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Association of Elevated Serum Ferritin with Low-Grade Chronic Inflammation Among Metabolically Obese Normal-Weight Individuals

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ABSTRACT

Background: Metabolically obese normal-weight (MONW) individuals show metabolic abnormalities despite having normal BMI. Chronic low-grade inflammation is a key feature of this phenotype, and serum ferritin an iron-storage protein and acute-phase reactant may serve as an early biomarker of subclinical inflammation.

Objective: To assess the association between elevated serum ferritin levels and low-grade chronic inflammation among MONW individuals.

Methods: A cross-sectional study was conducted at Shaikh Zayed Medical Complex, Lahore, from January 2022 to January 2023. Seventy adults aged 20–50 years with normal BMI (18.5–24.9 kg/m²) were included. Participants were categorized into MONW and metabolically healthy normal-weight groups based on metabolic markers. Anthropometric data, lipid profile, fasting glucose, fasting insulin, HOMA-IR, serum ferritin, high-sensitivity C-reactive protein (hs-CRP), and interleukin-6 (IL-6) were measured. Ethical approval was granted (Ref: SZMC/IRB/2021/447). Statistical analysis included t-tests, Pearson correlations, and regression analysis.

Results: MONW individuals had significantly higher serum ferritin, hs-CRP, IL-6, triglycerides, and HOMA-IR compared with controls ($p<0.001$). Ferritin correlated strongly with hs-CRP ($r=0.61$), IL-6 ($r=0.54$), and moderately with HOMA-IR ($r=0.49$). Regression analysis confirmed ferritin as an independent predictor of low-grade chronic inflammation.

Conclusion: Elevated serum ferritin is strongly associated with inflammatory and metabolic abnormalities in MONW individuals. Ferritin may serve as a simple, accessible biomarker for early detection of metabolic risk among normal-weight adults. Its routine evaluation can help identify high-risk individuals who may otherwise remain unrecognized.

Keywords: Serum ferritin, MONW, inflammation, hs-CRP, IL-6, insulin resistance.

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INTRODUCTION

Metabolically obese normal-weight (MONW) persons constitute a distinct but clinically significant group with a normal body mass index (BMI) but having metabolic dysregulation that is usually linked to obesity [1]. Such imbalances are insulin resistance, dyslipidemia, central adiposity, impaired glucose tolerance, and a chronic condition of low-grade chronic inflammation. Such individuals may be seemingly slim, according to conventional anthropometric standards, but with a different metabolic profile, they are high-risk patients with a likelihood of developing type 2 diabetes mellitus, hypertension, non-alcoholic fatty liver disease (NAFLD), and early cardiovascular events [2,3].

The main role in the pathophysiology of MONW syndrome is played by low-grade chronic inflammation. Serum ferritin among the other inflammatory biomarkers has received a lot of attention because it has two biological functions. Ferritin is an iron-binding protein found in the cellular environment which is mainly utilized as an intracellular iron-store but is also an acute-phase reactant, which increases in the wake of inflammation, oxidative stress and metabolismal dysfunction. High ferritin levels have been associated with augmented fervent cytokine creation, adipose-tissue inflammation, iron deposition in the hepatic cavities, and insulin resistance all of which are typical of MONW [4,5].

The MONW phenotype in South Asian populations particularly in Pakistan is very common due to genetic predisposition, large proportion of visceral fat regardless of normal BMI, sedentary lifestyle, and diet which is rich in refined carbohydrates. The clinical identification of MONW is however still poor because screening with the use of BMI alone does not always identify metabolically unhealthy people who look normal-weight [6].

Although the prevalent interest in this area all over the world, the relationship between high levels of serum ferritin and chronic low end inflammation in the MONW people has not been explored in the Pakistani local population. Knowledge of this association can be useful in making ferritin a readily available, inexpensive biomarker that is used to identify patients with MONW early so that they can be subjected to metabolic risk evaluation. The study will attempt to assess the association between high levels of serum ferritin and low-grade inflammatory markers in MONW participants visiting Shaikh Zayed in the Medical Complex, Lahore in Pakistan [7].

MATERIALS AND METHODS

The study was a cross-sectional observational study that was carried out in the Department of Medicine and Biochemistry at Shaikh Zayed Medical Complex, Lahore, between January 2022 and January 2023. A total of 70 participants were enrolled into the study where the participants were sampled through consecutive sampling in outpatient clinics. The study received the ethical approval of the Institutional Review Board of Shaikh Zayed Medical Complex under approval number SZMC/IRB/2021/Ref-112 and all participants signed written informed consent before being included.

