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EDITORIAL

Holistic Care of Women: Mind, Body, and Hormones

Syeda Batool Mazhar

Doctors today practice allopathic medicine, an evidence-based system of care, where effective treatments are based on trials and studies. A scientific alternative system is osteopathic medicine, focusing on holistic approach by including mind and spirit in addition to the body. Homeopathic and Ayurvedic medicine are included in alternative therapeutic options with less support from the global scientific community. Currently, in the developed countries, modern medicine is transitioning to client centered care and shared decision making in clinical practice. This is driven by the educated, well aware and discerning clients presenting in their clinics and hospitals.

The biopsychosocial model, proposes that health and illness are consequences of complex interplay of biological, psychological, and social factors.[1] Engel, a lead proponent of this model suggests that a physician's "basic professional knowledge and skills must span the social, psychological, and biological, for his decisions and actions on the patient's behalf to involve all three." [2] Mind & Body medicine can therefore provide a unique approach to health promotion in the community.

The linkage of public health with clinical medicine for primary, secondary and tertiary prevention of diseases can also be pivotal for change.[3] The non-communicable conditions affecting women reproductive health such as polycystic ovary syndrome (PCOS), endometriosis, adenomyosis, anemia and subfertility followed by post reproductive problems like menopause transition are increasingly being managed in a holistic fashion rather than with just polypharmacy.

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PCOS is an endocrine disorder with varying degrees of hyperandrogenism, insulin resistance and metabolic syndrome. It affects 1 in 15 women globally. While there is no cure for PCOS, several medical treatments, such as the combined oral contraceptive pill, can help manage its symptoms. However, increasingly a more natural approach is being preferred which includes weight loss, exercise, dietary changes, herbal supplements and probiotics to improve the immune system. In PCOS associated anovulatory subfertility, extracts from aloe vera and chamomile increase the number of ovarian follicles thereby assisting conception. Similarly, de chiro inositol, cinnamon and ginseng improve impaired glucose tolerance in PCOS patients. As side effects are minimal, patient satisfaction is improved although the treatment takes longer to be effective compared to standard medications.[4]

Endometriosis, another common chronic condition, is associated with pelvic pain and subfertility. Sometimes conventional medical and surgical treatments do not provide effective pain relief and side effects of medications may limit their use. The holistic strategies for managing endometriosis related pelvic pain include nutritional interventions, cognitive behavioral therapy, acupuncture, traditional Chinese medicine and transcutaneous electrical nerve stimulation. Such holistic management strategies are increasingly being incorporated into routine counselling when offering conservative, medical and or surgical treatments for endometriosis.[5]

In a longitudinal study in Australia, analyzing pregnant women's attitudes towards the use of Complementary and Alternative Medicine (CAM) products in pregnancy, one third of 1835 respondents used herbal products. The women using CAM, like aromatherapy and homeopathy wanted greater personal control over their body. Their personal experience of CAM benefits led to preference for alternatives over the maternity care providers' standard advice.[6]

Finally, all women menstruating during the reproductive years will go through menopause with decrease in the hormones, estrogen and

progesterone. The common symptoms women experience during perimenopause include hot flashes, night sweats with sleep disturbance, mood swings, forgetfulness, weight gain and fatigue. Hormone therapy (HT) remains the most effective treatment for vasomotor symptoms and can be advised in selected menopausal women within 10 years of their last menstrual period. For women with contraindications to HT like estrogen-dependent cancers or cardiovascular disease or personal preference, it is important for doctors to be well informed about nonhormone treatment options that are supported by evidence.[7]

Choices commonly used by women in dealing with menopause symptoms include intake of natural soya products, flaxseeds and sprouted legumes which have plant estrogens. These phytoestrogens may help relieve some symptoms like hot flashes and poor sleep. Drinking eight to ten glasses of water per day can help with bloating and vaginal dryness caused by hormone fluctuations. Supplements like Black Cohosh, Vitex or Chasteberry also relieve hot flashes. Exercise, Acupuncture, Aromatherapy, Volunteering, Spiritual practices, including meditation are useful for managing stress at menopause.[8] The importance of this concept is highlighted by the choice of the theme of world menopause day by International Menopause Society on 18th October 2025 is "Life Style Medicine in Menopause".

It is time to rethink alternative medicine and this should be offered in our clinics and hospitals. This can contribute to increased patient satisfaction and contribute to better outcomes in managing these complex conditions.

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ORIGINAL ARTICLE

Short-Term Outcomes of Immediate Postpartum Intrauterine Device Insertion

Sana Hafeez[1], Hafsa Irshad[2], Fareeha Usman[3], Aiman Yousuf[4], Joveria Sadaf[5], Sana Aara[6]

ABSTRACT

Objective: To determine the short-term outcomes of intrauterine contraceptive device insertion performed immediately after childbirth.

Study Design: Descriptive case series.

Place and Duration of Study: The department of Obstetrics & Gynaecology, Shahida Islam Medical and Dental College (SIMDC), Lodhran, from April 23, 2021 to October 22, 2021.

Materials and Methods: One hundred and fifty women were selected by non-probability consecutive sampling. The patients requiring post-partum contraception and fulfilling selection criteria were included in the study after informed consent. Follow up was done for 3 months after insertion of IUCD and complications such as expulsion, vaginal discharge, menstrual irregularities and lost string, were recorded on a pre-designed proforma. The SPSS version 27.0 was used for data analysis. Women's age, BMI and parity were analysed as mean and standard deviation. Complications of insertion of IUCD were recorded as frequency and percentage. Chi-square test was applied to check post stratification statistical significance. The *p* value ≤ 0.05 was considered statistically significant.

Results: The mean age of the women was 26.79 ± 4.48 years. Thirty-nine (26%) women delivered vaginally and 111 (74%) women by caesarean section. The mean body mass index of women was 26.16 ± 5.44 kg/m^2. Seventeen (11.3%) females had menstrual disturbance, 24 (14.7%) had vaginal discharge, 47 (31.3%) reported with lost string and 10 (6.7%) with IUCD expulsion. Out of these reported complications, only vaginal discharge demonstrated a statistically significant association (p = 0.013).

Conclusion: The postpartum IUCD insertion is safe and effective method of contraception, with minimal complications such as expulsion, vaginal discharge, menstrual irregularities and lost string, none of which are life threatening.

Key Words: *Contraception, copper IUCD, expulsion, insertion, postpartum, PPIUCD (postpartum intrauterine contraceptive device).*

Introduction

Family planning during the postpartum period is a crucial component of maternal and reproductive health. Historically, emphasis has been placed on interval contraception, often overlooking the risk of unintended pregnancies soon after childbirth. Most couples express the desire to delay the next pregnancy following delivery. Howe, a significant proportion of couples lack adequate awareness or access to contraception, which contributes to unplanned pregnancies within short intervals.[1]

It is estimated that a substantial number of women conceive within 18 months of childbirth, [2] and globally, millions of pregnancies are classified as unintended each year, many of which result in induced abortion.[3] In countries like Pakistan, despite the availability of family planning services, contraceptive uptake remains suboptimal, ranging from 16–46%, and only about 32% of couples report using a family planning method. [4] In Sub-Saharan Africa and other low-income settings, only 25% of the population uses contraception, further exacerbating the rate of unplanned pregnancies. [5]

The postpartum period presents an ideal opportunity for initiating contraception, as couples are often more receptive to family planning during this time. While contraception is conventionally started at the six-week postnatal visit, many women

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miss follow-ups later due to their busy schedule, which makes them vulnerable to early, unintended pregnancies. Recognizing this, various global health bodies have emphasized the importance of integrating contraceptive counselling and services into the immediate postpartum period.[6,7,8]

The postpartum intrauterine contraceptive device (PPIUCD) is a significant advancement in immediate postpartum contraception. It can be inserted within 10 minutes to 48 hours after placental delivery and offers several advantages: it is long-acting, reversible, safe during breastfeeding, and provides immediate and effective protection against pregnancy and is associated with high continuation rates when properly inserted.[2]

Despite these benefits, the global uptake of PPIUCD remains inconsistent. This is due to a range of barriers, including sociocultural beliefs, limited public awareness, and inadequate provider training. Financial constraints and access issues also play a critical role, with around 17% of women citing such reasons for non-use of contraception.[9,10] While the method is globally endorsed, there remains limited local data on the short-term outcomes of PPIUCD use from Pakistan, especially concerning expulsion rates, lost strings, bleeding irregularities, infection, and patient satisfaction in low-resource settings. Most exiting research focuses on long-term outcomes or lacks context-specific findings.[4]

To address this gap, we conducted a study to evaluate the short-term clinical outcomes of IUCD insertion immediately following childbirth. Furthermore, the aim was to contribute to the evidence-based guide for future implementation strategies, that could provide training in similar contexts.

Materials and Methods

This descriptive case series study was conducted in the Obstetrics and Gynaecology Department of Shahida Islam Medical and Dental College, Lodhran, over six months duration starting from April 23, 2021 to October 22, 2021, after obtaining approval from the ethical review committee (ERC letter no. SIMC/H.R./7250/21).

The sample size was calculated using 95% confidence level, a 6% margin of error, and an expected copper IUCD expulsion rate of 12%.[13] A total of 150 patients were enrolled through non-probability consecutive sampling, after obtaining verbal informed consent outlining the benefits and potential risks of the procedure.

Married women aged 20–35 years, admitted for either caesarean section or normal vaginal delivery, requiring postpartum contraception were included in the study.

Exclusion criteria included fever >100°C, vaginal infections, membrane rupture >24 hours, uterine anomalies on ultrasound, manual placenta removal, and primary postpartum haemorrhage (>500 ml in vaginal delivery, >1000 ml in caesarean section).

The IUCD insertion was followed by monthly assessments for three months, with complications recorded on a structured proforma by the researchers. The proforma's internal consistency was assessed with a Cronbach's alpha of 0.82, indicating good reliability. The age, body mass index (BMI), parity, mode of delivery and complications of PPIUCD, such as expulsion, vaginal discharge, menstrual irregularities and lost string, were recorded. Lost thread and abnormal vaginal discharge were confirmed on per speculum examination and ultrasound was done to confirm the presence of copper IUCD in the uterus.

Data was analysed by using SPSS version 27.0. The age, body mass index (BMI), and parity were expressed as mean ± standard deviation, while qualitative variables (IUCD insertion complications) were reported as frequencies and percentages. Post-stratification statistical significance was analysed using the Chi-square test. The p value ≤ 0.05 was considered statistically significant.

Results

The distribution of the females based on their age, BMI, parity and mode of delivery is shown in Table I, in terms of mean ± SD and percentages. The short-term complications including menstrual disturbance, vaginal discharge, lost strings and expulsion of IUCD are shown in Table II and III.

The mean age of women was 26.94 ± 4.48 years. Regarding parity, 67 women (44.7%) were para 1 while 83 (63.3%) were para ≥ 2. The mode of delivery was vaginal in 39 (26%) females and 111 women (74%) were delivered by caesarean section. The mean BMI was 26.16 ± 5.45 kg/m^2.Vaginal discharge was seen more frequently in the group in whom

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PPIUCD was placed vaginally as compared to caesarean section and was statistically significant (*p* value = 0.013).

Regarding complications 17 (11.3%) females had menstrual disturbance (17.9 % in those who delivered vaginally and 10 % with caesarean section), 22 (14.7%) had vaginal discharge (2.6% v/s 18.9%), 47 (31.3%) reported with lost string and 10 (6.7%) had expulsion of IUCD 7.7% v/s 6.3 %).

Discussion

This study evaluates short-term outcomes of PPIUCD insertion. The findings include menstrual disturbances in 11.3% (p=0.130), vaginal discharge in 14.7% (p=0.013), lost IUCD strings in 31.3% (p=0.129), and expulsion in 6.7% (p=0.765). These outcomes reinforce that while PPIUCD is an effective and reversible contraceptive option and only the vaginal discharge may influence user continuation and satisfaction.

The expulsion rate in this study was 6.7%. This aligns

Table I: Demographic Variables (n=150)

Demographic Variables	Subgroups	Number of patients (n=150)	Percentage (%)	Mean±SD
Age in years	20-29	106	70.66 %	26.49 ± 4.48
	30-35	44	29.33 %	
BMI (kg/m^2)	Under Weight	18	12 %	26.16 ± 5.44
	Normal	45	30 %	
	Overweight	39	26 %	
	Obese	48	32 %	
Parity	Primipara	67	44.66%	1.55 ± 0.50
	Multipara	83	55.33%	
Mode of delivery	Vaginal delivery	39	26%	1.74 ± 0.44
	C section	111	74%	

Table II: Short Term Complications (n=150)

		Menstrual Disturbance		Vaginal Discharge		Lost strings		Expulsion of IUCD	
		Yes (n=17)	No (n=133)	Yes (n=22)	No (n=128)	Yes (n=47)	No (n=103)	Yes (n=10)	No (n=140)
Age in years	20-29 (n=106)	12 (11.3%)	94 (88.7%)	16 (15.6%)	90 (84.9%)	32 (30.2%)	74 (69.8%)	6 (5.7%)	100 (94.3%)
	30-35 (n=44)	5 (11.4%)	39 (88.6%)	6 (13.6%)	38 (86.4%)	15 (34.1%)	29 (65.9%)	4 (9.1%)	40 (90.9%)
	p value	0.155		0.426		0.961		0.533	
BMI (Kg/m2)	Under Weight (n=18)	1 (5.6%)	17 (94.4%)	1 (5.6%)	17(94.4%)	6 (33.3%)	12 (66.7%)	1 (5.6%)	17 (94.4%)
	Normal (n=45)	9 (20.0%)	36 (80.0%)	8 (17.8%)	37 (82.2%)	15 (33.3%)	30 (66.7%)	5 (11.1%)	40 (88.9%)
	Over weight (n=39)	4 (10.3%)	35 (89.7%	4 (10.3%)	35 (89.7%)	11 (28.8%)	28 (71.8%)	2 (5.1%)	37 (94.9%)
	Obese (n=48)	3 (6.3%)	45 (93.8%)	9 (18.8%)	39 (81.3%)	15 (31.3%)	33 (68.8%)	2 (4.2%)	46 (95.8%)
	p value	0.155		0.426		0.961		0.533	

*The *p* value ≤ 0.05 was considered statistically significant .

Table III short Term Complications

		Menstrual Disturbance		Vaginal Discharge		Lost string		Expulsion	
		Yes (n=17)	No (133)	Yes (n=22)	No (n =128)	Yes (n=47)	No (n=103)	Yes (n=10)	No (n=140)
Parity	**Primi (n=67)**	7 (10.4%)	60 (89.6%)	11 (16.4%)	56 (83.6%)	24 (35.8%)	43 (64.2%)	5 (7.5%)	62 (92.5%)
	Multi (n=83)	10 (12.0%)	73 (88.0%)	11 (13.3%)	72 (86.7%)	23 (27.7%)	60 (72.3%)	5 (6.0%)	78 (62.5 %)
	P value	0.759		0.586		0.287		0.725	
Mode of delivery	**Vaginal (n=39)**	7 (17.9%)	32 (82.1%)	1 (2.6%)	38 (97.4%)	16 (41.0%)	23 (59.0%)	3 (7.7%)	36 (29.3%)
	C section (n=111)	10 (9%)	101 (91%)	21 (18.9%)	90 (81.1%)	31 (27.9%)	80 (72.1%)	7 (6.3%)	104 (93.7%)
	P value	0.130		0.013*		0.129		0.765	

*The *p* value ≤ 0.05 was considered statistically significant.

with Dorairajan *et. al.,*[11] who reported a 5% expulsion rate, and is lower than Nahas *et. al.,*[12] who noted 8.5% and Ashraf *et. al.,*[13] who reported 11%. Our comparatively lower rate could be due to 74% of insertions performed during caesarean delivery, allowing direct visualisation and precise fundal placement. Like the findings of Levi *et. al.,*[14] caesarean-based insertions tend to result in fewer expulsions than vaginal insertions, likely due to more controlled insertion conditions.

In our study, 31.3% of participants experienced missing IUCD strings. This finding aligns with a multicenter study conducted across six countries, which reported missing strings in 29% of cases, with a higher incidence following caesarean deliveries compared to vaginal deliveries.[15] Similarly, a study by Gurney *et. al.,*[16] found that 23.5% of women had no visible strings at six weeks postpartum after vaginal delivery. The higher incidence of missing strings in caesarean deliveries may be due to the difficulty in ensuring proper string placement during surgery. Adequate training in string management and follow-up techniques, such as ultrasound localization, can mitigate concerns.[17]

Menstrual disturbances occurred in 11.3% of patients. This is in line with the study by Mishra *et. al.,*[18] which observed menstrual irregularities in 13.3% of PPIUCD users. A study conducted in Pakistan reported menstrual irregularities in 30.1% of PPIUCD users. The lower rate in our study could be due to differences in patient populations, insertion techniques, or reporting methods.[19] These symptoms are typically due to local endometrial inflammation caused by the copper ions, as supported by Che *et. al.,*[20] who noted changes in cervical mucus and suppression of the endometrial lining. Variability may stem from baseline differences in menstrual patterns or from cultural perceptions of normal bleeding.

Vaginal discharge was reported in 14.7% of participants. Similar findings were documented by Pati *et. al.,*[20] who found vaginal discharge in 13% of PPIUCD users. However, higher rates (up to 19%) were reported by Singh *et. al.,*[21] in a community-based Indian study. Differences may be due to variations in hygiene practices, insertion techniques, or patient education on normal versus pathological discharge. It is important to distinguish physiological discharge from infection-related symptoms, which require prompt assessment.

Our high caesarean delivery rate (74%) likely contributed to reduced expulsion rates, consistent

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with findings from Levi *et. al.,*[14] and Grimes *et. al.,*[23] who showed lower expulsions when IUCD was inserted during caesarean section. Visual confirmation of placement and uterine closure over the IUCD minimise chances of malposition and expulsion.

Our study observed an expulsion rate of 6.7%. This finding aligns with a recent systematic review and meta-analysis, which reported that IUD expulsion rates vary by delivery method: 14.8% for vaginal deliveries and 3.8% for caesarean deliveries.[23] Similarly, a prospective observational study found that patients who delivered vaginally were 4.23 times more likely to experience IUD expulsion compared to those who had caesarean sections.[24] The higher expulsion rates associated with vaginal deliveries may be due to uterine contractions and anatomical changes postpartum. In contrast, caesarean deliveries allow for direct visualization and placement of the IUD at the fundus, potentially reducing expulsion risk.

Pre-insertion counselling plays a vital role in patient satisfaction and continuation. Raghuwanshi *et. al*.,[25] stressed antenatal counselling as essential to reduce anxiety and improve acceptance of potential side effects. Additionally, early follow-up ensures identification of complications such as expulsion or infection. Training clinicians to check device positioning via ultrasound at six weeks can further improve retention.

The study was limited by a short follow-up period and lack of hormonal IUCD comparison.

Consistency with regional studies supports generalisability, while minor variations emphasise the ongoing need for clinician training, patient counselling, and postpartum follow-up.

Conclusion

The postpartum IUCD insertion is safe and effective method of contraception, with minimal complications such as expulsion, vaginal discharge, menstrual irregularities and lost string, none of which are life threatening.

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CONFLICT OF INTEREST

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DATA SHARING STATEMENT

The data that support the findings of this study are available from the corresponding author upon request.

ORIGINAL ARTICLE

Interobserver Variability in HER2 Breast Biomarker Reporting: Implications for Diagnostic Consistency and Treatment Precision

Hira Batool, Sameen Afzal, Fatima Khalid, Saira Javeed, Zonaira Rathore, Akhter Sohail Chughtai

ABSTRACT

Objective: To assess the interobserver variability in HER2 immunohistochemical stain interpretation by pathologists of different strata of experience.

Study Design: Cross-sectional observational study.

Place and Duration of Study: Chughtai Institute of Pathology at Lahore, during a three-month interval from 01/6/2024 to 31/8/2024.

Materials and Methods: Fifty cases (n=50) of invasive breast cancer were included by random probability sampling and blocks were retrieved through respective biopsy reports by the laboratory information system. All the cases of ductal carcinoma in situ (DCIS) and salivary gland-like tumors of the breast were excluded. HER2 antibody was applied to these cases and interpreted by four histopathologists with varying years of reporting experience. Interobserver variability was observed by using the Cohen's and Fleiss kappa tests. A *p-value* of ≤0.05 was considered statistically significant.

Results: All patients were female, with a mean age of 46.3 years ± 12.87. The highest concordance was observed at a score of 3, while the greatest discordance occurred at a score of 2, with kappa values of 0.81 and 0.35, respectively, and a p-value of <0.01.

Conclusion: The highest interobserver variability was observed in the assessment of HER2 score 2, highlighting the challenges in interpreting equivocal cases.

Key Words: *ASCO Guidelines, Equivocal Cases, Human Epidermal Growth Factor Receptor 2, Interobserver Variability, Invasive Breast Cancer.*

Introduction

Breast cancer is one of the most prevalent cancers in the world. Its incidence is 12% all over the world.[1] Various risk factors are associated with the occurrence of breast cancer, and they include age, with higher prevalence in women more than 50 years, family history, obesity, and excessive alcohol consumption along with hormone replacement therapies.[2-4] Multifaceted treatment options are available for breast cancer. One of the commonly employed treatment options is targeted therapy given against estrogen receptors (ER), progesterone receptors (PR), and human epidermal growth factor receptor 2 (HER2).[5,6] Various immunohistochemical tests are done on tissue biopsies of breast tumors to detect the expression of these biomarkers.[7]

Approximately 20-25% of breast cancers are positive for HER2 immunohistochemical stain.[8] HER2 is a transmembrane receptor with tyrosine kinase activity and plays a pivotal role in cell signaling, differentiation, and angiogenesis and therefore plays an important role in malignant transformation.[9, 10] Breast cancers can exhibit a 40 to 100-fold increase in HER2 protein.[11] According to 2018 the American Society of Clinical Oncology (ASCO) guidelines, HER2 expression has been categorized as a score of 0, 1, 2, or 3 based on the intensity of membranous expression. Recent 2023 ASCO Guidelines have suggested recategorization of HER2 scores to ultra-low expression at score 0, low HER2 expression at scores 1+ and 2+ In Situ Hybridization (ISH) negative, and high expression at score 3+ due to a recently conducted trial on the trastuzumab response in patients with HER2 Score 1 or 2. It was observed that those patients responded well to anti-HER2 therapy, and the overall survival rate was also increased.[12-13] However, the College of American Pathologists (CAP) and ASCO guidelines 2023 have not yet applied the

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results of this study to the treatment regimen as this study excluded the treatment response of HER 2 score 0 as it is thought that in the future these tumors might show expression of HER2 by sensitive techniques. Due to the higher predictive power of HER2 immunostaining, the present practice of oncologists is to treat patients with trastuzumab who present with metastatic disease or early-stage breast cancer with HER2 score of 3 on immunohistochemistry and HER2 equivocal score, which is further amplified on fluorescence in situ hybridization (FISH) studies.[14,15] Scores 0 and 1 are contemplated as not eligible for treatment. However, these results are subject to variability owing to different aspects, such as preanalytical variables, the types of antibodies used, staining methods, and interpretation by different histopathologists. Due to the difference in ethnicity of our region, we expect different results and therefore, it is important to score this biomarker meticulously for optimal management.[16] It is evident that HER2 biomarker expression is of pivotal importance in the diagnosis and devising treatment regimen, however, the major caveat is the variation in the interrater variability in its scoring. In recent years, the issue has been studied well internationally, however, there is a dearth of research focused on the interrater variability in our region, where differences in laboratory practices, pathologist training, and, adherence to international guidelines can significantly influence diagnostic accuracy and consistency. Therefore, the study is novel and to the best of our knowledge, is the first of its kind in Pakistan. This study was designed to assess the inter-rater variation in the immunohistochemical staining interpretation of HER2 antibody among pathologists and to highlight the significance of accurately scoring this parameter according to internationally recommended guidelines to ensure optimal treatment of breast cancer patients.

Materials and Methods

This cross-sectional observational study was conducted at the Chughtai Institute of Pathology (CIP), Lahore lasting three months from 01/06/2024 to 31/8/2024 after getting IRB approval (IRB#1277/IRB/ CIP). Fifty diagnosed and reported cases of invasive breast cancer booked in the mentioned period were selected by random probability sampling techniques after retrieving respective laboratory reports by the laboratory information system. Cases of ductal carcinoma in situ (DCIS) and salivary gland-like tumors of the breast were excluded. HER2 immunohistochemical stains were employed on slides prepared from paraffin-embedded tumor blocks. The type of antibody applied was polyclonal rabbit anti-human c-erbB-2 oncoprotein using Dako Link 48 automatic stainer. External control was applied to each batch of cases for quality assurance. Four pathologists interpreted the results, of which three were general histopathologists and the fourth was breast subspecialist histopathologist. The three general histopathologists hold different years of reporting experience upto 5 years, are of Pakistani nationality, and have an age range from 35 to 40 years. These three general histopathologists independently scored all fifty slides of HER2 hormone receptor antibody according to 2018 ASCO guidelines which define a score 0 if there is no staining or less than 10% expression on tumor cell membranes, a score of 1 if the weak expression on membranes of more than 10% tumor cells, score 2 if there is moderate but patchy expression on membranes in more than 10% neoplastic cells, or absolute expression on membranes in more than 10% neoplastic cells, score 3 if there is peak, complete staining on membranes in more than 10% tumor cells and individually submitted their results.[9] All were blinded to each other's assessment and designated observers 1, 2, and 3. Then a consensus opinion on the HER2 score of each case was made by all three general histopathologists along with the most experienced fourth breast subspecialist histopathologist allotted as observer 4 having experience of up to 10 years in reporting breast hormone receptors, Pakistani nationality, and 45 years of age. This consensus score was considered a gold standard score, and results were submitted as reported by observer 4. The statistical analysis was done by entering the scores of all 50 cases submitted by all four observers into SPSS version 29. A *p-value* of ≤0.05 was considered statistically significant. The concordance between observers 1,2 and 3 scores was calculated with the consensus score conferred by observer 4 one by one by applying Cohen's kappa test. Further, interrater agreement among all the observers was measured by using the Fleiss multi-rater kappa test which is an

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extended form of Cohen's kappa. Kappa value was interpreted as no agreement at a score range of 0-0.20, minimal agreement with a score range of 0.21-0.39, weak agreement with a score range of 0.40-0.59, moderate agreement with a score range of 0.60-0.79, strong agreement with a score range of 0.80-0.90 and almost perfect agreement with a score above 0.90.

