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EDITORIAL

Nutrition assessment in surgical patients: The strategic way to improve outcomes

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Introduction

Malnutrition remains a significant but often under-recognized challenge in the management of surgical patients worldwide. It is estimated that a substantial proportion of patients undergoing major surgery, particularly those with gastrointestinal or oncologic diseases, suffer from some degree of malnutrition.[1,2] The physiological stress induced by surgery, characterized by a hypermetabolic state and systemic inflammatory response, exacerbates existing nutritional deficits.[3] This synergistic effect leads to impaired immune function, delayed wound healing, increased muscle wasting, and a higher predisposition to postoperative complications such as sepsis and anastomotic leakage.[1,4] Consequently, malnutrition is directly linked to prolonged hospital stays, increased healthcare costs, and higher mortality rates.[2,5] Therefore, early and systematic nutrition assessment is no longer optional but a fundamental pillar of perioperative care.[4]

The landscape of nutrition screening and assessment

The primary goal of nutritional screening is to identify individuals who are at risk of malnutrition and are likely to benefit from nutritional support. Several tools have been validated for use in the clinical setting, including the Malnutrition Universal Screening Tool (MUST), Nutrition Risk Screening 2002 (NRS-2002), and the Subjective Global Assessment (SGA).[2] Recent systematic reviews and meta-analyses have underscored the importance of tool validity. For instance, MUST has shown high sensitivity (0.84) and specificity (0.85) in predicting adverse outcomes in general surgical populations.[2] However, the choice of tool often depends on the clinical setting and the specific patient demographic. In elderly critically ill patients, prognostic indices such as the Geriatric Nutritional Risk Index (GNRI) and the Prognostic Nutritional Index (PNI) have gained traction.[5] These indices utilize objective laboratory data, such as serum albumin levels and lymphocyte counts, combined with physical measurements like body weight. Comparative studies have indicated that both GNRI and PNI are strong predictors of mortality in the elderly, although GNRI may offer slightly better prognostic performance in certain intensive care scenarios.[5]

Nutrition assessment tools in the Thai context: BNT/NT

In Thailand, the development and implementation of localized tools have been crucial in addressing the specific needs of the population and the healthcare system's structure. The Bhumibol Nutrition Triage (BNT), also referred to as Nutrition Triage (NT), is a prominent tool developed by Thai experts.[1,6] Unlike some international tools that rely heavily on subjective parameters, the BNT/NT incorporates objective data including Body Mass Index (BMI), recent weight changes, current energy intake, age, and the severity of

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the primary disease.[6] The BNT/NT categorizes patients into four risk levels (Class I to IV). Evidence from the multicenter THAI-SICU study, which involved 1,685 patients across major Thai medical centers, has demonstrated a clear correlation between BNT/NT classification and clinical outcomes.[1,6] Patients classified as BNT/NT Class III and IV exhibited significantly higher ICU mortality and 28-day mortality rates compared to those in lower risk classes.[6] Specifically, the odds ratio for mortality increases significantly as the BNT/NT class progresses, highlighting its utility as a robust prognostic tool in high-acuity surgical settings within the Thai healthcare context.[1,6]

Specialized surgical populations and PNI

In specialized fields such as gynecologic oncology, the role of the Preoperative Prognostic Nutritional Index (PNI) is becoming increasingly evident.[3] Patients undergoing major surgery for gynecologic cancer often present with compromised nutritional status due to the malignancy itself. Research has shown that a low preoperative PNI is an independent predictor of postoperative complications, including surgical site infections and prolonged ileus.[3] This suggests that a multi-faceted approach—combining standardized screening like BNT/NT with specific prognostic indices like PNI—could provide a more comprehensive risk profile for surgical patients.[3,5]

The path to improved outcomes

The ultimate objective of nutritional assessment is to guide intervention. Identifying a patient at high nutritional risk should immediately trigger a personalized nutritional care plan.[4] This may involve preoperative nutritional optimization, such as the use of oral nutritional supplements or immunonutrition, and early postoperative enteral feeding.[4,7] In Thailand, nationwide surveys have indicated that while awareness of nutritional importance is growing, there remains a gap in the consistent application of these tools across all hospital levels.[7] Standardizing the use of validated tools like BNT/NT, SGA, or the others and integrating them into the surgical "check-list" are essential steps toward improving the quality of care. Moreover, the integration of the Global Leadership Initiative on Malnutrition (GLIM) criteria and muscle mass measurement provides a new framework for diagnosing malnutrition globally, which clinicians are increasingly adopting to align local practices with international standards.[2,8]

Conclusion and recommendations

Nutrition assessment is the gateway to improving surgical outcomes. The evidence is clear: malnourished patients fare worse. Tools like BNT/NT in Thailand or other standard assessment tools have proven their worth in predicting mortality and morbidity in critically ill surgical patients.[1,6] To move forward, healthcare systems must:

1. Mandate nutritional screening for all elective and emergency surgical admissions using validated tools.[4]
2. Utilize objective indices like PNI and GNRI to supplement general screening, especially in high-risk groups like the elderly and oncology patients.[3,5]

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3. Foster multidisciplinary "Nutrition Support Teams" (NST) to bridge the gap between screening and action.[7]
4. Implement standardized protocols for perioperative nutritional support based on the identified risk levels.[4]

Conflict of interest

The authors declare that there is no conflict of interest related to the study.

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SYSTEMATIC REVIEW AND META-ANALYSIS

Prognostic performance of GNRI versus PNI for predicting mortality in elderly critically ill patients: A systematic review and meta-analysis

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Abstract

Background: Malnutrition significantly impacts outcomes in elderly critically ill patients. The Geriatric Nutritional Risk Index (GNRI) and Prognostic Nutritional Index (PNI) are two established tools to assess nutritional status and predict mortality. However, their comparative prognostic performance in this population remains unclear.
Objective: This study aimed to compare the predictive ability of GNRI and PNI for mortality among elderly ICU patients.
Methods: We conducted a systematic search in PubMed, Scopus, and Web of Science for studies assessing GNRI and/or PNI in relation to mortality in ICU patients aged ≥60 years. We extracted mean and standard deviation values for survivors and non-survivors. Meta-analyses were conducted to calculate pooled mean differences (MD) with 95% confidence intervals (CI), and heterogeneity was evaluated using the I^2 statistic.
Results: Eight studies involving 6,217 ICU patients were included. Both GNRI and PNI scores were significantly lower in non-survivors. The pooled MD for GNRI was −8.99 [95% CI −9.71 to −8.27] (I^2 = 86%), and for PNI was −4.45 [95% CI −4.94 to −3.96] (I^2 = 47%). GNRI showed a larger effect size but greater heterogeneity, while PNI results were more consistent. Most studies had low to moderate risk of bias based on the ROBINS-E tool.
Conclusion: GNRI and PNI are valid prognostic tools for predicting mortality in elderly ICU patients. GNRI may provide stronger predictive value, whereas PNI offers more consistent prognostic performance.

Keywords: GNRI, PNI, elderly, ICU, mortality, nutritional assessment

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Introduction

Malnutrition is highly prevalent among elderly individuals admitted to the intensive care unit (ICU), with estimates ranging from 30% to 60% depending on the population and diagnostic criteria used[1]. This condition is associated with impaired immune responses, prolonged hospital stays, increased complication rates, and higher mortality. Elderly patients are especially vulnerable due to multiple comorbidities, reduced physiological reserves, and altered metabolic responses to critical illness.[1]

To assess nutritional risk and predict adverse outcomes in this population, various screening tools have been developed. Among them, the Geriatric Nutritional Risk Index (GNRI) and the Prognostic Nutritional Index (PNI) are widely used due to their simplicity, reliance on routinely available laboratory parameters, and reported prognostic value. GNRI incorporates serum albumin and the ratio of actual to ideal body weight, whereas PNI is calculated from serum albumin and total lymphocyte count, reflecting both nutritional and immunological status.[3]

Previous studies have demonstrated the association between low GNRI or PNI values and increased mortality in various populations, including patients with sepsis, trauma, cardiovascular disease, and elderly ICU patients. However, comparative evidence on the predictive strength of GNRI versus PNI in critically ill elderly patients remains inconsistent. For instance**,** Kim et al. found GNRI had better predictive accuracy than PNI for in-hospital mortality after acute myocardial infarction, while Shao et al.[2] reported similar prognostic abilities of both indices in a large ICU cohort. Furthermore, studies by Soylu et al**.** and Taskın et al.[9] in older ICU patients supported the prognostic value of both indices, but with varying cutoff sensitivities and specificities.

Given these variations and the lack of a definitive comparison, this study aimed to systematically review and quantitatively synthesize the current evidence on the prognostic performance of GNRI and PNI in predicting mortality among elderly critically ill patients. Clarifying which index provides superior prognostic performance is clinically important, as it may guide ICU clinicians in selecting a more reliable, simple, and cost-effective tool for early risk stratification and timely nutritional interventions, thereby potentially improving survival outcomes in elderly critically ill patients.

Methods

Search strategy

This systematic review and meta-analysis were conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines.[5] The review protocol was registered in PROSPERO under the registration number CRD420251086421. A systematic search was conducted in PubMed, Scopus, and Web of Science databases from inception to July 2025. The search strategy used Boolean operators and MeSH terms, combining the following keywords: "Geriatric Nutritional Risk Index", "GNRI", "Prognostic Nutritional Index", "PNI", "elderly", "intensive care", "ICU", and "mortality". The complete search strings for each database are presented in Supplementary Table S1 to ensure reproducibility. For example, the PubMed search strategy was: (“Geriatric Nutritional Risk Index” OR GNRI) AND (“Prognostic Nutritional Index” OR PNI) AND (elderly OR aged OR “older adults”) AND (“intensive care unit" OR ICU) AND (mortality OR survival). Equivalent search terms and syntax were adapted for Scopus and Web of Science. In addition to database searches, we also screened grey literature sources including ClinicalTrials.gov, medRxiv, and relevant conference abstracts to minimize potential publication bias. However, no additional eligible studies were identified from these sources. The full search strategy is available upon request. References of relevant articles were also manually screened to identify additional eligible studies.

Eligibility criteria

We included original observational studies (cohort or cross-sectional) that evaluated the prognostic utility of the Geriatric Nutritional Risk Index (GNRI) and/or Prognostic Nutritional Index (PNI) in predicting mortality among elderly critically ill patients aged ≥60 years admitted to the intensive care unit (ICU). Studies were eligible if they reported GNRI and/or PNI values (mean ± standard deviation) for survivors and non-survivors. Only studies published in English were included. Studies involving pediatric populations, non-ICU settings, or lacking outcome data were excluded.

Study selection

All reviewers independently screened titles and abstracts. Full texts of potentially relevant articles were assessed against the eligibility criteria. Discrepancies were resolved by consensus or consultation with a third reviewer. The selection process is depicted in the PRISMA 2020 flow diagram. In line with PRISMA 2020 recommendations, the flow diagram provides a transparent overview of the number of records identified, screened, excluded, and finally included.

Data extraction

Data were extracted using a standardized form and included: author name, publication year, country, patient population, sample size, mean ± SD of GNRI and/or PNI for both survivors and non-survivors, and mortality outcomes. Data extraction was independently performed by two reviewers (DP and AH) to ensure accuracy.

Quality of assessment

The ROBINS-E (Risk of bias in non-randomized studies of exposures) tool was applied to evaluate the methodological quality across seven domains, including confounding, selection of participants, classification of exposures, and outcome measurement. The risk of bias in each study was classified as low, some concern, high, or very high according to the ROBINS-E criteria.

Data synthesis and statistical analysis

Meta-analyses were performed using Review Manager (RevMan) version 5.4.1**.** Continuous outcomes (GNRI and PNI scores) were summarized using pooled mean differences (MDs) with 95% confidence intervals (CIs)**.** Heterogeneity was assessed using the I^2 statistic**,** with values >50% considered substantial. Both fixed-effect and random-effects models were applied for sensitivity analysis. Forest plots were generated to visualize pooled effects. Funnel plots were used to explore potential publication bias.

Results

Study selection

A total of 148 records were identified through database searching. After removing 36 duplicates, 112 titles and abstracts were screened. Of these, 21 full-text articles were assessed for eligibility. Thirteen studies were excluded due to insufficient data or ineligible outcomes, resulting in 8 studies included in the final meta-analysis. The selection process is illustrated in the PRISMA flow diagram (**Figure 1**).