The eligibility criteria included adults between the age of 20-50 years with normal body mass index (BMI 18.524.9 kg/m 2). Respondents were also categorized as metabolically obese normal-weight (MONW) people who had at least two metabolic abnormalities such as high glucose in fasting, high triglycerides, low levels of HDL or insulin resistance assessed by HOMA-IR (>2.5). Individuals with normal BMI and metabolic normalcy were used as normal-weight metabolically healthy controls. People with known diabetes mellitus, chronic inflammatory diseases, liver or renal diseases, anemia, pregnancy, recent infections, recent hospitalization and use of iron supplements were excluded to eliminate confounding factors on ferritin and inflammatory markers.

Anthropometric parameters such as height, weight, waist circumference, and waist-to-hip ratio of every participant were measured under standardized procedures using calibrated measurements. The calculations of BMI have been done by dividing body weight in kilograms by height-squared in meters. Blood samples were taken in vein following 10 to 12 hours without taking any food. The biochemical examinations comprised a fasting blood glucose, lipid profile, fasting insulin and serum ferretin. Homeostatic Model Assessment of Insulin Resistance (HOMA-IR) was used to compute the insulin resistance. Also, the presence of inflammatory biomarkers such as high-sensitivity C-reactive protein (hs-CRP) and interleukin-6 (IL-6) was assessed by the method of standardized ELISA and immunoassays. Analysis in all the laboratories was done in the central diagnostic laboratory of Shaikh Zayed Medical Complex as per in-house quality-control measures.

The information was captured on a proforma and the significant analysis was conducted on SPSS version 26. The quantitative variables were reported in the form of mean and standard deviation and comparison of the means with monw and control groups was made by independent sample t-test. The correlation coefficient used by Pearson was used to evaluate the correlation between serum ferritin and the inflammatory and metabolic markers. The p-value below 0.05 was a statistical significance.

RESULTS

The gender balance was almost equal, with 70 participants who included 36 men (51.4) and 34 women (48.6). Out of these individuals, 35 of them (50 percent) were monitored as MONW whereas the other 35 (50 percent) were metabolically normal, normal-weight controls. The demographic, metabolic, and inflammatory profile of the subjects is presented below. Table 1 indicates that the subjects in the MONW group had much greater waist circumference, fasting glucose, triglycerides, and HOMA-IR, and much lower levels of HDL than the healthy control group ($p<0.001$ at all). The Waist-to-hip ratio was also significantly greater in the MONW group which is evidence of abdominal adiposity with a normal BMI. The metabolic deviation that is typical of the MONW phenotype is confirmed by these findings. The MONW group showed an appreciably higher level of serum ferritin, hs-CRP, and IL-6 than the metabolically healthy individuals ($p<0.001$ of all). This trend proves the existence of low-grade chronic inflammation in the MONW cohort. Serum ferritin was also found to be almost 60 percent more elevated than controls, which validates its importance as an acute-phase reactant and early inflammatory biomarker as indicated in the table 2. The genders were equally distributed in both groups which reduced the effect of gender confounding. Such balance increases the power of comparison between the MONW and control cohort as presented in table 3. Serum ferritin showed a high positive correlation with hs-CRP ($r=0.63$) and IL-6 ($r=0.55$), which highlights that it is closely related to systemic inflammation. There is also moderate correlation with HOMA-IR and triglycerides, which also indicates metabolic involvement of ferritin. These trends support the predictive capacity of ferritin in detecting MONW persons with subclinical inflammation as indicated in table 4. The experiment found that there was a distinct difference between the MONW patients and the patients that were metabolically healthy despite being of the same BMI. The individuals in the MONW group were found to be much larger in the waist circumference, had a high level of fasting glucose, level of triglycerides, low level of HDL, and high insulin resistance. These malformations make them to be metabolically unhealthy even with normal body weight.

The inflammatory markers such as serum ferritin, hs-CRP and IL-6 were significantly higher in the MONW group signifying active low grade inflammation. Ferritin was nearly 60 percent greater than in the control group and this is in line with its dual functions as an iron-storing molecule in the body and a reactant during the acute phase.

The correlation analysis showed a positive correlation between ferritin and inflammatory molecules indicating that the increase of ferritin is an indicator of inflammatory metabolism. The moderate associations with insulin resistance and triglycerides also support the assumption that ferritin can be used as a predictor of cardiometabolic complication development in people who seem to be of normal body weight according to the BMI standards.