Results

The mean age of patients in 50 selected cases was 46.3 years, with a standard deviation of 12.87. All patients belonged to the female gender (100%). The most frequent breast cancer in this study was invasive breast carcinoma (IBC) of No Special Type (NST) 47 (94%), and the commonest grade was II 29 (58%) (Table I). According to the categorical scale mentioned in materials and methods, the interpretation of Cohen's kappa value following analyzing interobserver concordances of HER 2 scores (0-3) among observers 1, 2, and 3 was compared to the interpretation of results by observer 4. The results showed weak agreement between observers 1 and 3, with observer 4 having Cohen's kappa values of 0.54 and 0.57, respectively, and moderate agreement between observers 2 and 4 with a Cohen's kappa value of 0.71 (Table II). The Kappa value for the multi-rater Fleiss Kappa analysis was 0.65, which indicated moderate agreement among all observers (Table III). Interrater agreement on HER2 scores 0,1,2 and 3 was also acquired. The results illustrated nearly perfect agreement on score 3, moderate agreement on scores 0 and 1, and weak agreement on an equivocal score of 2 (p value<0.01). (Table IV).

Table I: Histopathological Features of Breast Cancer Cases Included in This Study

Attributes		N (%)
Histologic type	IBC NST	47 (94%)
	Mucinous carcinoma	1 (2%)
	Pleomorphic lobular carcinoma	1 (2%)
	Invasive lobular carcinoma	1 (2%)
Histologic grade	Grade I	2 (4%)
	Grade II	29 (58%)
	Grade III	19 (38%)
Estrogen receptor (ER)	Positive	31 (62%)
	Negative	18 (36%)
	Not applied	1 (2%)
Progesterone receptor (PR)	Positive	30 (60%)
	Negative	19 (38%)
	Not applied	1 (2%)

IBC NST: Invasive Breast Carcinoma, No Special Type

Table II: Interobserver/Interrater Cohen's Kappa Value for The Degree of Concordance Between Observers 1-3 With Observer 4

Inter-observer comparison	Cohen's Kappa value	p-value*
Observer 1 and 4 concordances	0.54	<0.01
Observer 2 and 4 concordances	0.71	<0.01
Observer 3 and 4 concordances	0.57	<0.01

***Statistically significant p-value <0.05**

Table III: Multi-Rater Fleis Kappa Statistics Value for The Overall Degree Of Concordance

Overall comparison	Fleiss Kappa value	p-value*
Overall concordance	0.65	<0.01

***Statistically significant p-value <0.05**

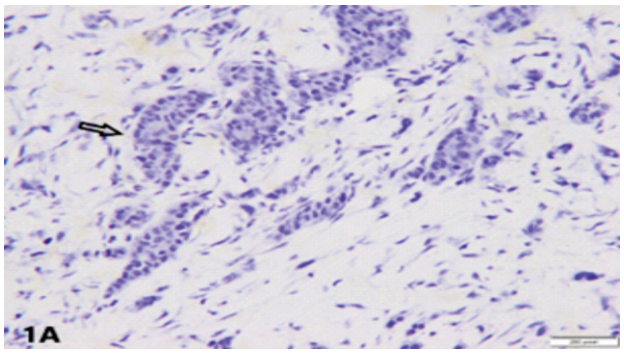
Table IV. Individual HER2 Score Agreement Status by Fleiss Kappa Statistics Value

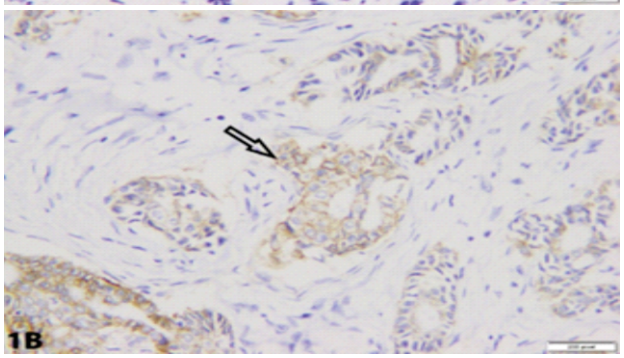
HER2 Score	Fleiss Kappa value	p-value*
0	0.73	<0.01
1	0.65	<0.01
2	0.35	<0.01
3	0.81	<0.01

***Statistically significant p-value <0.05**

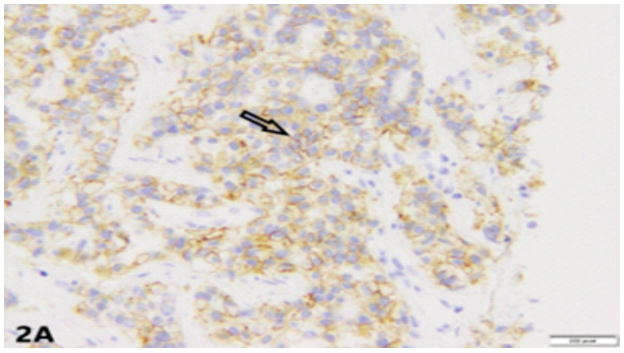
Discussion

The scoring of HER2 was done following the categorization by ASCO guidelines 2018 as negative at scores 0 (Figure 1A) and 1 (Figure 1B), equivocal at score 2 (Figure 2A), and positive at score 3 (Figure 2B).[17,18] Overall agreement by the Fleiss kappa test revealed moderate agreement among all the observers with a kappa value of 0.65 (p value < 0.01). The results showed the greatest conflict at HER2 score 2 (kappa value of 0.35; p value < 0.01) and the highest agreement at HER2 score 3 (kappa value of 0.81; p value < 0.01). Therefore, reporting score 2 cases can be the most challenging and this area needs to be improved as if scored erroneously this could affect the individual management of breast cancer patients.





1B. (400X magnification) manifests weak incomplete membranous staining of HER2 antibody in >10% neoplastic cells, scored 1



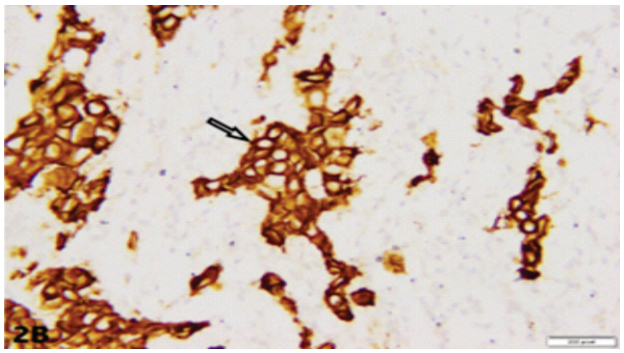


Figure 2A. (400X magnification) reveal moderate incomplete membranous staining in >10% neoplastic cells for HER2 antibody, scored 2 and Figure 2B. (400X magnification) depicts strong membranous immunostaining in >10% neoplastic cells for HER2 antibody, scored 3

Casterá and Bernet [19] found low to moderate interobserver concordance, with a kappa value of 0.2 to 0.4 among five observers, and also compared HER2 immunostain expression with ISH results. Concordance of HER2 immunostain was higher in ISH-positive cases as opposed to ISH-negative cases. The probable reason for the difference in opinion was the personalized interpretation of this biomarker. The analysis done by Sun *et al.,*[20] showed excellent agreement among observers and with digital image analysis as all the pathologists had expertise in breast cancer reporting in contrast to our study showing moderate concordance among general histopathologists as well as breast expert histopathologist with an overall kappa value of 0.65.

A study by Baez-Navarro *et al.,*[21] revealed low agreement at scores of 1 due to difficulty in the distinction between score 0 and 1 nonspecific staining and evaluating staining in 10% of tumor cells. This was in contrast to our study which had a moderate level of agreement at a score of 1. Umemura *et al.,*[22] conducted a research study and established a good level of agreement in immunostain interpretation among 10 laboratories and disagreement in results was due to different staining procedures in institutions. In contrast, our research study calculated interobserver concordance in one institution. Cross-institutional assessment by Robbins *et al.*[23] found substantial discordance at scores 1 and 2 using the 4-category scoring system (0,1,2, and 3) and higher agreement using the 3-category scoring system (0, low, and 3). The higher concordance in the latter 3-tier scoring system was due to the assembling of scores 1 and 2 as low scores, which made the interpretation untroubled.

Recently conducted studies by Baez Navarro et al.,[21] and Robbins et al.,[23] exhibited low concordance at scores 1 and 2 similar to our study which manifests discordance at scores 1 and 2, maximum at the latter. Among the 50 cases, 22 (44%) had discrepancies for multiple reasons encountered by the pathologists including faint membranous staining, conglomeration of the tumor, missing maximum interest area of HER2 antibody expression, and lack of experience. Among all the cases with ambiguity in our study, equivocal score 2 was the most controversial, because score 2 lies in the borderline

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category, neither positive nor negative making it a difficult zone for overall general pathologists, suggesting that such cases should be reported after receiving a second opinion from another pathologist having expertise in reporting breast pathology to counteract incorrect scoring practices and acquiring efficient training for HER2 reporting skills.

Recommendations and Limitations:

We did not correlate HER2 equivocal/score 2 with the fluorescence in situ hybridization (FISH) technique. So, we recommend that future studies should be conducted with a correlation of score 2 with the FISH studies.

Conclusion:

Based on our study objective, we found moderate interobserver concordance among pathologists with varying years of reporting experience in interpreting HER2 immunostain from scores 0 to 3. HER2 equivocal score 2 results, however, indicated significant interobserver variability. Thus, in order to minimize diagnostic discrepancies and to ensure optimal diagnosis, pathologists should be properly trained and consult interdepartmentally before interpreting HER2 immunostains.

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CONFLICT OF INTEREST

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DATA SHARING STATEMENT

The data that support the findings of this study are available from the corresponding author upon request.

ORIGINAL ARTICLE

Evaluation of Cross Match to Transfusion Ratio as a Tool of Quality Working In Tertiary Care Transfusion Services

Rabiah Asghar, Ayesha Junaid

ABSTRACT

Objective: To evaluate the cross match to transfusion (CT) ratio, transfusion probability (%TP), and transfusion index (Ti) of packed red cells as a tool of quality working in the blood bank.

Study Design: Descriptive observational study

Place and Duration of Study: This study was carried out from all indoor patient departments and blood bank over a 06 month period, from April 2024 to October 2024 at Shifa International Hospital

Materials and Methods: After receiving Institutional Review Board approval,
the sample size was calculated using the WHO Calculator 2.0, data was collected through blood bank (HMIS) and department wise CT ratio, TP% and TI were calculated, entered and analysed using SPSS version 26.

Results: 527 packed red cell products (RCC) were prepared after cross-matching, 198 (38%) were transfused, leaving 329(62%) unused with an overall cross CT of 2.6. These results showed that overall CT of blood bank was very close to target CT ratio . Departmental variations were observed, with surgery having a CT ratio of 2.1 indicating significant blood usage while Gynecology/Obstetrics and Liver transplant having 6.6, indicating over-requesting of blood products.

Conclusion: The study found that blood usage is generally acceptable, with a CT ratio of 2.6. However, significant variation was seen across departments: the surgical department had an efficient CT ratio of 2.1, while Gynecology/Obstetrics and Liver Transplant showed higher ratios (6.6), pointing to possible over-ordering and wastage. The results emphasize the need for targeted approaches, including department-specific protocols and regular audits, to optimize blood utilization.

Key Words: *Blood Typing, Cross Matching, Red Cells.*

Introduction

Transfusions of blood is a very useful therapeutic technique in hospitals. Obtaining whole blood from healthy donors, properly screening and making its components is included in blood transfusion services .The first blood transfusion was documented by James Bundell (obstetrician and physician) in December 22, 1818.[1]

The most important service of the blood bank is therapeutic rather than diagnostic. "Vein to vein" process incorporates all the stages starting from blood donation to patient transfusion.[2] A cross match test between a patient and a donor's blood is essential before any blood transfusion. As per the standard operating procedure, when blood centres receive requests for a specific number of blood units, the required units are reserved for the designated department after the routine cross-match is completed. Once cross-matching is done, the units are unavailable for other patients, ensuring that the blood products are allocated to the intended recipient. Furthermore blood units that are cross-matched several times but not issued may ultimately be discarded when they expire.[8]

A crucial indicator for evaluating the effectiveness of blood use and assisting in the prediction of excessive blood demand is CT ratio. It was introduced by Boral Henry in 1975, since then the C/T ratio has since been widely utilized by various researchers to analyse and evaluate blood transfusion practices. This ratio provides a valuable measure for ensuring that blood products are ordered and utilized in a manner that aligns with clinical needs, helping to improve resource management and reduce unnecessary transfusions.[3,4]

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By analysing this ratio, healthcare facilities can optimize their blood management practices and improve overall resource allocation.[5]

Over-ordering of blood units is commonly observed among patients that are scheduled for elective surgery. These pre-operative requisitions are often based on assumptions of worst-case scenarios or an overestimation of intra-operative or post-operative blood loss, leading to excessive demands for red cell concentrates (PRBCs).[4]

Utilizing and managing blood products requires a multidisciplinary approach in order to minimize waste and reduce complexity. The amount of blood products collected by transfusion services worldwide reflects the ongoing rise in hospital blood product demand.[6] Before requesting different blood components, clinicians should carefully consider whether the indications are appropriate. This will help to avoid blood wastage, unnecessary patient exposure to various transfusion-transmitted illnesses, and the formation of antibodies.[1] The Hospital Transfusion Committee (HTC) should conduct a thorough evaluation and audit of the procedures for ordering and using blood. In order to improve blood transfusion services and put policies in place that can improve the blood center's offerings, the gathered data can be used for discussions at HTC meetings, which should involve all relevant clinical and administrative departments.[1]

This study was conducted with the objective to evaluate the CT ratio of various departments in a hospital setting to assess the patterns of blood component demand and its utilisation. By evaluating our data, our study can help to reduce unnecessary transfusions and guide necessary improvements in the use of red cell concentrates within the hospital.

Materials and Methods

Descriptive observational study carried out at Shifa International Hospital (blood transfusion services). This study was conducted after obtaining approval from Institutional Review Board (IRB#398-23). The span of study was 06 months from March 2024 till September 2024. This study was done by collecting information through blood bank information system after obtaining informed consent from all in-patient departments.

527 recipients and their donors who needed red cell concentrates from in-patient departments (Surgery, Medicine, Paeds, Gyne/obs, Surgical ICU, Medical ICU, Paediatric ICU, Neurology, Oncology, Orthopaedic, Liver transplant, Kidney transplant, Gastroenterology, Emergency) were enrolled in the study.

Blood products that were provided by a blood transfusion services other than the blood transfusion services of Shifa International Hospital (SIH) were excluded from the study although according to policy of our blood bank these blood bank can be used on demand.

The sample size was determined with the help of WHO calculator 2.0. Data was entered & analysed with the help of SPSS (Version-26). Categorical variables were depicted as frequencies & percentages. CT ratio, Transfusion probability and transfusion index were calculated by using these formulas:Cross-match to transfusion ratio (C/T ratio) = number of units cross-matched/number of units transfused. A ratio of 2.5 and below is considered indicative of significant blood usage.[6]

Transfusion probability (%T) = number of patients transfused/number of patients cross-matched × 100. A value of 30% and above was considered indicative of significant blood usage.[6]

Transfusion index (TI) = number of units transfused/number of patients cross-matched. A value of 0.5 or more was considered indicative of significant blood utilization.[6]

Results

In six-month study, over all 527 packed red cell products (RCC) were prepared after cross-matching, 198 (38%) were transfused, leaving 329(62%) unused with an overall cross CT of 2.6. These results showed that overall CT of blood bank was very close to target CT. The data retrieved from various units of the hospital with significant and effective blood utilization included the Emergency Unit, with CT ratio of (2.1) . Surgery Unit showed CT ratio of (2.5). Medical Unit yielded CT ratio (2.1). Gastroenterology unit had CT ratio (2). Oncology presented with a CT ratio (1.27). Paediatric ICU had CT ratio of 1.

The data recovered from various units of the hospital with insignificant and ineffective blood consumption comprised the Gynaecology/Obstetrics Department that showed CT ratio of (6.6). The Liver Transplant Department had CT ratio of (4.28). Surgical ICU had CT ratio of (2.8). Medical ICU, gave CT ratio of (4.1).

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Neurology Department had CT ratio (5). Nephrology Department generated CT ratio of (2.7). Orthopaedic Department had CT ratio (3.2). Kidney Transplant Department generated CT ratio of (1). Paediatric Department had CT ratio of (4) . In order to achieve more significant or efficient blood product usage by lowering CT ratio, it is very important to evaluate the indication for cross match generated from various department.

Table I: Overall Cross match to transfusion ratio, transfusion probability and transfusion Index

Total number of cross matches	Total no of bag used	Total no of bags unused	Cross match to transfusion ratio	Transfusion probability	Transfusion index
527	198	329	2.66	38	0.38

Table II: Department wise C: T ratio, transfusion probability and transfusion index

Departments	No of Cross Match	No of Bags Issued	No of Bags Cross Matched but not Issued (Wastage)	Cross Match to Transfusion Ratio(C:T Ratio)	Transfusion Probability (TP)	Transfusion Index (TI)
Emergency	24	11	13	2.1	45	0.45
Medicine	30	14	16	2.1	47	0.47
Surgery	113	45	68	2.5	40	0.40
Liver transplant	30	07	23	4.28	23.2	0.23
Medical ICU	33	08	25	4.1	24	0.24
Surgical ICU	14	05	09	2.8	36	0.36
Neurology	10	02	08	5.0	20	0.20
Gastroenterology	39	19	20	2.0	49	0.49
Pediatrics	04	01	03	4.0	25	0.25
Pediatric ICU	03	03	00	1.0	100	1.0
Nephrology	25	09	16	2.7	36	0.36
Oncology	55	43	12	1.27	78	0.78
Gyne/Obs	111	17	94	6.6	15	0.15
Orthopedic	32	10	22	3.2	31	0.31
Kidney transplant	04	04	00	1.0	100	1.0

(n=527)

Cross match to transfusion ratio, Transfusion index, Transfusion probability

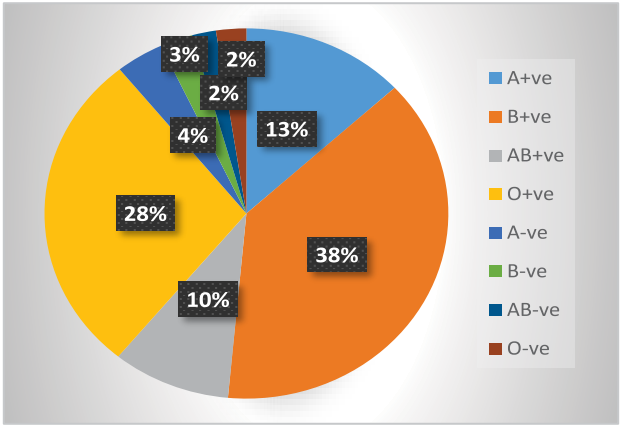

Figure-1: Frequency of blood groups among Donors (n=527)

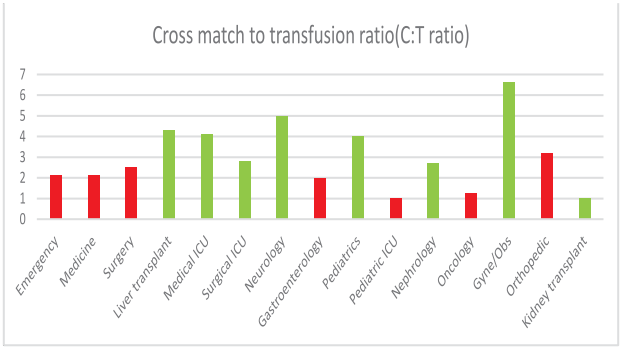

Figure 2: Cross match to transfusion ratio of various departments (n=527)

Significant CT ratio<2.6
Insignificant CT ratio >2.6

Discussion

Blood transfusions are often based on the subjective expectation of blood loss rather than estimations of evidence based blood loss during certain surgeries. CT ratio below 2.5 is considered indicative of significant blood usage that means at least 30% of the cross-matched blood should have been needed for transfusion.[1] The cross match process for packed red blood cells is a significant test done at our blood center, in addition to blood type and serum screening for the corresponding patient. Testing using the gel card method for patient serum incompatibility with donor cells is done. Cells from the patient undergo the typing process, after which they are examined for ABO and Rd (D) using the appropriate anti-serum.[1]

A study done by Yasmeen et al in North India showed overall CT was 1:1, (TP %) was 68% and Transfusion index was 1. These three blood utilization indices indicated that blood products were efficiently utilized in their hospital that was relatable to our study that also showed overall CT ratio (2.6), TP (38%) & TI (0.38).[10]

A study conducted in Nepal by Amar et al showed CT ratio of emergency department was 1.72 and TI came out to be 0.88 that was related to our study that showed CT ratio of 2.5 & TI (0.40). These comparable results indicate that the emergency department was effectively utilizing blood products.[8]

A Study done by Akansha sharma et at in Obstetric and Gynaecological department Sikkim India in 2023 presented with C:T ratio (6.6), TP (12%) & TI (0.23) comparable with the our results that showed CT ratio (6.6), TP (15%) and TI (0.15) . Most of cross-matched red cell concentrates were not transfused. The high CT ratio in both studies were due to over ordering of blood products driven by over estimation of intra-operable blood loss. [9] In order to prevent ineffective utilisation of blood products, it is important to review the indications required for transfusion.

A study done in surgical department of a hospital in Ethopia in 2023 revealed CT ratio (2.26), TP (22.7) &TI (0.5) that was relatable with our study.[12] In a 2022 study conducted in hospital located in South India by Pruthvi Raj et al included all departments who had elective surgeries, the CT ratio was found to be 4.57 that was not comparable with our study results as our study includes all surgical departments that performed both elective and emergency surgeries.[13]

In our study B+ve came out to be commonest blood type that was cross matched. However, study led by Sehar K et al in Rawalpindi found that blood group O had the highest rate.[14] Another study conducted in 2021 at PIMS, Islamabad showed, blood group B had the greatest rate, then blood groups O, A, and AB amongst donors, which had comparable outcomes with our study.[15] We emphasized on most common and rarest blood group distribution among persons living in north of Pakistan by determining the frequency of blood groups among blood donors. This would help blood bank to maintain their blood product storage according to the demand.

As this is a single-centre study, our findings may not be applicable to other centre that follow different transfusion practices and technical protocols for various surgical procedures.

Another limitation of this study is lack of information regarding indications for blood transfusion requests generated by various departments. This research gap can be addressed in future studies to provide a more thorough analysis in order to prevent over ordering and cross matching.

Conclusion

The study demonstrated that the overall cross-match to transfusion (CT) ratio of 2.6 is close to the targeted standard, indicating acceptable blood utilization practices at the blood bank. However, significant departmental differences were observed. The surgical department's CT ratio of 2.1 reflects efficient blood usage, whereas the higher ratios in Gynaecology/Obstetrics and Liver Transplant (6.6) suggest over-ordering and potential wastage of blood products. These findings underscore the importance of implementing targeted strategies—such as developing department-specific blood ordering protocols and regular audits—to optimize blood usage and improve overall quality management in the blood bank.

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Conflict of interest: Authors declared no conflicts of Interest.

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CONFLICT OF INTEREST

Authors declared no conflicts of Interest.

GRANT SUPPORT AND FINANCIAL DISCLOSURE

Authors have declared no specific grant for this research from any funding agency in public, commercial or nonprofit sector.

DATA SHARING STATEMENT

The data that support the findings of this study are available from the corresponding author upon request.

ORIGINAL ARTICLE

Computer Vision Syndrome Among Computer Users in Muzaffarabad, Azad Jammu and Kashmir

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ABSTRACT

Objective: To determine the prevalence of Computer Vision Syndrome (CVS) among computer users in Muzaffarabad, Azad Jammu and Kashmir.

Study Design: Cross-sectional observational study.

Place and Duration of Study: Department of Ophthalmology, Abbas Institute of Medical Sciences (AIMS), Muzaffarabad from April 1, 2022 to September 30, 2022.