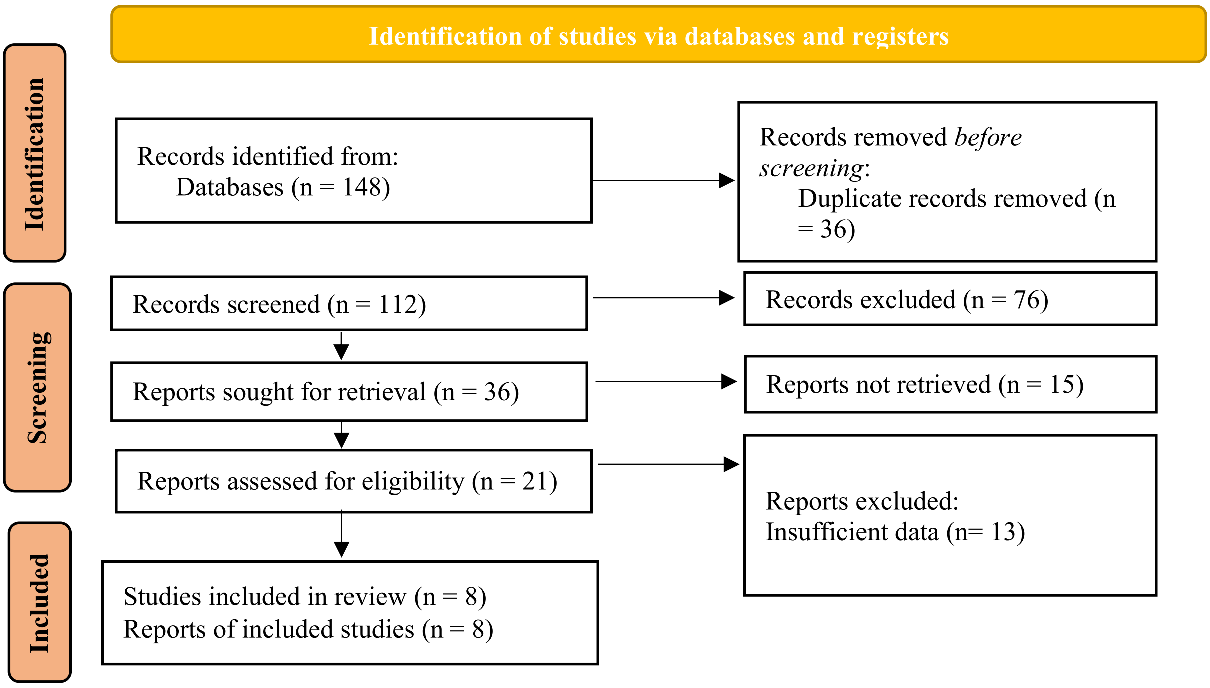


Figure 1. Prisma flowchart, stages of study selection flowchart for systematic review and meta-analysis

Study characteristics

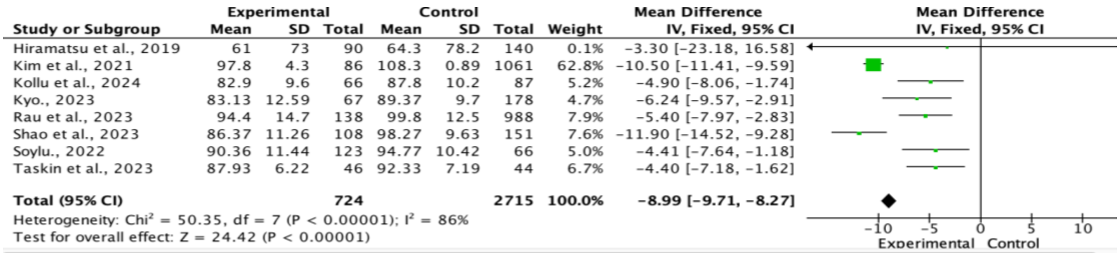
The 8 included studies involved a total of 6,217 elderly ICU patients. Sample sizes ranged from 91 to 2,060 participants, with populations including trauma patients, sepsis cases, very elderly (≥85 years), and patients on mechanical ventilation. GNRI and PNI scores were reported as mean ± standard deviation (SD) for both survivors and non-survivors. **Table 1** summarizes the study characteristics and findings.

Table 1. Study characteristics and findings

Author, Year	Country	Population	Number of Samples		GNRI Score (Mean ± SD)		PNI Score (Mean ± SD)		Outcome
			Death	Survivor	Death	Survival	Death	Survival	
Rau et al., 2023 [6]	Taiwan	ICU trauma patients (n=1126)	138	988	94.4 ± 14.7	99.8±12.5	41.6 ± 11.4	44.8±9.4	GNRI significantly predicted mortality, PNI was not significant
Hiramatsu et al., 2019[7]	Japan	Elderly undernourished patients (n=230)	90	140	61.0 ± 73.4	64.3 ± 78.2	23.3 ± 32.5	25.8 ± 34.5	GNRI slightly better but not statistically significant
Kim et al., 2021[8]	Republic of Korea	Acute myocardial infarction patients (n=1147)	86	1061	97.8 ± 4.30	108.30 ± 0.89	49.03 ± 3.33	54.30 ± 0.81	GNRI had significantly higher predictive accuracy (AUC) compared to PNI
Kollu et al., 2024[1]	Turkey	Elderly ICU patients (≥65 years, n=153)	66	87	82.9 ± 9.6	87.8 ± 10.2	33.6 ± 7.5	37.5 ± 7.5	Both GNRI and PNI significantly predicted ICU mortality; similar predictive performance (AUC)
Soylu et al., 2022 [3]	Turkey	Very elderly ICU patients (≥85 years, n=189)	123	66	90.36± 11.44	94.77±10.42	32.04 ±6.54	34.32±6.40	GNRI slightly better with higher sensitivity & specificity
Kyo et al., 2023[4]	Japan	Patients with sepsis (n=32,159)	67	178	83.13 ± 12.59	89.37 ± 9.7	32.77 ± 5.93	36.57 ± 6.07	Both GNRI and PNI significantly predicted mortality, sharp increase risk GNRI<100, PNI<40
Shao et al., 2021[2]	USA	ICU patients (n=2060)	108	151	86.37 ± 11.26	98.27 ± 9.63	34.67 ± 4.59	38.63 ± 4.59	Both GNRI and PNI significantly predicted ICU mortality, similar predictive ability
Taşkın et al., 2023 [9]	Turkey	ICU patients on mechanical ventilation (n=91)	46	44	87.93 ± 6.22	92.33 ± 7.19	31.87 ± 4.74	36.27 ± 3.78	Both GNRI and PNI significantly predicted mortality

GNRI and PNI performance on mortality prediction

Across all studies, both GNRI and PNI scores were consistently lower in non-survivors compared to survivors. Pooled analysis demonstrated that non-survivors had significantly lower GNRI scores, with a mean difference (MD) of −8.99 [95% CI: −9.71 to −8.27], indicating a strong association between poor nutritional status and higher mortality. The forest plot illustrating this result under the fixed-effect model is shown in **Figure 2**. However, due to considerable statistical heterogeneity (I^2 = 86%), we performed a sensitivity analysis using a random-effects model, which yielded comparable results, confirming the robustness of the finding (**Figure 2**).

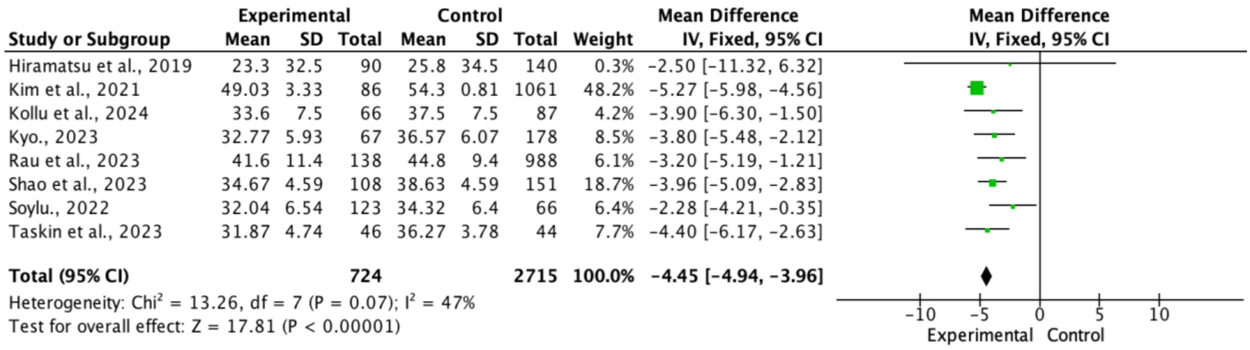


Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Hiramatsu et al., 2019	61	73	90	64.3	78.2	140	0.1%	-3.30 [-23.18, 16.58]
Kim et al., 2021	97.8	4.3	86	108.3	0.89	1061	62.8%	-10.50 [-11.41, -9.59]
Kollu et al., 2024	82.9	9.6	66	87.8	10.2	87	5.2%	-4.90 [-8.06, -1.74]
Kyo., 2023	83.13	12.59	67	89.37	9.7	178	4.7%	-6.24 [-9.57, -2.91]
Rau et al., 2023	94.4	14.7	138	99.8	12.5	988	7.9%	-5.40 [-7.97, -2.83]
Shao et al., 2023	86.37	11.26	108	98.27	9.63	151	7.6%	-11.90 [-14.52, -9.28]
Soylu., 2022	90.36	11.44	123	94.77	10.42	66	5.0%	-4.41 [-7.64, -1.18]
Taskin et al., 2023	87.93	6.22	46	92.33	7.19	44	6.7%	-4.40 [-7.18, -1.62]
Total (95% CI)			**724**			**2715**	**100.0%**	**-8.99 [-9.71, -8.27]**

Heterogeneity: Chi^2 = 50.35, df = 7 (P < 0.00001); I^2 = 86%
Test for overall effect: Z = 24.42 (P < 0.00001)

Figure 2. Forest plot showing the association between GNRI and mortality under the fixed-effect model.

Similarly, analysis of PNI showed that lower PNI scores were significantly associated with mortality**,** with a pooled mean difference of −4.45 [95% CI: −4.94 to −3.96]**.** The heterogeneity for PNI was moderate (I^2 = 47%)**,** and the consistency of the outcome across studies was better than that for GNRI. Forest plots of PNI under both fixed-effect and random-effects models are shown in **Figures 3**, respectively.



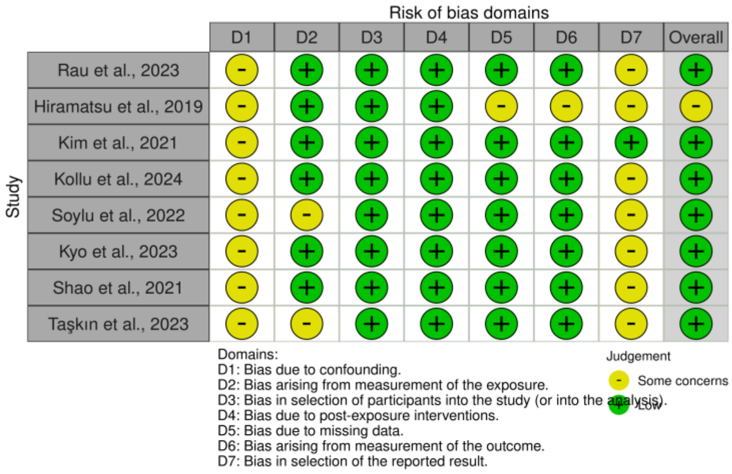
Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Hiramatsu et al., 2019	23.3	32.5	90	25.8	34.5	140	0.3%	-2.50 [-11.32, 6.32]
Kim et al., 2021	49.03	3.33	86	54.3	0.81	1061	48.2%	-5.27 [-5.98, -4.56]
Kollu et al., 2024	33.6	7.5	66	37.5	7.5	87	4.2%	-3.90 [-6.30, -1.50]
Kyo., 2023	32.77	5.93	67	36.57	6.07	178	8.5%	-3.80 [-5.48, -2.12]
Rau et al., 2023	41.6	11.4	138	44.8	9.4	988	6.1%	-3.20 [-5.19, -1.21]
Shao et al., 2023	34.67	4.59	108	38.63	4.59	151	18.7%	-3.96 [-5.09, -2.83]
Soylu., 2022	32.04	6.54	123	34.32	6.4	66	6.4%	-2.28 [-4.21, -0.35]
Taskin et al., 2023	31.87	4.74	46	36.27	3.78	44	7.7%	-4.40 [-6.17, -2.63]
Total (95% CI)			**724**			**2715**	**100.0%**	**-4.45 [-4.94, -3.96]**

Heterogeneity: Chi^2 = 13.26, df = 7 (P = 0.07); I^2 = 47%
Test for overall effect: Z = 17.81 (P < 0.00001)

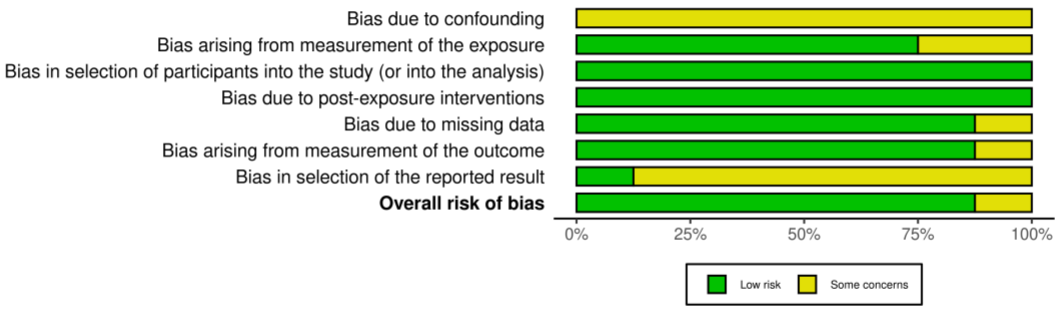
Figure 3. Forest plot showing the association between PNI and mortality under the fixed-effect model.

