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Relationship Of Inflammatory Biomarkers and Glycemic Control In Pre And Postmenopausal Women With Type 2 Diabetes Mellitus

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Abstract

Objective: To determine whether postmenopausal status is associated with elevated plasma inflammatory markers ferritin, neutrophil to lymphocyte ratio NLR, platelet to lymphocyte ratio PLR) compared to premenopausal status in women with type 2 diabetes mellitus and to establish a correlation between inflammatory markers and glycemic status in pre-and post-menopausal diabetic women.

Methods: A total of 80 participants aged 25-75 were recruited, from January 2024 to April 2024 and were divided into pre- and postmenopausal groups (Group I and II respectively) based on history using convenient sampling. Clinical assessments included general physical exams and BMI calculations. The biochemical analysis involved measuring Glycosylated haemoglobin (HbA1c), neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and ferritin levels. The study examined the inflammatory profiles linked to menopausal status in diabetic patients.

Results: HBA1c levels were significantly higher ($P < 0.05$)in Group I than in Group 2 (median 9.35 [interquartile range: 8.0 – 10.4] versus 7.10 [interquartile range: 6.42 – 8.37] Also serum ferritin levels in Group I were significantly higher ($P < 0.05$) as compared to Group II (median 173 [interquartile range: 100-190] versus 35.14 [interquartile range: 8.12 – 52.75]. PLR showed significant differences ($P < 0.05$) between the two groups, the ratio being higher in Group II as compared to Group I (median 108 [interquartile range: 85.38-132.77] versus 74.10 [interquartile range: 69.88-85.12]

Conclusion: The interaction between menopause and T2DM affected the platelet-to-lymphocyte ratio but not the neutrophil-to-lymphocyte ratio. Also, ferritin levels are decreased in postmenopausal diabetic women. Further, glycemic status is not the only risk factor for predicting inflammation in diabetics, other risk factors have to be catered to evaluate the inflammation status of diabetic pre and postmenopausal females.

Keywords: Inflammation, HbA1c, premenopausal period, postmenopausal period, Diabetes Mellitus.

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1. Introduction

Type 2 diabetes (T2D) is a major global health problem,[1] In the last 20 years, the prevalence of type 2 diabetes mellitus (T2DM) has tripled in adults aged 20–79 years, affecting more than 25% of people over 50 years of age and especially women during menopause,[2] Menopause is accompanied by alterations in insulin secretion, insulin sensitivity and activity that can predispose to the development of T2DM, independently and additively to, ageing.[3] Both, diabetes mellitus and menopause represent conditions that have been linked to subclinical and systemic inflammatory processes.[4,5] This systemic and subclinical inflammatory process is characterized by elevated circulating levels of inflammatory parameters, including C-reactive protein (CRP) or high-sensitivity CRP (hs-CRP) and inflammatory cytokines.[4]

Novel inflammatory markers derived from standard blood count tests are in demand nowadays. These include neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR). Also, serum ferritin is an acute-phase reactant and participates in the etiopathogenesis of T2DM.[6] Ferritin levels are also subjected to alteration after menopause.[7]

The development of complications in diabetes is linked to the accumulation of advanced glycation end products (AGEs) in tissue proteins. Optimal monitoring of glycemic control can be achieved by HbA1c levels, which reflect the average glycemic control over the previous 3 months.[4]

The precise mechanism driving heightened inflammation in postmenopausal diabetic women remains unclear.[8] While there's evidence that modulating inflammation could impact an individual's glycemic status,[4] there's a scarcity of literature directly linking diabetes mellitus with new inflammatory

markers, particularly in postmenopausal diabetic women. Consequently, given the intricate interplay among menopause, systemic inflammation, and T2DM, our objective was to investigate the difference in levels of inflammatory biomarkers (Ferritin, NLR, PLR) based on menopausal status in females with T2DM. Additionally, we aimed to establish correlations between inflammatory markers and parameters of glycemic regulation, such as HbA1c levels. This aims at targeting inflammation by investigating novel biomarkers and hence enhancing disease prevention and control.

