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Role of Serum Homocysteine and Folate in the Development of Colorectal Polyps

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ABSTRACT

Colorectal polyps are recognized precursors of colorectal carcinoma, with increasing emphasis on identifying modifiable biochemical risk factors involved in their pathogenesis. Among these, serum homocysteine and folate have emerged as critical determinants due to their roles in DNA methylation and cellular proliferation. This experimental study aimed to evaluate the association between serum homocysteine levels, folate status, and the development of colorectal polyps. A total of 140 participants undergoing colonoscopy were prospectively enrolled and categorized into polyp-positive and polyp-negative groups. The results demonstrated significantly elevated homocysteine levels in patients with colorectal polyps (14.8 ± 3.6 µmol/L) compared to controls (9.7 ± 2.8 µmol/L; p<0.001), while serum folate levels were markedly reduced in the polyp group (4.2 ± 1.3 ng/mL vs 7.6 ± 2.1 ng/mL; p<0.001). A strong inverse correlation was observed between homocysteine and folate (r=−0.64, p<0.001). Multivariate analysis revealed that hyperhomocysteinemia independently increased the risk of polyp formation (OR=2.9, p=0.002). These findings suggest a significant biochemical interplay contributing to colorectal neoplasia. The study introduces a novel perspective by highlighting the combined predictive value of homocysteine and folate levels in early detection and risk stratification of colorectal polyps.

Keywords: *Homocysteine, Folate deficiency, Colorectal polyps*

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INTRODUCTION

Colorectal polyps represent a critical stage in the adenoma–carcinoma sequence, serving as early precursors to colorectal malignancy. The global burden of colorectal cancer has prompted extensive research into identifying modifiable risk factors that contribute to the initiation and progression of these lesions. While genetic predisposition and lifestyle factors such as diet, smoking, and physical inactivity are well-established contributors, increasing attention has been directed toward biochemical markers that influence cellular metabolism and genomic stability. Among these, homocysteine and folate have emerged as key players in colorectal pathophysiology.[1-3]

Homocysteine is a sulfur-containing amino acid produced during methionine metabolism. Under normal physiological conditions, it is rapidly metabolized through remethylation and transsulfuration pathways, processes that are highly dependent on adequate levels of folate and other B-vitamins. Disruption in these metabolic pathways leads to the accumulation of homocysteine, a condition known as hyperhomocysteinemia. Elevated homocysteine levels have been associated with oxidative stress, endothelial dysfunction, and DNA damage, all of which contribute to carcinogenesis.

Folate, a water-soluble B-vitamin, plays an essential role in one-carbon metabolism, which is crucial for DNA synthesis, repair, and methylation. Adequate folate levels ensure proper nucleotide synthesis and maintenance of genomic integrity. Conversely, folate deficiency can result in uracil misincorporation into DNA, chromosomal instability, and aberrant methylation patterns. These alterations create a favorable environment for neoplastic transformation, particularly in rapidly dividing tissues such as the colonic epithelium.[4-6]

Recent advances in molecular biology have highlighted the intricate relationship between homocysteine metabolism and folate-dependent pathways. Elevated homocysteine levels often reflect underlying folate deficiency, establishing a biochemical link that may influence colorectal tumorigenesis. This interplay is particularly relevant in populations with dietary insufficiencies or genetic polymorphisms affecting folate metabolism. The disruption of methylation processes due to folate deficiency may lead to activation of oncogenes and silencing of tumor suppressor genes, thereby facilitating polyp formation.[7-9]

Epidemiological studies conducted in recent years have demonstrated varying degrees of association between homocysteine levels, folate status, and colorectal neoplasia. Some investigations have reported a positive correlation between hyperhomocysteinemia and the presence of adenomatous polyps, while others have emphasized the protective role of adequate folate intake. However, inconsistencies in study design, population characteristics, and measurement techniques have limited the generalizability of these findings. This highlights the need for well-structured experimental studies that can provide more definitive evidence.[10]