Risk of bias

Risk of bias for each study was assessed using the ROBINS-E (Risk of bias in non-randomized studies of exposures) tool. Most studies were judged to be of low risk to some concern, with no study excluded due to critical bias. A visual summary of the risk assessment across seven domains is presented in **Figures 4.**



(A)



(B)

Figure 4. Risk of bias of the entire study (A) ROBINS-E Traffic-light plot; (B) ROBINS-E Summary plot.

Heterogeneity and sensitivity analysis

Substantial heterogeneity was observed among studies evaluating GNRI ($I^2 = 86\%$), while PNI showed moderate heterogeneity ($I^2 = 47\%$). To account for this, we applied random-effects models in the meta-analysis. Under the random-effects model, GNRI remained significantly lower in non-survivors, with a pooled mean difference of −8.99 [95% CI: −9.71 to −8.27] (**Figure 5**). Similarly, PNI also showed a significant pooled difference of −4.45 [95% CI: −4.94 to −3.96] (**Figure 6**). The direction and magnitude of the effect remained consistent across models, indicating that the findings were robust and not driven by any single study**.**

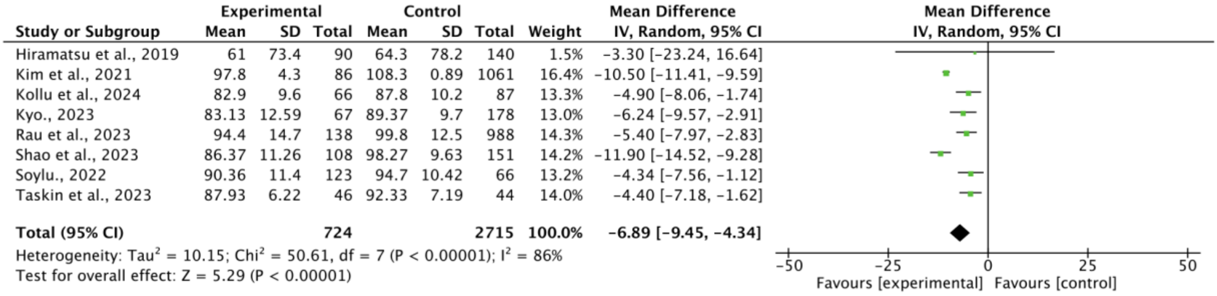


Figure 5. Forest plot showing the association between GNRI and mortality under the random-effects model.

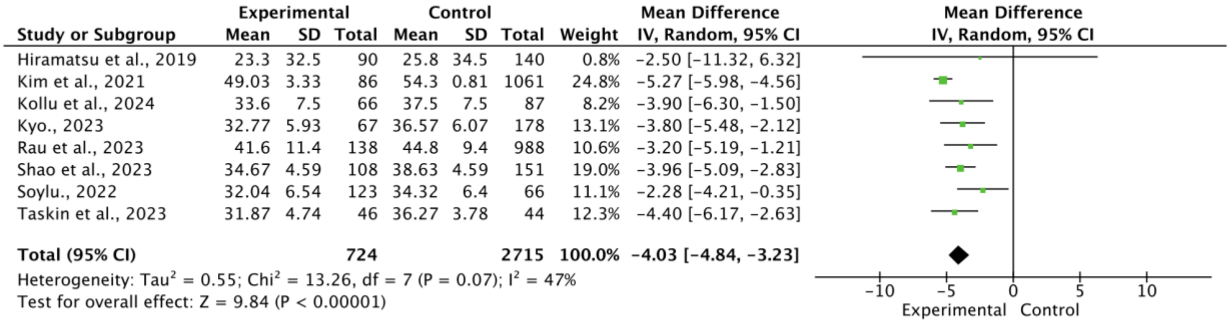
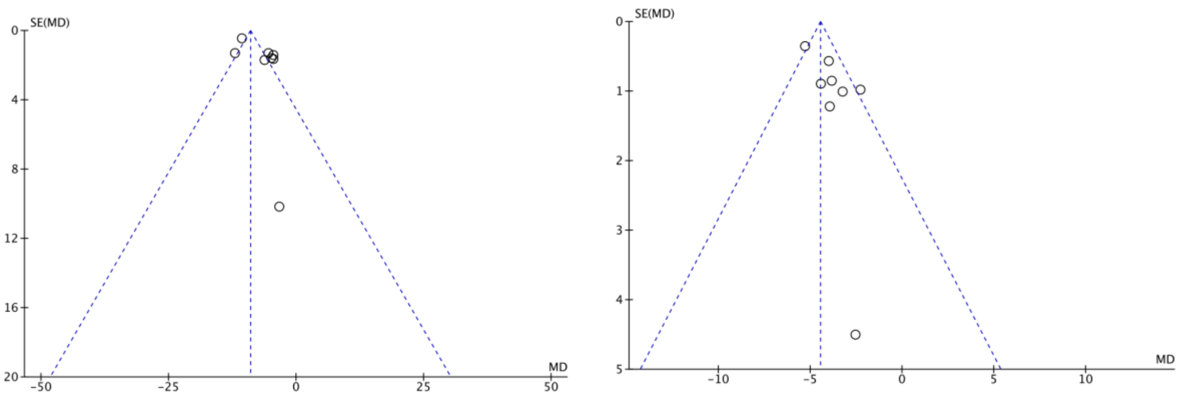


Figure 6. Forest plot showing the association between PNI and mortality under the random-effects model.

Publication bias

Visual inspection of the funnel plots for both GNRI and PNI (**Figure 7**) revealed symmetrical distribution of effect sizes, suggesting the absence of significant publication bias among the included studies. The plots showed no evidence of small-study effects or asymmetry, supporting the reliability of the pooled estimates. Although primarily used to detect reporting bias, the funnel plots also contribute to sensitivity analysis by evaluating the influence of study size and consistency across the evidence base. The symmetry observed in both plots further reinforces the robustness of the meta-analysis results.



(A) (B)

Figure 7. Funnel plot. (A) Funnel plot of GNRI. (B) Funnel plot of PNI

These results demonstrate that both GNRI and PNI are reliable indicators of mortality risk in elderly ICU patients, with GNRI showing a larger effect size but greater variability, and PNI showing more consistent performance across diverse populations and clinical contexts.

Discussion

This systematic review and meta-analysis demonstrated that both the Geriatric Nutritional Risk Index (GNRI) and Prognostic Nutritional Index (PNI) are valid predictors of mortality in elderly ICU patients. Pooled analyses revealed that non-survivors had significantly lower scores for both indices, with GNRI showing a larger effect size but greater heterogeneity, while PNI had a smaller effect size with more consistent results across studies.

Our findings are consistent with previous literature highlighting the prognostic utility of nutritional indices in critically ill populations. For instance, Kim et al.[8] reported that GNRI had a better predictive value for in-hospital mortality than PNI in elderly patients with acute myocardial infarction.[3] Similarly, Taskın et al.[9] showed that both GNRI and PNI were significantly associated with 28-day mortality in ICU patients on mechanical ventilation.[9]

Despite differences in populations and settings, several studies included in this review supported the predictive value of both indices. Shao et al.,[2] using a large cohort of 2,060 ICU patients, found no significant difference in prognostic ability between GNRI and PNI.[4] Meanwhile, Soylu et al.[16] suggested that GNRI may offer better sensitivity and specificity in very elderly ICU patients (≥85 years), aligning with our result that GNRI had a larger pooled effect size.[5]

In elderly critically ill patients, nutritional status is not only influenced by acute illness and age-related sarcopenia, but also by underlying metabolic factors such as obesity and genetic predisposition**.** Studies have suggested that gene polymorphisms, particularly those related to fat mass and obesity-associated (FTO) genes. In Asian populations, the AA genotype of the rs9939609 variant is associated with a greater risk of obesity compared to other genotypes.[10] This genotype may alter inflammatory responses and metabolic regulation during critical illness, thereby modifying prognostic indicators such as GNRI and PNI.

The greater heterogeneity observed in GNRI (I^2 = 86%) may reflect variability in patient conditions and weight-based calculations, which are often imprecise in ICU settings. In contrast, PNI showed more homogenous performance (I^2 = 47%), likely due to its reliance on stable laboratory parameters. Importantly, our funnel plot analyses showed no evidence of publication bias, and sensitivity analyses confirmed that findings were robust, with consistent results under random-effects modelling. These results strengthen the validity of both indices in predicting mortality, despite inter-study variability.

Some limitations should be acknowledged. First, the number of included studies is relatively limited (n = 8), and most were observational, introducing possible residual confounding. Second, GNRI and PNI cutoff values were inconsistent, and adjustments for disease severity were variably reported. Finally, our study did not explore the temporal change of nutritional indices during ICU stay, which may have additional prognostic value.

Nonetheless, the current evidence supports the incorporation of GNRI and PNI in routine ICU assessment for elderly patients. These indices offer simple, accessible, and cost-effective tools to support prognostication and guide early nutritional interventions.

Conclusion

Both GNRI and PNI are valuable tools for predicting mortality in elderly critically ill patients. Our pooled analysis indicates that GNRI demonstrates a stronger prognostic effect size, suggesting it may be more sensitive in detecting mortality risk. However, this comes with greater heterogeneity across studies, likely due to variability in weight-based parameters. In contrast, PNI showed more consistent predictive performance across diverse ICU populations, reflecting the stability of its laboratory-based components. Taken together, GNRI may be preferable when higher prognostic sensitivity is required, whereas PNI may be more reliable for routine clinical use due to its consistency and ease of application. These findings underscore the complementary roles of GNRI and PNI in supporting early risk stratification and guiding nutritional interventions in elderly ICU patients.

Conflict of interest

The authors declared no conflict of interest regarding this article.

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Author Contributions

DP: Conceptualization, data acquisition, formal analysis, interpretation of results, drafting the manuscript, and final approval of the version to be published; IWAH: Supervision, critical revision of the manuscript, interpretation of data, and final approval of the version to be published; MS: Conception and design of the study, critical revision of the manuscript for important intellectual content, and final approval of the version to be published.

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ORIGINAL PAPER

The preoperative prognostic nutritional index in patients undergoing major gynecologic oncology surgery and its association with postoperative outcomes

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Abstract

Background: Patients undergoing major surgery for gynecologic cancer often experience postoperative complications. Postoperative complications are influenced by various factors, one of which is nutritional status. The preoperative prognostic nutritional index (PNI), calculated from serum albumin levels and lymphocyte count, is used as a preoperative nutritional parameter and has been associated with postoperative outcomes.

Objective: To investigate the association between preoperative PNI and postoperative outcomes in patients undergoing major gynecologic oncology surgery.

Methods: This prospective observational study was conducted at Dr. Cipto Mangunkusumo National General Hospital in August-December 2024. Subjects were gynecologic cancer patients aged 18-65 years who underwent major surgery. PNI was calculated based on preoperative serum albumin levels and lymphocyte count. Postoperative complications were assessed within 30 days following surgery using the Clavien-Dindo classification. Statistical analysis was performed using Chi-square or Fisher's exact test, followed by multivariable logistic regression.

Results: A total of 56 subjects were included, with a mean age of 47.8 ± 12.3 years and a median PNI of 50.2 (28.9-61.3). Postoperative complications occurred in 35.7% of subjects, with surgical site infections being the most common. The median PNI was lower in the complication group, although the difference was not statistically significant. In multivariable analysis, advanced tumor stage was the only independent predictor of postoperative complications (odd ratio [OR] 4.74, 95% CI 1.26–17.83, p = 0.021). Low PNI showed a nonsignificant trend toward higher odds of complications (OR 1.71, 95% CI 0.47–6.28, p=0.420).

Conclusion: PNI was not statistically significant but showed a trend toward association with postoperative complications, suggesting its potential importance of preoperative nutritional status. Advanced tumor stage was an independent predictor of complications. Further multicenter studies are needed to confirm the prognostic role of PNI in gynecologic oncology surgery.