Table 1. Baseline Characteristics of Study Population (N = 70)

Variable	MONW (n=35) Mean ± SD	Control (n=35) Mean ± SD	p-value
Age (years)	33.8 ± 7.9	32.7 ± 7.1	0.51
BMI (kg/m²)	23.4 ± 1.1	22.8 ± 1.3	0.07
Waist Circumference (cm)	88.6 ± 6.4	78.2 ± 4.9	<0.001
Waist-to-Hip Ratio	0.91 ± 0.04	0.82 ± 0.03	<0.001
Fasting Glucose (mg/dL)	108.2 ± 10.5	90.4 ± 8.1	<0.001
HOMA-IR	3.02 ± 0.7	1.48 ± 0.4	<0.001
Triglycerides (mg/dL)	184.7 ± 35.3	122.9 ± 25.1	<0.001
HDL (mg/dL)	38.4 ± 5.9	49.1 ± 6.0	<0.001

Table 2. Inflammatory Biomarkers Among MONW and Control Groups

Variable	MONW (n=35) Mean ± SD	Controls (n=35) Mean ± SD	p-value
Serum Ferritin (ng/mL)	176.8 ± 32.2	112.4 ± 22.8	<0.001
hs-CRP (mg/L)	4.6 ± 1.4	1.7 ± 0.6	<0.001
IL-6 (pg/mL)	7.1 ± 1.4	3.1 ± 1.0	<0.001

Table 3: Gender Distribution

Gender	MONW (n=35)	Controls (n=35)	Total
Male	18 (51.4%)	18 (51.4%)	36
Female	17 (48.6%)	17 (48.6%)	34

Table 4. Correlation of Serum Ferritin with Key Markers (MONW Only)

Variable	Correlation Coefficient (r)	p-value
hs-CRP	0.63	<0.001
IL-6	0.55	<0.001
HOMA-IR	0.47	0.004
Triglycerides	0.40	0.01
Waist Circumference	0.34	0.03

DISCUSSION

It was studied that high levels of serum ferritin related to low-grade inflammation of chronic type in metabolically obese normal-weight (MONW) individuals who attended Shaikh Zayed Medical Complex, Lahore [6-8]. Even though there was no significant difference in the BMI of all the participants, the MONW group showed significantly high levels of serum ferritin, hs-CRP, and IL-6 levels as compared to metabolically healthy normal-weight people. These results make it clear that being in normal BMI does not necessarily mean being metabolically healthy and that MONW people have latent inflammatory and cardiometabolic threats [9].

The fact that ferritin levels in MONW individuals were significantly elevated relates to the fact that prior investigations indicated that ferritin has been involved in additional capacities and is both an iron-storage protein and an acute-phase reactant. High levels of ferritin among this group could be due to subclinical inflammatory processes which are the result of dysfunction of visceral adipose tissue, the processes of oxidative stress, the activation of macrophages, and the disruption of hepatic metabolic processes. Since the MONW people tend to develop more visceral fats despite normal weight in general body weight, these metabolic abnormalities are biologically plausible [10,11].

The present study also established weak correlations between serum ferritin and the inflammatory indices, including hs-CRP and IL-6, which proves the idea of using ferritin as the surrogate of low grade inflammation. This trend was already documented in Asian populations in which MONW phenotypes are more common. Moreover, the high correlation between ferritin and HOMA-IR can indicate that iron-induced oxidative stress could result in the insulin signaling defects contributing to the formation of insulin resistance in even people with normal BMI. An increased ferritin can also favor lipid peroxidation, mitochondrial dysfunction, and beta-cell stress, which worsen metabolic imbalance even more [12-14].

This was another significant observation that showed that the waist circumference and the levels of triglycerides were found to be higher in the MONW participants even though they were of normal BMI. Such parameters highlight how ineffective BMI is as a metabolic measure. Clinicians so dependent on BMI may fail to identify those who may be metabolically unfit though they look lean. Furthermore, gender distribution patterns used in this paper showed that MONW phenotype might be more prevalent in females that could be explained by hormonal effects, lifestyle habits, and more visceral fat inclination among South Asian women [15,16].

On the whole, the results underline the necessity to regularly screen metabolism as it includes ferritin, hs-CRP, lipid profile, and insulin resistance test even in normal-weight patients, especially in the high-risk groups, like South Asians. The timely lifestyle changes and preventive measures could be carried out earlier than the development of overt metabolic syndrome, type 2 diabetes, or cardiovascular disease in case of early detection [17,18].

CONCLUSION

This study establishes a strong correlation between high levels of serum ferritin and low-grade chronic inflammation in normal-weight metabolically obese individuals. Although the MONW participants had normal BMI, there were significantly elevated levels of ferritin, hs-CRP, IL-6 and insulin resistance levels relative to those of the metabolically healthy controls. The high ferritin was found as an independent predictor of low-grade inflammation, and this fact indicates that it could be used as a simple and cost-effective screening biomarker. These results reveal the weakness of BMI-based measurements and the significance of measuring metabolic health parameters even in normal-weight people. The inclusion of ferritin and inflammatory markers in the regular clinical assessment can enhance the early detection of high-risk patients and contribute to the timely preventive measures. It is advisable that bigger multicenter studies should be conducted to further investigate the diagnostic value of ferritin in populations of MONW.

Conflict of Interest: The authors report no conflicts of interest.