Materials and Methods: A cross-sectional study was conducted among 346 computer users aged 18–40 years, using digital devices. Participants with pre-existing eye disease (e.g., glaucoma, cataract, dry eye), or pregnancy were excluded. Quantitative data included age, screen time, duration of use, and symptom frequency, while qualitative data covered demographic characteristics, work environment, and subjective experiences of eye strain. Data were entered and analyzed using SPSS version 26. Descriptive statistics such as means, standard deviations, and frequencies were computed and associations between categorical variables (e.g., screen time and CVS symptoms) were analyzed. A p-value ≤ 0.05 was considered statistically significant.

Results: CVS symptoms were reported by 63.5% of respondents. Ocular complaints were more frequent (65%) than extra-ocular (35%), with eye fatigue (37.8%) and headaches (42.7%) being the most common symptoms. Neck or shoulder pain was reported by 33.4% of symptomatic individuals. Most users (62.1%) preferred medium screen brightness, and symptom relief was universally reported with increased screen breaks, although no statistically significant correlation was found between break frequency and symptom severity.

Conclusion: We found computer vision syndrome in 63.5% of who use electronic devices. These findings underscore the need for targeted ergonomic interventions and public education on safe screen practices.

Key Words: *Computer Vision Syndrome, Digital Eye Strain, Headache, Neck Pain, Screen time.*

Introduction

The abundant integration of electronic devices, particularly computers and mobile phones, has become an essential aspect of modern life. Beyond personal use, digital technology has saturated professional fields workplaces, educational institutions, recreational centers, and homes now rely heavily on screen-based interfaces. Professions such as accounting, graphic design, banking, engineering, air traffic control, and journalism depend on prolonged screen exposure, making digital visual tasks a central aspect of occupational performance. Globally, it is estimated that between 45 and 70 million people spend significant portions of their workday in front of screens, contributing to a surge in visual and musculoskeletal complaints categorized under computer vision syndrome (CVS).[1]

CVS is a cluster of ocular and extra-ocular symptoms resulting from sustained exposure to digital screens. These symptoms are broadly classified into visual (e.g., blurred vision, focusing difficulties), ocular surface (e.g., dryness, irritation), asthenopic (e.g., eye fatigue, strain), and extra-ocular (e.g., headaches, neck or shoulder pain) categories.[2] Extended screen use may impair accommodative function and exacerbate symptoms, particularly in the presence of poor posture, incorrect viewing angles, uncorrected refractive errors, dry eyes, or

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environmental discomfort.[3] Numerous risk factors further heighten CVS vulnerability. Chief among them is prolonged screen time without adequate breaks, poor ergonomic practices, inadequate lighting, digital multitasking, and pre-existing ocular conditions such as dry eye or uncorrected vision.[4]

Recent systematic reviews confirm that CVS is a global public health concern, with pooled prevalence rates ranging between 60% and 70%.[4,5] During the COVID-19 pandemic, this figure rose to approximately 74% due to increased reliance on remote work and online education.[6] Prevalence varies by population and region, with particularly high rates observed among university students, healthcare workers, and IT professionals.[7]

Pakistan has been identified as having one of the highest recorded CVS prevalence rates globally. A meta-analysis by Noreen *et. al.,*[8] reported high prevalence of CVS at 98.7% among participants in Pakistani computer users, especially among student and office-based cohorts. This alarming figure likely stems from extended screen exposure, low awareness of preventive strategies, limited access to eye care, and suboptimal workstation ergonomics.[3] Azad Jammu and Kashmir (AJK) reflects these national trends but remains underrepresented in research. The aim of this study was to fill that gap by quantifying CVS prevalence among computer users in Muzaffarabad, AJK by identifying risk factors and symptom patterns specific to the region. This study was designed for public education initiatives, ergonomic reforms, and its access to eye care services.

Materials and Methods

A cross-sectional observational study was conducted over a six-month period from April 1, 2022 to September 30, 2022 in the Department of Ophthalmology at Abbas Institute of Medical Sciences (AIMS), Muzaffarabad. The study received ethical approval from the Institutional Review Committee (AJKMC/HRC/2023-12) and written informed consent was obtained from all participants. Sample size was determined using the OpenEpi sample size calculator (version 3.01), applying a 95% confidence level, 5% margin of error, and a conservatively estimated prevalence of 70% based on findings from systematic reviews and national-level studies.[4,5] A total of 384 participants was initially selected using non-probability purposive sampling.

Data were collected using a structured, self-administered questionnaire adapted from the Computer Vision Syndrome Questionnaire (CVS-Q©), originally developed and validated by Seguí *et. al.,*[2,3] and it has demonstrated good internal consistency (Cronbach's $\alpha = 0.87$) and test-retest reliability ($\kappa = 0.81$), making it a reliable tool for assessing digital eye strain symptoms. It gathered information on participant demographics (age, gender, occupation), screen usage patterns (daily hours, device type), and the presence and frequency of CVS-related symptoms.

Inclusion criteria included adults aged 18 to 40 years who had used a digital screen for a minimum of one hour daily during the past month.[1] Individuals with diagnosed eye disorders (e.g., refractive errors, cataract, glaucoma, dry eye disease), a history of ocular surgery, or current pregnancy were excluded due to the potential confounding effects on ocular surface physiology. Both quantitative data (e.g., age, usage time, symptom frequency) and qualitative inputs (e.g., ergonomic conditions, self-reported symptom improvement) were gathered. Data were analyzed using SPSS version 26.0. Descriptive statistics were used to summarize variables (mean, SD, frequency, percentages). Associations between categorical variables were tested using Chi-square tests & t-tests and ANOVA were employed for continuous variables. A p value ≤ 0.05 was considered statistically significant.

Results

Out of the 384 participants initially approached, 38 questionnaires were excluded due to incomplete data, leaving a final sample size of 346 participants for analysis. The gender distribution was nearly equal, with 45.4% males (n =157) and 48.6% females (n =168), while 6% (n =21) did not disclose their gender. The age range of participants was 18 to 40 years, with the majority (86.4%, n= 299) falling within the 18–30-year age group.

Overall, 63.5% (n = 220) of the participants reported experiencing at least one symptom of Computer Vision Syndrome (CVS). Among those with symptoms, 65% (n = 143) reported ocular complaints, whereas 35% (n = 76) experienced extra-ocular symptoms. The most common ocular symptoms included eye fatigue (37.8%, n=131), eye

irritation (24.2%, n=84), and a burning sensation (11.0%). Among extra-ocular symptoms, headaches were the most frequently reported (42.7%, n=148), followed by neck or shoulder pain (33.4%, n=116). A chi-square test showed a statistically significant difference in the distribution of ocular and extra-ocular symptoms, favoring ocular symptoms (χ^2 = 19.25, p < 0.001). (Table I)

Analysis of symptom frequency revealed that 49.7% of participants occasionally experienced a burning sensation in the eyes, and 11.8% reported it as a persistent issue. Itchy eyes were occasionally reported by 62.1% and persistently by 25.7%. Tearing was reported occasionally by 43.9% and consistently by 29.8%, while 48.3% of participants experienced eye redness occasionally. Occasional reports of eye pain and dryness were noted by 39.6% and 44.2% of participants, respectively. Headaches were experienced occasionally by 46.2% of respondents, and neck or shoulder pain was commonly marked as a persistent complaint.

Chi-square analysis indicated a significant association between increased screen time and CVS symptom prevalence (χ^2 = 16.83, p = 0.002). Independent samples t-test revealed that symptomatic users had significantly higher mean screen time (6.40 ± 1.50 hours/day) compared to asymptomatic users (4.90 ± 1.20 hours/day), with a mean difference of 1.50 hours (t = 5.03, df = 344, p < 0.001). (Table II)

In terms of brightness settings, 62.1% (n = 215) used medium brightness, 24% (n = 83) preferred bright settings, and 13.9% (n = 48) used dull screens. Although most participants subjectively reported symptom improvement with frequent screen breaks, a one-way ANOVA showed no statistically significant relationship between break frequency and CVS symptom severity (F = 1.91, df = 2,343, p = 0.152) (Table III).

Table I: Distribution of Ocular and Extra-Ocular Symptoms in CVS

Symptom Type	Observed (n)	Expected (n)	Residual
Ocular Symptoms	143	109.5	+33.5
Extra-Ocular Symptoms	76	109.5	−33.5
Total	**219**		
(χ^2 = 19.25, df = 1, p < 0.001)			

Table II: Comparison of Mean Screen Time Between Symptomatic and Asymptomatic Participants

Group	n	Mean ± SD (hours/day)	Mean Difference	95% CI
Symptomatic	220	6.40 ± 1.50		
Asymptomatic	126	4.90 ± 1.20	1.50	0.91 to 2.09
(t = 5.03, df = 344, p < 0.001)				

Table III: Association of Break Frequency with CVS Severity

Break Frequency	n	Mean Severity Score ± SD
Rare	98	3.40 ± 0.60
Occasional	134	3.20 ± 0.50
Frequent	114	2.90 ± 0.70
(F = 1.91, df = 2,343, p = 0.152)		

Discussion

The present study found a prevalence of CVS at 63.5% among digital device users in Muzaffarabad, aligning with similar regional findings in Ghana (71.2%) and Ethiopia (69.5%).[9, 10] Global estimates range from 42.2% to 89.9%, with variability likely attributable to methodological heterogeneity including case definitions, sampling strategies, population demographics, and symptom assessment tools.[11] Our sample predominantly consisted of young adults aged 18–30 years (86.4%), a group recognized for higher CVS risk due to prolonged screen exposure related to education, work, and social media use.[12] While some international studies[13] report higher CVS prevalence in females, our analysis found no statistically significant gender association. This discrepancy may reflect differing screen time behaviors, reporting accuracy, or sociocultural roles influencing device use.

Ocular symptoms were commonly reported, with eye fatigue (37.8%) and irritation (24.2%) leading complaints—consistent with findings from previous studies[14] and supported by broader research into symptom drivers such as sustained accommodative effort, reduced blink rate, and tear film instability during prolonged screen exposure.[1 5] Extra-ocular symptoms such as headache (42.7%) and neck/shoulder discomfort (33.4%) were also prevalent, corroborating previous studies from Saudi Arabia and West Africa.[10,12] These symptoms reflect the ergonomic strain of suboptimal workstation

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setups and prolonged static posture. While we observed subjective symptom relief with increased screen breaks, statistical analysis did not establish a significant association between break frequency and symptom severity, suggesting that break timing, quality, and ergonomic context may be important confounders.[11]

Screen brightness was evaluated as a modifiable ergonomic factor. A majority (62.1%) of participants reported using medium brightness levels, aligning with best-practice ergonomic guidelines. Previous research suggested that screen brightness adjustment is among the most frequently adopted personal interventions to manage CVS symptoms. [13] Our study's granular reporting of symptom frequency (e.g., occasional vs. persistent) provides a valuable contribution to CVS literature. Notably, symptoms such as burning (49.7%), itching (62.1%), and tearing (43.9%) were frequently reported as occasional, reflecting a chronic but fluctuating symptom pattern. However, neck pain was disproportionately reported as a persistent issue, suggesting ergonomic strain beyond transient visual discomfort [10,12]

Our findings regarding the symptomatology and prevalence of CVS in our study population are largely congruent with existing regional and international literature. However, the precise relationship between the severity of CVS symptoms and mitigating behaviors, such as the frequency of visual breaks, remains to be definitively established. [11] This highlights the ongoing need for more rigorous investigations employing objective assessments of visual performance, detailed ergonomic parameters, and analysis of blink dynamics to fully elucidate this complex interaction.

This study is subject to several limitations inherent to its design. Primarily, the reliance on self-reported data introduces the potential for recall bias and potential misclassification of both symptom frequency and behavioral practices. Furthermore, the absence of a control group and the lack of objective ophthalmologic evaluations conducted within the study design preclude the establishment of strong causal inferences regarding the observed associations. To enhance reproducibility and facilitate more robust comparisons across studies, future research endeavors should ideally incorporate clinical diagnostic criteria for CVS, utilize stratified sampling techniques to ensure representativeness, and employ standardized, validated assessment tools.

Despite these limitations, this study possesses notable strengths that contribute valuable insights to the field. It represents the inaugural documented assessment of CVS prevalence and symptom patterns specifically within Muzaffarabad, Azad Jammu and Kashmir, a region that has previously lacked dedicated epidemiological data concerning digital eye strain. The relatively substantial sample size enhances the statistical power and generalizability of our findings within this population. Moreover, the use of a structured questionnaire adapted from validated instruments strengthens the internal validity of our results and facilitates meaningful comparisons with regional and global datasets on CVS. The detailed categorization of symptom frequency into occasional and persistent categories provides a more granular understanding of CVS symptomatology than studies that solely report binary prevalence, offering a nuanced view often underreported in the literature. By examining ergonomic factors such as screen brightness preference in conjunction with reported symptomatic relief obtained from screen breaks, the study offers multifaceted insights into modifiable behavioral practices that are relevant for both clinical management and public health interventions aimed at reducing digital eye strain. This study is also distinct in providing a comprehensive breakdown of both ocular and extra-ocular CVS symptoms using frequency categories (never, occasional, always), a level of detail often absent in prior regional studies. Unlike investigations that primarily emphasize overall prevalence figures, this study dissects the distribution of specific symptoms, such as persistent neck pain, and explores their correlation with reported ergonomic practices. This detailed profiling of symptoms not only enhances our understanding of patient discomfort but also provides a foundation for developing more tailored ergonomic and behavioral interventions. Furthermore, the study highlights the nuanced but ultimately non-significant relationship observed between break frequency and symptom severity, underscoring the ongoing need for more

detailed prospective ergonomic assessments to fully understand the impact of such behaviors.

Based on the findings of this study, several recommendations are proposed to mitigate the burden of CVS in the region. It is recommended that routine ophthalmic screening programs be implemented, particularly targeting frequent computer users within educational institutions and occupational settings, to facilitate early detection and management of CVS. Awareness campaigns on Computer Vision Syndrome and the principles of ergonomics should be conducted to educate the public about preventive strategies, such as adhering to the 20-20-20 rule and optimizing screen adjustment practices. [15] Employers should be encouraged to promote the establishment of ergonomically designed workstations and support policies that allow for regular visual breaks to reduce ocular and musculoskeletal strain among their employees. Integrating visual hygiene practices into public health and digital literacy programs is also crucial, with a specific focus on educating younger populations who are increasingly exposed to digital screens. [16,17,18] For future research, it is recommended that studies incorporate longitudinal study designs, include appropriate control groups for comparison, and employ objective clinical measures to more accurately evaluate the long-term effects of CVS and assess the efficacy of various ergonomic interventions.

Conclusion

We found a high prevalence (63.5%) of computer vision syndrome among digital device users in Muzaffarabad, with ocular symptoms being more common than extra-ocular ones. Prolonged screen time was significantly associated with symptom severity, while screen breaks alone showed no statistical protective effect. These findings underscore the need for targeted ergonomic interventions and public education on safe screen practices.

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Ethics: The study was conducted in adherence to the Helsinki Declaration and human ethics protocols.

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CONFLICT OF INTEREST

Authors declared no conflicts of Interest.

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DATA SHARING STATEMENT

The data that support the findings of this study are available from the corresponding author upon request.

ORIGINAL ARTICLE

Inflammatory Markers and Their Significance in Glycemic Control among Type 2 Diabetes Patients

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ABSTRACT

Objective: To compare serum C-reactive protein and Ferritin levels between type 2 diabetes mellitus patients and healthy individuals and also to assess their association with HbA_1clevels.

Study Design: Comparative cross-sectional study

Place and Duration of Study: This study was carried out from March 2024 to October 2024 at the Department of Pathology, Fauji Foundation Hospital, Rawalpindi.

Materials and Methods: Total 300 participants were divided into diabetic and non-diabetic groups. Diabetic group included 195 known type 2 diabetes patients having diabetes for at least 5 years. Non-diabetic group included 105 apparently healthy subjects. Patients having type-1 Diabetes, hemochromatosis, acute or chronic infection/inflammation, hypertension, pregnancy, anaemia, hemoglobinopathy, recent blood loss, blood transfusion/donation or those taking iron supplements were excluded. All demographic and clinical details were noted followed by blood sample collection and Laboratory analysis for serum Ferritin, CRP, fasting plasma glucose and plasma HbA_1c. Results were statistically analyzed on SPSS 22.

Results: The study comprised of 300 participants who were stratified into diabetic and non-diabetic groups. Elevated levels of serum Ferritin and CRP were observed in diabetic patients compared to healthy subjects; serum Ferritin level 165(98.50-190.00) ng/ml vs. 85.00(55.20-105.25) ng/ml (p = 0.036) and serum CRP level 8.50(5.70-11.10) mg/l vs. 2.80(2.30-4.00) mg/l (p <0.001) respectively. Significant positive correlation was also noted between these inflammatory markers and plasma HbA_1c; for serum CRP, r=0.464, p <0.001 and for serum Ferritin, r=0.231, p =0.001.

Conclusion: Our study revealed significantly elevated levels of serum CRP and Ferritin in type 2 Diabetes patients as compared to healthy subjects. Serum CRP and Ferritin are positively correlated with HbA_1c in patients with type 2 diabetes. These findings support the hypothesis that inflammatory markers may reflect glycemic control status in type 2 diabetes patients.

Key Words: *CRP, Ferritin, HbA_1c, Inflammation, Type 2 Diabetes.*

Introduction

Diabetes Mellitus (DM) is a disorder of multi-factorial involvement including genetic and environmental factors that cause either suppressed insulin secretion, action or both; ultimately resulting in hyperglycemia.[1] Pakistan holds 3rd rank in the world regarding prevalence of diabetes following China and India and IDF report has documented that 26.7% adult population in Pakistan is already having diabetes.[1,2] In recent years, a link has been suggested between inflammatory markers and glycemic control in type 2 diabetes (T2D) patients.[3,4] Elevated inflammatory markers like C-reactive protein (CRP) and Ferritin have been attributed to cause insulin resistance, poor glycemic control and other associated complications in diabetic patients.[5,6] Due to the potential implications of these inflammatory markers on T2D management and complications, the current study was planned to evaluate the association between inflammatory markers and glycemic marker in our diabetic population.

CRP is secreted by hepatocytes in response to cytokines released during an infective or inflammatory condition playing an important role in

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defense system of host.[3] Several viral, noninfectious inflammatory states and malignancies also lead to increased serum CRP levels. CRP values rise quickly in two hours and attain a peak at 48 hours, making it an early and reliable marker for monitoring disease.[7] Elevated CRP levels have been documented to be present in T2D patients with poor glycemic control and also have been found to be correlated with plasma HbA_{1c} level in these subjects.[3,5] It is postulated that CRP leads to phosphorylation of serine at insulin receptor, resulting in impaired ability of the receptor to activate phosphatidyl inositol 3-kinase, ending up in the development of insulin resistance and poor glycemic control.[3]

Serum Ferritin level is routinely used to reflect the iron stores in individuals but it also serves as an important acute phase reactant indicating inflammation. High serum Ferritin levels have been associated with hyperglycemia in T2D patients and have also been linked to increased frequency of chronic complications of T2D such as retinopathy, nephropathy, and vascular dysfunction.[4,8] It is suggested that hyperglycemia leads to increased glycation of hemoglobin in red cells releasing free iron from them. Free iron then initiates redox reactions leading to free radical synthesis that damages β-cells of pancreas and further augments the inflammatory response.[6] Damage to β-cells contributes to decreased insulin secretion and abnormally high blood glucose levels. It is also documented that high Ferritin may influence the expression of glucose transporters (GLUT4) in muscles and adipose tissue. This may influence signaling pathways related to glucose uptake and may disturb GLUT4 translocation to the cellular membrane with decreased entry of glucose into the cells and hyperglycemia.[9]

Available literature suggests an important role of inflammatory markers in glucose regulation among T2D patients, although their cause and effect relationship is still not fully known. In a research carried out in Pakistan, influence of serum Ferritin on glycemic control was studied in T2D patients and significantly elevated Ferritin levels were found to be associated with poor glycemic control 19. International literature from India, Ethiopia and Egypt also revealed markedly high serum Ferritin and CRP levels in T2D patients when compared to their healthy counterparts [3, 4, 5]. Kant and colleagues and Elimam and colleagues also studied correlation of inflammatory markers Ferritin and CRP with HbA1c and documented a positive correlation between these markers, indicating the involvement of inflammation in pathogenesis of diabetes.[3,5] A Quasi-experimental study conducted in Iran investigated serum Ferritin levels in T2D patients with poor glycemic control and reported significant decrease in Ferritin levels by controlling hyperglycemia after the study.[10]

In the light of growing evidence associating inflammation to the metabolic regulation in T2D and scarcity of local literature on this subject, this study was aimed to estimate serum Ferritin and CRP levels in T2D patients and to determine the their association with HbA_1c. We hypothesized that elevated serum CRP and Ferritin levels occur in T2D patients and are correlated with high HbA1c levels in them. Our study underscores the potential of utilizing these inflammatory biomarkers as indicators of metabolic dysregulation and disease severity in T2D patients.

Materials and Methods

This comparative cross-sectional study was conducted at Pathology Department of Fauji Foundation Hospital Rawalpindi from March 2024 to October 2024 after getting approval from Institutional Ethical Review Committee (No. 701/RC/FFH/RWP). The 300 participants included in this study were recruited from medical outpatient department through non-probability consecutive sampling. We stratified the study participants into two groups based on whether they were diagnosed with type 2 diabetes or not. “Diabetic group” comprised of 195 T2D patients who were already diagnosed by the physician, fulfilling American Diabetes Association (ADA) criteria [11] and had T2D for minimum 05 years. Second group labeled as “non-diabetic group” included 105 age and sex-matched healthy subjects. Sample size was estimated through WHO sample size calculator with type 2 diabetes prevalence in Pakistan 26.7%, confidence level 95% and margin of error 5% [1].

Exclusion criteria included age of the subjects < 18 years or >65 years, duration of T2D less than 5 years and medical evidence or history of any of the following condition: type-1 Diabetes mellitus,

hemochromatosis, acute or chronic infection/inflammation, hypertension, pregnancy, recent blood loss, intake of iron supplements or anti-inflammatory drugs, history of blood transfusion or donation during past three months, history of any hemoglobinopathy or presence of anemia.

After getting written informed consent of the subjects, demographic and clinical details were recorded on a structured questionnaire. Blood samples were then collected using EDTA tube for HbA_1c and blood complete picture (CP) while blood specimen in gel separator tube was used for performing serum Ferritin and CRP. Blood for fasting plasma glucose (FPG) was collected in sodium fluoride tube. Blood CP was performed on fully automated hematology analyzer (Beckman Coulter). Plasma HbA_{1c} was performed by immuno-turbidimetric technique on fully automated chemistry analyzer (Atellica CH by Siemens, Germany). FPG was also measured on same chemistry analyzer by hexokinase method.

Samples collected in gel separator tube were initially placed at room temperature, followed by centrifugation at 3000 rpm for serum separation. Serum was utilized for estimating Ferritin by Chemiluminescence immunoassay (Atellica IM by Siemens, Germany) and for quantitative estimation of CRP by enzyme-linked immunosorbent assay (MicroLISA by Amgenix International, USA; sensitivity: 0.01 mg/l, linearity: 160 mg/l). Intra-assay precision was also checked by randomly selecting few samples and running them along with their duplicates for calculating their mean, standard deviation and percent coefficient of variation (CV %). All samples were analyzed along with the routine Laboratory tests after checking daily internal quality control results. Laboratory technicians were blinded and were unaware of the groups assigned to the samples.

Diagnosis of patients with T2D was already done by the Physician according to ADA guidelines having either plasma HbA_1c level > 6.5%, FPG >7.0 mmol/l, post-prandial blood glucose > 11.0 mmol/L or 2hr blood glucose level > 11.0 mmol/L after 75g OGTT [11]. Based on ADA guidelines, FPG level ≥ 5.6 mmol/l in healthy subjects and ≥ 7.0 mmol/l in T2D patients was considered elevated while HbA_1c level ≥ 5.7% in healthy individuals and ≥ 6.5% in diabetic patients was considered elevated [11]. According to WHO guidelines, serum Ferritin level > 200ng/ml was considered elevated for males while serum Ferritin > 150ng/ml was taken elevated for females [12]. Serum CRP level > 6.0 mg/L was considered elevated [13]. Hemoglobin (Hb) level <12g/dl in females or <13 g/dl in male participants was defined as anemia according to WHO [14].

Data were analyzed on SPSS version 22. Data was assessed for distribution by Kolmogorov-Smirnov Test of Normality. Median and inter-quartile ranges were calculated for variables with non-parametric distribution. For categorical variables, frequency and percentage (%) was calculated. Categorical variables were compared across the study groups by Chi square test. Continuous biochemical and clinical parameters were compared between the study groups by Mann Whitney U test. Correlation of serum CRP and Ferritin with HbA_1c was determined by Spearman correlation. The probability value (p) was significant when it was less than 0.05.

Results

There were 300 participants in this study which were divided into two groups: diabetic and non-diabetic. Diabetic group comprised of 195 known patients with T2D while non-diabetic group included 105 non-diabetic healthy subjects. Median age of the study participants was 55 years. In diabetic group, 136(69.7%) were females and 59 (30.3%) were male subjects while in non-diabetic group, 73(69.5%) were female and 32(30.5%) were male. Since we included age and sex-matched subjects in both groups, no significant difference was noted in age and gender between the two study groups as shown in Table I.