Keywords: gynecologic cancer, major surgery, postoperative complications, preoperative malnutrition, prognostic nutritional index

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Introduction

Gynecologic cancers account for more than 1.3 million cases globally, with mortality rates reaching up to 47%.[1] In Indonesia, cervical and ovarian cancers are the most common gynecologic malignancies and are leading causes of cancer-related deaths among women.[2] Surgery remains the cornerstone of treatment for these cancers, particularly in the early stage. Due to their complexity and invasiveness, major gynecologic oncology surgeries are associated with a higher risk of adverse postoperative outcomes, which may increase the length of hospital stay, risk of readmission, and overall cost of care.[3,4]

Preoperative nutritional status is one of the key factors influencing postoperative outcomes. Malnutrition is common in gynecologic cancer and is driven by systemic inflammation, altered energy metabolism, inadequate nutrient intake, and adverse effects of cancer therapy.[5–7] Chronic malnutrition in cancer is associated with impaired immune function, particularly reduced lymphocyte levels and function, and may lead to hypoalbuminemia. These alterations are linked to increased postoperative morbidity and mortality.[6–8]

Several parameters can be used to assess preoperative nutritional status; however, many of them still have some limitations. Subjectivity, lack of comprehensive data, and interference from tumor mass or fluid retention may lead to inaccurate assessment.[9,10] Therefore, a simple and objective nutritional parameter is needed. The prognostic nutritional index (PNI) is a parameter that reflects both nutritional and immune status, calculated based on serum albumin levels and total lymphocyte count.[11–13] Low PNI is associated with preoperative malnutrition and poor surgical outcomes in several malignancies.[6]

Although previous studies have investigated the prognostic role of PNI in gastrointestinal, hepatobiliary, and cardiac surgeries, evidence in gynecologic cancer surgery remains inconclusive.[14–19] Yet prospective data focusing specifically on gynecologic oncology surgery are scarce, particularly in Indonesia. Therefore, this study aimed to investigate preoperative nutritional status using PNI and its association with postoperative complications in patients undergoing major gynecologic oncology surgery.

Methods

This prospective observational study was conducted at Dr. Cipto Mangunkusumo National General Hospital (RSCM), Jakarta, Indonesia, from August to December 2024. A total of 60 consecutive patients met the eligibility criteria during the study period. The study protocol was approved by the Health Research Ethics Committee of the Faculty of Medicine, Universitas Indonesia (KET-865/UN2.F1/ETIK/PPM.00.02/2024).

Study participants

Inclusion criteria were female patients aged 18-65 years with gynecologic cancer undergoing major surgery. Major gynecology oncology surgery was defined as laparotomy for resection of the genital organs (uterus, ovaries, fallopian tubes, vulva, or vagina) as well as adjacent structures that may serve as metastatic pathways, including pelvic and/or para-aortic lymph nodes, omentum, appendix, and peritoneal metastases.[4] Subjects with sepsis or severe infection, chronic liver disease, autoimmune disease, concurrent malignancies, ongoing chemotherapy or radiotherapy, and taking immunosuppressive drugs (except low-dose corticosteroids <10 mg or non-steroidal anti-inflammatory drugs [NSAIDs]) were excluded.

Data collection

Demographic and clinical data, including age, cancer site, tumor stage, comorbidities, and history of perioperative blood or albumin transfusions, were obtained from medical records. Dietary intake was assessed using food recall and food records collected 3 days preoperatively and up to 30 days postoperatively. Energy intake was categorized using a cut-off of 25 kcal/kg body weight, and protein intake using 1.5 g/kg body weight.[20] Anthropometric measurements were obtained by estimating body weight using mid-upper arm circumference (MUAC) based on the formula by Cattermole et al.,[21] and estimating body height using the formula by Wong et al.[22] Nutritional status was assessed by using Global Leadership Initiative on Malnutrition (GLIM) criteria, and subjects were categorized as malnourished or not malnourished.[23]

Laboratory data

Laboratory data were collected preoperatively (within three weeks prior to surgery), including hemoglobin (Hb) levels, serum albumin, and total lymphocyte count. Subjects were categorized as having low or normal albumin using a cutoff of 3.5 g/dL. The PNI was calculated using the formula by Onodera et al.[24]: PNI = [10 × serum albumin (g/dL)] + [0.005 × total lymphocyte count (/µL)]. PNI with a cut-off value of 45 was used as a nutritional parameter; subjects were categorized as having low PNI (<45) or high PNI (≥45).[25]

Postoperative outcomes

Postoperative complications were assessed within 30 days after surgery, based on medical records and confirmed by the attending physicians. Postoperative complications were classified using the Clavien–Dindo system, which is widely used in major gynecologic oncology surgery.[26] For analysis, complications were grouped as minor (grades I–II) or major (grades III–V) (**Table 1**).

Table 1. Clavien-Dindo classification of surgical complications[26]

Grade	Definition
I	Any deviation from the normal postoperative course without the need for pharmacological treatment or surgical, endoscopic, and radiology interventions Allowed therapeutic regimens are: drugs as antiemetics, antipyretics, analgetics, diuretics, electrolytes, and physiotherapy. This grade also includes wound infections opened at the bedside.
II	Requiring pharmacological treatment with drugs other than such allowed for grade I complications Blood transfusions and total parenteral nutrition are also included
III	Requiring surgical, endoscopic or radiological intervention
IIIa	Intervention not under general anesthesia

Grade		Definition
	IIIb	Intervention under general anesthesia
IV		Life-threatening complication (including CNS complications)* requiring IC/ICU management
	IVa	Single organ dysfunction (including dialysis)
	IVb	Multiorgan dysfunction
V		Death of a patient

*Brain hemorrhage, ischemic stroke, subarrachnoidal bleeding, but excluding transient ischemic attacks.
CNS, central nervous system; IC, intermediate care; ICU, intensive care unit.

Results

A total of 60 patients met the eligibility criteria. Four patients were dropped out because they did not complete the study or were lost to follow-up. Finally, 56 patients were included in the analysis. The study flow is shown in **Figure 1**. Based on the GLIM criteria, 50% of subjects were malnourished, including 23.3% with moderate malnutrition and 26.8% with severe malnutrition. Body mass index (BMI) was 23.7 ± 5.8 kg/m². Ovarian cancer was the most common diagnosis. Most patients had early-stage tumors (I–II), although stage III was the most frequently observed (33.9%), followed by stage I (32.1%), stage II (21.4%), and stage IV (12.5%). Advanced stage (III–IV) was significantly associated with a higher risk of postoperative complications. The most common comorbidities were cardiovascular diseases, followed by diabetes mellitus. Other comorbidities included respiratory diseases (9.4%), renal and urinary tract diseases (9.4%), and cholecystitis (3.1%).

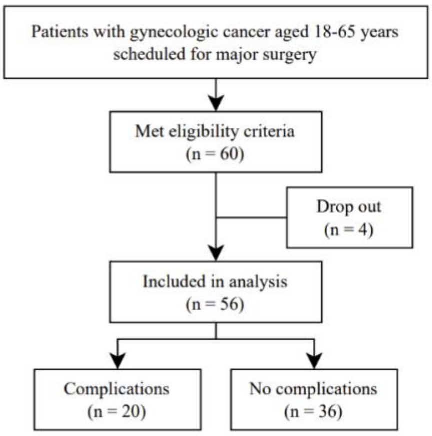

Figure 1. Study flow

Low preoperative albumin was significantly associated with postoperative complications. The median preoperative PNI was lower in patients who experienced postoperative complications compared to those without complications, although the difference did not reach statistical significance. Low PNI was observed in 33.9% of subjects. Postoperative complications occurred in 47.4% of subjects with low PNI compared to 29.7% of those with high PNI. However, this difference was not statistically significant.

Preoperatively, energy intake requirements were met by most subjects, with a median intake of 1,280 (600–1,700) kcal/day. However, protein intake was insufficient in most subject (48.1 ± 14.3 g/day). Postoperatively, 69.6% of subjects met their energy requirements, while only 33.9% met protein targets (52.5 ± 14.6 g/day). Perioperative blood transfusion was significantly associated with postoperative complications, with a higher proportion of complications observed among patients who received transfusions compared to those who did not.

Table 2. Subject characteristics (n=56)

Variable	Results	Complication		p-value
		Yes (n=20)	No (n=36)	
Age	47.8 ± 12.3*	49.3 ± 12.1*	47.2 ± 12.6*	0.762[a]
Nutritional status based on GLIM criteria (n, %)				
Malnourished	28 (50)	13 (46.4)	15 (53.6)	0.246[c]
Not malnourished	28 (50)	7 (25)	21 (75)	
Cancer site (n, %)				
Ovary	32 (57.1)	11 (34.4)	21 (65.6)	0.963[d]
Endometrium	19 (33.9)	7 (36.8)	12 (63.2)	
Cervix	5 (8.9)	2 (40)	3 (60)	
Vulva/vagina	0 (0)	0 (0)	0 (0)	
Tumor stage (n, %)				
I-II	30 (53.6)	5 (16.7)	25 (83.3)	0.002[c#]
III-IV	26 (46.4)	15 (57.7)	11 (42.3)	
Comorbidities (n, %)	26 (46.4)	11 (42.3)	15 (57.7)	0.408[d]
Diabetes mellitus	9 (28.1)	3 (33.3)	6 (66.7)	
Cardiovascular diseases	16 (50)	6 (37.5)	10 (62.5)	
Others	7 (21.8)	4 (57.1)	3 (42.9)	
Preoperative albumin (g/dL)	3.9 (2.3-4.8)†	3.7 (2.3-4.8)†	3.9 (2.5-4.8)†	0.173[b]
Low (n, %)	13 (23.2)	8 (61.5)	5 (38.5)	0.046[d#]
Normal (n, %)	43 (76.8)	12 (27.9)	31 (72.1)	
Preoperative total lymphocyte count (/µL)	1750 (645-3655)†	1751 (645-3160)†	2047 (878-3655)†	0.156[b]
Preoperative PNI	50.2 (28.9-61.3)†	45.1 (29-61)†	49.8 (31-61)†	0.067[b]
Low (≤45) (n, %)	19 (33.9)	9 (47.4)	10 (52.6)	0.224[c]
High (>45) (n, %)	37 (66.1)	11 (29.7)	26 (70.3)	
Preoperative Hb (g/dL)	11.2 ± 1.6*	10.4 ± 1.9*	11.7 ± 1.2*	0.002[a#]
Preoperative energy intake (kcal/kg body weight)	25.9 ± 6.0*	25.1 ± 6.6*	26.4 ± 5.7*	0.474[a]

Variable	Results	Complication		p-value
		Yes (n=20)	No (n=36)	
Insufficient (n, %)	23 (41.1)	10 (43.5)	13 (56.5)	0.311[c]
Sufficient (n, %)	33 (58.9)	10 (30.3)	23 (69.7)	
Preoperative protein intake (g/kg body weight)	0.99 ± 0.30*	0.98 ± 0.33*	0.99 ± 0.29*	0.358[a]
Insufficient (n, %)	39 (69.6)	13 (33.3)	26 (66.7)	0.573[c]
Sufficient (n, %)	17 (30.4)	7 (41.2)	10 (58.8)	
Postoperative energy intake (kcal/kg body weight)	26.9 ± 6.7*	25.0 ± 9.1*	27.9 ± 4.6*	0.112[a]
Insufficient (n, %)	17 (30.4)	9 (52.9)	8 (47.1)	0.076[c]
Sufficient (n, %)	39 (69.6)	11 (28.2)	28 (71.8)	
Postoperative protein intake (g/kg body weight)	1.07 ± 0.28*	1.02 ± 0.35*	1.10 ± 0.23*	0.272[a]
Insufficient (n, %)	37 (66.1)	13 (35.1)	24 (64.9)	0.900[c]
Sufficient (n, %)	19 (33.9)	7 (36.8)	12 (63.2)	
Perioperative blood transfusion (n, %)				
Yes	11 (19.6)	7 (63.6)	4 (36.4)	0.041[d#]
No	45 (80.4)	13 (28.9)	36 (71.1)	
Perioperative albumin transfusion (n, %)				
Yes	10 (17.9)	2 (20)	8 (80)	0.304[d]
No	46 (82.1)	18 (16.4)	28 (60.9)	

*mean ± standard deviation; †median (minimum-maximum); [a]independent t test; [b]Mann-Whitney U test; [c]chi-square test; [d]Fisher test; #p<0.05.
GLIM, Global Leadership Initiative on Malnutrition; Hb, hemoglobin; PNI, prognostic nutritional index.

The proportion of postoperative complications in this study was 35.7%, with minor complications being the most common. The most common type of complication was surgical site infections (SSIs). Among SSIs, 16.9% were superficial wound infections and 3.6% were sepsis. Other complications are pneumonia (3.6%), and pulmonary embolism (1.8%). The 30-day mortality rate was 3.6%, primarily caused by sepsis due to complicated intra-abdominal infections.