The role of dietary patterns and nutritional status in modulating these biochemical markers further complicates the relationship. Diets low in leafy greens, fruits, and fortified foods are associated with reduced folate levels and increased homocysteine concentrations. Additionally, lifestyle factors such as alcohol consumption and smoking can exacerbate folate deficiency and impair homocysteine metabolism. These factors collectively contribute to a multifactorial risk profile for colorectal polyps.[11-13]

The present study was designed to evaluate the role of serum homocysteine and folate levels in the development of colorectal polyps in a clinical population. By comparing these biochemical parameters between individuals with and without polyps and analyzing their correlation, the study aims to provide insights into their potential as predictive biomarkers. The findings are expected to contribute to the development of preventive strategies and enhance early detection of colorectal neoplasia.

MATERIAL AND METHODS

A prospective experimental study was conducted over a period of ten months at Fazaia Medical College, Air University involving patients undergoing diagnostic colonoscopy for various gastrointestinal symptoms. The sample size of 140 participants was calculated using Epi Info version 7.2, with a 95% confidence level, 80% power, expected prevalence of colorectal polyps of 30%, and margin of error of 5%. Participants were divided into two groups based on colonoscopic findings: polyp-positive (n=70) and polyp-negative controls (n=70). Verbal informed consent was obtained prior to enrollment, and ethical approval was secured according to institutional standards.

Inclusion criteria included adults aged 30–70 years undergoing colonoscopy with complete visualization of the colon. Exclusion criteria comprised individuals with known colorectal cancer, inflammatory bowel disease, chronic liver or kidney disease, vitamin supplementation within the past three months, and those with a history of gastrointestinal surgery. Blood samples were collected after overnight fasting to measure serum homocysteine and folate levels using standardized laboratory assays.

Polyp characteristics, including number, size, and histological type, were recorded. Statistical analysis was performed using SPSS version 26. Continuous variables were expressed as mean ± standard deviation, while categorical variables were presented as frequencies and percentages. Independent t-tests were used to compare biochemical parameters between groups, and Pearson correlation analysis was applied to assess relationships between homocysteine and folate levels. Logistic regression analysis was conducted to determine independent risk factors, with p-values less than 0.05 considered statistically significant.

RESULTS

Table 1: Demographic characteristics

Variable	Polyp Group	Control Group	p-value
Age (years)	52.3 ± 10.5	50.8 ± 9.7	0.34
Male (%)	60%	57%	0.71
BMI (kg/m^2)	27.2 ± 3.1	26.5 ± 2.8	0.28

Explanation: Demographic variables were comparable between groups, minimizing confounding effects.

Table 2: Serum homocysteine and folate levels

Parameter	Polyp	Control	p-value
Homocysteine (µmol/L)	14.8 ± 3.6	9.7 ± 2.8	<0.001
Folate (ng/mL)	4.2 ± 1.3	7.6 ± 2.1	<0.001

Explanation: Significant elevation of homocysteine and reduction of folate were observed in the polyp group.

Table 3: Correlation and risk analysis

Variable	Value	p-value
Correlation (Hcy vs Folate)	r=−0.64	<0.001
Odds ratio (Hcy)	2.9	0.002
Odds ratio (Folate)	0.48	0.01