In our study, 90(46.7%) diabetic patients had 5-10 years of disease duration, followed by 57(29.2%) subjects having 10-15 years duration, 24(12.3%) patients were diabetic for more than 20 years and 23(11.8%) were diagnosed with diabetes for 15-20 years. Among the participants, 105 (53.8 %) diabetic patients exhibited poor glycemic control as reflected by raised plasma HbA_1c levels while only 7 (6.7%) non-diabetic subjects had abnormal HbA_1c level (p<0.001). Similarly 111(56.9%) diabetic patients had raised fasting plasma glucose levels while only 11(10.5%) non-diabetic subjects had abnormal FPG levels (p<0.001). Serum CRP and serum Ferritin levels

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which indicate inflammation were also markedly elevated in diabetic group as compared to non-diabetic group. CRP was high in 53 (27.2%) diabetics while serum Ferritin was raised in 26 (13.3%) diabetic patients in this study (p<0.001). Comparison of frequencies of these variables by Chi square test is shown in Figure 1.

Fasting plasma glucose and plasma HbA_1c levels were significantly elevated among T2D patients than in healthy subjects in our study (median values 8.70 mmol/l vs. 4.60 mmol/l for FPG and 7.5% vs. 5.1% for HbA_1c respectively). On comparing median values of fasting plasma glucose and HbA_1c by Mann Whitney U test, significant difference was observed between diabetic and non-diabetic groups (Table II).

Upon investigating the levels of inflammatory markers in study groups, higher levels of serum Ferritin and CRP were noted in subjects having T2D compared to the non-diabetic healthy individuals (median levels of 165 nmol/l vs. 85 nmol/l for serum Ferritin and 8.50 mg/l vs. 2.80 mg/l for serum CRP respectively). Comparison of median values of these parameters by Man Whitney U test also showed significant difference between the two groups (Table II).

In order to determine the occurrence of any linear relationship between HbA_1c and inflammatory markers in T2D patients, Spearman correlation coefficient test was applied. It was revealed that among diabetic patients, a weak but statistically significant positive correlation was found between serum Ferritin and HbA_1c ($r = 0.231$, $p = 0.001$) while a moderate correlation was observed between serum CRP and HbA_1c ($r = 0.464$, $p < 0.001$), as displayed in Table III.

Discussion

Diabetes mellitus has become a very common health issue nowadays and the number of affected individuals is exponentially increasing with each passing year. Inflammatory markers have been attributed to be involved in the pathogenesis of T2D, since they may lead to decreased insulin sensitivity, poor glycemic control and associated complications.[5] Our study estimated serum Ferritin and CRP levels in T2D patients and age-matched healthy subjects. We also determined correlation of these inflammatory markers with HbA_1c in T2D patients.

In the current study, serum CRP level was significantly higher in T2D patients than in healthy

Table I: Comparison of Age and Gender Distribution between the Study groups (n=300)

Variables		Diabetic group N= 195	Non-diabetic group N= 105	*p*-value
Age (years) Median(IQR)		55.00 (51.00-67.00)	55.00 (50.00-64.00)	0.121
Gender n (%)	Male	59 (30.3%)	32 (30.5%)	0.487
	Female	136 (69.7%)	73 (69.5%)	

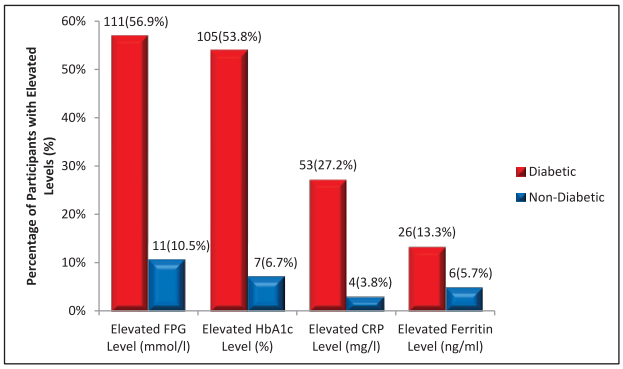

Figure 1: Frequency of Elevated Glycemic and Inflammatory Biomarkers in Diabetic vs. Non-Diabetic Groups.

Table-II: Comparison of Median and Inter-quartile Range (IQR) of Biochemical Parameters between study groups (n=300)

Variables	Study Groups		*p*-Value
	Diabetic (n=195) Median(IQR)	Non-Diabetic (n=105) Median(IQR)	
Fasting Plasma Glucose (mmol/l)	8.70 (6.50 - 13.00)	4.60 (4.20 - 4.90)	<0.001*
Plasma HbA_1c (%)	7.50 (7.00 - 9.30)	5.10 (4.80 - 5.40)	<0.001*
Serum Ferritin (ng/ml)	165.00 (98.50-190.00)	85.00 (55.20 - 105.25)	0.036*
Serum CRP (mg/l)	8.50 (5.70 - 11.10)	2.80 (2.30 - 4.00)	<0.001*

*p <0.05: significant

Table-III: Correlation of serum Ferritin and CRP Levels with plasma HbA_1c in T2D patients.

	Plasma HbA_1c	
	r	*p*-Value
Serum Ferritin	0.231	0.001
Serum CRP	0.464	<0.001

r = Spearman correlation coefficient; 0.00-0.19: very weak, 0.20-0.39: weak, 0.40-0.59: moderate, ≥ 0.60: strong

subjects. Similar to our finding, significantly higher CRP levels in T2D patients have been documented in several other studies.[5,13,15,16] Patne, Hisalkar and Dubey determined the association between CRP and HbA_1c in T2D patients and noted significantly elevated CRP levels in them.[17] This can be due to the fact that CRP can impart indirect effect on insulin sensitivity and its production from beta cells of pancreas by altering immune response through augmenting systemic inflammation.[13] A study by Lima and colleagues, however, contradicted our finding as they did not report a significant difference of serum CRP levels between diabetic and healthy individuals.[18] This discrepancy can be due to the difference in ethnicity or inclusion of diabetic patients with variable duration of disease which can cause variable degree of inflammation.

Significantly elevated serum Ferritin levels were also noted in T2D group than in non-diabetic group in our study. Consistent to our results, a research carried out in Pakistan also reported significantly elevated Ferritin levels in T2D patients with poor glycemic control.[19] International literature also revealed markedly high serum Ferritin levels in T2D patients compared to their healthy counterparts in studies conducted across India, Ethiopia and Egypt.[3,4,5]

A strong positive correlation between CRP and HbA_1c was found in diabetic patients in the current research. Similar relationship has been noted between CRP and glycated hemoglobin in studies conducted across the globe. A research conducted in Menoufia University, Egypt observed a positive correlation between CRP and HbA_1c in diabetics which is consistent with our results.[5] Likewise, studies done by Gautam and colleagues in Nepal and another study by Patne and colleagues in India assessed the relationship between inflammatory and glycemic control markers among T2D population and concluded a positive correlation between serum CRP and HbA_1c in these subjects.[13,17] This significant positive correlation indicates that increase in CRP level may be associated with elevated HbA_1c level and hence poor glycemic control in T2D patients. Therefore serum CRP can be postulated to serve as a useful tool in determining glycemic control and possible risk of complications in diabetic population. However, further studies are needed to validate this idea.

Serum Ferritin exhibited a significant positive correlation with HbA_1c levels among T2D patients in our study indicating that increased serum Ferritin is associated with increased plasma HbA1c level and hence poor glycemic control in these individuals. Supporting our results, Bayih et al and Elimam H et al also reported significant positive correlation between serum Ferritin and HbA_1c in their studies conducted in Ethiopia and Egypt respectively.[4,5] Similarly, Shubham J, et al. conducted a study in India to determine serum Ferritin level and its correlation with HbA1c in diabetic individuals and concluded a significant positive correlation between them.[8] This correlation can be attributed to the synthesis of advanced glycosylation end products (AGEs) which can occur due to hyperglycemia, since hyperglycemia leads to the release of free iron and other elements that have toxic potential associated with oxidative stress and inflammation [5]. Our finding contradicts the results reported by Al Argan and colleagues, who determined association between Ferritin and HbA_1c in Saudi population. In their study, they observed significantly raised serum Ferritin levels in diabetic patients similar to our study but contrary to us, they did not find any significant correlation between serum Ferritin and HbA_1c.[20] This difference can be attributed to the different ethnic origins, difference in duration of diabetes having different degree of inflammation or variable anti-diabetic regime given to the patients in both studies.

The findings of our study, consistent with the existing literature, suggest an association of inflammatory markers serum Ferritin and CRP with HbA_1c among T2D patients. These findings highlight the important role of monitoring inflammatory markers in diabetic patients. Elevated levels of inflammatory markers may be employed as indicators of poor glycemic control in these subjects. This may also help in monitoring diabetes worsening and progression towards its complications. Our findings also provide an insight for treating physicians and pharmaceuticals to consider inflammatory markers as a possible therapeutic target for better glycemic control in diabetic population. More prospective researches in this aspect are still needed to explore the underlying causative mechanisms and to validate the potential role of inflammation in glycemic control and disease outcomes in diabetic population.

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There were few limitations of our study, majority of the participants in this study were of female gender because our hospital mainly caters for the families of the ex-service men. Secondly, adjustment for the key confounding factors especially body mass index and metabolic syndrome could not be done in our study. Further prospective, multi-centered studies comprising of both genders along with adjustment of key confounding factors and including larger panel of inflammatory markers are needed across the national and international level to strengthen this idea.

Conclusion

Significantly elevated levels of serum Ferritin and CRP occur in type 2 Diabetes patients as compared to healthy subjects. Furthermore, a significant positive correlation exists between inflammatory markers; serum Ferritin and CRP, and glycemic marker plasma HbA_1c in T2D patients. These findings suggest an important role of inflammation in glycemic control among diabetics.

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Disclaimer

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Conflict of Interest

Authors declare no conflict of any financial, personal or professional interest.

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DATA SHARING STATEMENT

The data that support the findings of this study are available from the corresponding author upon request.

ORIGINAL ARTICLE

Evaluating Activity and Chronicity Indices in Lupus Nephritis Using the Recent NIH-Modified Activity Index Scores: A Comprehensive Correlation Analysis with Renal Function

Rabia Saleem, Humaira Nasir, Zafar Ali, Kanza Huma Zia, Anum Iqtidar, Nadia Hassan

ABSTRACT

Objective: To study the correlation between activity and chronicity indices in renal biopsies and renal functions among lupus nephritis patients.

Study Design: Prospective cross-sectional study**.**

Place and Duration of Study: This study was carried out from October 2021 to 2022 at Department of Histopathology, Shifa International Hospital Islamabad.

Materials and Methods: Clinical data, including history, age, serum creatinine, serum and urine albumin levels, ANA and Anti Ds DNA status, were obtained from the hospital's medical electronic records. Renal biopsies for light microscopy were assessed and scored for activity index and chronicity index using the recent (2018) NIH-modified activity and chronicity index scores (Table I). Immunofluorescence slides were viewed for full house deposits of IgG, IgA, IgM, C3 and C1q as seen in lupus nephritis. Data was incorporated into data management software, and statistical analysis was conducted using IBM SPSS version 23.0.

Results: Among the 91 renal biopsies, 12 (13.2%) were male patients and 79 (86.8%) were female patients. The mean activity index score was 6.42±3.9 (ranging from 0 to 16 out of 24), while the mean chronicity score was 2.25±2.0 (ranging from 0 to 8 out of 12). Comparisons of activity and chronicity index scores with lupus classes revealed a significant association. Mean activity scores for lupus Class 1 to 5 were 2.07±1.6, 3.40±2.3, 8.21±3.3, 3.00±2.3, and 5.00±0.5 respectively, similarly mean chronicity scores for lupus grade 1 to 5 were 0.50±0.5, 0.80±0.8, 2.75±1.9, 3.00±2.7, and 7.00±0.5 respectively. These scores were compared with lupus classes, revealing significantly higher mean activity and chronicity index scores for higher lupus classes. A positive correlation between index scores and elevated creatinine levels ($p<0.001$) was observed.

Conclusion: The study concludes that NIH-modified activity index and chronicity index scores are positively associated with lupus classes and clinical parameters, including serum creatinine, albumin, and urine protein.

Key Words: *Activity Index, Chronicity Index, Lupus Nephritis, Serum Creatinine.*

Introduction

Systemic lupus erythematosus (SLE) is a multisystemic, chronic autoimmune illness that affects almost every organ in the body.Renal involvement, which occurs in more than 50% of patients within the first year of diagnosis, is associated with higher morbidity and mortality.[1]After diabetes mellitus, lupus nephritis (LN) is the second most prevalent cause of renal impairment overall2.Its etiology is complex and includes environmental variables, complement activation, autoantibodies, and genetic factors.[2] Advances in therapeutic approaches have improved the prognosis and outcomes of lupus nephritis over the last decade. Renal biopsy remains the gold standard for diagnosis and managementz.[3]

When examined under a light microscope, lupus nephritis can have morphological characteristics that range from normal findings to severe symptoms including glomerulosclerosis, crescents, and endocapillary hypercellularity. Immunofluorescence often shows sub-endothelial deposits in addition to granular full-house deposits in the tubular basement membrane and mesangio-capillary pattern.[4]

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More over 10% of patients develop endstage renal disease within 15 years, demonstrating the substantial impact of LN on morbidity and mortality.[5] The International Society of Nephrology and Renal Pathology Society (ISN/RPS) classified LN into six classes in 2003, which were updated in 2008 to include Class I: Minimal Mesangial Lupus Nephritis, Class II: Mesangial Proliferative Lupus Nephritis, Class III: Focal Lupus Nephritis, Class IV: Diffuse Lupus Nephritis, Class V: Membranous Lupus Nephritis, Class VI: Advanced Sclerosing Lupus Nephritis.[6,7,8]

Recent studies have underscored the importance of assessing activity and chronicity indices in renal biopsies of LN patients.[9,10] This may be due to limited data in several studies, producing false negative correlations. International renal societies have advocated for incorporating these indices into LN workup to enhance the prognostic value of renal biopsy.[11]

This study aimed to correlate renal functions with activity and chronicity indices in renal biopsies of lupus nephritis patients and establish a model of histological features associated with long-term kidney function impairment in the Pakistani population.

Materials and Methods

The study included 91 adequate renal biopsies from diagnosed/ suspected systemic lupus erythematosis patients (ANA/ Anti Ds DNA positive/ clinical picture) that were prospectively analyzed between October 2021 and 2022 at Shifa International hospital after approval by the Institutional Review Board (IRB). Clinical data, including history, age, serum creatinine, serum and urine albumin levels, ANA, and Ds DNA levels, were accessed from hospital's electronic records. Only cases with adequate renal biopsies, with separate cores for light microscopy (LM) and immunofluorescence (IF), were included. Biopsies lacking glomeruli or consisting entirely of globally sclerosed glomeruli were excluded. Hematoxylin and eosin staining was performed on all renal biopsies, cut at 6 microns, with additional special stains (PAS, Jones silver, Trichrome). Direct immunofluorescence testing was applied separately to cores submitted in normal saline, using IgG, IgA, IgM, C3, and C1q immunofluorescence antibodies. Clinical details of each case were recorded on a specifically designed questionnaire, including history, age, serum creatinine, serum and urine albumin levels, ANA, and Ds DNA levels. Renal biopsies were evaluated and calculated for activity and chronicity indices using standard chart(Table I) biopsies were also assessed for ISN/RPN lupus classes histologically and confirmed through special stains. Data were incorporated into data management software, and statistical analysis was conducted using IBM SPSS version 23.0.

Descriptive statistics, including frequency and percentage for categorical variables, and mean values with standard deviations for continuous variables, were reported. Gender and comorbid conditions such as hypertension, diabetes mellitus, Anti Ds antibodies, and ANA antibodies were qualitative variables, while activity index score, chronicity index score, serum creatinine, serum protein, and urinary protein levels were quantitative variables.

Spearman correlation tests were used to to measure the monotonic association between activity and chronicity scores with lupus classes, with results reported as correlation coefficients and significance values. Additionally, one-way ANOVA tests were used to compare means of activity and chronicity scores with mean values of serum creatinine, albumin, and urinary protein. A significance level of $p \leq 0.05$ was considered statistically significant.

Results

A total of 91 renal biopsies of either known SLE or suspected cases were included out of all the renal biopsies between the time frame in the study, including 12 (13.2%) males and 79 (86.8%) females. The majority of participants, 38 (41.8%), fell within the 21-30 years age group, while 21 (23.1%) patients belonged to the 11-20 years age group. Among the participants, 54 (59.3%) had elevated creatinine values, 41 (45.0%) had low serum albumin levels, 58 (63.7%) exhibited high urinary protein levels, 32 (35.2%) had decreased serum C3 and C4 complement levels, and 59 (64.8%) tested positive for anti-dsDNA antibodies.

Lupus class distribution among the study participants is illustrated in Figure 1, with 14 (15.4%) classified as lupus class 1 (mesangial expansion), 10 (11.0%) as lupus class 2 (Mesangioproliferative), 61 (67.0%) as lupus class 3 (focal lupus nephritis), 5 (5.5%) as lupus class 4 (diffuse lupus nephritis), and 1

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(1.1%) as lupus class 5 (membranouslupus nephritis) Direct immunofluorescence showed predominantly full-house deposits as seen in lupus nephritis.

Activity and chronicity index scores were calculated for each participant. The mean activity index score was 6.42±3.9 (ranging from 0 to 16 out of 24), while the mean chronicity score was 2.25±2.0 (ranging from 0 to 8 out of 12). Comparisons of activity and chronicity index scores with lupus classes revealed a significant association, as depicted in Figure 3. Mean activity scores for lupus class 1 to 5 were 2.07±1.6, 3.40±2.3, 8.21±3.3, 3.00±2.3, and 5.00±0.5 respectively, similarly mean chronicity scores for lupus class 1 to 5 were 0.50±0.5, 0.80±0.8, 2.75±1.9, 3.00±2.7, and 7.00±0.5 respectively.

Exploration of the correlation between lupus classes and activity index score yielded a significant positive correlation (r=0.446, p<0.001), as did the correlation between lupus class and chronicity index score (r=0.495, p<0.001).

Furthermore, the association of activity and chronicity index scores with clinical and laboratory parameters was assessed (Table 3). Significant associations were found between creatinine levels and both activity index (p=0.008) and chronicity index (p=0.001), with higher scores observed in patients with elevated serum creatinine levels. While higher scores were noted for patients with lower serum albumin, raised urinary protein, positive anti-dsDNA test results, and low C3 and C4 complement levels compared to those with normal results.

Table I: Modified NIH Indices (2018) Activity and Chronicity Index Score

MODIFIED NIH ACTIVITY INDEX	SCORE
Endocapillary hypercellularity	0 - 3
Neutrophils and/ or karyorrhexis	0 - 3
Fibrinoid necrosis	(0 – 3) x 2
Hyaline deposits	0 - 3
Cellular and / or fibro -cellular crescents	(0 – 3) x 2
Interstitial inflammation	0 - 3
Total	0 - 24
MODIFIED NIH CHRONICITY INDEX	**Score**
Global sclerosis	0 - 3
Fibrous crescents	0 - 3
Tubular atrophy	0 - 3
Interstitial fibrosis	0 - 3
Total	0 - 12

Table II: Association of mean activity and chronicity score with clinical/laboratory parameters

	Activity score (mean)	P value	Chronicity score (mean)	P value
Creatinine				
• < 1	• 4.3	0.008	0.86	0.001
• 1.1-2.0	• 7.5		2.1	
• 2.1-3.0	• 7.7		2.5	
• >3	• 7.9		3.3	
Serum albumin				
• <1.5	• 3.2	0.349	0.8	0.477
• 1.6-2.5	• 7.2		2.3	
• 2.6-3.5	• 6.0		1.9	
• >3.5	• 6.0		1.0	
Urine protein				
• <3 gm	• 4.7	0.071	1.5	0.291
• >3 gm	• 7.2		2.2	
Serum C3 and C4				
• Low	• 7.2	0.155	2.6	0.590
• Normal	• 5.6		2.2	

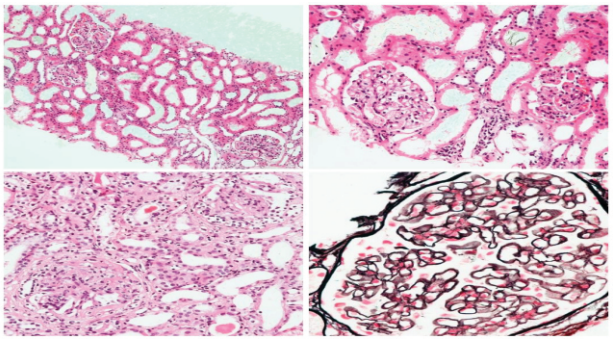

Figure 1: [Left upper: Class II(Mesangial hypercellularity), Right upper: Class III(Endocapillary proliferation less than 50%) Left lower: Class IV(Endocapillary proliferation more than 50%) Right lower: Class V(Membranous GN)

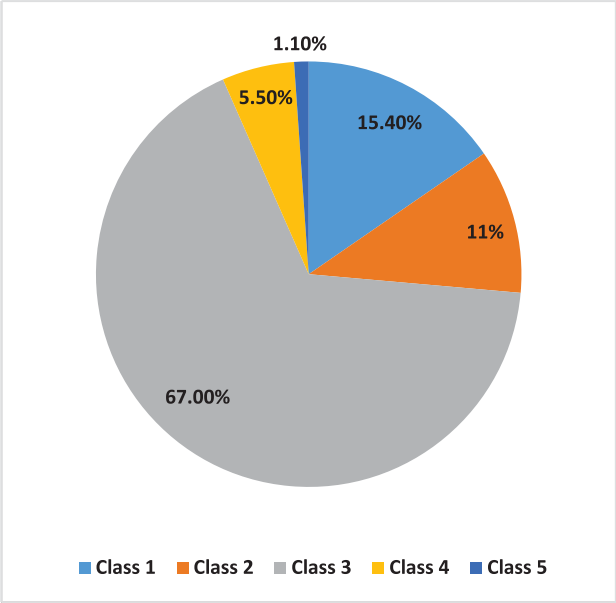

Figure 2: Distribution of Study Participants as per Lupus Nephritis Class

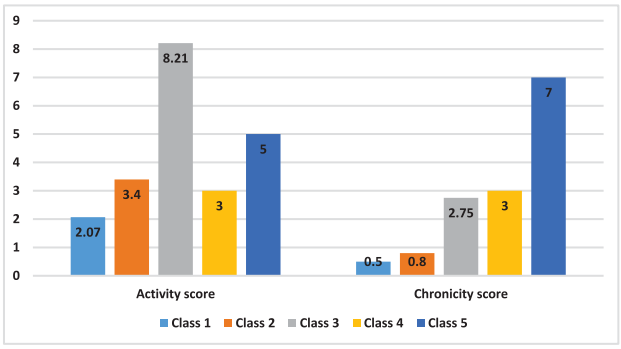

Figure 3: Mean Activity and Chronicity Score as per Lupus Grade among Study Participants (n=91)

Discussion

Renal biopsy is the most accurate way to diagnose lupus nephritis and assess the chronicity and activity of the condition to predict how renal function would deteriorate over time.

In our cohort, a substantial proportion of participants fell within the 21-30 years age group, followed by the 11-20 years age group. This age distribution reflects the peak onset period for lupus nephritis, which typically occurs during young adulthood. However, participants across a wide age range were included in the study, indicating the relevance of lupus nephritis across different age groups. 79 (86.8%) female patients and 12 (13.2%) males in our study reflects the female predominance of the disease process.

The distribution of creatinine levels provides insights into renal function among the participants. A considerable number of participants had creatinine levels above 1 mg/dL, indicating impaired renal function, while a notable portion had creatinine levels within the 1.1-2.0 mg/dL range. This underscores the significance of monitoring renal function in lupus nephritis patients, as elevated creatinine levels can indicate renal damage and disease progression. Serum albumin levels were also assessed, with a substantial proportion of participants having albumin levels less than 1.5 g/dL, with significant proteinuria (>3 grams) reflecting protein loss in the urine.

Assessment of serum C3 and C4 levels revealed that a considerable proportion of participants had low levels of complement components, which is commonly observed in active SLE and lupus nephritis. The presence of low complement levels suggests ongoing immune dysregulation and complement consumption. Anti-dsDNA levels were positive in 59 (64.8%) patients, and 19 (20.9%) patients were diagnosed to have SLE after diagnosis of lupus nephritis on renal biopsy.

The activity index in renal biopsy evaluates the severity of active inflammation and injury, while the chronicity index assesses the extent of irreversible structural changes and scarring within renal tissues. The majority of participants exhibited varying degrees of activity index ranging from endocapillary proliferation, glomerular neutrophilic infiltration, and cellular crescents, reflecting ongoing immune-mediated injury. Fibrinoid necrosis/karyorrhexis, although less commonly observed, is a hallmark feature of significant vascular injury and thrombotic microangiopathy. The majority of participants in this study did not exhibit significant fibrinoid necrosis/karyorrhexis, indicating a lower prevalence of severe vascular lesions in the cohort. The presence of hyaline deposits reflects previous episodes of glomerular injury and repair. Similarly, the majority of participants displayed varying degrees of chronicity index ranging from global sclerosis, fibrous crescents, tubular atrophy, and interstitial fibrosis, reflecting poor long-term outcomes.

Table II presents the association of mean activity and chronicity scores with various clinical and laboratory parameters in the study cohort, shedding light on the relationship between histopathological features and disease severity.