Table 3. Postoperative complications

Variable	Results (n=56)
Complication (n, %)	
No	36 (64.3)
Yes	20 (35.7)
Clavien-Dindo classification (n, %)	
Minor	12 (21.4)
Grade I	2 (3.5)
Grade II	10 (17.9)
Major	8 (14.2)
Grade III	3 (5.3)
Grade IV	3 (5.3)
Grade V	2 (3.6)

Variable	Results (n=56)
Type of complication (n, %)	
Surgical site infections	11 (19.6)
Hemorrhage	5 (8.9)
Ileus	5 (8.9)
Others	3 (5.4)

In the multivariable logistic regression model including PNI, preoperative Hb, tumor stage, and perioperative blood transfusion, only advanced tumor stage (III-IV) was independently associated with postoperative complications (OR 4.74, 95% CI 1.26–17.83, p=0.021). Subjects with low PNI tended to have higher odds of complications, although the association was not statistically significant (OR 1.71, 95% CI 0.47–6.28, p=0.420). Preoperative Hb <12 g/dL and perioperative blood transfusion were also not significant predictors. Serum albumin was not included in the regression model since it is a direct component of the PNI and would introduce collinearity.

Table 4. Multivariate analysis of factors associated with postoperative complications

Variable	B	Wald	p-value	OR	CI 95%
Low PNI (<45)	0.536	0.652	0.420	1.709	0.465–6.283
Preoperative Hb <12 g/dL	0.430	0.330	0.566	1.537	0.355-6.660
Tumor stage III-IV	1.555	5.291	0.021#	4.737	1.259-17.826
Perioperative blood transfusion	0.936	1.391	0.238	2.549	0.538-12.066

#p<0.05
CI, confidence interval; Hb, hemoglobin; OR, odd ratio; PNI, prognostic nutritional index.

Discussion

In this prospective study, we investigated the PNI and postoperative outcomes in patients undergoing major gynecologic oncology surgery. According to GLIM criteria, the prevalence of malnutrition in this study was 50%, which was higher than that observed when using BMI alone (19,7%).[23] This highlights the importance of considering etiological and functional aspects in the nutritional assessment of gynecologic cancer patients. Although not statistically significant, postoperative complications were more frequent among malnourished patients. Loss of muscle mass can lead to a blunted inflammatory response, impaired wound healing and has been associated with poor surgical outcomes.[27]

Most subjects were diagnosed with ovarian cancers, in alignment with previous studies.[4,28] Complications were most commonly observed in subjects with cervical cancer. Cervical cancer is often asymptomatic and frequently diagnosed at advanced stage, which is associated with a higher surgical risk.[4] Postoperative complications tended to be more frequent in subjects with comorbidities, although not statistically significant. Comorbidities may contribute to increased oxidative stress and immune dysregulation, increasing susceptibility to postoperative complications.[4,29]

Subjects with complications had significantly lower preoperative Hb compared to those without complications. Preoperative anemia may reduce tissue oxygenation, increase oxidative stress, and suppress immune response and activity.[30,31] In addition, both preoperative and postoperative protein intake were generally insufficient in subjects with and without complications. Low protein intake during both preoperative and postoperative period is associated with prolonged hospital stay and a higher risk of complications.[20,32–34] Perioperative blood transfusion was significantly associated with postoperative complications, consistent with prior studies suggesting that patients who received transfusions often had more severe clinical conditions and may also experience adverse immunomodulatory effects of transfusion products.[35,36]

The proportion of postoperative complications in this study was 35.7%, slightly higher than previous studies. This difference may be explained by our inclusion of only major gynecologic oncology procedures, which are more extensive than laparoscopy or transvaginal approaches reported in other studies.[4,37] Surgical site infections (SSIs) were the most common complication. Hypoalbuminemia, perioperative anemia, and perioperative blood transfusions are an independent predictor of SSIs. Low albumin and anemia impair immune function and wound healing process, potentially increasing the risk of SSIs.[30,38,39]

In multivariate analysis, advanced tumor stage (III-IV) was identified as the only independent predictor of postoperative complications. This is consistent with the notion that advanced disease requires more complex surgical procedures, thereby contributing to the risk of postoperative complications.[29,40] Previous studies have also suggested that malnutrition is more prevalent in advanced-stage cancer, which triggers a more severe inflammatory and surgical stress response, thereby increase the risk of complications.[41,42]

Although PNI was not statistically significant, it showed a trend toward higher odds of complications, suggesting that nutritional and immune status remain important contributors to postoperative outcomes. This finding is in line with the significant association observed between low preoperative albumin and complications, as albumin is a major component of the PNI. Preoperative Hb and perioperative blood transfusion were not independent predictors in the adjusted model, indicating that their effects may be mediated through other clinical factors.

Our findings differed from previous studies, which reported significant associations between low PNI and postoperative complications.[18,19] This discrepancy could be explained by differences in PNI cut-off values; the inclusion of only major laparotomy procedures in our study, whereas other studies included less complex procedures such as laparoscopy or transvaginal surgery, which may affect complication risk. In addition, the relatively small sample size in our study may have limited statistical power, although a trend toward increased complications in the low-PNI group was observed.

The molecular mechanisms underlying the relationship between PNI and postoperative complications are complex and multifactorial. Malnutrition and systemic inflammation lead to lymphocyte suppression and hypoalbuminemia.[7,8] Lymphocytes are involved in modulating inflammation and promoting wound healing, while albumin plays a critical role in immune response, collagen synthesis, and granuloma formation. Low lymphocytes count and hypoalbuminemia may compromise immune function and impair wound healing, therefore increasing the risk of postoperative complications.[5,38,43]

This study has several strengths, including its prospective design and the use of the Clavien-Dindo classification, which allows standardized reporting of both minor and major complications. The use of the GLIM criteria as an indicator of nutritional status also reduces potential bias caused by tumor mass or fluid retention. Nonetheless, some limitations should be acknowledged. Dietary intake was collected only during hospitalization and may not reflect habitual intake. The sample size was relatively small, and the single-center design may limit the generalizability of the findings.

Conclusion

In conclusion, although PNI did not reach statistical significance, it showed a trend toward association with postoperative complications, highlighting the potential importance of preoperative nutritional status. Advanced tumor stage, however, was identified as an independent predictor of complications. Larger multicenter studies are warranted to further establish the prognostic role of PNI in gynecologic oncology surgery.

Conflict of interest

The authors declared no conflict of interest regarding this article.

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Author Contributions

All authors contributed equally to the conception and design of the study, data acquisition, analysis and interpretation of data, drafting and critical revision of the manuscript, and final approval of the version to be published. All authors have read and approved the final manuscript.

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ORIGINAL PAPER

Changes in postprandial plasma malondialdehyde levels between consumption of brown rice compared to white rice in sedentary workers

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Abstract

Background: Office workers are prone to sedentary behavior and low physical activity, which can increased oxidative stress. The effect of dietary carbohydrates on oxidative stress can be assessed through changes in Malondialdehyde (MDA) levels, typically observed 2-4 hours of postprandially. In Indonesia, white rice remains the dominant carbohydrate source, whereas brown rice is known to contain antioxidants and dietary fiber that help counteract free radicals.
Objective: The study aimed to compare the effect of brown rice and white rice consumption on postprandial plasma MDA levels.
Methods: A total 28 sedentary workers subjects from FKUI Salemba participated in this open label, randomized, parallel clinical trial using consecutive sampling. Subjects were allocated to consume either 150 g of white rice (IR-64/*Setra Ramos* variety) or 150 g of brown rice (*Aek Sibundong* variety). Each meal was given once accompanied by 60 g of omelette, 70 g of tofu stew, and 220 ml of water. The participants were aged 23-48 years, with 80% being female, and all had normal BMI.
Results and Conclusion: Significant differences in energy intake (p=0.026) and protein intake (p=0,014) were observed between the groups. Postprandial plasma MDA levels in the brown rice group tended to decrease, though not -significantly. (p=0.0649), whereas the white rice group showed a significant increase (p=0.01). No significant difference was found between the two groups (p=0.065). Nevertheless, brown rice can still be considered a better alternative staple food than white rice, as its antioxidants and higher fiber content can protect the body's cells from diet-induced oxidative stress.

Keywords: brown rice, oxidative stress, postprandial MDA, sedentary workers, white rice

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Introduction

Office workers frequently engage in sedentary behaviors—characterized as waking activities performed while seated or reclined with an energy expenditure of ≤ 1.5 METs—mainly due to extended periods of sitting.[1,2] In Southeast Asia, approximately 35% of women and 18% of men aged 18–44 exhibit such inactivity, accounting for an estimated 500 million non-communicable disease events projected between 2020 and 2030.[3] The high rate of sedentary behavior in the office, coupled with low levels of daily physical activity, is currently considered a risk factor for chronic diseases. This is partly due to the dysregulation of cellular redox homeostasis, decreased mitochondrial function, and increased activity of Nicotinamide Adenine Dinucleotide Phosphate (NADPH) oxidase, which leads to increased oxidative stress. Oxidative stress is known to have a linear relationship with the incidence of metabolic and chronic diseases. It is generally defined as an imbalance between pro-oxidants and antioxidants that causes disruption of reduction-oxidation (redox) signaling and control. This imbalance produces unstable molecules or Reactive Oxygen Species (ROS) that can cause molecular damage in the body. Increased generation of ROS can have detrimental effects on vital cellular components, including proteins, lipids, and DNA as a result of oxidative stress. This can induce tissue damage in the body's cells, which can result in a number of chronic diseases.[4-6] Over time, persistent sedentarism exerts sustained pressure on mitochondrial systems and diminishes the effectiveness of enzymatic antioxidants, thereby weakening the primary cellular defense mechanism against ROS and further exacerbating oxidative damage.[7] In contrast, Perez et al. reported a significant negative correlation between levels of moderate-to-vigorous physical activity and plasma malondialdehyde (MDA)—a biomarker of lipid peroxidation—particularly among men.[8]

As mentioned before, one important process that reduces enzyme function and molecular signaling pathways, ultimately leading to tissue damage, is oxidative stress.[9] Reactive Oxygen Species-induced lipid membrane degradation can increase the fluidity and permeability of the membrane, allowing water and Na to enter and causing cell enlargement and ultimately lysis. Protein damage, on the other hand, includes enzyme inactivation, peptide chain breakage, aggregation of cross-linked reaction products, changes in electrical charge, modifications to specific amino acid positions, and vulnerability to proteolysis. Finally, ROS can break DNA strands, remove nucleotides, alter bases, cause DNA-protein crosslinking and cause damage to DNA by deoxyribose oxidation.[10]

One of the byproducts of polyunsaturated fatty acid peroxidation, malondialdehyde (MDA) is well known for being one of the most sensitive indicators of lipid oxidative damage.[11] The body reacts to oxidative stress circumstances in two stages. Within minutes after eating (postprandial), the first phase starts, and it often peaks two to four hours later. The immune system stabilizes or homeostatic metabolism returns to normal, during the second phase, which is known as the adaptation phase. The stress reaction will last for a long time and progress to a condition of dysmetabolism or failure to balance the redox system if both phases are disturbed, either because the first phase's effect is too great or the adaptation phase does not proceed smoothly.[12,13]

In reaction to oxidative stress, body cells employ an antioxidant defense system that is primarily an endogenous antioxidant and consists of a number of enzyme components, including glutathione peroxidase (GPx), catalase (CAT), and superoxide dismutase

(SOD).[6] Superoxide anion is broken down by SOD into oxygen (O_2) and hydrogen peroxide (H_2O_2), which is subsequently transformed back into water (H_2O) and oxygen by CAT and GPx.[14,15] The three endogenous antioxidants can cooperate to defend against ROS-induced cell damage thanks to this mechanism.[16] One dietary element that has an impact on oxidative stress is carbohydrates. In general, excessive intake of glucose and fatty acids causes an increase in the production of acetyl coenzyme A (acetyl CoA), an enzyme that plays a role in cellular metabolism. Increased acetyl CoA levels result in increased NADH formation in the tricarboxylic acid (TCA) cycle. As a result, mitochondria are stimulated to produce excess superoxide in the electron transport chain, thereby increasing superoxide levels in the mitochondria. This leads to excessive production of ROS, damaging mitochondrial proteins, deoxyribonucleic acid (DNA), and lipids. It then activates redox-sensitive transcription factors and triggers an inflammatory cascade.[17]

In Indonesia, white rice, a refined grain, serves as the primary energy source. Rice consumption is dominated by household consumption, followed by consumption in industry, hotels, and restaurants. Data shows that consumption of white rice processed into white rice reaches 80 kilograms per person per year.[18] As public awareness of health issues increases, the cultivation of other types of rice, such as brown rice, has also begun to increase. However, its cultivation has not yet received as much attention as white rice.[19] Because it contains phenolic compounds, flavonoids, anthocyanins, proanthocyanidins, tocopherols, tocotrienols, and phytic acid, brown rice, a type of whole grain, has a high degree of antioxidant activity in addition to white rice, which is a refined grain. Proanthocyanidin is the primary secondary metabolite found in brown rice, while genes that create anthocyanins—natural pigment compounds that combat free radicals—are found in the aleurone portion of the grain.[20] Brown rice can avoid an excessive rise in blood glucose because of its low glycemic index and rich nutritious content, including fiber, vitamins, and minerals.[21] Postprandial oxidative stress can be prevented by combining physical activity with the consumption of foods that possess antioxidant properties. In this context, the researcher aims to investigate the effect of dietary choices by comparing brown rice and white rice consumption, specifically examining their impact on postprandial plasma MDA levels in healthy adult sedentary worker volunteers.