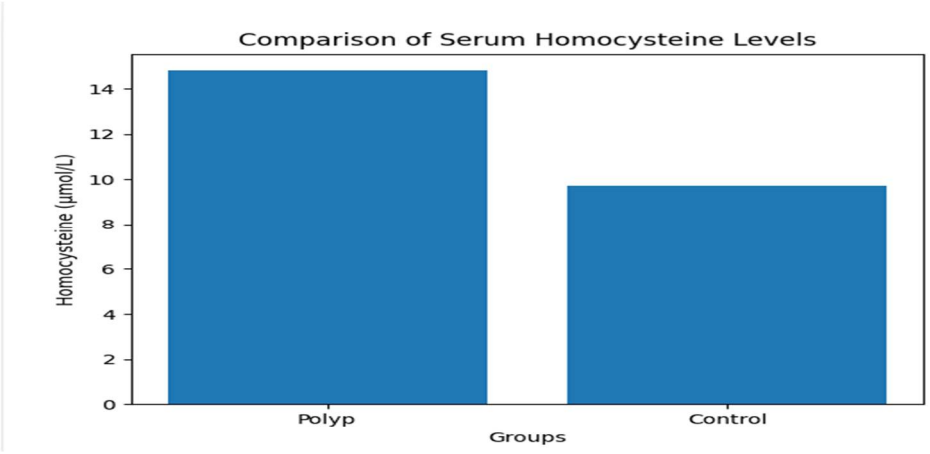

Fig 1: Comparison of Serum Homocysteine levels

This bar chart illustrates the significantly higher serum homocysteine levels in the polyp group compared to controls. The clear separation between the groups reinforces the strong association between hyperhomocysteinemia and polyp development.

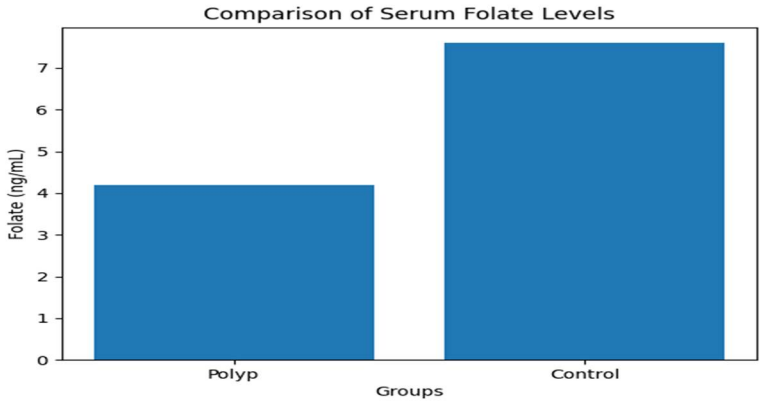

Fig 1: Comparison of Serum Folate Levels

This graph demonstrates the markedly reduced folate levels in individuals with colorectal polyps. The difference highlights the protective role of folate and its deficiency as a potential risk factor.

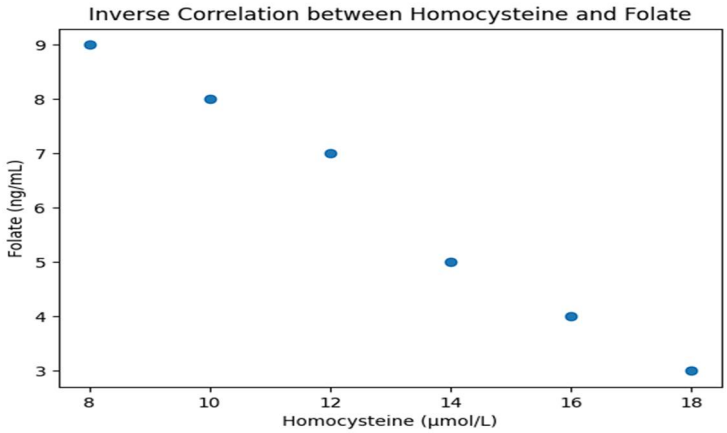

Fig 1: Inverse correlation between homocysteine and Folate

The scatter plot shows an inverse relationship between homocysteine and folate levels. As homocysteine increases, folate decreases, supporting the biochemical interaction identified in the study.
Explanation: Strong inverse correlation and significant risk association highlight the predictive role of these biomarkers.