Higher mean activity and chronicity scores were significantly associated with elevated creatinine levels (>1 mg/dL), with larger number associated with activity. A retrospective study by Prasan wong et al. examined 38 patients and noted significant correlations between serum creatinine. They concluded that the modified National Institutes of Health (NIH) scoring system showed stronger associations with clinical and outcome indicators compared to traditional scores.[12]

In another retrospective cohort study conducted by Nakagawa et al. involving Japanese population with biopsy-proven LN, 66 subjects with a mean age of 31 years were included. They observed that a higher chronicity index correlated with an increased cumulative incidence of primary outcomes ($p<0.001$).[13]

Another study by Moroni et al. followed 203 lupus

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nephritis (LN) patients for 14 years. They reported significant correlations between components of the activity, chronicity index and clinical-laboratory indicators like serum creatinine levels.[6]

In a study involving 301 patients with biopsy-proven lupus nephritis (LN), it was reported that the presence of globally sclerotic glomeruli predicted kidney survival in univariate analysis but not in multivariate analysis.[15] Instead, in a cohort of 105 patients followed for 9.9 years, factors such as fibrinoid necrosis, fibrous crescents, interstitial fibrosis/tubular atrophy, deranged renal function, and non-White race were predictive of end-stage kidney disease (ESKD).[16]

Furthermore, in another similar study, the revised ISN/RPS classification was utilized to assess the outcome of 101 Chinese patients with LN over approximately 10 years, elevated chronicity index emerged as independent risk factors for a composite renal outcome, which includes a reduction in estimated glomerular filtration rate (eGFR) of 30% or more, ESKD, and mortality.[17]

Although there are variations in findings, all the studies affirm the effectiveness of NIH-modified activity index and chronicity index scores in forecasting prognosis and the likelihood of future complications in lupus nephritis patients.

Conclusion

This study supports that the NIH-modified activity index and chronicity index scores demonstrate positive associations with key clinical parameters such as serum creatinine, albumin, and urine protein. This scoring system holds promise for predicting the prognosis and assessing the risk of future complications among patients with lupus nephritis.

Limitation

Lower serum albumin raised urinary protein, positive anti-dsDNA test results, and low C3 and C4 complement levels compared to those with normal results were seen with higher activity chronicity indices but results were not statistically significant. This is because we do not find all the laboratory parameters with each biopsy as we receive bulk of biopsies from outside Shifa international hospital.

Conflict of Interest: None

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CONFLICT OF INTEREST

Authors declared no conflicts of Interest.

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DATA SHARING STATEMENT

The data that support the findings of this study are available from the corresponding author upon request.

ORIGINAL ARTICLE

Postpartum Depression in Females Presenting with Poor Sleep Quality During Third Trimester of Pregnancy

Nida Siddique[1], Aneela Nadeem[2], Nishat Akram[3], Huma Afridi[4], Shazia Tazion[5], Fahad Usman[6]

ABSTRACT

Objective: To assess the frequency of postpartum depression in females presenting with suboptimal sleep quality in the third trimester of pregnancy.

Study Design: It was an Analytical Prospective study

Place and Duration of Study: Department of Obstetrics & Gynecology, Imran Idrees Teaching Hospital, Sialkot. Duration of study was 10 months from 28th February 2024 to 15th December 2024.

Materials and Methods: A total of 200 females meeting the inclusion criteria were enrolled through non-probability consecutive sampling. Women aged 18–40 years with gestational age ≥34 weeks and poor sleep quality were included, while those with multiple fetuses, systemic diseases (e.g., pre-eclampsia, gestational diabetes, renal or liver disease, and anemia) were excluded. After delivery, participants were followed for one month and evaluated for postpartum depression with the Edinburgh Postnatal Depression Scale (EPDS) by a consultant psychiatrist at Imran Idrees Teaching Hospital, Sialkot. Data were recorded and analyzed using SPSS version 23, with Chi-square applied for stratified analysis.

Results: Mean maternal age was 28.7 ± 6.7 years, mean gestation age 37.8 ± 1.8 weeks. Sleep disturbance was pervasive (PSQI 13.3 ± 4.4 > cut‑off 5), and 56 of 200 mothers (28 %) screened positive for postpartum depression (PPD). PPD prevalence did not differ by age group (<30 vs >30 y, p = 0.653), parity (p = 0.271), or delivery mode (p = 0.280) thus, poor sleep quality, rather than obstetric factors, was the key correlate of PPD.

Conclusion: The frequency of postpartum depression was high in females presenting with poor sleep quality during third trimester of pregnancy

Key Words: *Depression, Maternal Health, Pregnancy, Sleep Quality, Third Trimeste.*

Introduction

Postpartum depression is characterized by occurrence of mild to severe depressive symptoms within 1 year after childbirth.[1] Females face a heightened risk of mood disorders during the postpartum period, with poor postpartum sleep potentially serving as a modifiable risk factor for depression.[2]

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In the postpartum phase, mothers who were not engaged in employment, did not have access to childcare assistance, or regarded the infant's nocturnal sleep behavior as a considerable issue encountered elevated levels of exhaustion.[3] The female with depression cannot cope with her baby like she is unable to maintain breastfeeding, positions the infant incorrectly during sleep, neglects to ensure timely vaccinations for the infant, does not prioritize the infant's safety, exhibits frequent irritability, provides insufficient comfort during initial interactions with the infant, repeatedly contemplates inflicting harm upon the infant, and, in certain instances, engages in abusive behavior towards the infant.[4]

Limited research has been conducted on maternal fatigue, specifically concerning its presence during the entirety of gestation and the subsequent postpartum phase.[5] Research on the relationship between depressive symptoms and prenatal subjective sleep quality has revealed that pregnant women who screen positive or fit the diagnostic

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criteria for depression report far lower levels of felt sleep quality.[6] There is general agreement that there is a reciprocal relationship between mood and sleep since disrupted (low quality) sleep is strongly linked to depression. During pregnancy and the postpartum period, sleep disturbances are frequent in women's lives. It has been proposed that sleep disruption is an additional element that might explain why women are more likely to experience depression during the postpartum period than throughout other times of their lives. Although postpartum depression is common and linked to sleep disorders, some research has tried to offer pregnant women a sleep-focused intervention to see if it can enhance sleep and, in turn, the mood of the mother after giving birth, but this hasn't been successful.[7] A study reported that 38.88 % of mothers experienced poor sleep quality and 19 % developed postpartum depression, while a 2023 investigation found that within the first three months after delivery the overall incidence of depression was 12.1 %, of which 7.1 % represented severe cases.[8,9] In 2021, according to a research, the prevalence of depression six weeks after giving birth was 17.4% (95% CI 16.73–18.17) of the world's population, with 18.6% (95% CI 18.0–19.2) in lower and middle income countries.[10] Another study conducted in Japan found the period prevalence of 11.5% in 6–12 months after birth.[11] Poor subjective sleep quality during pregnancy independently predicts the emergence of postnatal depressive symptoms as seen in another study that showed that six weeks postpartum mothers reporting poor sleep quality were almost three times more likely to screen positive for depression than their well-rested counterparts (31.2 % vs. 10.5 %), highlighting the critical interplay between early postnatal sleep disturbance and maternal mental health[12,13] So the aim of this study is to assess the frequency of postpartum depression in females presenting with poor sleep quality during the third trimester of pregnancy. It has been noticed from literature that different regions of the world showed varied frequency of postpartum depression among females who had poor sleep quality in pregnancy especially during the third trimester. But we have not been able to find any local evidence which can help us in deciding the extent of the problem in the local population. In a country like Pakistan, the females usually ignore such conditions and these lead to more hazardous outcomes. So we want to conduct this study to get local evidence regarding the extent of the problem as well as update local guidelines to screen such cases on an early basis and prevent the patients from developing hazardous conditions.

Operational Definition

- **Poor sleep quality**

It was defined as score≥5 by using Pittsburgh Sleep Quality Index (PSQI) during the third trimester of pregnancy.[14]

- **Postpartum depression**

It was labelled if Edinburg Postnatal Depression Scale (EPDS) score was >10 after 1 month of delivery[15]

Materials and Methods

It was an Analytical Prospective study that took place in Department of Obstetrics & Gynecology Imran Idrees Teaching Hospital, Sialkot after taking approval from IRB no (ref: 2024/IITH/RA/0026). The duration of the study was from 28th February 2024 to 15th December 2024. The sample size of 200 were calculated using Raosoft online sample size calculator with 95% confidence level, 5% level of significance and taking expected percentage of postpartum depression i.e. 17% in females presenting with poor sleep quality during the third trimester of pregnancy.[16] The sample selection was non probability, consecutive sampling. According to the operational definition, women between the ages of 18 and 40 who had poor sleep quality and a gestational age of at least 34 weeks (as determined by LMP) were eligible for participation. The exclusion criteria was the presence of Multiple fetus (on USG), Females with systemic problems e.g. PIH (BP≥140/90mmHg) or pre-eclampsia (Bp≥140/90mmHg with or without proteinuria ≥+1 on dipstick method), gestational Diabetes (BSR>186mg/dl and on medical record), renal disease (creatinine >1.2mg/dl), liver problem (ALT>40IU, AST>40IU), anemia (Hb<10mg/dl). 200 females who fulfilled the inclusion criteria were enrolled in the study by convenience sampling. Informed consent was obtained. Additionally, all of the fundamental demographic data (name, age, gestational age, and parity) was recorded. Then females were followed-up till delivery. Mode of delivery was noted. After delivery, females were followed-up for 1 month.

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After one month, females were assessed for postpartum depression by using Edinburgh Postnatal Depression Scale EPDS scale by a consultant psychiatrist. Patients were referred to the Department of Psychiatry, Imran Idrees Teaching and Allied Hospitals Sialkot. If a major depressive disorder took place within 4 weeks after delivery, then postpartum depression was labeled (as per operational definition). To address the recognized difficulty of re-engaging SVD mothers in routine OPDs at discharge each participant received an appointment card for a twice-weekly postpartum mental health checkup, women who missed these slots were screened during their infant's scheduled immunization visit. All antenatal data was entered on a standard form by two obstetric residents while the one-month Edinburgh Postnatal Depression Scale (EPDS) assessments were administered by a senior psychiatry resident. All this information was recorded through questionnaire. The collected data was analyzed statistically by using SPSS version 23. Quantitative variables like age, gestational age Pittsburgh Sleep Quality Index PSQI score and EPDS score were presented as mean ± S.D. Qualitative variables like postpartum depression and mode of delivery (vaginal cesarean) were presented as frequency and percentage was calculated for parity. Data was stratified for age, parity and mode of delivery. Chi square was applied to compare postpartum depression between stratified groups. P-value <0.05 was considered as significant.

Results

Table I shows the mean age of participants was 28.68 ± 6.67 years, ranging from 18 to 40 years. The mean gestational age at delivery was 37.75 ± 1.75 weeks, with a minimum of 35 weeks and a maximum of 40 weeks. Sleep quality and mental health assessments, the mean Pittsburgh Sleep Quality Index (PSQI) score was 13.3 ± 4.37, indicating poor sleep quality among participants, with scores ranging from 6 to 20. The mean Edinburgh Postnatal Depression Scale (EPDS) score was 9.15 ± 8.42, with a minimum of 0 and a maximum of 30, reflecting varying levels of postpartum depressive symptoms.

Table II shows that vaginal delivery was the most common mode, observed in 74 participants (37.0%), followed by cesarean section in 67 participants (33.5%) and instrumental delivery in 59 participants (29.5%), with a total of 200 deliveries recorded. In terms of parity distribution, 54 participants (27%) were nulliparous, while 55 participants (27.5%) had one prior birth, 47 participants (23.5%) had two, 25 participants (12.5%) had three, and 19 participants (9.5%) had four previous births, making a total of 200 women.

Table III shows that for age, among 120 women aged <30 years, 35 (29.2%) had PPD, while 85 (70.8%) did not. Among 80 women aged >30 years, 21 (26.3%) had PPD, while 59 (73.8%) did not with the p-value of 0.653.

For parity, 109 women were primi, of whom 34 (31.2%) had PPD, whereas 75 (68.8%) did not. Among 91 multiparous women, 22 (24.2%) had PPD, while 69 (75.8%) did not, with a p-value of 0.271.

Mode of delivery shows 67 women had a cesarean section, with 14 (20.9%) experiencing PPD and 53 (79.1%) not affected. Among 74 women who had vaginal delivery, 23 (31.1%) developed PPD, while 51 (68.9%) did not. Among 59 women with instrumental delivery, 19 (32.2%) had PPD, while 40 (67.8%) did not with a p-value of 0.280.

Table I: Descriptive Statistics of Maternal Characteristics, Sleep Quality, and Depression Scores (n= 200)

Parameter	Mean	Minimum	Maximum
Age (years)	28.68±6.67	18	40
Gestational Age (weeks)	37.75±1.75	35	40
PSQI score*	13.3±4.37	6	20
EPDS score**	9.15±8.42	0	30

*** Pittsburgh Sleep Quality Index**
****Edinburgh Postnatal Depression Scale**

Table II: Distribution of Delivery Modes and Parity (n= 200)

	Frequency	Percent
MOD		
Cesarean section	67	33.5
Vaginal delivery	74	37.0
Instrumental delivery	59	29.5
Total	200	100.0
Parity		
Nulliparous	54	27
One	55	27.5
Two	47	23.5
Three	25	12.5
Four	19	9.5
Total	**200**	**100.0**

Table III: Comparison of Postpartum Depression with Age, Parity, and Mode of Delivery (MOD)

Parameter	Category	Postpartum Depression: Yes (n)	Postpartum Depression: No (n)	Total (n)	Chi Value	p-value
Age (years)	<30	35	85	120	0.203	0.653
	>30	21	59	80		
Parity	Primary	34	75	109	1.21	0.271
	Multiple	22	69	91		
Mode of Delivery (MOD)	Cesarean Section	14	53	67	0.28	
	Vaginal Delivery	23	51	74	2.54	0.280
	Instrumental delivery	19	40	59		

Discussion

A major public health issue that impacts both mother health and baby care is postpartum depression (PPD). Pregnancy-related sleep issues, especially during the third trimester, have been found to be possible risk factors for the emergence of PPD. The demographic characteristics of the study population provide valuable context for interpreting the findings. The participants' average age was 28.68 ± 6.67 years, ranging from 18 to 40 years while the mean gestational age was 37.75 ± 1.75 weeks, with a range of 35 to 40 weeks, indicating that most participants were in the later stages of pregnancy, when sleep disturbances tend to peak due to physiological and psychological stressors. The results revealed a frequency of 28% for PPD, as measured by the Edinburgh Postnatal Depression Scale (EPDS), while the mean Pittsburgh Sleep Quality Index (PSQI) score of 13.32±4.37 indicated significant sleep disturbances. These findings provide critical insights into the association between prenatal sleep quality and postpartum mental health in a resource-constrained setting.

The frequency of PPD (28%) observed in this study is consistent with findings from other low- and middle-income countries (LMICs). A study in Ethiopia reported a PPD prevalence of 33% among women with poor sleep quality during pregnancy, emphasizing the interplay of psychosocial stress and insufficient mental health resources.[16] Similar findings were observed in Brazil, where the PPD prevalence was 31%, with poor prenatal sleep identified as a key contributor.[17] These rates are notably greater than those recorded in nations with high incomes (HICs), where PPD prevalence ranges from 9-13%.[9,18] For instance, a large longitudinal study from the United States in 2021 found that women with poor sleep quality during the third trimester had a PPD prevalence of 15%, suggesting disparities in healthcare access, socioeconomic factors, and cultural influences.[19] Several recent Asian studies corroborate these findings. Wu et al. (2020) identified a PPD prevalence of 22.14% among Chinese women with poor prenatal sleep, illustrating the adverse effects of sleep disturbances on mental health outcomes.[20] In South Asia, a study revealed PPD rates ranging between 24.3 % (95% Confidence Interval (CI) 19.03 to 30.47), with poor sleep quality emerging as a primary modifiable risk factor.[21] These findings suggest that women in LMICs may be disproportionately affected by PPD due to compounding stressors, including limited healthcare access, sociocultural expectations, and economic challenges. Additionally, the bidirectional relationship between poor sleep quality and depression has been extensively documented. Insufficient sleep exacerbates mood disorders, while depression disrupts sleep architecture, creating a vicious cycle. A cross sectional study conducted in 2024 reinforced this, showing that women with sleep disturbances during pregnancy are at a threefold higher risk of developing PPD.[22] The physiological basis of this relationship has also been explored in recent studies. Ko et al. (2020) demonstrated that disrupted sleep patterns during pregnancy may dysregulate cortisol levels and inflammatory responses, both of which are implicated in the pathogenesis of PPD.[23]

The elevated PSQI scores observed in our study (mean 13.32±4.37) are higher than those reported in studies from HICs. For instance, research in Japan found mean PSQI scores of 8.6 during the third trimester, with a PPD prevalence of 11.5%. [24] This discrepancy underscores the role of sociocultural and economic factors in exacerbating sleep and mental health challenges in LMICs. The current study highlight the significant association between poor sleep quality and PPD, suggesting that sleep disturbances during pregnancy act as a precursor to postpartum mood disorders. In Pakistan's sociocultural context, stressors such as financial instability, gender-based roles, and limited family

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support may amplify the impact of poor sleep on maternal mental health. [25]Addressing these factors is essential to reduce the burden of PPD in resource-limited settings. The findings of this study have important clinical implications. Screening for sleep quality during antenatal visits using validated tools such as the PSQI can aid in early identification of at-risk individuals. Interventions targeting sleep disturbances during pregnancy, such as cognitive behavioral therapy for insomnia (CBT-I) or mindfulness-based therapies, have demonstrated significant improvements in sleep quality and reductions in PPD risk. [26] Additionally, healthcare providers should consider integrating psychosocial support into antenatal care programs to address the sociocultural stressors that may contribute to poor mental health outcomes. From a public health perspective, raising awareness about PPD and its link with prenatal sleep quality is critical. Maternal age, parity, and delivery route showed no statistically significant relationship with postpartum depression once severe third-trimester sleep disturbance was accounted for. This pattern likely reflects a dominant mediating effect of poor sleep quality, which can mask smaller obstetric influences, and is compounded by wide confidence intervals around subgroup estimates.

Community-based programs that educate families about the importance of maternal mental health and provide support networks could help alleviate societal barriers to care. In resource-limited settings like the Department of Obstetrics & Gynecology, Imran Idrees Teaching Hospital, integrating mental health screening and interventions into routine obstetric care is a feasible and effective strategy. The strengths of the study include its setting in a tertiary care teaching hospital, which allowed for a diverse sample of participants. Additionally, the use of validated tools such as the PSQI and EPDS enhances the reliability of the findings. By following participants into the postpartum period, the study provides valuable insights into the temporal relationship between poor prenatal sleep quality and PPD.

Conclusion

This study shows a strong correlation between poor sleep quality during the third trimester of pregnancy and an increased prevalence of postpartum depression (28%). These findings highlight the need for early screening and interventions targeting sleep disturbances to reduce the risk of postpartum depression. Integration of mental health support into routine antenatal care and raising awareness about maternal mental health are key steps, especially in resource-poor settings. Although there are certain limitations, the study provides local insights and shows the requirement for further research to come up with effective strategies in preventing and managing postpartum depression.

Limitation of the Study

The study's limitations include its single-center, non-probability consecutive sampling design, which constrains external validity and may introduce selection bias. Moreover, the deliberate exclusion of obstetric comorbidities such as pre-eclampsia, gestational diabetes, and anemia likely led to an underestimation of postpartum-depression prevalence. Additionally, reliance on self-administered psychometric instruments (PSQI and EPDS) renders the findings susceptible to measurement error and response bias. Furthermore, the follow-up horizon was limited to one month postpartum, potentially missing late-onset depressive episodes.

Future Implications

Future studies should aim to explore the long-term consequences of poor sleep quality during pregnancy on both maternal and infant health outcomes. Prospective longitudinal studies with extended follow-up periods would help clarify the trajectory of PPD and its associated factors. Randomized controlled trials evaluating the efficacy of sleep-focused interventions during pregnancy in reducing PPD risk are also warranted. Expanding the scope of research to include diverse populations across LMICs and HICs could provide a more comprehensive understanding of the sociocultural and economic factors influencing maternal mental health.

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CONFLICT OF INTEREST

Authors declared no conflicts of Interest.

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DATA SHARING STATEMENT

The data that support the findings of this study are available from the corresponding author upon request.

ORIGINAL ARTICLE

Aromatase Activity and Its Association with Coronary Artery Disease in Males

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ABSTRACT

Objective: To determine the association among aromatase activity, testosterone-to-estradiol (T/E2) ratio, body mass index (BMI), and coronary artery disease in males.

Study Design: Comparative cross- sectional study.

Place and Duration of Study: Department of Chemical Pathology, from Feb2023 –Jan2024.

Materials and Methods: This cross-sectional study used the T/E2 ratio as a marker for aromatase activity and assessed the levels of plasma testosterone, estradiol, and T/E2 in 300 males. In order to evaluate the evolution of CAD, T/E2 was compared across serum quartiles and cardiac calcium score groups using ANOVA. It also showed correlations with atherosclerotic plaque, CRP, cholesterol, and BMI.

Results T/E2 ratio and plaque calcification score were found to be negatively correlated in atherosclerotic plaques. These effects were observed to be greater in men with elevated body mass indexes (BMI). BMI, CRP, and Calcium Score show statistically significant differences across the three T/E2 ratio groups

Conclusion: Males with low T/E2 ratio had higher levels of calcified plaque, systemic inflammation and evident atherosclerosis. These effects were strongest in men with higher BMI, which increased risk of future major acute coronary event.

Key Words: *BMI; Cardiac Calcium Score; Coronary Artery Disease; CT Angiography; Testosterone to Estradiol Ratio; Myocardial Infarction.*

Introduction

The development of atherosclerotic plaques in the arterial lumen is a typical sign of coronary artery disease. This results in decreased blood flow, Consequently, this hinders the myocardium's capacity to take in oxygen.[1] Superimposed atherothrombosis and subsequent artery blockage can result from plaque erosion or rupture, this may result in cardiovascular (CV) events such as myocardial infarction (MI), stroke, limb ischemia, and death from CV.[2] Age is the most significant risk element for coronary heart disease development and mortality after coronary atherosclerosis appears.[3] CAD affects the lives of almost four million people annually in the 49 nations that make up Europe and Northern Asia. An estimated 1.5 million Americans suffer a heart attack or stroke every year.[4] In 2019, CADs accounted for up to 32% of all deaths worldwide, with myocardial infarction and stroke accounting for 85% of these deaths.[5]

There is still uncertainty regarding the connection between testosterone and cardiovascular health. While some research indicates testosterone has a preventive impact, other studies imply it raises the chance of cardiovascular incidents.[6] The enzyme aromatase, which changes testosterone into estrogen, has been discovered to play a major role in the development of CAD.[7] Heart disease (CAD) and poorer cardiovascular outcomes are linked to a low serum testosterone/estradiol (T/E2) ratio, which indicates aromatase enzyme activity in males.[8] Systemic inflammation, bigger plaque size, and an increased risk of cardiovascular events are associated with low testosterone/estradiol (T/E2) ratios, which are regulated by testosterone being converted into estradiol by white fat cells.[9] There are a number of known direct and indirect effects on artery health of steroid hormones related to testosterone and estrogen, including 17β estradiol. An elevated BMI is associated with coronary artery disease because estradiol depends on both aromatase and circulating free testosterone.

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Because of the increased white adipose tissue, an elevated BMI raises aromatase activity, which increases the production of estrogen and upsets the hormonal balance.[10]

Although there has been progress in identifying the hormonal factors involved in coronary artery disease (CAD), the aromatase activity, as measured by the testosterone-to-estradiol (T/E2) ratio, is poorly comprehended in men. Earlier reports have shown mixed results on its relationship with systemic inflammation, coronary calcification, and obesity-related risks and there is an urgent need to fill this knowledge gap. The study was conducted to fill this gap and examine the relationship between aromatase activity, which is assessed by T/E2 ratio, and CAD and its associations with clinical markers including BMI and coronary calcification. The results are to elucidate the influence of hormonal imbalances on the cardiovascular pathology and guide the development of better risk assessment and specific treatment.

Materials and Methods

In this comparative cross-sectional study, conducted at Department of Chemical Pathology, Armed Forces Institute of Pathology, Rawalpindi, in collaboration with the Armed Forces Institute of Cardiology, Rawalpindi, from Feb2023 –Jan2024. Blood samples and data was collected after taking informed consent from every patient and the institutional review board's ethical clearance of participating centres - IRB letter no.2773 dated 27.7.24. Following a comprehensive review of the literature, we used the WHO calculator to determine a sample size of 300, maintaining a 5% margin of error, a 95% confidence level, and an 80% test power.[11]

All male patients (40-60 years) presenting to Institute of Cardiology for coronary CT angiography were incorporated into the research. Patients on hormone replacement therapy, diagnosed with testosterone producing tumors, diabetics and patients on insulin therapy, hypertensive patients, patients on lipid lowering drugs, patients with history of angioplasty or previous myocardial infarction, acute and chronic inflammatory conditions were taken out of the study.

Blood samples were drawn at the time of cannulation of patient for CT angiography. Using an automated analyzer and the CHOD-PAP enzymatic colorimetric technique, serum total cholesterol was measured. Serum testosterone and estradiol levels were analyzed by chemiluminescence dedicated reagent method on Advia centaur XPT. CRP was performed on Roche Cobas 600 through Turbidimetric inhibitory immunoassay (TINIA).

