/m^2. The mean BMR was 1545.0 ± 163.9 kcal/day. Anthropometric measures, such as WC (94.5 ± 9.9 cm) and hip circumference (122.4 ± 9.5 cm), along with a WHR of 0.8 ± 0.1, suggest central adiposity. Metabolic parameters included total cholesterol (5.2 ± 1.2 mmol/L), HDL-C (1.4 ± 0.4 mmol/L), LDL-C (3.2 ± 0.8 mmol/L), and glucose (5.2 ± 1.4 mmol/L), with a median triglyceride level of 1.2 mmol/L. Insulin resistance, assessed via HOMA-IR, had a median of 2.1. Markers of gut barrier function, which included CD14, FABP2, and endotoxin, showed wide variability, with medians of 1585.9 pg/mL, 349.1 pg/mL, and 173.6 EU/mL, respectively. The rest of the measured parameters have been shown in Table 1. It is worthy to note that if the definition of prediabetes used HbA1c (>5.7) instead of glucose (>5.6), then 17 of the participants would not be considered as having MHO.

Table 2 shows Pearson correlation coefficients (R) between the markers of gut barrier function and insulin resistance—CD14, FABP2, endotoxin, and C-peptide—with various cardiometabolic parameters. CD14 showed a significant positive correlation with FABP2 (R =

Table 1.
Clinical characteristics of participants.

Parameters (N = 100)	Mean ± SD
Age (years)	31.0 ± 7.1
Weight (kg)	88.4 ± 12.5
BMI (kg/m²)	35.1 ± 4.7
Basal metabolic rate (kcal)	1545.0 ± 163.9
Waist (cm)	94.5 ± 9.9
Hips (cm)	122.4 ± 9.5
WHR	0.8 ± 0.1
FAT free mass	48.5 ± 5.1
Total body water (kg)	35.5 ± 3.7
Triglycerides (mmol/L)	1.2 (0.9 - 1.7)
Total cholesterol (mmol/L)	5.2 ± 1.2
HDL-cholesterol (mmol/L)	1.4 ± 0.4
LDL-C (mmol/L)	3.2 ± 0.8
Glucose (mmol/L)	5.2 ± 1.4
Hba1c (%)	4.7 ± 0.9
Insulin (μIU/mL)	9.6 (7.3 - 14.0)
HOMA-IR	2.1 (1.5 - 3.3)
HOMA-β	1.5 (1.1 - 2.1)
C-peptide (ng/mL)	.4 (.2 – .8)
CD14 (pg/mL)	1585.9 (695.4 - 2491.3)
FABP2 (pg/dL)	349.1 (52.5 - 747.0)
Endotoxin (pg/mL)	173.6 (81.3 - 480.1)

Note: Data presented as Mean ± SD for normal variables and Median (Quartile 1 – Quartile 3) for non-normal variables; $p < 0.05$ considered significant.

0.23, p = 0.02. CD14 also exhibited a significant inverse correlation with C-peptide (R = -0.37, p = 0.02). Additionally, CD14 showed a borderline-significant positive correlation with HOMA-IR (R = 0.32, p = 0.05. On the other hand, FABP2 was inversely associated with age (R = -0.21, p = 0.04) and glucose levels (R=-0.22, P=0.03). It also showed a significant positive correlation with HbA1c (R = 0.24, p = 0.02. Endotoxin was significantly inversely associated with BMI (R = -0.21, p = 0.04) and HC (R = -0.24, p = 0.02). Lastly, C-peptide showed a significant inverse correlation with height (R = -0.29, p = 0.05) and a borderline-significant inverse correlation with LDL-C (R = - 0.27, p = 0.08). A sub-analysis was done removing all participants with HbA1c >5.7 (n=17) and found no significant associations between variables of interest (not shown in Table 2).

Stepwise linear regression analyses were used to identify significant predictors of CD14, FABP2, and endotoxin levels with cardiometabolic variables measured as shown in Table 3. For CD14, the only significant predictor was Log HOMA-β, with a regression coefficient of 0.8 ± 0.3; p = 0.02 (Fig. 1). The model explains 15% of the variability in insulin sensitivity (adjusted $R^2 = 0.15$; p = 0.02). For FABP2, the only significant predictor was log triglycerides, with a regression coefficient of -2.7 ± 1.0 and a p-value of 0.016 (Fig. 2). The model explains 17% of the variance perceived in triglyceride levels (adjusted $R^2 = 0.17$; p = 0.02). Lastly, no significant predictors were identified for endotoxin (Table 3).

4. Discussion

This cross-sectional study aimed to investigate the relationships between markers of gut barrier function and metabolic parameters in Arab women with MHO, an under-investigated population in the context of obesity and gut health. The study results showed that CD14 was significantly associated with FABP2 and inversely associated with C-peptide in women with MHO, suggesting that higher levels of CD14 may indicate gut barrier dysfunction, which in turn disrupts lipid metabolism and contributes to increased insulin resistance.