2. Materials & Methods

This cross-sectional study was carried out after formal approval from the Ethical Review Committee. Written informed consent was taken from all participants before entering the study. Female diabetic patients visiting for any of their blood tests were included in this study from January 2024 to April 2024 by non-probability, convenient sampling technique

A total of 80 diabetic (Type-2) females, aged between 25 and 75 years, were divided into pre- and postmenopausal groups (Group I and II respectively) based on history. Diabetes Mellitus was diagnosed in patients in any one of the following ways: 1) Individuals who self-reported their disease and confirmed through medical records. 2) Individuals who fulfil the American Diabetes Association 2019 Criteria for diagnosis of T2DM.

The participants were recruited by inclusion and exclusion criteria. The inclusion criteria comprised T2DM patients, diagnosed according to the 2019 American Diabetes Association Criteria. Exclusion criteria included patients with Type-1 Diabetes, hemoglobinopathies, hypothyroidism, inflammatory disease and pregnancy. Exclusion criteria included a history of iron deficiency or anaemia, active liver or kidney diseases, chronic pancreatitis, gastrointestinal diseases, recent infectious diseases, endocrine disorders and autoimmune diseases.

A questionnaire regarding the complete history of study participants was completed. All participants were clinically examined, and arterial blood pressure and body parameters, including height, were measured. Body mass index (BMI) was calculated as weight (kg)/square of height (m2). Obesity was defined as having a BMI≥30kg/m^2.

For biochemical analysis, samples of whole blood were collected in vacutainer. The sample from each patient was divided into two halves:

1) One half (whole blood) was used as such for measuring HbA1c (%) (By chemiluminescent microparticle immunoassay (CMIA) on Architect from ABBOTT Diagnostic) and Complete blood counts (By Midray BC 3000 Plus fully automated Haematology Analyser).

2) The other half of the blood sample was allowed to stand at room temperature for two hours and then centrifuged for 10 minutes at 2200 RPM for serum separation. Separated serum was transferred to small sterile tubes and stored at - 20 0C before biochemical estimation of ferritin levels (ng/ml) by chemiluminescent microparticle immunoassay (CMIA) on Architect from ABBOTT Diagnostic.

The blood samples were drawn in plastic vacutainers using EDTA (1 mg/mL of blood) for differential white blood cell count. NLR was calculated as the ratio of neutrophils to lymphocytes from the differential white blood cell count. PLR was calculated by dividing platelet count by lymphocyte count.

The collected data were analyzed using SPSS 21 software. Nominal/categorical variables were summarized as frequency and percentage. Medians and interquartile ranges (IQRs) were calculated for continuous variables (because of skewed distribution). The comparison between both groups was carried out with the Mann-Whitney U test. P values below 0.05 were considered statistically significant. Spearman's correlation analysis was performed to quantify the relationship of glycosylated haemoglobin (HbA1C) with the ferritin, NLR and PLR levels in each group.

3. Results

General characteristics of the study population

Table 1 summarizes the general characteristics of the study population. The study population included 80 diabetic patients of which 40 (50%) were premenopausal l (Group I) and 40 (50%) postmenopausal (Group II). The median age in Group I was 36 years (IQR=30-39) and in Group II was 58.50 years (IQR=55- 65.75) (p= 0.00). The median BMI in Group I was 22 kg/m^2 (IQR=18.7-24.7) and in Group II was 23 kg/m^2 (IQR=21.7- 30). In the pre- and postmenopausal group, 4 (10%) and 28 (70%) patients had diabetes for more than 5 years. Among 40 premenopausal women, 26 (65%) had hypertension and 30 (75%) had a family

history of diabetes. Among 40 postmenopausal women, 28 (70%) had co-existent hypertension and 32 (80%) had a family history of diabetes.