Methods

Subjects and research location

This clinical trial research has been ethically approved by the Research Ethics Committee of the Faculty of Medicine, Universitas Indonesia (FMUI) with the letter KET-1779/UN2.F1/ETIK/PPM.00.02/2024. The sample size was 24 people (intervention group 12, control 12) with an estimated dropout of 20%, so the total minimum sample size was 30 people. During the intervention period, two subjects from the intervention group dropped out, one because they did not consume the intervention food (brown rice) and the other because of difficulties in taking blood samples, so that the subjects could not continue to the next stage of the study. The total number of subjects analyzed was 28 subjects, which 15 subjects were in the control group, and 13 subjects were in the intervention group. The sample was collected using a consecutive sampling technique from administrative workers of FKUI Salemba. Inclusion criteria included healthy administrative employees, age 21-59 years, normal body mass index (18.5-22.9 kg/m^2), low physical activity (≤600 METs minutes/week), and informed consent. Exclusion criteria included pregnancy/breastfeeding/menopause, consumption of herbal medicines and/or vitamin supplements within 24 hours before data collection, history of diabetes mellitus (DM), cardiovascular disease (CVD), cancer, hypertension, hypercholesterolemia, vegan, smoker/alcohol drinker, allergy to intervention food ingredients. Informed consent was signed after a full explanation of the purpose, methods, and risks of the study. This study was a clinical or experimental open-label trial, parallel, with random allocation using the randomlist.com application.

Feeding modifications and procedures

Two types of rice were used in this study: control, 150 g white rice of the IR-64/*setra ramos* variety and intervention, 150 g brown rice of the *aek sibundong* variety. Each rice was given a combination of 60 g of omelet and 70 g of tofu stew, and 220 ml of water. The white rice was cooked using a rice cooker until the marker changed from "cook" to "warm" after washing twice, with the ratio of white rice and water when cooking as much as 150 g: 246 mL. After that, the rice was left in the rice cooker for 15 minutes before stirring and serving.[21] Meanwhile, brown rice was cooked by soaking brown rice first for 2 hours after washing twice so that the development of rice is better so that the texture of the rice is more like white rice and acceptable to the subject.[22] Then brown rice was cooked according to the same processing method as white rice using a rice cooker, but with a ratio of rice to water, namely 1: 2.[21-23] The results of the 2007 NutriSurvey in the control group included energy 403 kcal, carbohydrates 51 g, protein 20.9 g, fat 12.3 g, and fiber 2.8 g. While the intervention group has nutritional values based on NutriSurvey 2007, including energy 376 kcal, carbohydrates 43.4 g, protein 19.9 g, fat 13.2 g, and fiber 2.8 g.

The research subjects fasted from 9.30 pm to 07.30 a.m (10 hours) the next day before being given the research food once during breakfast. Then the subject was given a breakfast according to the modified food made by the researcher and asked to finish the food within 15 to 20 minutes. During the observation period, no additional calories or excessive activity beyond daily work habits were allowed. Observation was conducted for 4 hours after consumption of the study meal. At 12:00 p.m. (4 hours later), the subjects were recollected for blood collection as a measure of postprandial plasma MDA, which was then taken to the Biochemistry and Molecular Biology laboratory of FKUI.

Data collection

Sociodemographic data collection in the form of gender and age, anthropometric measurements, physical activity assessment, calorie needs, along with macronutrients and fiber, as well as basal plasma MDA levels was carried out before the intervention (baseline), while postprandial plasma MDA levels were taken 4 hours after the intervention (endline). Anthropometric measurements were carried out to obtain body mass index (BMI) data by measuring height using a shorrboard with an accuracy of 0.1 cm and weight using a SECA scale with an accuracy of 0.1 kg.

Physical activity assessment using the international physical activity questionnaire short-form version (IPAQ-SF) questionnaire was carried out to equalize the subject's physical activity level, which was sedentary. This questionnaire consists of 7 questions based on the physical activity performed by the subject during the last 7 days. Then food intake was assessed using a 1 x 24-hour food recall sheet which was interviewed directly by the researcher on 1 working day without comparing it with holidays to describe a diet similar to the real situation in the daily work of the subjects.

Blood sample collection and examination

Venous blood of 5 ml was collected into two different heparin tubes, before and 4 hours after dieting. Blood storage was placed in a refrigerator at 4^0C and transportation was performed using a cool box with ice blocks by maintaining the same temperature as storage. Malondialdehyde levels were then measured with TBARS assay or Will's method, using a spectrophotometer in the biochemistry and molecular biology laboratory of FKUI.[24]

Statistical analysis

Data were analyzed using SPSS (version 26). Univariate tests assessed the characteristics of age, gender, BMI, caloric intake, macronutrients (carbohydrate, protein, and fat), and fiber intake, as well as basal MDA levels. Results with normal distribution were written as mean±SD, while results with abnormal distribution were written as median (minimum-maximum). Bivariate tests were conducted to assess changes in MDA levels of each group before and after the intervention using paired T test if the distribution was normal/Wilcoxon if the distribution was not normal, while the final result to see the difference in changes in MDA levels between groups using unpaired T statistical test if the distribution was normal/Mann-Whitney if the distribution was not normal. Significant is set for $p < 0.05$.

Results

Selection of research subject

There were 28 subjects who participated in this study until the end. All subjects signed informed consent at the beginning of the study and continued with a characteristic interview, screening criteria for research subjects, anthropometric assessment, physical activity assessment, and food intake assessment. The researcher then conducted group matching by equalizing the gender distribution in each group and using simple randomization techniques on eligible subjects for the division of control and intervention groups. Subject scheduling was carried out to proceed to the dietary intervention stage and blood sampling for plasma MDA examination. The stages of selection of research subjects can be seen in **Figure 1**.

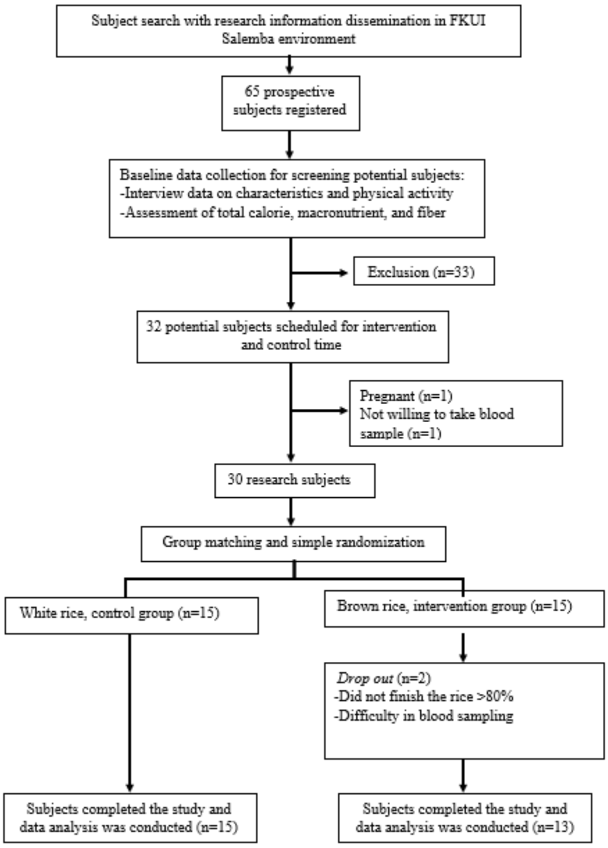

Figure 1. Research subject selection chart

Characteristics of the study subjects

Based on the results of univariate analysis, the age of the subjects in this study had a median of 27 years (23-48 years) for the whole subject, and so did the control group, while the average age of the subjects in the intervention group was 30 ± 6.7 years. There were 6 male subjects, with each group having the same proportion of 3 subjects each, fewer than females in both the control group (80%) and intervention group (76.9%). The body mass index (BMI) of the subjects in this study has been selected with normal BMI inclusion criteria (18.5-22.9 kg/m2), so the results of BMI distribution are not much different. There was no significant difference between the two groups in terms of characteristics tested by bivariate analysis (p>0.05) in **Table 1**.

Table 1. Characteristics of study subjects

	Total subjects (n=28)	White rice group (n=15)	Brown rice group (n=13)	P value
Age (years)	27 (23-48)	27 (23-48)	30±6.7	0.711[a]
Gender, n (%)				
Male	6 (20)	3 (20)	3 (23.1)	0.84[b]
Female	24 (80)3	12 (80)	10 (76.9)	
Body mass index (kg/m^2)	20.97±1.24	20.94±1.20	21±1.34	0.87[c]

[a]*Mann-Whitney test*
[b]*Chi-square test*
[c]*Unpaired T-test*

Energy, carbohydrate, protein, fat, and fiber intake

The energy and macronutrient intake of the study subjects assessed using 24h food recall according to **Table 2**, had a normal distribution, with significant differences between the two groups in total energy intake (p=0.02) and protein intake (p=0.014), while other intakes, such as carbohydrates and fats did not have significant differences between groups. Total energy intake in the control group had an average of 1,709 ± 341.5 kcal, while the intervention group tended to be lower at an average of 1346 ± 467.7 kcal. Likewise, the average protein intake in the control group was higher (63 ± 11.1 kcal) compared to the intervention group (47.9 ± 18.6 kcal). In contrast to the normal distribution of energy and macronutrient intake, fiber intake assessed by a similar method resulted in data with abnormal distribution in all subjects, with a median value of 7.1 g/day (2.3-20.4 g/day) but was normally distributed in each group.

Table 2. Energy, macronutrient, and fiber intake of study subjects

	Total subjects (n=28)	White rice group (n=15)	Brown rice group (n=13)	P value
Energy intake (kcal)	1540±437.9	1709±341.5	1346±467.7	0.026*
Carbohydrate intake (g/day)	168.8±52.8	182.7±52.9	152.8±49.9	0.138
Protein intake (g/day)	56.0±16.6	63±11.1	47.9±18.6	0.014*
Fat intake (g/day)	72.3±30.9	81.7±28.8	61.4±30.7	0.083
Fiber intake (g/day)	71 (2.3-20.4)	8.8±4.9	7.5±4.3	0.472

**Unpaired T-test*

Plasma MDA levels

In **Table 3**, it can be seen that the basal MDA assessment in all subjects was normally distributed (p>0.05), which means that the subjects' baseline values were the same. Basal MDA and postprandial MDA levels in both groups did not have significant differences. The brown rice group showed a non-significant change in plasma MDA levels (p=0.0649), whereas the white rice group exhibited a significant increase in plasma MDA levels (p=0.01). There was no significant difference in plasma MDA levels between the consumption of brown rice compared to white rice (p=0.065).

Table 3. Changes in plasma MDA levels

	Total subjects (n=28)	White rice group (n=15)	Brown rice group (n=13)	P value*
Basal plasma MDA levels (nmol/mL)	0.75±0.17	0.68 (0.41-0.82)	0.83±0.18	0.051[a]
Postprandial plasma MDA level (nmol/mL)		0.84 (0.28-1.01)	0.85 (0.31-1.05)	1.00
Difference (nmol/mL)		0.14±0.2	-0.006±0.21	0.065[b]
P value[c]		0.01	0.649	

[a]*Mann-Whitney test*
[b]*Unpaired T-test*
[c]*Wilcoxon test*

Discussion

The age of the subjects who participated until data analysis in this study ranged from 23 years to 48 years, with a median of 27 years in the control group, while the average age of subjects in the intervention group was 30 years. The age range obtained in the subjects of this study is by data from the Central Statistics Agency in 2024 regarding the Labor Force in Indonesia, where the age group of 25-44 years is the largest age group of workers in Indonesia.[25] Likewise, the prevalence of employees with low physical activity according to Adawiyah, et al.[26] research was found to be more at the age of 19-44 years compared to the older group, namely 45-65 years. Male subjects in both groups amounted to 3 subjects or less than 25%, less than women, both in the control group which dominated up to 80% and the intervention group with the distribution of women reaching 76.9%. The gender distribution of subjects in this study has gone through a matching process to equalize the characteristics between groups for a more normal distribution. Research by Khakim, et al[27] and Abadini, et al[28] found that sedentary behavior was more prevalent in female office employees. In addition, global data conducted by the Lancet 2024 study stated that from 2000 to 2022, women were physically inactive with an average percentage of 5% higher than men.[29]

The subjects in this study were limited to the normal BMI category. This IMT restriction was carried out because of the possibility of increased oxidative stress in overweight and obese subjects (IMT> 22.9 kg/m2), which could affect the results of the MDA examination. Excessive fat accumulation in obesity can cause a pathological increase in serum free fatty acid (FFA) concentration, which can interfere with glucose metabolism, stimulate the accumulation of energy substrates (glucose and fat) into the liver, muscle, and fat tissues, and trigger mitochondrial and peroxisomal oxidation. Increased oxidative damage leads to higher cytokine production, ROS synthesis, and an increased rate of lipid peroxidation.[30]

All intake data in this study were obtained using the 24-hour food recall method on weekdays. Food intake can be influenced by various factors, such as age, gender, weight and height, environmental temperature, hormonal status, and dietary patterns.[31] The work environment, such as interaction and support among coworkers, working time, and eating habits inside and outside the office are also taken into consideration in assessing the subject's food intake.[32] Research conducted on office workers in Japan showed that office workers who ate lunch in the office canteen had a Healthy Eating Index value in 2015 (HEI-2015) followed by workers who brought home-made food. This is in contrast to workers who choose to eat lunch from fast food restaurants or takeaways due to overwork and therefore shorter mealtimes.[33]

The statistically similar basal MDA levels in this study indicate that both groups had similar levels of oxidative stress before treatment, so basal plasma MDA levels are not expected to affect the results after treatment. The increase in oxidative stress that occurred after consumption of the study food would be biased due to uneven basal oxidative stress levels in the subjects. The tendency to decrease postprandial oxidative stress in the brown rice group proves that the consumption of brown rice has an effect in reducing oxidative stress that occurs after consuming daily food when compared to white rice which actually increases postprandial plasma MDA levels.