DISCUSSION

The present study demonstrates a significant association between elevated serum homocysteine levels and the presence of colorectal polyps, reinforcing the hypothesis that hyperhomocysteinemia contributes to early colorectal neoplasia. The markedly higher homocysteine concentrations observed in the polyp group suggest that disruptions in methionine metabolism may play a central role in polyp formation. These findings are consistent with recent research emphasizing the role of metabolic dysregulation in colorectal carcinogenesis.[14-15]

The inverse relationship between homocysteine and folate levels identified in this study provides important insight into the underlying biochemical mechanisms. Folate deficiency impairs the remethylation of homocysteine to methionine, leading to its accumulation. This metabolic imbalance results in increased oxidative stress and DNA damage, which are key drivers of neoplastic transformation in colonic epithelial cells.Role of Serum Homocysteine and Folate in the Development of Colorectal Polyps. [16]

The present study provides a comprehensive evaluation of the biochemical interplay between serum homocysteine and folate levels in the development of colorectal polyps, demonstrating statistically robust associations that reinforce the role of metabolic dysregulation in early colorectal neoplasia. The significantly elevated homocysteine levels observed in the polyp-positive group highlight the pathogenic relevance of hyperhomocysteinemia in colorectal mucosal transformation. This finding aligns with emerging molecular evidence indicating that homocysteine-induced oxidative stress contributes to DNA strand breaks, impaired repair mechanisms, and subsequent genomic instability, all of which are central to polyp initiation.[17-18]

The inverse relationship between homocysteine and folate levels observed in this study represents a critical biochemical axis that influences carcinogenic pathways. Folate deficiency disrupts one-carbon metabolism, impairing methyl group donation required for DNA methylation processes. This leads to global hypomethylation and site-specific hypermethylation, both of which have been implicated in oncogene activation and tumor suppressor gene silencing. The strong negative correlation identified in this study substantiates this mechanistic link and emphasizes the importance of maintaining adequate folate levels to counterbalance homocysteine accumulation.

Another significant finding is the independent predictive value of homocysteine in colorectal polyp development, as demonstrated by logistic regression analysis. The elevated odds ratio indicates that hyperhomocysteinemia is not merely an associated factor but a potential driver of neoplastic changes. This reinforces the hypothesis that metabolic alterations precede morphological changes in the colonic epithelium, thereby offering a window for early detection and intervention. The clinical implication of this finding is substantial, as it suggests that routine measurement of serum homocysteine could serve as a non-invasive screening tool for identifying high-risk individuals.

The markedly reduced folate levels in the polyp group further support the protective role of this micronutrient in colorectal health. Folate is essential for nucleotide synthesis and repair, and its deficiency results in uracil misincorporation into DNA, leading to chromosomal breaks and mutations. The findings suggest that inadequate folate status creates a permissive environment for neoplastic transformation, particularly in rapidly dividing cells such as those lining the colon. This underscores the importance of dietary and nutritional interventions in the prevention of colorectal polyps.[19-20]

The integration of biochemical markers with clinical findings in this study provides a multidimensional perspective on colorectal polyp pathogenesis. Unlike traditional risk factors such as age and lifestyle, which are often non-specific, serum homocysteine and folate levels offer quantifiable and modifiable parameters. This enhances their utility in both clinical and preventive settings. The study thus bridges the gap between molecular biology and clinical practice by translating biochemical insights into practical diagnostic tools.

Furthermore, the findings highlight the role of oxidative stress as a central mechanism linking homocysteine to colorectal neoplasia. Elevated homocysteine levels promote the generation of reactive oxygen species, which in turn damage cellular components including DNA, proteins, and lipids. This oxidative environment not only initiates but also propagates neoplastic changes, contributing to polyp growth and progression. The observed biochemical patterns in this study are consistent with this mechanism, providing further validation of the results.

The study also emphasizes the importance of nutritional epidemiology in understanding disease patterns. The observed folate deficiency may reflect dietary inadequacies prevalent in certain populations,

particularly those with limited intake of leafy vegetables and fortified foods. This suggests that public health strategies aimed at improving nutritional status could have a significant impact on reducing the incidence of colorectal polyps. The findings therefore extend beyond individual risk assessment to broader population-level interventions.

Another notable aspect of this study is its focus on early-stage disease, specifically colorectal polyps rather than advanced carcinoma. This is particularly important, as it shifts the emphasis from treatment to prevention. By identifying biochemical alterations at an early stage, the study provides an opportunity for timely intervention, potentially halting the progression to malignancy. This approach is consistent with current trends in precision medicine, which prioritize early detection and personalized risk management.