SPSS version 26 was used to do the statistical analysis for this investigation. The Shapiro-Wilk test was used to assess the normality of the data prior to analysis. The median and interquartile ranges (IQR) were given for data that was not regularly distributed, whereas the mean and standard deviation (SD) were computed for variables that were normally distributed. The testosterone to estradiol (T/E2) ratio was initially treated as a continuous variable and expressed as median (IQR) due to non-normal distribution. For additional analysis, the T/E2 ratio was also categorized into three groups to assess its relationship with BMI and calcium score. The groups were defined using tertiles as follows: Low T/E2 ratio (<1.41), Normal T/E2 ratio (1.41–1.89), and High T/E2 ratio (>1.89). To compare the testosterone to estradiol (T/E2) ratio, CRP levels, and total cholesterol between two groups based on BMI (High BMI >25 kg/m², and Normal BMI <25 kg/m²), the Mann Whitney U test was applied. The Kruskal Wallis Test was used for comparison of BMI and Calcium Score across T/E2 Ratio Groups. For pairwise comparisons among the three T/E2 ratio groups (Low, Normal, and High), Dunn's Post Hoc Test was employed because of the data's non-parametric character. Spearman The association between the T/E2 ratio and BMI was investigated using correlation analysis. Significant p-Values were those that were less than 0.05.

Results

This study covered 300 patients in total. The patients' median age was 46.00 years, with an 11-year IQR.

The table I presents a comparison of various biochemical and clinical variables between two BMI groups: Normal BMI (<25 kg/m²) and High BMI (>25 kg/m²). The significant differences was found between BMI groups for the T/E2 ratio, CRP levels, and calcium score, with p-values of <0.001 for each, demonstrating substantial statistical significance. In contrast, the p-value for total cholesterol is 0.626 mmol/L showing no significant difference between the two groups. These findings suggest that

individuals with higher BMI have increased aromatase activity, inflammation, and coronary artery calcification.

TABLE I: Comparison of T/E2 Ratio, CRP, Total Cholesterol, and Calcium Score across BMI Groups (n=300)

Variables	BMI Groups		p-Value
	Normal (<25 kg/m²) Median, IQR (n=98)	High (>25(<25 kg/m²) Median, IQR (n=202)	
T/E2 ratio	1.52 (1.98-0.96)	0.54 (0.79-0.34)	<0.001
CRP (mg/L)	9.50 (15.00-5.00)	29.00 (61.00-7.00)	<0.001
T. CHOL (mmol/L)	4.00 (5.00-2.18)	4.20 (6.40-1.90)	0.626
Calcium score	50.00 (100.00-10.00)	110.00 (412.00-60.00)	<0.001

The table-II compares BMI and calcium score across three T/E2 ratio groups: Low (<1.41), Normal (1.41-1.89), and High (>1.89). For BMI, the group with a low T/E2 ratio has a significantly higher median compared to the Normal and High groups, having a p-value of <0.001, suggesting a strong connection between T/E2 ratio and BMI. Similarly, the calcium score is highest in the Low T/E2 ratio group compared to the Normal and High groups, with a p-value of <0.001, showing vital differences in coronary artery calcification among the groups with T/E2 ratios.

Table II: Comparison of BMI and Calcium Score across T/E2 Ratio Groups (n=300)

Variables	T/E2 Ratio Groups			p-Value
	Low (<1.41) (n=236)	Normal (1.41-1.89) (n=25)	High (>1.89) (n=39)	
BMI (kg/m²)	29.00 (32.00-26.00)	23.00 (25.10-21.50)	21.00 (23.00-21.00)	<0.001
Calcium Score	100.00 (410.00-50.00)	50.00 (100.00-10.00)	50.00 (90.0-0.00)	<0.001

T/E2 ratio groups were defined using tertiles: Low (<1.41), Normal (1.41–1.89), High (>1.89).

The Table-III presents a pairwise comparison of BMI and calcium score among the T/E2 ratio groups (n=300). For BMI, no significant difference was found between the High and Normal T/E2 ratio groups (p=0.721). However, significant differences were observed between the High and Low groups (p<0.001) and the Normal and Low groups (p<0.001), indicating a relationship between lower T/E2 ratios and higher BMI. For the calcium score, there was no significant difference between the High and Normal T/E2 ratio groups (p=1.00), but significant differences were found between the High and Low groups (p<0.001) and the Normal and Low groups (p=0.002), suggesting a greater coronary artery calcification in the Low T/E2 ratio group.

TABLE III: Pairwise Comparison of BMI and Calcium Score among T/E2 Ratio Groups (n=300)

Variables	T/E2 Ratio Groups		p-Value
	(I) Ratio group	(J) Ratio group	
BMI	High	Normal	0.721
	High	Low	<0.001
	Normal	Low	<0.001
Calcium Score	High	Normal	1.00
	High	Low	<0.001
	Normal	Low	0.002

The table-IV shows the correlation between T/E2 ratio and BMI, with a correlation coefficient of r = -0.641, indicating a strong negative correlation between these two variables. The p-value of <0.001 suggests that this correlation is statistically significant. This means that as the T/E2 ratio increases, BMI tends to decrease.

Table IV: Correlation of T/E2 Ratio with BMI

	T/E2 Ratio	
	r	p-Value
BMI	-0.641	<0.001

Discussion

The importance of the testosterone-to-estradiol (T/E2) ratio as a possible indicator of coronary artery disease (CAD) risk is highlighted in the current study, especially in people with high body mass indexes (BMIs). Prior studies have demonstrated a substantial correlation between systemic inflammation and vascular calcification and hormonal abnormalities, which are manifested by low T/E2 ratios. A major cause of morbidity and death globally, coronary artery disease (CAD) is influenced by intricate interactions between hormonal, metabolic, and inflammatory pathways. New research identifies the testosterone-to-estradiol (T/E2) ratio as a crucial indicator of hormonal imbalance and a possible predictor of CAD; low T/E2 ratios have been linked to increased vascular calcification and systemic inflammation.[12] Due to the greater buildup of white adipose tissue, elevated BMI raises aromatase activity, which in turn converts testosterone to estrogen. Obesity-related metabolic and cardiovascular risks are associated with this hormonal imbalance, which is characterized by higher levels of estrogen than testosterone.[13]

The results of this research serve as evidence of the complexity of the connection between the

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testosterone-to-estradiol (T/E2) ratio, BMI, and the coronary artery calcification. Decreased T/E2 ratio was significantly related to higher BMI, more systemic inflammation as shown by CRP levels, and more coronary artery calcification. This implies that the hormonal imbalance that is caused by the high activity of aromatase in those with higher BMI can be a contributing factor to the pathogenesis of coronary artery disease (CAD). Elevated C-reactive protein (CRP) levels indicate systemic inflammation and calcified plaques, which are linked to low T/E2 ratios in males. Higher BMI individuals experienced these effects more strongly, indicating that white adipose tissue's elevated aromatase activity is a key factor in the development of atherosclerosis. Prior research has similarly shown that increased systemic and plaque inflammation is associated with lower T/E2 ratios, highlighting the part aromatase plays in cardiovascular risk (van Koeverden et al., 2019). These results align with the research of Naftolin et al., 2016 states that low T/E2 ratios exacerbate vascular inflammation and atherosclerosis through aromatase-mediated conversion of testosterone to estradiol, and the observed differences in calcium scores and BMI across T/E2 quartiles further support the role of hormonal imbalance in CAD progression. The importance of the T/E2 ratio as a possible biomarker for determining CAD risk is emphasized in the study.

The rate of coronary artery calcification was much more in the low T/E2 ratio group than in the normal and high ratio group, which shows that the severity of vascular calcification is strongly associated with hormonal imbalances. The absence of a strong association between the cholesterol levels and BMI groups supports the hypothesis that the classical markers of lipids might not be sufficient in reflecting the metabolic and inflammatory pathways involved in the development of CAD.[16] The T/E2 ratio shown a substantial connection with CAD markers, in contrast to conventional markers like cholesterol levels, which did not demonstrate any significant changes between BMI groups ($p = 0.626$). This implies that it might be useful as a diagnostic instrument. These findings align with the study of Huang et al., 2019 showing that hormonal abnormalities, rather than traditional lipid profiles, are more important in the development of CAD.

According to the study's findings, a higher BMI is linked to higher T/E2 ratio quartiles, which probably explains the connection between raised T/E2 and higher CRP levels as well as enhanced arterial wall inflammation. Given its association with atherosclerosis and cardiovascular control, this implies that the T/E2 ratio, which represents aromatase activity, may be a valuable indicator for determining a person's personal cardiovascular risk. The results emphasize how important it is to keep researching the metabolic and hormonal processes. More details about the relative contributions of this ratio in men would be beneficial to better understand the possible application of T: E2 ratio as a clinical biomarker (Wang et al., 2019).

Our study compared the T/E2 ratio in CAD patients grouped on basis of cardiac calcium score on CT angiography while a study by Van et al and Huang et al had a significant difference in groups based on T/E2 ratio when compared to endarterectomy patients results of plaque's histological appearance, type of plaque and their 3 year survival rate and future occurrence of MACE Van Koeverden D. et al. (2019) and HTERT expression in patients with worse cardiovascular status respectively (Huang et al., 2019).

Recent studies of Kusters et al., 2024 also confirm the mechanistic connection between increased expression of aromatase in adipose tissue and systemic inflammatory markers in obese men. In their observation, they found a correlation between production of adipose tissue-derived estrogens and elevated levels of C-reactive protein (CRP) and interleukin-6 (IL-6), which are major mediators of vascular inflammation. This is similar to our observation that people with lower T/E2 ratio have higher levels of CRP, highlighting the inflammatory process in case of hormonal imbalance. Inflammation plays a crucial role in CAD, with the T/E2 ratio emerging as a potential measure for aromatase activity, particularly in obese patients. Increased systemic inflammation and vascular calcification are associated with low T/E2 ratios. Our findings add relevance to the idea that a key connection between obesity and CAD may be disrupted sex hormone balance, which is triggered by elevated aromatase activity in the setting of higher BMI. This is in line with the data of the van

Koeverden et al., 2019, which showed that lower T/E 2 ratios correlate with higher systemic and plaque inflammation, higher calcification and twofold risk of major adverse cardiovascular events in overweight men.

Thirumalai et al., 2022 elucidate the simultaneous functions of estrogen and testosterone in cardiovascular health. Although men have historically been at higher risk for CAD due to testosterone, new research indicates that aromatase may be able to reduce some of these risks by converting testosterone to estrogen.

Conclusion

This study emphasize the prospect of the testosterone to estradiol (T/E2) ratio as a measure of coronary artery disease (CAD) risk, especially among males with high body mass index (BMI). The fact that low T/E2 ratio is strongly linked to systemic inflammation, vascular calcification, hormonal imbalance highlights the significance of dealing with metabolic and hormonal aspects of CAD management. This highlights the wider aspect of the hormonal pathways aim of reducing cardiovascular risk. The research needs to be conducted in the future to examine the potential role of T/E2 modulation in therapeutic approaches and its relevance in various populations to improve cardiovascular outcomes.

Future recommendations: Long-term, randomized, double-blind, placebo-controlled studies to assess the effects of aromatase blockers on cardiovascular disease, cardiovascular death, and all-cause death in men with low testosterone estradiol levels could be extremely useful in advancing our understanding of the atherosclerotic process.

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CONFLICT OF INTEREST

Authors declared no conflicts of Interest.

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DATA SHARING STATEMENT

The data that support the findings of this study are available from the corresponding author upon request.

ORIGINAL ARTICLE

Comparison of Lower Incisor Gingival Recession in Nonextraction Orthodontic Patients with Class I Crowding and Class II Malocclusion

Sadia Naureen, Huma Ghazanfar Kiani

ABSTRACT

Objective: To compare lower incisor gingival recession (GR) in non extraction orthodontic patients with Class I crowding and Class II malocclusion treated using Class II elastics.

Study Design: A cross sectional comparative study.

Place and Duration of Study: Orthodontic Department, Rawal Institute of Health Sciences (RIHS), from February 10, 2024 to August 10, 2024.

Materials and Methods: Pre and post-treatment casts of 42 orthodontic patients were divided into two groups: Class I crowding (C1) and Class II elastic treatment (E2). Clinical crown height (CCH) of the lower left central incisor was measured. GR was determined as the difference in CCH before and after treatment. The data was analyzed by SPSS v.20.0. Descriptive statistics like frequency of gender and mean age in C1 and E2 group were calculated. Paired sample t-test for intra group GR (pre and post treatment) and independent sample t-test for inter group GR were applied to analyze GR between two groups. The p value ≤ 0.05 was considered statistically significant.

Results: Both groups showed an increase in GR after treatment. The mean GR1 value was slightly higher (.5214mm) than GR2 (.4262mm) depicting that the C1 group had slightly more GR than the E2 group, though this difference was not statistically significant.

Conclusion: Both treatment modalities in non extraction cases resulted in increased GR, emphasizing the need to consider periodontal implications during orthodontic planning.

Key Words: *Class II Elastics, Gingival Recession, Orthodontic Treatment, Periodontal Health.*

Introduction

Gingival recession (GR) is a common periodontal condition which is characterized by the subjection of the root surface due to the gingival margin's advancement to the cementoenamel junction, often resulting in aesthetic concerns and dentinal hypersensitivity.[1] This condition involves the loss of attachment and exposes the tooth root to the oral environment. GR can lead to discomfort and may contribute to the development of both carious and non-carious cervical lesions.[2] The condition is most frequently observed in mandibular incisors, affecting approximately 43% of cases.[3] Among the various etiological factors contributing to GR, dental alignment and occlusal relationships are particularly significant.[3] GR has been associated with the buccolingual thickness of the gingival tissue, as well as orthodontic forces that displace teeth beyond the alveolar bone's boundaries, potentially inducing localized bone dehiscence and fenestrations.[4,5] Nevertheless, some studies have reported no significant differences in the occurrence and severity of GR between patients who are orthodontically treated and their matched untreated controls.[6,7]

There is a historical concern that moving lower incisors forward (proclination) during orthodontic treatment could lead to gum recession, especially in cases with pre-existing thin gum tissue or bone.[8] Research has shown that when we treat lower incisor crowding by nonextraction orthodontic treatment the teeth align by proclination of the lower incisors. For every millimeter of crowding alleviated, there's an expected increase in proclination of around 0.5 degrees and a slight protrusion of 0.2 mm, which can lead to GR.[9] On the other hand, research also indicates that this is not a strong or consistent correlation. Jati and Firquim[10] found no significant

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link between changes in lower incisor inclination (whether through orthodontic treatment or other factors) and the development of gingival recession.

Similarly, when class II malocclusion is treated by nonextraction orthodontic treatment by class II elastics it also leads to proclination of the lower incisors which can result in GR if excessive.[11] According to a recent systematic review, Class II elastics are efficacious in correcting Class II malocclusions, with their primary effects being dentoalveolar.[12] Conversely, GR was not found in patients, who were orthodontically treated using intermaxillary elastics and the Twin Force appliance.[13,14] These conflicting findings underscore the necessity for further investigation.

In nonextraction cases, orthodontic movements, especially in the mandibular anterior region, can influence the gingival margin's stability and the underlying periodontal support. Therefore, this study was conducted to "evaluate and compare the extent of gingival recession in nonextraction orthodontic patients with Class I crowding and those treated with Class II elastics." This study will help orthodontists identify and analyze improved orthodontic treatment modalities that prioritize both aesthetic and periodontal health outcomes.

Materials and Methods

This cross-sectional retrospective study was conducted at Rawal Institute of Health Sciences (RIHS) Islamabad, approved by Institutional Review Board (IRB) of RIHS (RIHS/IRB/D/24/003). The duration of study was six months from February 10, 2024 to August 10, 2024. The sample size was 42, that was calculated by using the prevalence of GR 40%,[15] a 95% confidence level, and a 5% margin of error, by single population proportion formula:

$$n = \frac{Z^2\ [p(1-p)]}{d^2}$$

Where n is sample size, Z is 1.96 i.e. the Z-score for 95% confidence level, *p* is the estimated prevalence of GR (as a proportion), and d is margin of error i.e. 0.05.

Non-probability purposive sampling technique was done. We evaluated the amount of GR in lower incisors among two patient groups: those presenting with moderate crowding and those with Class II malocclusion treated using elastics in nonextraction cases.

Patients were divided in two groups lower incisor crowding group (C1) and class II elastic group (E2). Each group consisted of 21 patients. The inclusion criteria which was: (i) age of the patients ranged from 16 to 30 years with good oral hygiene, (ii) all patients were treated without extraction with fixed orthodontic mechanotherapy, (iii) patients having thick attached gingiva, lower incisor to mandibular plane angle not more than 95°, (iv) patients in the lower incisor crowding group should not have crowding more than 5mm, patients in the class II elastic group should have no crowding in the lower arch. The thickness of gingiva was assessed manually by a single investigator by inserting periodontal probe in the gingival sulcus. The exclusion criteria included (i) patients with a history of periodontal disease (ii) treatment prior to orthodontic intervention (iii) patients with systemic conditions affecting periodontal health and (iv) patients who underwent additional dental procedures affecting the gingiva during or after orthodontic treatment.

Dental casts taken were labeled as pre (T0C1) and post-treatment (T1C1) in C1 group. Similarly, in E2 group pretreatment casts were labelled as T0E2 and post treatment as T1E2, respectively. The dental casts were utilized to assess alterations in the clinical crown height (CCH) of the lower left central incisor following incisor proclination, as illustrated in Figure I. Dental casts after treatment (T1) were obtained one-month post-debonding. Scaling was also done at the time of debonding to eliminate potential effects of bracket-induced gingival inflammation on measurement. The CCH of the lower left central incisor was determined using a vernier caliper, measuring the perpendicular distance from the incisal edge to the most apical point of the free gingival margin. The net GR was calculated as the difference between pre and post-treatment CCH values, designated as GR1 for the C1 group and GR2 for the E2 group. To evaluate the measurement method's precision, a single operator repeated all plaster model measurements after a week. An intra class correlation coefficient (ICC) was then computed between the two measurement sets, resulting in a value of 0.96, indicating high reliability.

Descriptive statistics for both C1 and E2 groups were calculated by using SPSS 20. Data distribution was studied using a Shapiro–Wilk normality test. Paired

sample t test was used to compare intragroup pre-treatment and post-treatment values of GR. Whereas, inter group comparison was done on the differences of pre-treatment and post-treatment in CCH comprising "GR1 for C1" and "GR2 for E2" group by using independent sample t-test. The *p* value of ≤ 0.05 was considered statistically significant.

Results

The frequency of males and females was 8 (32%) and 13 (68%) in crowding (C1) group, while in Class II elastic group (E2) group it was 9(43%) and 12 (57%) respectively as shown in Figure II. The mean value for age, pre and post treatment CCH and net GR is shown in Table I for both C1 and E2 groups. Shapiro–Wilk normality test showed equal distribution of data. Results of paired sample t-test (Table II) were statistically significant (p=0.001) for both C1 and E2 groups. These results revealed that GR occurred in both groups after orthodontic treatment. Mean GR1 value was slightly higher (.5214mm) than GR2 (.4262mm) depicting that the C1 group had slightly more GR than the E2 group. However, it was not statistically significant when independent sample t-test was applied as shown in Table III (p =0.418).

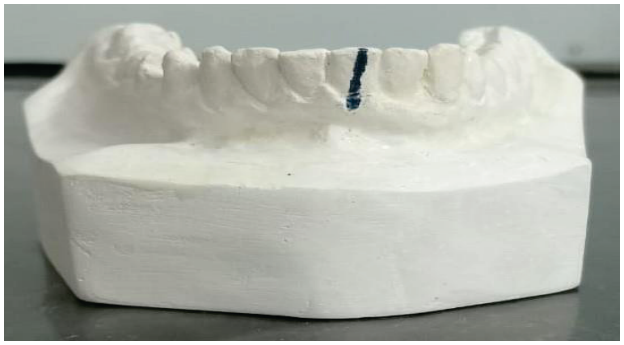

Figure 1: Measurement of CCH from incisal edge to deepest gingival crevice.

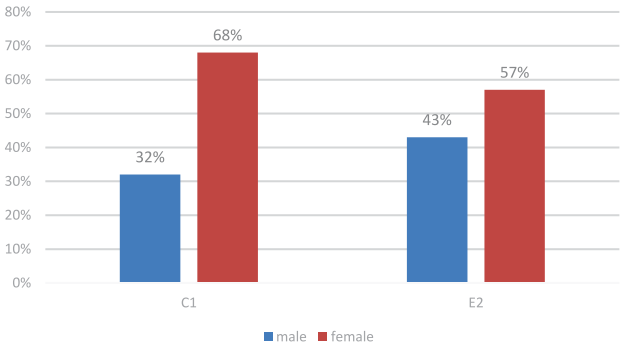

Figure 2: Percentage of males and females in C1 and E2
C1= Crowding group E2= Class II elastic group

Table I: The mean of pre and post treatment CCH in C1 and E2 groups

	n	Mean ± SD
Crowding group (C1) Age	21	16.238 ± 1.81
T0C1 (CCH)	21	7.8238 ± .814
T1C1 (CCH)	21	8.3429 ± .817
GR1	21	.5214 ± .404
Class II elastic group (E2)		
Age2	21	16.9524 ± 2.51
T0E2 (CCH)	21	7.6619 ± .780
T1E2 (CCH)	21	8.0714 ± .698
GR2	21	.4262 ± .347
Valid n (listwise)	21	

Discussion

Our study showed that significant amount of GR occurred in the post treatment phase of both class II elastics and nonextraction crowding groups. Similar to this Bin Bahar and Alkhalidy[16] revealed that while treating Class II nonextraction cases using Class II inter maxillary elastics, the lower incisors frequently procline. This proclination of the lower incisors is inevitable, and in certain cases particularly in dolichofacial individuals with a slender cortical bone structure in the mandibular symphysis—may experience periodontal complications like GR as a result of this movement. Tsolaki *et. al.,*[11] demonstrated that multibracket orthodontic treatment utilizing Class II elastics alone leads to a rapid and undesirable inclination of the labial incisors causing GR.[17]

However, in contrast to our results Rongo *et. al.,* [18] demonstrated that using Class II elastics in combination with aligners leads to effective control of lower incisors, which means less GR. Tehnia and Carlos[5] found no association between appliance-induced labial movement of mandibular incisors and GR, rather it is associated with thin thin gingiva. Additionally, according to a recent systematic review there is not enough evidence to definitively state that the forward tipping of incisors caused by fixed appliances negatively affects periodontal health. As a result, additional research is required to address this issue.[19]

This controversy also extends to cases of mild Class I crowding. In the front part of the lower jaw, significant correlations have been found between

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Table II: Intragroup paired sample t-test

		Paired Differences				t	df	Sig. (2-tailed)
		Mean	Std. Error Mean	95% CI Difference Lower	Upper			
Pair 1	T0C1 - T1C1	-.519±.405	.08847	-.70359	-.33450	-5.867	20	0.001
Pair 2	T0E2 - T1E2	-.409±.359	.07850	-.57327	-.24578	-5.217	20	0.001

The *p* value of ≤ 0.05 was considered statistically significant.

Table III: Inter group Independent Sample T-Test

Gingival recession		Levene's Test for Equality of Variances		t-test for Equality of Means						
		F	Sig.	t	df	Sig. (2-tailed)	Mean Difference	SE of Difference	95% CI Difference Lower	Upper
GR	Equal variances assumed	.016	.900	.819	40	.418	.09524	.11635	-.13992	.33040
	Equal variances not assumed			.819	39.1	.418	.09524	.11635	-.14008	.33056

The *p* value of ≤ 0.05 was considered statistically significant.

incisor crowding and the advancement of periodontal disease.[20] Changes in soft tissues can be associated with the thickness of the labial gum tissue and the amount and type of orthodontic forces that push the teeth outside the alveolar bone envelope, leading to localized bone loss and GR.[4] In our study we have controlled this factor by including patients with thick gingival biotype on lower incisors.

On the other hand, Nastri *et. al.,*[21] found no correlation between GR and the final lower incisor to mandibular plane angle (IMPA), even when this angle exceeded 95°. Orthodontic tooth movement can cause dehiscence at the bone crest when a tooth is moved into an area of thin bone before the occurrence of actual GR. Ideally, tooth movement should only occur within the trabecular space of the alveolar bone; however, some movements may compromise the outer cortical plate, leading to dehiscence and fenestration. Labial cortical bone thickness can only be accurately assessed using cone-beam computed tomography (CBCT). In our study we selected patients with thick attached gingiva but could not assess the thickness of labial alveolar bone in lower incisors region due to the unavailability of CBCT. This might have led to biased results. Given the fragility of the periodontal labial structure and bone, careful orthodontic planning tailored to areas with thin buccal bone can help prevent GR.[22]

According to a local study done by Imtiaz and Baloch[23] most of the cases with fixed orthodontic appliances had no gingival tissue recession, only few cases were seen in Class I and Class II. However, this mild gingival tissue recession was significantly associated to oral hygienic index. Ideally, teeth should be fully "enveloped" by bone tissue on all surfaces, but this is often overlooked during treatment planning.[24] It can be concluded that it is not the orthodontic treatment itself, but rather inadequate planning, that leads to GR. In most of the cases, the incisors and canines labial surfaces—particularly the mandibular incisors—are so thin that no bone is anticipated on palpation. In such cases, applying controlled, light continuous orthodontic forces is the solution. This approach not only positions teeth toward the center of the bone but also enhances the structural thickness of the buccal periodontal tissues.[23] In contrast to this our study showed significant post treatment GR in both C1 and E2 groups.