Table 2.
Bivariate correlations between CD14, FABP2, Endotoxin, and C-peptide with cardiometabolic parameters in all participants.

	CD14		FABP2		Endotoxin		C-peptide	
	R	p-value	R	p-value	R	p-value	R	p-value
FABP2	.23*	.02	1.00		- .05	.65	.01	.96
Endotoxin	- .12	.25	- .05	.65	1.00		.21	.22
C-peptide (ng/mL)	- .37	.02	.01	.96	.21	.22	1.00	
Age	.10	.33	- .21*	.04	.02	.81	- .09	.57
Weight (kg)	- .07	.48	- .02	.81	- .14	.17	.09	.56
Height (cm)	.04	.67	- .03	.78	.11	.29	- .29	.05
BMI (kg/m²)	- .10	.34	- .01	.94	- .21	.04	.27	.08
BMR (kcal)	- .09	.35	.07	.50	- .09	.37	.09	.55
Waist (cm)	- .01	.95	- .09	.36	- .14	.17	.12	.44
Hips (cm)	- .01	.91	- .09	.37	- .24*	.02	.04	.78
WHR	0	.98	- .05	.65	.05	.61	.10	.50
Fat-free mass (kg)	- .10	.33	.05	.61	- .05	.63	.09	.56
Triglycerides (mmol/L)	- .11	.27	- .19	.06	.12	.24	.17	.27
Total cholesterol (mmol/L)	.05	.63	-.15	.14	- .05	.60	- .25	.10
HDL-C (mmol/L)	- .08	.45	.03	.77	- .13	.19	- .03	.83
LDL-C (mmol/L)	.10	.33	- .08	.46	.08	.45	- .27	.08
Glucose (mmol/L)	- .04	.72	- .22	.03	- .12	.24	- .06	.72
Hba1c (%)	0	.98	.24*	.02	.15	.14	.23	.14
Insulin (μIU/mL)	.28	.09	.13	.45	- .17	.33	.22	.16
HOMA-β	.10	.59	.33	.06	- .11	.55	.26	.11
HOMA-IR	.32	.05	- .03	.88	- .24	.16	.17	.28

Note: Data presented as Pearson correlation coefficient; R indicates correlation coefficient and p indicates p-values; * p<0.05 considered significant.

Table 3.
Predictors of CD14, FABP2, and endotoxin.

	CD14		FABP2		Endotoxin	
	B ± SE	p	B ± SE	p	B ± SE	p
CD14						
FABP2						
Endotoxin						
Age (years)						
BMI (kg/m²)						
Total cholesterol (mmol/L)						
HDL-C (mmol/L)						
Hba1c						
Log triglyceride (mmol/L)			-2.7 ± 1.0	0.016		
Log HOMA-β	0.8 ± 0.3	0.022				
Log HOMA-IR						
Adjusted R^2	15%		17%			

Note: Data presented as B ± SE and Adjusted R^2 obtained from three-stepwise linear regression equations using CD14, FABP2, and Endotoxin as dependent variables and all cardiometabolic parameters as independent variables. Significant at $p < 0.05$.

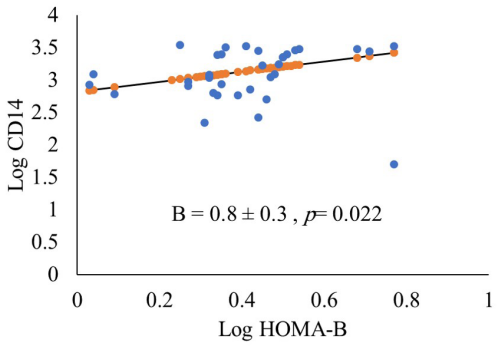

Fig. 1. Significant positive correlation between Log CD14 and Log HOMA-β.

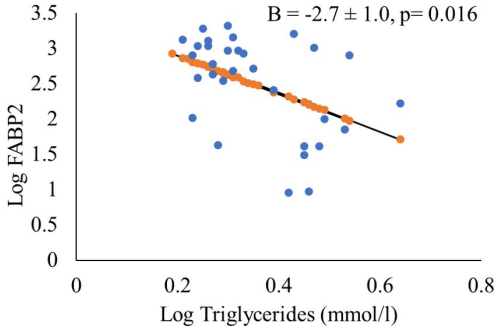

Fig. 2. Significant inverse correlation between log triglycerides and log FABP2.

The findings are in accordance with a recent observational study of randomly selected participants from the Reasons for Geographic and Racial Differences in Stroke (REGARDS) study, ascertaining CD14 and diabetes risk among whites and blacks, where higher CD14 levels were associated with 10% increase in incident diabetes among whites in particular (Cruden *et al.*, 2024). The significant association of CD14 with FABP2 reinforces the role of CD14 in adipose tissues and supports a recent animal study that showed CD14 deficiency in rats exhibited ideal body composition, resistance to high-fat diet, and may serve as a proangiogenic marker (Lv *et al.*, 2025). It is worthy to note that CD14 in the present study predicts a substantial variance in insulin sensitivity, as seen in HOMA-β. In a recent systematic review by Sharigyn and colleagues (2023), CD14 with endotoxin activates toll-like receptors (TLR) of the immune system, which in turn influences glucose responsiveness, adipose gene expression, and metabolism, with CD14-deficient mice showing increased resistance to obesity, insulin resistance, and cardiovascular disease, while also regulating SIRT1 activity, a major regulator of metabolism (Sharigyn *et al.*, 2023).