The decrease in postprandial MDA levels in the brown rice group can occur one of them because of the anthocyanin content in brown rice which has antioxidant effects and is not owned by white rice. Anthocyanins and anthocyanidins, like other polyphenols and flavonoids, have the ability to bind and eliminate free radicals such as reactive oxygen and nitrogen species (ROS and RNS) thus preventing oxidative stress.[34,35] Anthocyanin levels in the aek sibundong brown rice variety are 10.87 mg/100g, and in addition to the high antioxidant activity found, these levels also act as high anti-diabetic by preventing stress on the endoplasmic reticulum and inhibiting pancreatic lipase activity, resulting in improved glycemic control and lipidemia, and protecting the liver from insulin resistance caused by a high-fat diet.[36-38] Flavonoids in brown rice can also inhibit glucose uptake and prevent glucose-induced lipid peroxidation.[38]

Research from Wiedani, et al.[38] who examined bioactive activities such as anthocyanins in dragon fruit, which has an anthocyanin content of 8.8 mg/100g, found that there was a decrease in plasma MDA levels in experimental mice despite being given a high-fat diet. Another study that shows the effectiveness of anthocyanins against MDA is research with the herbal plant *Clitoria ternatea* (butterfly pea), which every gram can reduce postprandial MDA levels up to 2 hours after consumption of sucrose carbohydrates.[39] The high dietary fiber in *aek sibundong* brown rice, which is around 3.3 g/100 g, can also affect MDA inhibition. Compared to the white rice variety IR 64 / *setra ramos* which was the control food given in this study, it only contains 0.5 to 1 g/100 g of dietary fiber. Dietary fiber content has a negative relationship with the glycemic index value of food. The glycemic index value of white rice from the IR64 variety is 79, which is in the high category.[40] Meanwhile, brown rice from the *aek sibundong* variety has a glycemic index in the medium category, at 59.[41] Fiber functions to slow down the rate of food in the digestive tract and inhibit enzyme activity so that the digestive process, especially starch, is slowed down and the blood glucose response will be lower, thus the glycemic index value tends to be lower. If there is an increase in glucose in the blood, NADPH oxidase activity will increase and produce superoxide, which can eventually trigger lipid peroxidation. Lipids found in plasma, mitochondria, and endoplasmic reticulum membranes are the main targets of ROS attacks and peroxidation in most macromolecules. The end products of lipid peroxidation, known as lipid peroxides, can be toxic to any cell and require destruction by antioxidants such as glutathione.[42] This is reinforced by a study in Las Vegas that proved a decrease in MDA as well as an increase in serum antioxidant capacity in pregnant women who were given a blueberry diet supplemented with 12 g of soluble fiber for 8 weeks.[43]

This study has limitations in assessing healthy clinical status, which is the inclusion criterion of the subject, where only subjective anamnesis is carried out for the history of the subject's disease. At the very least, after history taking, simple laboratory tests such as lipid and glucose profiles should be performed to more objectively assess current metabolic disease status related to oxidative stress. In addition, the use of the food recall method to assess daily intake in this study risks recall bias even though the researcher has minimized the bias by modelling various food menus using a food photo book. A single intervention may not produce significant results in this study, although postprandial plasma MDA changes can occur within 2-4 hours after eating. The author suggesting that repeated interventions should be considered in future studies or adding more research samples.

Conclusion

The change in postprandial plasma MDA levels between the consumption of brown rice compared to white rice in sedentary workers was not significant. However, plasma MDA levels in the brown rice group tend to decrease, while MDA levels in the white rice group significantly increased. Therefore, brown rice can be considered a better alternative staple food option compared to white rice, because it contains antioxidants and higher fiber to protect the body's cells from diet-induced oxidative stress. This must be accompanied by a balanced diet and sufficient physical activity.

Conflict of interest

There was no conflict of interest related to this research. The authors have no personal or financial relationship that could influence the judgment or action.

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Author’s contribution

All authors contributed equally to the conception and design of the study, data acquisition, analysis and interpretation of data, drafting and critical revision of the manuscript, and final approval of the version to be published. All authors have read and approved the final manuscript.

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NARRATIVE REVIEW

Dissecting pathways of cancer-associated cachexia and its evidence-based relation to vitamin D

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Abstract

Introduction: Cancer-associated cachexia (CAC) is a complex metabolic syndrome. It affects 0,5-1% of the general population and 60-83% of cancer patients. Vitamin D has a potential immunological role in cancer cachexia. However, the mechanism remains unclear.

Method: This review outlines the complex mechanisms of CAC, a metabolic syndrome marked by muscle loss affecting 80% of cancer patients and the potential action of vitamin D. We highlight the limited studies exploring vitamin D's impact on CAC, based on cachexia parameters.

Result: The Warburg effects in CAC are understood to involve elevated energy use, driven by the tumor microenvironment (TME) and pro-inflammatory cytokines. This present review explores the mechanism of cachexia on skeletal, adipose tissue, liver and tumor microenvironment. At the same time vitamin D deficiency in cancer correlates with poor prognosis due to its critical role in immune modulation. Notably, various clinical trials showed the beneficial roles of vitamin D in reducing inflammation, pain and increasing weight.

Conclusion: Few studies had explored the beneficial effects of vitamin D in cancer; However, limited evidence exists on immunomodulatory effects of vitamin D. This critical gaps stressing the need for further clinical research across various cancer types.

Keywords: cancer-associated cachexia, vitamin D

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Introduction

Cachexia is a complex metabolic syndrome marked by muscle loss, often with fat loss, partially reversible with nutritional support.[1,2] It affects 0,5-1% of the general population and 60-83% of cancer patients.[1] It causes 20% of cancer deaths, often when weight loss exceeds 30-40%.[3] Diagnosis can use cachexia score (CASCO) or miniCASCO, or simplified criteria: > 5% weight loss in 6 months, or ≥ 2% with BMI < 20 kg/m^2 or sarcopenia.[1,4,5] Pre-cachexia and refractory cachexia also exist. About 60% of patients in hospital in their 70s face sarcopenia, frailty, cachexia, or malnutrition, worsening outcomes.[6] Cachexia affects 40-60% of older male and 40-50% of older female cancer patients.[7]

Low serum of 25-OH vitamin D is common in prostate, breast, ovarian, and colorectal cancers,[9] and it is linked to cancer risk and outcomes.[10] Vitamin D and its analogues may reduce metastasis and mortality.[11] However, European Society of Parenteral and Enteral Nutrition (ESPEN) states vitamin D does not prevent muscle loss in cancer.[11] Still, it has a potential anti-inflammatory effects, and immunological role by reducing T-cell and B-cell activity and cytokines (IFN-γ, IL-6, IL-2, TNF-α), key in cachexia development.[12] However, the underlying mechanism by which vitamin D influences cachexia and its interaction in cancer progression remains unclear, representing critical gap in current knowledge in cancer cachexia.

Cancer-associated cachexia

Cancer-associated cachexia is a complex interplay of metabolic dysregulation, characterized by systemic inflammation due to tumor-related factors. On clinical presentations, the patients appear cachetic with involuntary weight loss. The tumour energy demands range from 100–1400 kcal/day.[13] Cachexia risk varies by tumor type.[14] It involves a negative energy balance driven by the Warburg and reverse Warburg effects.[15,16] In the Warburg effect, tumor cells use inefficient aerobic glycolysis, leading to high glucose uptake and lactate production that acidifies the tumor microenvironment (TME), promoting immune evasion.[15,17] The Cori cycle adds to energy inefficiency by recycling lactate to glucose in the liver.[15] In the reverse Warburg effect, cancer-associated fibroblasts (CAFs) undergo glycolysis due to ROS and IL-6 exposure, releasing metabolites (lactate, pyruvate, ketones, glutamine) into the TME to fuel cancer growth and support metastasis and immune suppression.[13,15]

Liver, muscle, and adipose tissue support this altered metabolism. The liver compensates early on but later contributes to muscle wasting and lipolysis via IL-6.[18] Elevated bile acids also worsen muscle loss via TGR5 receptor activation.[14] Muscle loss occurs through increased proteolysis (via ubiquitine-proteasome system (UPS), calcium-activated systems, autophagy-lysosome) and reduced protein synthesis, with TNF-α-activated NF-κB increasing MuRF-1 expression.[14,18] Reduced mammalian target of rapamycin (mTOR) activity triggers abnormal autophagy and mitophagy via AMPK–FOXO–mTORC1 disruption.[19] Early-stage cachexia also involves white adipose tissue (WAT) lipolysis, releasing fatty acids and converting WAT into thermogenic beige cells, worsening energy imbalance.[14,20]

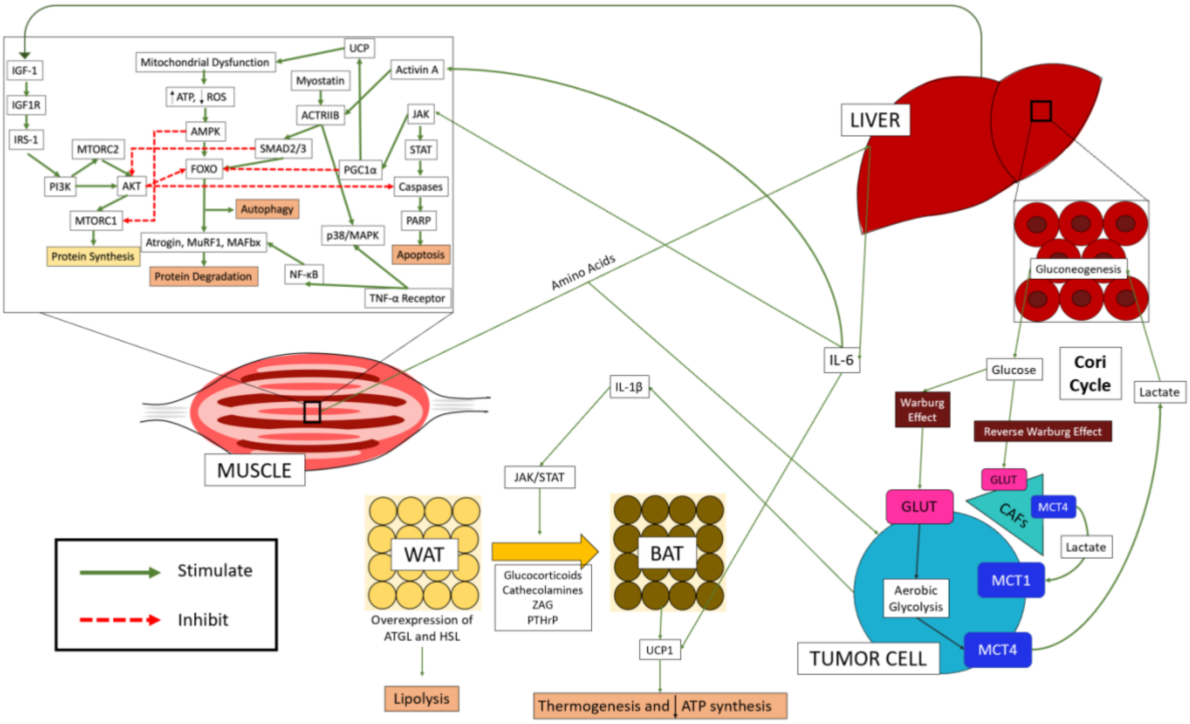

Figure 1. Mechanisms of cachexia in the skeletal muscle, adipose tissue, liver, and tumor microenvironment (TME). Tumor cells use glucose via the Warburg or reverse Warburg effect, producing lactate for energy. Interleukine-6 (IL-6) from the liver drives muscle wasting, thermogenesis, and reduced ATP via JAK/STAT and FGF/p38 MAPK pathways. In WAT, IL-6 and TNF-α induce lipolysis through ATGL and HSL, while adipocyte browning is promoted by glucocorticoids, catecholamines, ZAG, and PTHrP.