Potential limitations of our study include the reliance on historical records, which may lead to incomplete or missing data. Furthermore, the retrospective design may introduce biases related to patient selection and variability in treatment approaches. To gain a more comprehensive understanding of the

impact of different orthodontic treatment modalities on gingival health, future research should aim for larger sample sizes and extended follow-up periods.

These results highlight the need for careful consideration of periodontal health in orthodontic treatment planning, particularly in younger patients. In future studies we should use CBCT to assess the thickness of labial cortical plate and gingival tissue. We can assess the direct effect of orthodontic treatment mechanics on GR by controlling these factors.

Conclusion

Both Class I and Class II nonextraction orthodontic treatment plans were associated with gingival recession in lower incisors.

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REVIEW ARTICLE

Psychiatric and Psychological Perspectives on the Treatment of Obsessive-Compulsive Personality Disorder: A Narrative Review

Tania Qamar

ABSTRACT

Background: Obsessive-Compulsive Personality Disorder (OCPD) is known as excessive control, a rigid commitment to norms, and an overarching commitment to perfectionism. Despite its prevalence, OCPD often goes undiagnosed or unnoticed, which leads to considerable impairments in quality of life and psychological functioning.

Objective: The objective of this narrative review is to examine the perspective of psychiatric and psychological treatment approaches for OCPD.

Method: This narrative review focused on literature published between 2000 and 2024, covering adult populations with OCPD across North America, Europe, and Asia. This narrative paper reviewed the different pharmacological and psychological treatment options that used to help individuals with OCPD.

Results/Review: Findings shown that psychiatric or pharmacological treatments are found beneficial, and SSRIs reduce the emotional rigidity or anxiety associated with OCPD. On the other hand, Cognitive-Behavioural Therapy (CBT), psychodynamic therapy, and other new psychological therapies were also found effective. Despite numerous treatment claims, a limited empirical literature has not proven the effectiveness of any treatment for OCPD.

Conclusions: Although CBT seems to have the most empirical support as a treatment, it is promising for improving the conditions of patients with OCPD. Future studies could focus on developing standardized treatment guidelines and intervention models to enhance the quality of care for patients with OCPD. It includes an examination of relevant predictors of treatment response that could provide beneficial clinical care for patients with OCPD.

Key Words: *Obsessive-Compulsive Personality Disorder, SSRIs, Psychiatric Treatments, Psychological Treatment.*

Introduction

Clinical Context: Key Features and Functional Limitations

Obsessive-Compulsive Personality Disorder (OCPD) is a persistent medical condition characterised by extreme perfectionism, and an obsession with order and small details, and a strong desire to control one's environment. The Diagnostic and Statistical Manual-Fifth Edition-Text Revision (DSM-5-TR) describes OCPD as a pattern of symptoms that results in clinically significant distress or impairment in functioning. The American Psychological Association (APA) lists the following things as possible causes of OCPD symptoms: an unhealthy fixation on work or productivity, an unhealthy fixation on details and order, moral and ethical stubbornness, refusal to delegate, disengagement from oneself and others, and indecision.[1] Individuals with Obsessive-Compulsive Personality Disorder (OCPD) show a range of symptoms characterized by indecisiveness, emotional disconnection, and a rigid need for control.[1,2]

These include difficulty expressing emotions, extreme reactions to disruptions in control, resistance to changes in routine, procrastination driven by perfectionism, and obsessive attention to detail that often leads to inefficiency and missed deadlines.[3,4] Their compulsive behaviour extends to re-reading or re-watching materials due to fear of overlooking details. OCPD significantly impairs psychological well-being and social functioning, with studies[5,6] indicating comparable declines in quality of life to those seen in Obsessive Compulsive Disorder (OCD). Moreover, OCPD, often comorbid with

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borderline personality disorder, incurs significant economic costs due to healthcare needs and work disruptions. The disorder is marked by interpersonal difficulties, where individuals tend to be inflexible, demanding, and overly reliant on rigid standards, leading to frequent relational conflicts.[7]

In addition, individuals with OCPD have extremely high standards for the behaviour of others. A study found that people with OCPD are highly directing and cold in their relationships, and they also experience hostile-dominant interpersonal issues.[7] Some of the interpersonal issues that have been described are attributed to the fact that individuals with OCPD are less adept at empathic perspective-taking than healthy controls. Another study showed that emotionally sensitive people have the ability to understand the appropriate affective response to another person and to experience sympathy and concern for others.[8] However, they are limited in their ability to follow this intuition and indicate the adequate emotional responses in social situations or consider different points of view of others. Perfectionism is recognized as a fundamental characteristic of OCPD in both research and clinical reports, with perfectionism being a major cause of functional impairment.[8]

Obsessive-Compulsive Personality Disorder (OCPD) is strongly associated with maladaptive perfectionism and depressive symptoms, which significantly elevate the risk of suicidal ideation and behaviours.[9] Individuals with OCPD often believe that anything short of perfection is unacceptable and tend to derive self-worth from external validation, leading to emotional distress and poor relationship functioning. Compared to patients with depression alone, those with OCPD demonstrate a higher frequency of suicide attempts and experience fewer protective factors such as reduced anxiety or reasons to live.[10] The variety in OCPD, which comes from its subjective diagnostic criteria, shows up in different clinical styles, each with its own specific thinking, feelings, behaviours, and ways of interacting with others. Anxious types tend to procrastinate, fixate on details, and experience self-critical indecisiveness, while dominant types are more aggressive, skeptical, and inflexible.[11] These different emotional styles, persistent anxiety versus constant irritation, highlight the complexity and variety in OCPD cases, making it important to create specific treatment plans.

People who suffer from anxiety tend to be more submissive, people-pleasers, and conflict-averse, whereas individuals who are more dominant tend to be more critical, aggressive, and confrontational.[11] The literature provided a broad perspective at Cognitive-Behavioral Therapy (CBT) for OCPD. However, the treatment would work better for each patient depending on how they present and how much they are expected to lose in their daily life.[11] Individuals with the controlling personality type would benefit from developing emotion regulation abilities, whereas both types find it easier to acclimatize and tolerate distress through behavioral trials. Many diverse factors draw people with OCPD to treatment.[12] People with OCPD feel distressed when they can't complete work or school projects. This distress is typically either due to their inability to manage their time effectively or the quality of work they expect to complete.

Obsessive-Compulsive Personality Disorder (OCPD) is a prevalent yet underrecognized personality disorder, affecting 2% to 8% of the population[12]. Individuals with OCPD often experience a sense of being "stuck" in their professional or educational lives due to chronic self-criticism and unmet expectations of others, leading to persistent negative moods. These challenges frequently extend to intimate relationships, causing distress that prompts many to seek help in primary care or mental health settings.[13] Despite the high prevalence and notable impact of OCPD, there is a lack of public awareness, limited scientific literature, and a lack of treatment with proven efficacy. Moreover, mental health professionals often face difficulties in diagnosis due to inconsistent guidelines and insufficient familiarity with the disorder's distinct characteristics.[14,15] This situation points out the need for increased clinical attention and public education regarding OCPD.The rationale for this review is to synthesize psychiatric and psychological treatment perspectives to reduce the gaps in empirical evidence and guide future research and clinical practices.

Methods

This narrative review focused on literature published between 2000 and 2024, covering adult populations

with OCPD across North America, Europe, and Asia. The search strategy used keyword combinations such as "OCPD treatment," "Cognitive Behavioral Therapy OCPD," "SSRIs OCPD," and "psychotherapy for personality disorders" in databases including PubMed, PsycINFO, Scopus, and Google Scholar. Although the approach was not systematic, inclusion was based on relevance to psychiatric and psychological treatments, focusing on clinical trials, meta-analyses, and narrative syntheses from PubMed, PsycINFO, and Scopus databases. Inclusion criteria were peer-reviewed articles with clinical relevance to adult OCPD treatment.

Results

Evaluation and Treatment Interventions

Medical Intervention

Selective Serotonin Reuptake Inhibitors (SSRIs), including sertraline and fluoxetine, have been found to help individuals with Obsessive-Compulsive Personality Disorder (OCPD) experience a reduction in anxiety and rigidity.[16] As SSRIs change serotonin levels, the neurotransmitter is important in emotional regulation and compulsive behaviors. In a study, fluoxetine was shown to improve cognitive flexibility among subjects with OCPD, thereby lowering resistance to change.[17] Risperidone and other pharmacological treatments help with acute rigidity and emotional dysregulation.[18] However, concerns about the weight gain and sedating effects have led to a ban on its widespread use. In a brief study, mood stabilizers, particularly lamotrigine, were shown to decrease emotional instability for patients with OCPD.[19]

A study was conducted to examine the two groups of 24 people with DSM-IV OCPD who were randomly assigned to receive either fluvoxamine (50–100 mg/day) or a placebo for up to 12 weeks.[20] Results found an improvement in OCPD features in those who received fluvoxamine compared to the placebo group.[20] Additionally, literature studied that how SRI medications affect OCPD traits. For example,[21] administered sertraline and citalopram to 308 depressed patients with co-occurring personality disorders and found that both medication types were associated with reduced dysfunctional personality disorder traits; however, the most effective medication at reducing OCPD traits was citalopram. While SSRIs are reported to reduce OCPD rigidity (Fluoxetine and Citalopram), contradictory results exist regarding their efficacy. Some studies showed minimal changes in personality traits. Similarly, while CBT has showed improvements in trait perfectionism, its comparative efficacy to psychodynamic therapy remains debated due to the lack of head-to-head RCTs. A study found comparable results between both therapies, but limited by lack of OCPD-specific outcome measures.[21]

Another study examines two groups of OCD patients, which indicated that patients with OCPD who were taking clomipramine had significantly lower scores on a measure of OCPD features than did those who were taking imipramine[22]. Case reports studies have investigated the adaptability of OCPD characteristics to mood stabilisers and antipsychotics.[22] SRIs are the most prevalent pharmacological treatment for individuals with OCPD, yet more research into the medication treatment of primary OCPD is needed to provide the field with more high-quality evidence. Although no empirically validated gold standard treatment is available for OCPD, the therapy treatment is considered the best choice for intervention.[23] The next section reviews the available research on psychological and psychotherapies treatments for OCPD.

Psychodynamic Psychotherapy

Psychoanalytic explanations of Obsessive-Compulsive Personality Disorder (OCPD) attribute the cause of OCPD in children to either overly strict or overprotective parenting.[24] According to these theoretical models, OCPD traits develop due to the attachment insecurity experienced in early development[24]. Empirical research on the relationship between attachment and OCPD traits is limited. Though the timing is past-oriented, it is recently shown that the symptoms of OCPD were related to an ambivalent-avoidant attachment style in Iranian students.[25] A study indicated that individuals with OCPD showed more secure attachment styles compared to those with borderline personality disorder.[26] Prior to the emergence of OCPD, Freud posited a developmental link between the two disorders, indicating that OCPD features were already present.[27]

According to a study of adults, childhood OCPD traits are associated with an adult diagnosis of Obsessive-

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Compulsive Disorder (OCD).[28] At the same time[29] found that OCPD characteristics in adolescents were associated with simultaneous OCD symptoms in a cohort of children diagnosed with OCD. These findings provide support to the idea that OCPD features in childhood are associated with OCD (both current and future); however, further longitudinal research is required. The goal of insight-oriented psychodynamic treatment for OCPD is to identify the ways in which the symptoms of OCPD serve as a defense mechanism against the patient's own emotions of inadequacy and fear. After coming to this realization, patients strive to change their unyielding patterns and discard their unrealistic expectations of perfection in favour of a more realistic perspective.[29]

Patients suffering from personality disorders, such as OCPD, find relief through supportive-expressive psychodynamic therapy.[30] After 52 sessions, 14 patients with OCPD showed significant improvements in this study. However, there was no control group in this research[30]. In two more studies, Mixed personality disorder patients, especially some with OCPD, who received immediate psychodynamic therapies surpassed control group patients who had to wait.[31] However, findings did not directly evaluate changes in OCPD symptoms, and neither study specifically looked at improvement among people who had OCPD. Therefore, future researchers need to conduct further studies to evaluate the effectiveness of psychodynamic therapies.

Cognitive-Behavioural Therapy

Cognitive Behavioural Therapy (CBT) generally includes a mixture of perceptive and behavioural strategies. In order to address Obsessive-Compulsive Personality Disorder (OCPD), The general cognitive therapy dimension at involves finding and restructuring faulty ideas that lead to maladaptive behaviours.[32] Therapists instruct patients to consider the range of acceptable possibilities in order to challenge "all-or-nothing" thinking. Similarly, therapists also help patients to identify that when they exaggerate the repercussions of mistakes (catastrophizing) by asking them to consider the real impact of small mistakes. Behavioural components are also a part of CBT, and one of these is the use of behavioural trials to introduce the patient to stimuli and settings that trigger their fears.[32,16] Certain individuals diagnosed with OCPD experience challenges in forming connections, largely attributable to their inflexible cognitive frameworks and struggles with expressing emotions.

Young's schema-focused therapy[33] is designed to identify and restructure patients' maladaptive schemas as they are articulated during the therapy process, in light of this struggle. Despite the extensive description of numerous cognitive and behavioural approaches to OCPD[34], there is a lack of empirical research evaluating these treatments. A study was carried out involving individuals with severe depression who also fulfilled the DSM-IV criteria for OCPD. These participants received cognitive therapy specifically targeting OCPD. On average, after 22 sessions, all 10 patients reported decreased depression and anxiety, and 9 of those individuals no longer fulfilled the diagnostic criteria for OCPD. The limitations of this study were that it did not include a control group and had a small sample size.[35]

Another study that involved outpatients with OCPD (N=516) and avoidant personality disorder (N=524) who received cognitive treatment sessions up to 52 per week. 83% of OCPD patients experienced clinically significant improvements in symptom severity, whereas 53% improved depression severity.[36] However, definitive conclusions cannot be drawn about the effectiveness of CBT in treating OCPD because this open trial lacks a waitlist control group or alternative treatment. The most extensive cognitive-behavioral therapy research on OCPD was led.[37] Researchers in this study put together an open-label 10-week trial of group therapy for OCPD that included cognitive restructuring, psychoeducation, behavioral experiments, and planning for how to avoid relapse. The study was conducted with 116 outpatients who met DSM-IV criteria for OCPD. Results showed that treatment significantly reduced the severity of OCPD.[37]

Furthermore, after the intervention, individuals who showed reduced levels of trait anxiety and depression were more inclined to experience a reduction in their symptoms of OCPD. There was also predictive power in the level of distress prior to intervention.[37] However, a major limitation of this study was the lack of a control group. A study performed a randomized controlled trial of group

Cognitive Behavioral Therapy (CBT) that focused on clinical perfectionism instead of OCPD. Forty- Two participants with anxiety, eating, and mood disorders, as well as elevated perfectionism, were randomly assigned to a CBT group and a waitlist control group. The clinical perfectionism, dietary constraint, depressive symptoms, social anxiety, eating disorders, anxiety sensitivity, and ruminating behaviours of participants in the group CBT were considerably reduced.[38]

In addition, results showed a significant difference in the improvement of self-esteem and quality of life before and after treatment in the treatment group and between the two groups. The six-month follow-up confirmed the long-term maintenance of the CBT treatment. In addition to improving quality of life and self-esteem, the findings support the idea that CBT in a group setting is an effective strategy for addressing therapeutic perfectionism.[38] Due to the limited research that has directly compared psychodynamic and CBT, the available evidence does not prove the effectiveness of either approach in treating OCPD. For instance, in a prior study, 40 sessions of cognitive treatment (N=525) or short-term psychodynamic therapy (N=525; randomised) were administered to patients diagnosed with cluster C personality disorder[39].

Although OCPD was more commonly diagnosed in this sample, it was present in 17 people who met DSM-III criteria: the cognitive therapy group consisted of eight individuals (32%), while the psychodynamic group contained nine individuals (36%). Treatment and testing addressed symptom distress, interpersonal issues, and fundamental personality pathology. After two years, results showed that the symptoms among both patient groups were significantly improved. Furthermore, across all age groups, CBT and psychodynamic therapy both produced comparable levels of improvement. The cognitive-behavioural treatment used in this study was college-based and failed to emphasise a behaviour-focused approach[39]. This study did not compare treatment outcomes in OCPD patients specifically; therefore, more research is required to establish the effectiveness of both cognitive and psychodynamic treatment approaches for OCPD.

Other Psychological Treatments

A number of alternative treatments for Obsessive-Compulsive Personality Disorder (OCPD) have been evaluated using case-by-case analytic designs. For instance, two case studies were directed to adapt metacognitive therapy for individuals with OCPD.[40,41] Metacognitive therapy is meant to increase patients' awareness of their emotions and ability to understand and empathize with mental states while improving interpersonal functioning. The interpersonal difficulties typically experienced by patients with OCPD appear well-matched to this psychotherapy (although further study is necessary). Another study described Radically Open-DBT (RO-DBT) is a variation of Dialectical Behavioural Therapy (DBT) that targets emotional and cognitive restriction.[42]

They also documented a successful application of this adjustment with one person who presented with OCPD. In addition, previous research has issued a treatment manual for RO-DBT that addresses the treatment of overcontrol disorders, such as OCPD, as well as anorexia nervosa.[43] Acceptance and Commitment Therapy (ACT), considered a "third-wave" therapy, has also proven effective for personality disorders.[44] ACT is designed to facilitate a process of experiential acceptance by using metaphors, behavioral therapist approaches, and mindfulness training to help patients learn to act willingly and carry on with troubling internal experiences. In the context of OCPD, ACT assists with learning about the paradoxical effects of experiential avoidance.

The reason being, struggling coping mechanisms and unpleasant internal experiences (such emotions) frequently worsen when attempts to control or escape them are themselves challenging. In contrast, ACT treatment for OCPD encourages acceptance and tolerance of negative experiences rather than compulsive/controlling reactions. Patients learned to practice conscious toleration of distressing feelings related to their experience of imperfection or sudden disruptions in their structured routines, rather than reacting defensively by attempting to control their environment or the circumstantial challenge they encountered. There haven't been any ACT trials for OCPD, but a recent randomized controlled trial (RCT) study was conducted to

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explored that how well ACT works for clinical perfectionism.[45] Prior research showed that, a total of 53 participants were identified as having clinical perfectionism, and all consented to receive ACT (nobody was excluded) on an individual basis for a total of 10 weeks.

The ACT condition showed more improvement in all domains of clinical perfectionism, happiness, impaired functioning, stress, and change process than the comparison (waiting) group did. These data indicate that ACT for clinical perfectionism is feasible and useful.[45] Recently, a study adapted an effective General Psychiatric Management (GPM) for OCPD, which serve as a framework for mental health professionals in a more general approach to care[46]. GPM is based on current research in mental health treatment and can be adjusted for use with other personality disorders. GPM has some core ideas, which include informing the patient about their diagnosis, helping them feel positive about creating a life they are excited for, and dealing with any co-occurring disorders or concerns about safety.[46]

Proposed Model of Cognitive Behavioural Therapy for OCPD

This section suggests a new intervention that is based on and inspired by existing manualized Cognitive Behavioral Therapy (CBT) techniques. It includes skills training in how to control your emotions and relationships with others, Acceptance and Commitment Therapy (ACT) for perfectionism, and CBT for perfectionism. In CBT for Obsessive-Compulsive Personality Disorder (OCPD), it is essential for the therapist to emphasize that the goal is not to change the patient's fundamental character traits, lower their performance expectations, or make them content with average results. Rather, the objective is to help people replace their inflexible, internalised rules such as settling for "good enough" instead of perfection with more flexible and efficient principles.[47] Additionally, self-compassion replaces the constant cycle of harsh self-criticism.

Clinicians providing CBT for OCPD should encourage patients to reflect on their values and the ways that their OCPD characteristics affect their progress toward achieving those goals. For therapy to be successful, the therapist has to show the patient how changing their behaviour will align with their values.[47] It is common practice to advice patients to prioritize activities and tasks in a way that aligns with their beliefs while helping them with time management and activity planning. Mental health professionals can use the "dimmer switch of effort" as a helpful metaphor to recover time lost on strict, perfectionistic activities. The patient is advised to view the effort they exert on a task as a dimmer switch, one that can be adjusted in accordance with the perceived importance of the task, rather than as an on-off light switch that requires either the utmost effort or no effort.

In other words, one would put their best effort into things they deem important or that are in line with their values, while they deliberately put their least effort into things they deem mundane or unimportant, such as cleaning the dishes or vacuuming[47]. Therapists can encourage the patient to weigh the importance of each choice before investing time and resources in decision-making. For insignificant choices, they can flip a coin or make a "snap" decision; for decisions with higher importance compared to others. The patient can prioritize a specific value and engage in decision-making aligned with that value, even in the face of discomfort or tension arising from deviating from the conventional rule-based approach. Here, the current review used the analogy of a wallet or tank for mental resources to illustrate the initial phases of CBT for OCPD. Living under the constant pressure of strict regulations and perfectionistic practices, as well as the stresses of daily life, reduces one's mental capabilities.

Without enough resources, individuals suffering with OCPD are at a higher risk of experiencing burnout, which can take the form of sadness or worry, and they are also less inclined to resist the urge to exert control over their environment and other people. Self-care practices include obtaining sufficient sleep, adhering to a balanced diet, and participating in regular physical activity, engaging in leisure or pleasurable activities, and engaging in social interactions, are essential for the restoration of mental resources.[48] Problems with time management or putting things off until later, an unhealthy fixation on work or productivity, and unfavourable self-evaluation (such as feeling guilty or critical for failing to meet productivity targets) all have a negative effect on an individual's willingness

to engage in self-care.[49] Through the development of strategies to enhance within each of these areas of self-care, the patient could gradually reduce their susceptibility to low mood and distress, as well as enhance the psychological resources available for applying behavioural variations in CBT.

In addition, as indicated earlier, being open and willing to endure physical pain and unpleasant feelings is necessary to make these behavioural changes that prioritize self-care and balance. Individuals with OCPD, especially those who show a controlling presentation style, benefit considerably from acquiring the ability to control their negative emotions and be more adaptable in their relationships as a means of improving their ability to receive support from those around them, including their therapist.[50] In other words, the potential for changes in OCPD symptoms exists. Patients experience fewer connection breakdowns with their therapist and other supports; they are better able to manage their OCPD symptoms, which could be achieved through training in these skills. According to[51], behavioural experiments are a beneficial approach to evaluate perfectionism standards because they provide a chance to participants to gather their own data on the standard's validity and the probability of the undesirable event in a real-life setting. As a means of facilitating experiential learning, behavioral experiments involve working together; the patient and clinician determine which beliefs, rules, or standards are to be evaluated, and then the clinician devises an experiment to examine what happens when the patient deviates from the established norm. As an example of a behavioral experiment, one could sit down to dinner without completing the kitchen cleanup, wear new boots across grass, go to bed before roommates and let them sleep in, send a message or email without checking for errors, or leave home without a list of what to bring on vacation.

Discussion

This section provides an overview of some of the controversies and concerns that involve Obsessive-Compulsive Personality Disorder (OCPD).

Uncertainty Regarding the Nature of the Relationship between OCPD and OCD

Many people, including those seeking treatment, have long been confused about Obsessive-Compulsive Personality Disorder (OCPD) and Obsessive-Compulsive-Disorder (OCD) due to their shared nomenclature and strong historical affiliation. In informal settings, the term "OCD" is frequently used by the public to characterize rigid behavioural patterns or perfectionism is usually linked to presentations of OCPD. Classical historical accounts, such as some theorists[27,52] established a connection between the traits currently related to OCPD and the onset of OCD. However, according to the current theories, OCPD and OCD are separate disorders, and OCPD is not a "minor" form or prior to OCD, even if the two can co-occur.[53]

Even though both involve doing the same things over and over again, taking a lot of time, and following a set pattern (for example, composing and revising essays, putting everything in order, and creating lists), OCD is different because it involves disturbing and intrusive obsessions.[53,7] OCPD has ego-syntonic traits and behaviours, while OCD has ego-dystonic traits and behaviours. This difference is because the person with OCPD thinks these things are fitting and right (with their sense of self). Comorbidity studies highlight the uniqueness of both disorders by showing that few individuals who suffer from one of the illnesses also experience the other.[53,7] More public awareness and education campaigns about obsessive-compulsive disorder and other related disorders are needed to clear up the persistent misunderstandings about these two different disorders.

Is it more effective to conceptualize OCPD as a dimensional or categorical construct?

A large body of literature on Obsessive-Compulsive Personality Disorder (OCPD) and similar illnesses has taken a classificational approach, looking specifically for instances of distinctive personality disorders as they are now described in the DSM-5-TR. However, there are evolving theories in the field that place an emphasis on dimensional approaches to personality diseases. There is a hybrid dimensional-categorical model of personality pathology in Section III of the DSM-5-TR appendix. This model is made up of new measurements and models. This model could be looked into in more research in the future. Moreover, this model signifies an extensive revision of the OCPD construct. In particular, the new model states that in order to diagnose OCPD, one has to show rigid

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perfectionism as a core trait.

Other distinctive characteristics of OCPD, which are not mandatory but are recommended, include perseverance, restricted affectivity, and intimacy avoidance.[54,11] The extent to which this novel model enhances the current understanding of OCPD remains an open topic for future investigation. The recently suggested OCPD criteria seem to be more stringent, emphasizing perfectionism as a necessary trait while eliminating two previous diagnostic symptoms the unwillingness to let go of worn-out or useless things and miserliness. Validation of the other possible OCPD criteria introduced by the alternative conceptualization such as reduced affectivity and intimacy avoidance requires further research.