Another interesting finding in this population is the significant associations between FABP2 with glucose and HbA1c, suggesting that it could be a potential marker of early metabolic disturbance, especially among MHO individuals. The significant inverse association of FABP2 with glucose levels contradicts its positive correlation with HbA1c, the latter of which is more aligned with previous observations on its role in long-term glucose dysregulation. Previous studies on FABP2 indicate that higher levels were associated with increased diabetes-related complications and sub-atherosclerosis in children (El-Asrar *et al.*, 2023). FABP2, which is primarily a marker of intestinal lipid disturbance, has been studied mostly in genetics, since its polymorphisms have been associated with various cardiometabolic disorders in different ethnic groups such as MetS in Caucasians (Turkovic *et al.*, 2012) and ischemic stroke in ethnic Han Chinese (Cao *et al.*, 2023). The significant association between FABP2 and triglycerides in the present study are closely aligned with the findings from ethnic North Indians, where FABP2 polymorphisms have been associated with hypertriglyceridemia (Meena *et al.*, 2023).

Findings of the present study provide valuable insights into the complex interplay between gut barrier markers and metabolic health in this population, highlighting several important associations not seen in previous investigations.

Lastly, no significant predictors were found for endotoxin, indicating that other factors, such as gut microbiota composition or dietary influences, may be involved in determining endotoxin levels. This highlights the complexity of the gut barrier's role in metabolism and suggests that endotoxin levels may not be as strongly influenced by traditional metabolic parameters in this population. It is worthy to note, however, that at least in interventional studies done in the same Arab population, endotoxin was strongly associated with triglycerides and total cholesterol, most notably among obese participants with type 2 diabetes (Al-Daghri *et al.*, 2022). The lack of consistency in observations may also be attributed to the differences in assays used in these studies, apart from the fact that the participants had MHO in this study and no diabetes. Larger studies are needed to confirm these findings.

The authors recognize several limitations. The design of the study prevents causal conclusions on the relationship between gut barrier function and metabolic health. Longitudinal studies are needed to determine whether changes in gut barrier over time lead to metabolic dysfunction. Furthermore, the findings are only applicable to women with MHO, and as such, larger studies using diverse populations are necessary to validate and examine how the present findings apply to other groups. Lastly, several confounders not included in the study, such as diet and physical activity, may influence gut microbiota composition and should be considered in future studies for a more comprehensive understanding. Nevertheless, several strengths are noted in this study, as it is the only study to investigate the link between cardiometabolic parameters and gut barrier function in Arab women with MHO. The exclusion of several comorbidities and medications eliminates potential confounders and ensures that the results reflect the true associations of the studied parameters with metabolic status among MHO women. The study also collected a wide array of clinical parameters, which can lead to hypothesis generation in future studies.

5. Conclusion

In summary, the study provided preliminary evidence of a link between gut barrier function markers and metabolic parameters, particularly insulin resistance, in Arab women with MHO. The findings suggest that CD14 and FABP2, markers of gut permeability, may serve as early indicators of metabolic risk even in individuals who are not overtly unhealthy. Given the rising obesity rates in the Arab world, this study underscores the importance of exploring gut health as a potential therapeutic target in the management of obesity and metabolic disorders. Further research is needed to better understand

the mechanisms underlying these associations, particularly in diverse populations like Arab women, where genetic, dietary, and lifestyle factors may uniquely influence gut health and metabolic outcomes. Interventions that have positive modulatory effects on the gut microbiome, such as the consumption of the Mediterranean diet, may also provide additional understanding of how markers of gut permeability can be manipulated.

CRediT authorship contribution statement

Dara Aldisi: Conceptualization, supervision, funding acquisition; **Shaun Sabico:** Writing original draft, methodology; **Taghreed A Basaaed, Amani A Alfarraj:** Methodology, project administration; **Abeer A Almiman:** Methodology, project administration; **Kaiser Wani: Formal Analysis, Syed D Hussain and Mohammed G.A. Ansari:** Data curation; **Nasser Al-Daghri:** Conceptualization, writing – review and editing, supervision; **All authors:** writing – review and editing. All authors have seen and approved the final version of the manuscript

Declaration of competing 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.

Data availability

Data used for constructing the results in this study may be obtained from the corresponding authors through a reasonable request and under conditions set by the Ethics committee.

Declaration of Generative AI and AI-assisted technologies in the writing process

The authors confirm that there was no use of artificial intelligence (AI)-assisted technology for assisting in the writing or editing of the manuscript and no images were manipulated using AI.

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