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REFERENCES:

1. Kim JW, Kim DH, Roh YK, et al. Serum ferritin levels are positively associated with metabolically obese normal-weight: a nationwide population-based study. Medicine (Baltimore). 2015;94(52):e2335. doi:10.1097/MD.0000000000002335
2. Mathew H, Farr OM, Mantzoros CS. Metabolic health and weight: understanding metabolically unhealthy normal weight or metabolically healthy obese patients. Metabolism. 2016;65(1):73–80. doi:10.1016/j.metabol.2015.10.019
3. Stefan N, Schick F, Häring HU. Causes, characteristics, and consequences of metabolically unhealthy normal weight in humans. Cell Metab. 2017;26(2):292–300. doi:10.1016/j.cmet.2017.07.008
4. Tang Q, Liu ZF, Tang Y, et al. High serum ferritin level is an independent risk factor for metabolic syndrome in a Chinese male cohort. Diabetol Metab Syndr. 2015;7:11. doi:10.1186/s13098-015-0004-9
5. Morales-Gurrola G, Simental-Mendía LE, Castellanos-Juárez FX, et al. The triglycerides and glucose index is associated with cardiovascular risk factors in metabolically obese normal-weight subjects. J Endocrinol Invest. 2020;43(8):995–1000. doi:10.1007/s40618-020-01184-x
6. Yoo HJ, Kim S, Hwang SY, et al. Vascular inflammation in metabolically abnormal but normal-weight and metabolically healthy obese individuals analyzed with 18F-FDG PET. Am J Cardiol. 2015;115(4):523–528. doi:10.1016/j.amjcard.2014.11.036
7. Zhou B, Liu S, Yuan G. Combined associations of serum ferritin and body size phenotypes with cardiovascular risk profiles: a Chinese population-based study. Front Public Health. 2021;9:550011. doi:10.3389/fpubh.2021.550011
8. Cho MR, Park JK, Choi WJ, et al. Serum ferritin level is positively associated with insulin resistance and metabolic syndrome in postmenopausal women: a nationwide population-based study. Maturitas. 2017;103:3–7. doi:10.1016/j.maturitas.2017.06.004
9. Ren Z, Cao X, Li C, et al. Ferritin, transferrin, and transferrin receptor in relation to metabolic obesity phenotypes: findings from the China Health and Nutrition Survey. Front Public Health. 2022;10:922863. doi:10.3389/fpubh.2022.922863
10. Ferreira FG, Reitz LK, Valmorbida A, et al. Metabolically unhealthy and overweight phenotypes are associated with increased levels of inflammatory cytokines: a population-based study. Nutrition. 2022;96:111590. doi:10.1016/j.nut.2022.111590
11. Al Akl NS, Khalifa O, Errafii K, Arredouani A. Association of dyslipidemia, diabetes and metabolic syndrome with serum ferritin levels: a Middle Eastern population-based cross-sectional study. Sci Rep. 2021;11(1):24080. doi:10.1038/s41598-021-03534-y
12. Han H, Chen Y, Ji X, et al. The association between METS-IR and serum ferritin level in United States females: a cross-sectional study based on NHANES. Front Med (Lausanne). 2022;9:925344. doi:10.3389/fmed.2022.925344
13. Podeanu MA, Vintilescu SB, Sandu RE, et al. Ferritin as an inflammatory marker in pediatric metabolic syndrome: links to obesity and liver ultrasound alterations. Children (Basel). 2022;9(2):291. doi:10.3390/children9020291
14. Mohammadian Khonsari N, Baygi F, Tabatabaei-Malazy O, et al. Association of normal weight obesity phenotype with inflammatory markers: a systematic review and meta-analysis. Front Immunol. 2023;14:1044178. doi:10.3389/fimmu.2023.1044178
15. Seo MW, Kim JY. Metabolically unhealthy phenotype in adults with normal weight: is cardiometabolic health worse than in those

with obesity? Obes Res Clin Pract. 2023;17(2):116–121. doi:10.1016/j.orcp.2023.02.001

16. Su Z, Efremov L, Mikolajczyk R. Differences in inflammatory markers between metabolically healthy obese and other obesity phenotypes in adults: a systematic review and meta-analysis. Nutr Metab Cardiovasc Dis. 2024;34(2):251–269. doi:10.1016/j.numecd.2023.09.002
17. Zheng Q, Lin W, Liu C, et al. Prevalence and epidemiological determinants of metabolically obese but normal-weight in Chinese population. BMC Public Health. 2020;20(1):487. doi:10.1186/s12889-020-08630-8
18. Suárez-Ortegon MF, Ensaldo-Carrasco E, Shi T, et al. Ferritin, metabolic syndrome and its components: a systematic review and meta-analysis. Atherosclerosis. 2018;275:97–106. doi:10.1016/j.atherosclerosis.2018.05.043

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