The comprehensive evaluation of these models to ascertain whether they enhance the current categorical system may take some time, as dimensional approaches to OCPD are still in the early stages. Even in cases where a person does not fully show the symptoms of a personality disorder, their dimensional personality features can impact their functioning, highlighting the greater therapeutic relevance of this perspective. For example, even in people who have been diagnosed with OCPD, perfectionism can cause a lot of stress and make it hard to do things. This has been called a transdiagnostic phenomenon.[54,47] Treating OCPD and other mental health issues more effectively requires paying attention to characteristics like perfectionism.

Does OCPD Affect OCD Intervention?

A significant body of research has examined Obsessive-Compulsive Personality Disorder (OCPD) within the framework of Obsessive-Compulsive-Disorder (OCD). Whereas OCPD is a common co-occurring disorder, research on its influence on the treatment of obsessive-compulsive disorder has been completely inconsistent.[55] Treatment guidelines for adults with OCD suggest that SRI medications or Cognitive Behavioral Therapy (CBT), specifically Exposure with Response Prevention (EX/RP), is the most effective option. The efficacy of each treatment approach containing OCPD is in disagreement[56]. One study looking at SRIs found that individuals with OCD and concurrent OCPD had considerably fewer improvements in their OCD symptoms than those with OCD only.[55,56] However, a study on the treatment of OCD found a more favourable response to fluvoxamine in comorbid OCPD.[57] While CBT is widely endorsed for its focus on restructuring perfectionistic thinking, psychodynamic therapy provides a depth-oriented approach that could be better suited for personality-level restructuring. Critics argue that CBT oversimplifies the underlying emotional drivers of OCPD, whereas proponents cite its empirically measurable outcomes.[57]

Furthermore, further experiments of the medication suggested that comorbid OCPD did not correlate with outcomes in OCD.[58] The literature shows mixed results regarding the impact of comorbid OCPD on psychotherapy for OCD. For example, a study found in one EX/RP trial that comorbid OCPD was associated with worse outcomes in OCD.[59] EX/RP studies found that people with more severe OCPD symptoms who stuck to the 25 standard treatment sessions of the EX/RP course had a lower chance of getting better with their OCD symptoms.[60,2]. Patients who also had OCPD did better in cognitive-based CBT (which changes deeply held beliefs through cognitive restructuring and behavioral experiments) than patients who did not have OCPD[61]. These mixed and sometimes opposing results demonstrate the need for more research into how OCPD relates to the treatment of OCD. Future studies could consider the variation in OCPD traits for the outcome of various treatments.

Limitations and Recommendations

This review did not apply a systematic review methodology and have introduced selection bias. Literature was restricted to English language sources, and studies with small sample sizes or without control groups were included, which could affect generalizability. Future studies should implement standardized treatment protocols, use larger samples, and compare therapy modalities (e.g., CBT vs. psychodynamic therapy) via randomized controlled trials. Research on long-term treatment outcomes and dimensional assessments of OCPD traits is also recommended.

Conclusions

This review synthesized available evidence on psychiatric and psychological interventions for OCPD. While CBT holds the most empirical support,

emerging therapies like ACT and RO-DBT also showed significance. The review emphasizes the need for future trials with strong methodologies to compare treatment modalities, develop innovative interventions, and guide standardized care pathways. The findings highlight the complexity of OCPD and emphasis the need of multi-modal, individualized treatment approaches aligned with patients' unique personality profiles and emotional regulation needs. The review suggests that clinical practitioners should consider integrating emotion regulation training into CBT for OCPD to target rigid perfectionism and interpersonal dysfunction. There is a pressing need to increase OCPD awareness among clinicians and develop population-specific intervention manuals. These findings could inform training programs, clinical decision-making, and future guideline development for personality disorders.

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- Revised manuscripts are assessed on the appropriateness of response to recommendations during initial review. Once the editor is satisfied with the suitability of the manuscript, it is forwarded to subject experts for external peer review.

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- Manuscript suitable for publication is forwarded to two external peer reviewers to evaluate the suitability of the article for publication based on its quality, novelty, and relevance.
- A time frame of minimum 4 weeks is given to the reviewer to send their suggestions to the editor. In case of delay by the reviewer, a reminder is sent to the external reviewer.
- If a reviewer is unable to meet the time frame agreed upon or he declines to review the manuscript, the manuscript will be sent to another reviewer.

Final Decision

- The editor may ask reviewers to make recommendations regarding acceptance or rejection of manuscripts and gives weightage to the recommendations given by them, but the editor must be the one who makes the decisions.
- Suggested revisions by the reviewer are sent back to authors for corrections/revision and resubmission within 04 week. Authors are required to send a covering letter mentioning the details of corrections/amendments and revisions.
- If reviewers and editors are satisfied with the changes, the manuscript is accepted and assigned to the future issue for publication.
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- The editor may reject manuscripts without outside review, for example if the subject matter is outside the purview of the journal, a manuscript on the same topic is just about to be published, the quality of the manuscript is poor, or criteria for the submission of manuscripts are not met.

POLICY ON RESEARCH AND PUBLICATION ETHICS

JIIMC promotes research integrity and adherence to the basic values of research including honesty, objectivity, openness, and accountability. The researchers interested to submit their manuscripts to JIIMC are expected to follow the culture of responsible research. JIIMC follows the core practices of COPE and deals with the research and ethical misconduct as per COPE guidelines. We also follow the guidelines of International Committee of Medical Journal Editors (ICJME), World Association of Medical Editors (WAME) and Higher Education Commission of Pakistan (HEC) to meet the standards of publication ethics.

Research on Animals

Research conducted on animals is not published in JIIMC.

Research Approval from Ethical Committees/ Boards

- It is mandatory for the authors of original research to submit the permission/exemption by institutional ethical review board/committee at the time of the submission of manuscript.
- Authors will submit the permission of the head of the institution where research was conducted, if required.
- When reporting experiments on human subjects, indicate whether the procedures were followed in accordance with the ethical standards of the responsible committee on human experimentation (institutional or regional) and with the latest version of Helsinki Declaration. Anonymity of the patient's will be ensured by avoiding the use of patient name, initials, or hospital record numbers, especially in illustrative material.

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- JIIMC expects from the research authors to ensure the safety and protection of the research participants by adhering to national and international guidelines.
- The authors of research articles will submit testimony related to any issue with humanrights that may be inherent in their submissions.

- Articles under consideration that experiment on human subjects in research are required to have *institutional review committee/board approval* in accordance with ethical standards set forth in the ICMJE- Uniform Requirements for Manuscripts Submitted to Biomedical Journals.

HUMAN RIGHTS POLICY

- JIIMC follows ICMJE Recommendations on Protection of Research Participants and World Medical Association (WMA) Declaration of Helsinki – ethical principles for medical research involving human subjects.
- When reporting experiments on human subjects, indicate whether the procedures were followed in accordance with the ethical standards of the responsible committee on human experimentation (institutional or regional) and with the latest version of Helsinki Declaration.
- In case of doubts, authors will explain the justification for their approach and exhibit that the institutional review committee approved the doubtful aspects of research.

Informed Consent and Confidentiality of Research Participants

- In case of research on human subjects, in addition to an ethical approval certificate an undertaking that "informed consent to participate" was taken from adult participants and/or from parents/guardians of participants under 16 years of age will be submitted by the authors. This should also be mentioned in the material and methods section.
- Consent must be obtained for all Case Reports, Clinical Pictures, and Adverse Drug Reactions.
- Authors should avoid identifying patient information, including patients' names, initials, or hospital numbers, in written descriptions, photographs, and pedigrees unless the information is essential for scientific purposes and the patient (or parent/ guardian) gives written, informed consent for publication.
- Consents might be required by the editor on images from participants in the study. Consent form must be made available to Editors on request and will be treated confidentially.
- Informed consent should be obtained if there is any doubt that anonymity can be maintained, e.g., masking the eye region in photographs of patients is inadequate protection of anonymity."
- Masked Study Participants- If identifying characteristics are altered to protect anonymity, such as in genetic malformations, authors should provide written assurance to the editors that alterations do not distort scientific meaning.
- Authors are suggested to follow the CARE guidelines for case reports.

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JIIMC follows the standard definition/description of plagiarism and the recommendations/ guidelines of Committee of Publication Ethics (COPE) https://publicationethics.org/corepractices ,ICMJE www.icmje.org, WAME, https://www.wame.org/policies, Higher Education Commission (HEC) of Pakistan policies about plagiarism https://www.hec.gov.pk/english/services/faculty/Plagiarism/Pages/default.aspx. Authors are advised to go through these guidelines carefully before submitting their manuscript with JIIMC. The cases of plagiarism will be dealt with according to the rules/ regulations and recommendation of the ICMJE, COPE and WAME and HEC. The disciplinary committee of JIIMC comprises the Editor in Chief and Managing editor of the journal to deal with cases of plagiarism. All articles submitted to JIIMC are checked by anti-plagiarism software **"TURNITIN "** to determine Overall Similarity Index (OSI) and Single Matched Similarity Indexed (SMSI)..

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Corresponding authors of the published papers are entitled to receive the maximum of 3 copies of printed issue in which his/her paper is published.

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They can submit their complaints to the managing editor through following email: prh.jiimc@riphah.edu.pk. The matter will be investigated thoroughly and cautiously, and the explanation/decision will be communicated to the complainant as soon as possible. The management of the journal will publish all corrections, clarifications, retractions and apologies when needed.

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The Journal of Islamic International Medical College (JIIMC) is committed to achieve and uphold ethical values at every step of the publication process. Every effort is made to avoid mistakes/errors in the publication of JIIMC. However, at times mistakes may take place. Readers are welcome to submit their comments, questions, or criticisms about any manuscript published in JIIMC, issues related to inappropriate authorship, undeclared conflicts of interests, plagiarism, unethical research; manipulation/falsification of results, research standards violations, reviewer bias or any contribution to JIIMC that infringes copyright or other intellectual property rights. They can submit their complaints to the managing editor through following email: managing.editor@riphah.edu.pk, prh.jiimc@riphah.edu.pk. The matter will be investigated thoroughly and cautiously, and the explanation/decision will be communicated to the complainant as soon as possible. The management of the journal will publish all corrections, clarifications, retractions and apologies when needed.

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An erratum is referred to as a correction of errors in the article by the journal during editing, including errors of omission such as failure to make factual proof corrections requested by authors within the deadline provided by the journal and within journal policy. During the proofreading stage, the final copy of the manuscript is sent to the corresponding author for approval before its publication. Errors identified after publication by authors or readers are corrected in PDF copy of the online version. Errata are generally not published for simple obvious typing errors but are published when an apparently simple error is significant (for example, a Greek m for an 'm' in a unit, or a typing error in the corresponding author's email address). In case of a significant error in the figure or table, a corrected figure or table is published as an erratum.

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A corrigendum refers to a change the authors wish/want to make to their article at any time after its acceptance by the journal. Corrigenda submitted by the authors are published if scientific accuracy or reproducibility of the original paper is compromised. In case of an error in the published author list, JIIMC will publish a Corrigendum but not usually for overlooked acknowledgements. Authors should contact the editor JIIMC, who will determine the impact of the change and decide on an appropriate course of action.

Readers wishing to draw the journal's attention to a significant published error should submit their comments as a "Letter to the Editor". Such "Letters to the Editor" will be reviewed by unrelated and neutral referees. On editorial acceptance, the paper will be sent to the authors of the original paper for their early response.

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An addendum is decided on the significance of the addition to the interpretation of the original publication. Addenda do not contradict the original publication, but if the authors inadvertently omitted significant information available to them at the time of submission. This material will be published as an addendum after peer review.

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JIIMC can consider issuing an Expression of Concern (EOC) if editors have well-founded concerns and feel that readers should be made aware of potentially misleading information contained in an article. JIIMC will consider an expression of concern if they receive inconclusive evidence of research or publication misconduct by the authors, there is evidence of unreliable findings, or an investigation is underway, but a judgement will not be available for a considerable time.

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Research papers having serious errors to invalidate a paper's results and conclusions, or publication misconduct may require retraction. Retractions may be requested by an article's author(s), by an institution, by readers, or by the editor.

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- There is clear evidence that the findings are unreliable, either as a result of major error (e.g., miscalculation or experimental error), or as a result of fabrication (e.g., of data) or falsification (e.g., image manipulation)
- It constitutes plagiarism.
- The findings have previously been published elsewhere without proper attribution to previous sources or disclosure to the editor, permission to republish, or justification (i.e., cases of redundant publication).
- It contains material or data without authorization to use.
- Copyright has been infringed or there is some other serious legal issue.
- It reports unethical research
- It has been published solely on the basis of a compromised or manipulated peer review process.
- The author(s) failed to disclose a major competing interest that, in the view of the editor, would have unduly affected interpretations of the work or recommendations by editors and peer reviewers.

At times the article may occasionally be retracted for correction of errors in submission or publication and will be replaced with the corrected one.

Retraction Process

JIIMC adopts the following retraction process to ensure best practice of retraction:

1. An article requiring potential retraction will be brought to the attention of JIIMC editor.
2. Managing Editor will follow the step-by-step guidelines according to the COPE flowcharts and will seek the response from the author of the article as well.
3. JIIMC Publication & Research Integrity Committee will evaluate the evidence of misconduct and response of the authors. Based on the findings, the committee will recommend a final decision whether to retract the publication or otherwise.
4. The final decision is then communicated to the author and, if necessary, any other relevant bodies(PMC, HEC), or the author's institution as deemed appropriate.
5. The retraction-note titled "**Retraction: [article title]"** will be published in the paginated part of a subsequent issue of the journal and listed in the contents list.

6. The text of the retraction should explain why the article is being retracted.
7. The statement of retraction and the original article must be clearly linked in the electronic database so that the retraction will always be apparent to anyone who comes across the original article.
8. The relevant changes in the online version will be reflected through **Crossmark** icon.

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INSTRUCTIONS FOR AUTHORS

The material submitted for publication should be sent completely to the Journal of Islamic International Medical College, Pakistan. Research work that has already been reported in a published paper or is described in a paper sent or accepted elsewhere for publication should not be submitted. Duplicate submission of the same research work to another journal should be avoided as this falls into the category of publication misconduct. A complete report following publication of a preliminary report, usually in the form of an abstract, or a paper that has been presented at a scientific meeting, if not published in a full proceeding, may be submitted. Manuscripts are submitted online on the following link:

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- Publication Charges (Revised with effect from 01 February 2024) = PKR 12,000/-

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- Processing Charges (Revised with effect from 01 February 2024) = PKR 3,000/-
- Publication Charges (Revised with effect from 01 February 2024) = PKR 9,000/-

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MANAGING EDITOR JIIMC

Westridge-III, Pakistan Railway Hospital
Islamic International Medical College, Rawalpindi
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MATERIAL FOR PUBLICATION

The material submitted for publication may be in the form of an original research (Randomized controlled trial – RCT, Meta-analysis of RCT, Quasi experimental study, Case Control study, Cohort study, Observational Study with statistical support, etc.), a Review Article, a Case Report, Recent Advances, New Techniques, Debates, Book/CDs Review on Clinical/Medical Education, Adverse Drug Reports or a Letter to the Editor. Survey Articles and Studies more than five years old at the time of submission are not accepted for publication in JIIMC. Non-English articles are not accepted for publication in JIIMC.

ORIGINAL ARTICLES should report original research of relevance to clinical medicine and may appear either as papers or as short communications. The original paper should be of about 2000-2500 words excluding abstract and references. The abstract should be structured of about 250 words. Three to 10 keywords should be mentioned at the end of the abstract as per MeSH (Medical Subject Headings). There should be no more than four tables or illustrations. The data should be supported with 20 to 25 locals as well as international references. More than 50% of the references should be from the last five years.

SHORT COMMUNICATIONS should be about 1000 words, with a non-structured abstract, two tables or illustrations and 5 references.

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REVIEW ARTICLE should consist of structured overview of relatively narrow topic providing background and recent development with reference of original literature. An author can write a review article only if he/she has written a minimum of three original research articles and some case reports on the same topic. Review articles should be of 2500 to 3000 words with a non-structured abstract of 150 words and minimum 3 key words.

LETTERS TO THE EDITOR should normally not exceed 400 words, have no more than 05 references and be signed by all the authors-maximum 3 are allowed. Preference is given to those that take up points made in contributions published recently in a journal. Letters may be published with a response from the author of the article being discussed. Discussions beyond the initial letter and response will not be entertained for publication.

OBITUARIES should be of about 250 words.

EDITORIALS are written by invitation.

DISSERTATION/THESIS BASED ARTICLE An article based on dissertation/thesis submitted as part of the requirement for a postgraduate degree (M. Phil, FCPS, MS) can be sent for publication after it has been approved by the institution's ethical review board/committee and the college/university evaluation committee/board. The data should not be more than five years old. Thesis/dissertation-based articles will be assessed by proper review process. Once accepted for publication, disclosure will be made that 'it is a Dissertation based article.'

RANDOMIZED CONTROLLED TRIALS

- When reporting the results of a randomized trial, JIIMC requires a completed CONSORT 2010 checklist and flow diagram as a condition of submission.
  - o CONSORT 2010 checklist
  - o CONSORT 2010 flow diagram
- Templates for these can be readily accessible here or on the CONSORT website, which also describes several CONSORT checklist extensions for different designs and types of data beyond two group parallel trials
- Authors should ensure that your article, at minimum, reports content addressed by each item of the checklist. Meeting these basic reporting requirements will greatly improve the value of your trial report and may enhance its chances for eventual publication.
- As per recommendation of ICMJE, Journal of Islamic International Medical College requires registration of clinical trials in a public trials registry as a prerequisite for publication of all clinical trials.
- **Clinical Trials:** Clinical Trials submitted for publication must be registered in public registry, e.g., http://clinicaltrial.gov/ , must provide registration proof & all RCTs must be based on CONSORT statement. Unregistered trials will not be published.

  A clinical trial is any research study that prospectively assigns human participants or groups to one or more health-related interventions to assess their effects on health outcomes. These interventions can include drugs, surgical procedures, devices, behavioral treatments, dietary changes, and modifications in care processes. Health outcomes encompass any biomedical or health-related measures collected from patients or participants, including pharmacokinetic data and adverse events. Purely observational studies (those in which the assignment of the medical intervention is not at the discretion of the investigator) do not require registration.

GENERAL ARCHIVAL INSTRUCTIONS

The manuscript should be typed in MS Word. Each manuscript should include a title page (containing email address, cell numbers, institution, and postal address of the corresponding author), abstract, key words, text, acknowledgements (if any), references, tables (each table, complete with title and footnotes) and legends for illustrations and photographs. Each component should begin on a new page. Sub-headings should not be used in any section of the script except in the abstract.

TEXT ORGANIZATION

All manuscripts except Short Communication and Letter to the Editor should be divided into the following sections.

ABSTRACT

Abstracts of original article should be in structured with following sub-headings:

- Objective
- Study Design

- Place & Duration of Study
- Materials & Methods
- Results
- Conclusion

Four elements should be addressed: "why did you start?", "what did you do?", "what did you find?" and "what does it mean? “.” Why did you start?" is addressed in the objective. "What did you do?" constitutes the methodology and could include design, setting, patients or other participants, interventions, and outcome measures. "What did you find?" is the 'results', and "what does it mean?" would constitute the conclusions. Please label each section clearly with the appropriate sub-headings. Structured abstract for an original article, should not be more than 250 words. At least 3 key words should be written at the end of the abstract. Review articles, case reports and others require a short, unstructured abstract. Commentaries do not require an abstract.

INTRODUCTION

Write this section with references as per following instructions:

1. Give background information about the subject matter and the issues your study intends to address. Only strictly pertinent references should be cited, and the subject should not be extensively reviewed.
2. Describe what is known (in the literature) and what is not clear about the subject with reference to relevant literature thus identifying the literature gap.
3. You write the rationale (justification) of your study.
4. Finally, you mention the objective of your study

MATERIALS AND METHODS

Methodology is written in past tense.

Follow this sequence **without headings:**

- Study design
- Place and Duration of Study
- Sample size
- Sampling technique
- Mention about permission of the ethical review board and other ethical issues addressed.
- Inclusion and Exclusion Criteria
- Data collection procedure-
- Type of data: parametric or nonparametric
- Data analysis: including Statistical Software used, and statistical test applied for the calculation of p value and to determine the statistical significance. Exact p-values and 95% confidence interval (CI) limits must be mentioned instead of only stating greater or less than level of significance. All percentages must be accompanied with actual numbers.

RESULTS

These should be presented in logical sequence in the text, tables, and illustrations. All the data in the tables or illustrations should not be repeated in the text; only important observations should be emphasized or summarized. No opinion should be given in this portion of the text.

DISCUSSION

This section should include the author's comments on the results. Write in present tense, active voice except for results, which are written in past tense. It should be written in following sequence:

- First, very briefly summarize, Interpret and discuss main results and don't merely repeat the results.
- Discuss key studies relevant to your study.
- Compare your work with other's work.
- Describe limitations of your study.
- Suggest future work if necessary.

CONCLUSION

Conclusion should be provided under a separate heading. It should be in congruence with the objective. No recommendations are needed under this heading.

REFERENCES

References must be written in Roman Number and in the Vancouver Style only. References should be numbered in the order in which they are superscripted in the text. At the end of the article, the full list of references should give the names and initials of all authors (unless there are more than six when only the first six should be given followed by et al). The author's names are followed by the title of the article; title of the journal abbreviated according to the style of the Index Medicus (see “List of Journals Indexed”, printed yearly in the January issue of Index Medicus); year, volume, and page number, e.g., Hall, RR. The healing of tissues by C02 laser. Br J. Surg: 1970; 58:222-225. References to books should give the names of editors, place of publication, publisher, and year. The author must verify the references against the original documents before the

article. References to papers accepted but not yet published should be designated as "in press" or "forthcoming"; authors should obtain written permission to cite such papers as well as verification that they have been accepted for publication.

TABLES AND ILLUSTRATIONS

Tables and illustrations should be merged within the text of the paper, maximum number of tables and illustrations should not exceed four, and legends to illustrations should be typed on the same sheet. Tables should be simple and should supplement rather than duplicate information in the text; tables repeating information will be omitted. Each table should have a title and be typed in double space without horizontal and vertical lines on an 8 ½" x 11' paper. Tables should be numbered consecutively with Roman numerals in the order they are mentioned in the text. Page number should be in the upper right corner. If abbreviations are used, they should be explained in footnotes and when they first appear in text. When graphs, scattergrams, or histograms are submitted, the numerical data on which they are based should be supplied. All graphs should be made with MS Excel and be sent as a separate Excel file even if merged in the manuscript. For scanned photographs the highest resolution should be used.

S.I.UNITS

System International (SI) Unit measurements should be used. All drugs must be mentioned in their generic form. The commercial name may however be mentioned within brackets, if necessary.

PHOTOGRAPHS AND FIGURES

Figures and Photographs should only be included when data cannot be expressed in any other form. Figures and photographs must be cited in the text in consecutive order. Legends must be typed on the same paper. Legends for photomicrographs should indicate the magnifications, internal scale, and method of staining. Figures should be numbered in Arabic numbers.

OBLIGATORY FILES

Obligatory supporting documents for all types of Manuscripts except the letter to editor, without which JIIMC will not accept the manuscript for initial processing.

- Cover Letter
- JIIMC Checklist
- JIIMC Conflict of Interest Performa
- JIIMC CopyRight and Undertaking Agreement
- IRC Certificate
- Bank draft as initial processing fee (Original bank draft send in JIIMC office)

Template of these files is available in the download section.

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Any funding source for the research work must be informed at the time of submitting the manuscript for publication in JIIMC. Any associations that might be construed as a conflict of interest (stock ownership, consultancies, etc.) shall be disclosed accordingly. Examples of financial conflicts include employment, consultancies, stock ownership, honoraria, paid expert testimony, patents or patent applications, and travel grants, all within 3 years of beginning the work submitted. If there are no conflicts of interest, authors should state that. All authors are required to provide a signed statement of their conflicts of interest as part of the author's declaration.

FINANCIAL DISCLOSURE & ROLE OF THE FUNDING SOURCE

- Author is supposed to declare the funding source as acknowledgement at the end of the manuscript.
- Author will describe the role of the study sponsor (s), if any, in study design; in the collection, analysis, and interpretation of data; in the writing of the report; and in the decision to submit the paper for publication.
- If there is no Methodology section, the role of the funding source should be stated as an acknowledgment.
- The corresponding author should confirm that he/she had full access to all the data in the study and had final responsibility for the decision to submit for publication.
- JIIMC publishes FINANCIAL DISCLOSURE & ROLE OF THE FUNDING SOURCE statement for each article.

AUTHORSHIP CRITERIA

All those designated as authors should meet all four criteria for authorship as stated in *ICMJE recommendations (http://www.icmje.org/icmje-recommendations.pdf).* According to ICMJE recommendations authorship is based on the

following four criteria:

1. Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data; and
2. Have been involved in drafting the work or revising it critically for important intellectual content; and
3. Have given final approval of the version to be published; and
4. Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Each author should have participated sufficiently in the work to take public responsibility for appropriate portions of the content. We strongly discourage gift or ghost authorship. Mere supervision, collection of data, statistical analysis and language correction do not grant authorship rights. To avoid any dispute regarding authorship authors are advised to consult COPE guidelines to avoid authorship problems.

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