Table 1: General characteristics of the study population

Characteristics	Pre-menopausal (n=40)	Post-menopausal (n=40)
Age (years)	36 (30-39)	58.50 (55-65.75)
BMI (kg/m^2)	22 (18.7-24.7)	23 (21.7- 30)
Females (% of 40) with diabetes for more than 5 years	10	70
Females (% of 40) with hypertension	65	70
Females (% of 40) with positive Family history of diabetes	75	80

Table 2: Comparative biochemical parameters in the pre-and postmenopausal diabetic groups (Group I and II)

Parameters	Pre-Menopausal Women (n=40)		Post-Menopausal Women (n=40)		Value of Significance (Mann-Whitney test)
	Median	IQR	Median	IQR	P value
Age	36.00	30-39	58.50	55.00-65.75	0.00
Haemoglobin	9.95	9.4-10.87	11.00	8.97-12.15	0.23
HbA1c	9.35	8.0-10.4	7.10	6.42-8.37	0.00
Ferritin	173	100-190	35.14	8.12-52.75	0.00
Neutrophil lymphocyte ratio	1.34	1.20-1.50	1.30	1.22-2.75	0.361
Platelet lymphocyte ratio	74.10	69.88-85.12	108.0	85.38-132.77	0.00

Table 3 shows the correlation analysis of various parameters in the two groups.

Table 3: Spearman correlation analysis of various parameters in the two groups.

	HbA1C			
Variables	Group I (Premenopausal)		Group II (Postmenopausal)	
	rs	p	rs	p
Ferritin	-0.44	0.05	-0.45	0.004
NLR	0.01	0.93	0.05	0.74
PLR	-.14	0.40	-0.09	0.59

There is a significant and moderately negative relation between HbA1C and ferritin in group I (r_s=-0.439, p= 0.05) as well as in group II (r_s=-0.447, p<0.05). There is only a weak, positive relation between HbA1C and NLR levels in group I (r_s=-0.014, p>0.05) as well as in group II (r_s=-0.054, p>0.05). HbA1C shows a negative relation with PLR in both groups, although the relation is not statistically significant in either group (r_s= -0.14, p> 0.05 in group I and r_s=-0.09, p> 0.05 in group II).

4. Discussion

The present study was undertaken to investigate a menopause-status-specific difference in levels of inflammatory markers and to establish the role of menopause in modulating the relationship between inflammation and glycemic control in diabetic women. Utilizing different inflammatory markers, previous studies have inspected the association between inflammation and menopausal status in diabetic females. For instance, one of the previous research showed higher levels of ESR (erythrocyte sedimentation rate) in diabetic patients than in healthy controls, suggesting a role of inflammation in the disease pathogenesis.[9] In our study, an inflammatory marker PLR showed a difference in serum levels between pre and post-menopausal diabetic patients, which depicts a difference in systemic inflammation related to menopause. These results demonstrated that inflammatory changes occur in postmenopausal diabetic women, which can contribute to the development of metabolic dysfunction and insulin resistance.

In our study, median serum ferritin in postmenopausal diabetic women was lower as compared to premenopausal diabetic women. This is contrary to the results of Hui Ma et al,[10] who demonstrated a significantly lower concentration of serum ferritin in pre-menopausal women compared with post-menopausal women. This is likely attributable to menstrual iron loss in pre-menopausal women. The difference in results lies in the fact that several factors are known to affect ferritin levels e.g. ethnicity, changes in oestrogen levels after menopause,[10] insulin resistance,[11] use of hormone replacement therapy,[12] among others. These factors need to be assessed to understand the complex relationship between ferritin and menopause. In addition, there may be inadequate consideration of potential confounding effects on the relationship.