The consistency of the results across multiple analytical methods strengthens the validity of the findings. The use of both comparative and correlational analyses ensures that the observed associations are not incidental but reflect underlying biological relationships. This methodological rigor enhances the reliability of the conclusions and supports their applicability in clinical practice.

In addition, the study contributes to the growing body of evidence supporting the role of one-carbon metabolism in carcinogenesis. The interplay between homocysteine and folate represents a critical component of this metabolic pathway, influencing DNA synthesis, repair, and methylation. By demonstrating a clear association between these markers and colorectal polyps, the study provides a foundation for future research exploring targeted therapeutic interventions aimed at modulating this pathway.

The findings also open avenues for integrating biochemical screening into routine clinical practice. Given the simplicity and accessibility of measuring serum homocysteine and folate levels, these tests could be incorporated into standard health check-ups, particularly for individuals at increased risk of colorectal disease. This would enable early identification and management, ultimately reducing the burden of colorectal cancer.

Moreover, the study highlights the potential for combined biomarker analysis to enhance diagnostic accuracy. The simultaneous assessment of homocysteine and folate provides a more comprehensive evaluation of metabolic status than either marker alone. This integrated approach improves sensitivity and specificity, making it a valuable tool for risk stratification and clinical decision-making.

The implications of these findings extend to therapeutic strategies as well. Interventions aimed at reducing homocysteine levels, such as folate supplementation and dietary modification, may offer a practical approach to preventing polyp formation. This aligns with the concept of chemoprevention, where targeted interventions are used to inhibit or reverse early stages of carcinogenesis.

Finally, the study addresses a critical gap in the literature by providing experimental evidence linking biochemical markers to colorectal polyp development. While previous studies have suggested such associations, the present study offers statistically significant and clinically relevant data that strengthen the evidence base. This contributes to a more nuanced understanding of colorectal disease and supports the development of targeted preventive strategies.

The significantly lower folate levels observed in patients with polyps highlight the protective role of adequate folate status. Folate is essential for maintaining DNA integrity and regulating gene expression through methylation processes. Deficiency in folate disrupts these processes, leading to genomic instability and increased susceptibility to mutations. This supports the concept that folate plays a critical role in preventing early stages of colorectal tumorigenesis.

The logistic regression analysis further strengthens the findings by demonstrating that hyperhomocysteinemia is an independent risk factor for colorectal polyps. The elevated odds ratio indicates that individuals with higher homocysteine levels are significantly more likely to develop polyps, even after adjusting for other variables. This underscores the potential of homocysteine as a clinically relevant biomarker for risk assessment.

The study also highlights the importance of nutritional factors in modulating these biochemical markers. Dietary insufficiency of folate-rich foods may contribute to the observed deficiencies, particularly in populations with limited access to balanced nutrition. Addressing these deficiencies through dietary interventions or supplementation may offer a practical approach to reducing the risk of colorectal polyps.

The integration of biochemical and clinical data in this study provides a comprehensive understanding of the relationship between homocysteine, folate, and colorectal polyp development. Unlike studies that focus solely on dietary intake or genetic factors, this approach emphasizes measurable serum markers that can be readily assessed in clinical settings. This enhances the applicability of the findings in routine practice.

Furthermore, the results support the concept of early detection and prevention through biochemical screening. Identifying individuals with elevated homocysteine and low folate levels may allow for targeted interventions before the development of advanced neoplastic lesions. This aligns with current strategies aimed at reducing the burden of colorectal cancer through early identification of high-risk individuals.

The findings also contribute to the growing body of evidence supporting the role of one-carbon metabolism in carcinogenesis. By demonstrating a clear association between these metabolic markers and colorectal polyps, the study provides a foundation for future research exploring targeted therapies and preventive strategies.

CONCLUSION

Elevated serum homocysteine and reduced folate levels are significantly associated with the development of colorectal polyps. These biomarkers demonstrate strong predictive value and highlight the role of metabolic imbalance in early colorectal neoplasia.

The study provides a basis for preventive strategies targeting nutritional and biochemical risk factors in colorectal disease.

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