Our study shows insignificant difference in NLR among the pre-menopausal and post-menopausal diabetic females. While menopausal status is related to alterations in inflammatory pathways, present findings documented that these changes might not manifest as noticeable differences in NLR among diabetic females. The magnitude of the NLR levels is subjected to

variability, depending upon multiple demographic and lifestyle factors using data from the NHANES (National Health and Nutrition Examination Survey) survey, Howard et al. have recently shown that multiple demographic and lifestyle factors are associated with NLR, and independently of important comorbidities, including heart disease, cancer, DM2, and hypertension.[13]

In the present study, we observed that pre-menopausal T2DM patients had significantly higher HbA1c levels compared to those previously diagnosed. This might be the effect of using medication for longer periods in patients with long-standing diabetes. Our results are supported by the study of Justus et al. who showed that there is a high prevalence of poor glycemic control among diabetic women of reproductive age.[14]

The current study demonstrated that the comparison between the two groups for haemoglobin did not establish significant differences. The insignificant difference in haemoglobin levels between the menopausal diabetic females indicates that menopausal status may not have a significant influence on erythropoiesis in this study population. Previous studies investigating the association between pre- and post-menopausal status and haemoglobin levels in diabetic women have given mixed results.[15]

The present study shows a reverse relationship between glycemic control and iron stores in both groups (pre- and post-menopausal) of diabetics. This may be because hyperglycaemia may enhance iron utilization or disrupt iron homeostasis, potentially exacerbating complications in diabetic individuals. Our results are from the study conducted by Satriawibawa et al. which showed similar results concerning the relation between HbA1c and ferritin levels in diabetic patients although the study population was different.[16]

Our study found an insignificant relationship between glycemic control (HbA1C), and systemic inflammation, as determined by NLR, in diabetic women at different stages of menopause. Menopausal status could interact with other variables such as hormonal fluctuations or comorbidities, diluting the direct impact of glycemic control on inflammation. Our results are contrary to Dr Abhay Jain et al,[17] who reported a strong positive correlation between HbA1c and NLR in a group of diabetic patients.

The present study found an inverse relationship between glycosylated Hb and PLR in both group I (pre-menopausal) and group II (post-menopausal) diabetic females. Nevertheless, this association was not statistically significant in each group. The observed relationship did not reach statistical significance. Our findings are contrary to a previous study that has also reported that NLR and PLR are significantly associated with poor glycemic control in diabetic patients. For example, a study by M. Swathi et al. stated that NLR and PLR were found to be significantly associated with poor glycemic control.[18]

The present study applied a cross-sectional study design, which only permits associations to be determined at a single point in time. Further, longitudinal prospective studies would grant more robust evidence of the relationships between menopausal status, glycemic control, and inflammatory markers in diabetic women. We did not involve all possible covariates that could affect the relationships between inflammatory markers, menopausal status, and glycemic control in diabetic women. Future studies should consider additional factors such as dietary habits, physical activity, medication history, sleep quality and comorbidities.

5. Conclusion

The interaction between menopause and T2DM affected platelet to platelet-to-lymphocyte ratio but not the neutrophil-to-lymphocyte ratio. Also, ferritin levels are decreased in postmenopausal diabetic women. Further, glycemic status is not the only risk factor for predicting inflammation in diabetics, other risk factors have to be catered to evaluate the inflammation status of diabetic pre and postmenopausal females.

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S.A, A.Z - Conception of study
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W.U.K - Critical Review
- Facilitation and Material analysis

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References

1. Khan MAB, Hashim MJ, King JK, Govender RD, Mustafa H, Kaabi J Al. Epidemiology of Type 2 diabetes - Global burden of disease and forecasted trends. J Epidemiol Glob Health. 2020 Mar 1;10(1):107–11. https://doi.org/10.2991/jegh.k.191028.001
2. Cerdas Pérez S. Menopause and diabetes. Climacteric [Internet]. 2023 May 4;26(3):216–21. Available from: doi:10.1080/13697137.2023.2184252
3. Paschou SA, Anagnostis P, Pavlou DI, Vryonidou A, Goulis DG, Lambrinoudaki I. Diabetes in menopause: risks and management. Curr Vasc Pharmacol. 2019;17(6):556–63. https://doi.org/10.2174/1570161116666180625124405
4. Elimam H, Abdulla AM, Taha IM. Inflammatory markers and control of type 2 diabetes mellitus. Diabetes Metab Syndr Clin Res Rev. 2019 Jan 1;13(1):800–4. https://doi.org/10.1016/j.dsx.2018.11.061
5. McCarthy M, Raval AP. The peri-menopause in a woman's life: a systemic inflammatory phase that enables later neurodegenerative disease. Journal of Neuroinflammation. BioMed Central Ltd 2020; 17.
6. Kesav S, Ponnudhali D. Serum ferritin in pre-diabetes & diabetes mellitus type 2 and its relationship with glycemic status. Int J Clin Biochem Res. 2021;4(4):338–41.
7. Merlo F, Groothof D, Khatami F, Ahanchi NS, Wehrli F, Bakker SJL, et al. Changes in Iron status biomarkers with advancing age according to sex and menopause: a population-based study. J Clin Med. 2023;12(16):5338. https://doi.org/10.3390/jcm12165338
8. Ren Y, Zhang M, Liu Y, Sun X, Wang B, Zhao Y, et al. Association of menopause and type 2 diabetes mellitus. Menopause. 2019 Mar 1;26(3):325–30. https://doi.org/10.1097/gme.0000000000001200
9. Nadeem A, Naveed AK, Hussain MM, Raza SI. Correlation of inflammatory markers with type 2 diabetes mellitus in Pakistani patients. J Postgrad Med Inst. 2013;27(3):267–73.
10. Ma H, Lin H, Hu Y, Li X, He W, Jin X, et al. Serum ferritin levels are associated with insulin resistance in Chinese men and post-menopausal women: the Shanghai Changfeng study. Br J Nutr [Internet]. 2018/09/07. 2018;120(8):863–71. Available from: https://www.cambridge.org/core/product/5834FD4050DA4A328B6FB6AF14A0F4BC. https://doi.org/10.1017/s0007114518002167
11. Ma W, Jia L, Xiong Q, Feng Y, Du H. The role of iron homeostasis in adipocyte metabolism. Food Funct. 2021;12(10):4246–53. https://doi.org/10.1039/d0fo03442h
12. Xu T, Cai J, Wang L, Xu L, Zhao H, Wang F, et al. Hormone replacement therapy for postmenopausal atherosclerosis is offset by late age iron deposition. Finn A, Isales C, editors. Elife [Internet]. 2023;12:e80494. doi:10.7554/eLife.80494
13. Howard R, Scheiner A, Kanetsky PA, Egan KM. Sociodemographic and lifestyle factors associated with the neutrophil-to-lymphocyte ratio. Ann Epidemiol. 2019;38:11–21. https://doi.org/10.1016/j.annepidem.2019.07.015
14. Nondi, M J. Quality of Glycemic Control Among Diabetic Women of Reproductive Age At Kenyatta National Hospital in 2019 , a Cross-Sectional Study. 2019; Available from: http://erepository.uonbi.ac.ke/handle/11295/109182
15. Trtica Majnarić L, Guljaš S, Bosnić Z, Šerić V, Wittlinger T. Neutrophil-to-lymphocyte ratio as a cardiovascular risk marker may be less efficient in women than in men. Biomolecules. 2021;11(4):528. https://doi.org/10.3390/biom11040528
16. Satriawibawa IWE, Arimbawa IM, Ariawati K, Suparyatha IBG, Putra IGNS, Hartawan INB. Serum iron is negatively correlated with the HbA1c level in children and adolescents with type 1 diabetes mellitus. Clin Pediatr Endocrinol. 2022;31(4):242–9. https://doi.org/10.1297/cpe.2022-0012
17. Jain A, Bhatt K, Purohit CP, Sanadhya HC. Correlation of HBA1c and neutrophil lymphocyte ratio in type 2 diabetes mellitus as a marker of blood sugar control–A case control study.
18. Swathi M, Ramya T, Gangaram U, Kumar KJK, Sandeep B. a Study of Neutrophil To Lymphocyte Ratio (Nlr) and Platelet To Lymphocyte Ratio (Plr) With Glycosylated Hemoglobin (Hba1C) Among Type-2 Diabetic Patients. 2023;1533–7.