Note: GLUT1, glucose transporter 1; PEPCK, phosphoenolpyruvate carboxykinase; MCT4, monocarboxylate transporter 4; CAFs, cancer-associated fibroblasts; OXPHOS, oxidative phosphorylation; IL-6, interleukin-6; JAK, janus kinase; STAT, signal transducers and activators of transcription; FGF, fibroblast growth factor; MAPK, mitogen-activated protein kinase; UCP1, uncoupling protein 1; WAT, white adipose tissue; BAT, brown adipose tissue; ZAG, zinc-α2-glycoprotein; PTHrP, parathyroid-hormone-related protein. (Figure was modified from Archid R[13], Peixeto[14], Wang[18], and Bonaficio A[19]. This modification has not been published elsewhere).

Proteolysis and impaired protein synthesis in cardiac muscle resemble those in skeletal muscle.Insulin resistance, common in CAC, worsens muscle and fat loss by enhancing gluconeogenesis and disrupting PI3K/AKT/mTOR signaling; this often improves after tumor removal. In Drosophila, tumor secreted ImpL2 (an IGFBP analog) disrupts muscle metabolism.16,24 TNF-α also promotes insulin resistance by affecting insulin receptor signaling.[18]

The brain-gut axis regulates appetite and energy via neuropeptides (e.g., substance P, NPY, CGRP).[18] Hypothalamic pathway involving POMC, IL-6, leptin, ghrelin, GDF15, and others influence thermogenesis and lipolysis through neurons like AgRP and PVH.[18,21] Additional regulators include GLP-1, LCN2, and INSL3, which affect appetite via MC4R signaling.[21,22] Tumor derived factors like TNF-α, neutrophils, and sphingosine 1-phosphate can cross the blood-brain barrier, promoting anorexia. Macrophage inhibitory cytokine-1 (MIC-1) further suppresses appetite through TGF-β receptor interaction in the hypothalamus.[21]

Further involvement of cytokines and immune cells in the development of cachexia and cancer outcome

Pro-inflammatory mediators (TNF-α, IL-1, IL-6, IL-8, TGF-β, NF-κB) drive inflammation, anorexia, and muscle loss in CAC.[23,24] The special cluster of TNF superfamily, TWEAK (TNF-Related Weak Inducer of Apoptosis) induces atrophy via NF-κB.[23] Interleukin-1α (IL-1α) affects appetite, though IL-1β depletion did not ease fatigue.[21,23,25] Interleukin-2 (IL-2), IL-10, EGF, and IFN-γ activate JAK/STAT; IL-10 suppresses protein synthesis via mTOR, IL-6 promotes glycolysis, and IL-8 supports tumor growth.[14,26,27] Interferon-γ (IFN-γ), IL-20, Activin A worsen wasting, while IL-4 may be protective.[19,26,28] Tumor Growth Factor-β (TGF-β) and GDF-15 impair muscle via separate pathways.[23,26] Vitamin D promotes apoptosis via BAX/BCL-2 modulation, helping limit systemic damage in CAC.[29,30]

Tumor associated macrophages (TAMs) polarize to anti-tumor (M1) or pro-tumor (M2); high M2 or low M1/M2 ratio correlates with poor prognosis.[31,33] The CD47 and SIRPα+ macrophages are negative markers in sarcoma.[32] Interleukine-4 (IL-4) improves muscle and survival in colon cancer.[33] High neutrophils (NLR > 3.15) predict cachexia and worse outcomes in several cancers.[34,35] In mice, glycolysis inhibition raised neutrophils and accelerated cachexia.[36] The CD4+ T-cells aid macrophages and improve outcomes; CD8+ T-cells may reduce cachexia when depleted.[36-38] Naive CD4+ CD44low cells may preserve muscle.[39] The B-cells, NK cells, MDSCs, and mast cells have unclear roles, though MDSCs and CAFs promote WAT browning, IL-6, TGF-β, and PTHrP release, and M2 polarization, worsening cachexia.[23]

Anti-inflammatory effect of vitamin D in cancer-associated cachexia patients

Vitamin D is a fat-soluble vitamin. Its main source of vitamin D is direct exposure to sunlight which provides ultraviolet B (UVB) photons wavelength 285-320 nm to allow the penetration in dermis and epidermis, which then undergoes metabolism and activation in liver and kidney. The classic function of vitamin D is to promote the intestinal absorption of calcium by mediating active calcium transport across the intestinal mucosa. If the levels of 25(OH) vitamin D are low, only a small fraction of dietary calcium is absorbed, which leads to increase bone turnover and reduces bone mineral density. Therefore, for the optimal musculoskeletal and bone health, the levels of 25(OH) vitamin D should be at least 30 ng/ml.[40]

Beyond its well-known role in bone, vitamin D also serves in numerous extraskeletal function. Vitamin D, particularly $1,25(OH)_2D_3$, modulates innate immunity by stimulating defensin β2 and CAMP in monocytes and macrophages, enhancing chemotaxis, autophagy, and IL-15 secretion.[12,27] It also affects keratinocytes and various epithelial cells. Vitamin D receptor (VDR) is expressed in T cells, B cells, and macrophages. Vitamin D inhibits dendritic cell maturation and B-cell activity, promotes Th2 (via IL-4, IL-5, IL-10), and suppresses Th1 cytokines (e.g., IL-12, IFN-γ, TNF-α).[12] It also reduces Th17 through Foxp3+ Treg induction and IL-10 production. However, human studies vary due to differences in vitamin D levels and analogues used.

Vitamin D deficiency correlates with cancer and poor prognosis. Its anticancer roles include anti-inflammation, autophagy, apoptosis, antiproliferation, and differentiation.[27,41] It modulates TME via IL-10 upregulation, IL-6/IL-8 inhibition, TGF-β suppression, MKP5 promotion, NF-κB inhibition, and reduced prostaglandin and COX-

2/PGE2 pathways. The COX-2 suppression limits VEGF-driven angiogenesis.[27] Calcitriol plus progesterone reduces CXCL1/2 and proteins linked to metastasis and survival.[42] It also reduces DC activation markers (CD40, CD80, CD86), decreases IL-12, and increases IL-10, lowering T-cell activation.[27]

Despite these roles, studies linking vitamin D and cachexia remain scarce. A PubMed search (November 2022-2023) using 'cachexia' and CASCO parameters revealed inconsistent results **(Table 1).**

Table 1. Evidence of vitamin D and individual aspects of cachexia according to CASCO.

Type of Study	Author (Year)	Types of Cancer	Intervention	Related Findings
In-vitro study	Sustova H, et al (2019)[43]	Mimic cancer (Lewis lung carcinoma)	co treatment with 25 Vit D or 1,25 Vit D in C2C12 myotubes induced muscle wasting by administering combination of TNF-α , IFN-γ or IL-6	25 Vit D prevented the reduction in myotubes diameter through activation of Akt signaling. However, 1,25 (OH)2 D showed had no protective effect on myotubes as it was associated with an increased Fox03 expression.
Animal study	Camperi A et al.[44]	Rats induced hepatoma	10 nM concentration of 1,25 (OH)2 D	Administration of 1,25 (OH)2 D to mice bearing tumor does not modify the kinetic of cachexia appearance, in terms of both muscle wasting and adipose tissue depletion, whereas it further increases muscle VDR expression. There is lack of a direct link between cachexia and circulating Vit D levels
Clinical trial	Van Veldhuizen et al. (2000)[45]	Metastatic prostate cancer	Vitamin D 2000 IU/day for 12 weeks	Improvement of pain (25%) and muscle strength (37%)
	Hoffer et al. (2016)[46]	Advanced lung cancer	Consumption of 20,000 IU vitamin D daily with the largest meal of the day for 14 days followed by 10,000 IU per day for a further 7 days.	C-reactive protein (CRP) levels at baseline, 14 days (280,000 IU), and 21 days (350,000 IU) are 20.9 ± 36.8 mg/L, 17.0 ± 22.1 mg/L, and 16.7 ± 22.0 mg/L respectively, which showed a decreasing trend but not statistically significant.
	Haidari et al. (2020)[47]	Stage II or III colorectal cancer	Randomization to 4 groups of treatments for 8 weeks : Control group received a vitamin D placebo weekly + 2 omega-3 fatty acid placebo capsules daily Omega-3 fatty acid group received 2 omega-3 fatty acid capsules (each	No significant differences were observed in weight, BMI, and FFM% among four groups at baseline and after intervention. However, mean changes in these parameters were significantly different post-intervention ($p < 0.01$), with notable improvements in the three intervention groups compared to control ($p < 0.01$ for all). Within-group analysis showed that intervention groups

Type of Study	Author (Year)	Types of Cancer	Intervention	Related Findings
			capsule containing 330 mg of omega-3 fatty acids) daily + a vitamin D placebo weekly Vitamin D group received a 50,000 IU vitamin D soft gel weekly + 2 omega-3 fatty acid placebo capsules daily Cosupplementation group received a 50,000 IU vitamin D soft gel weekly + 2 omega-3 fatty acids capsules (each capsule containing 330 mg of omega-3 fatty acids) daily.	experienced significant increases in weight, BMI, and percentage of fat-free mass, along with reductions in CRP, TNF-α, and IL-6, while the control group showed declined in those parameters. Serum IL-6, TNF-α, and CRP changes differed significantly among groups ($p < 0.001$), with the largest IL-6/CRP reduction in the vitamin D group, and greatest TNF-α reduction in the co-supplementation group. Pairwise comparisons confirmed significant drops in TNF-α and IL-6 in the vitamin D group ($p < 0.001$) and in all markers in the co-supplementation group ($p < 0.001$). The omega-3 group also showed significant reduction in TNF-α ($p = 0.01$) and CRP ($p = 0.04$) compared to control. Albumin levels significantly differed across groups at baseline ($p = 0.01$) and post intervention ($p < 0.01$). Within- group comparisons revealed significant albumin decreases in the control group ($p < 0.01$) and a smaller but significant decrease in the vitamin D group ($p = 0.02$).
	Peppone et al. (2018)[48]	41 females diagnosed with breast cancer (stage 0-III) within the previous five years.	The 4 treatment groups were: group 1 receiving high-dose weekly calcitriol (ChromaDex), group 2 performing individualized home-based progressive walking and resistance exercise program (EXCAP), group 3 receiving a combination of both treatments, and group 4/control group receiving a daily multivitamin (contained 400 IU of vitamin D and 200 mg of calcium) for 12 weeks	No significant difference between the four groups in BMI, VO_2max, handgrip, chest press, leg extension.
	Chandler et al. (2020)[10]	Invasive cancer (VITAL study)	Vitamin D3 (cholecalciferol, 2000 IU/d) and	Among Non-Hispanic White participants (163 vitamin D3, 205 placebo), vitamin D3

Type of Study	Author (Year)	Types of Cancer	Intervention	Related Findings
			marine omega-3 fatty acids (1 g/d)	reduced cancer mortality (HR, 0.80; 95% CI, 0.65-0.98; P = 0.03). In patients with BMI < 25 kg/m^2, cancer mortality was lowest in the vitamin D group (HR 0.58 (0.39-0.86; p=0.007), with a significant interaction by BMI (p = 0.02). Similarly, total metastatic cancer and cancer mortality were lowest in the lower BMI group with vitamin D (HR 0.62 (0.45-0.86; p = 0.004), with BMI interaction p = 0.03).
	Brenner et al. (2021)[49]	Invasive cancer (VITAL study)	Vitamin D3 (cholecalciferol, 2000 IU/d) and marine omega-3 fatty acids (1 g/d)	Vitamin D3 supplementation was linked to a 14% significant reduction in advanced cancer risk (RR 0.86; 95% CI, 0.74-0.99). Among normal-weight participants, the risk of any and advanced cancer was lower but not statistically significant compared to obese participants (RR 0.86; 95% CI, 0.71-1.03 and RR 0.85; 95% CI, 0.59-1.2). The protective effect decreased with higher BMI, though not significantly.
Observational	Analan et al. (2020)[50]	Breast cancer	Division to lymphedema and control groups	Serum 25(OH)D3 levels did not show statistically significant differences between groups ($p > 0.05$). There was no correlation in the BCRL group between 25(OH)D3 levels and the VAS and Q-DASH scores or the diametric and volumetric differences of extremities ($r \leq 0.3$; $p > 0.05$).
	Dev et al. (2011)[51]	Advanced cancer patients	-	70% of fatigue and anorexic patients had vitamin D insufficiency (< 30 ng/mL) and 47% had 25(OH) vitamin D levels <20 ng/mL.
	Klement et al. (2021)[52]	Breast, rectal, and head and neck cancer patients.	-	Strongest correlation was an inverse correlation between vitamin D concentration and leucocyte count (Kendalls' $\tau = -0.173$, $p = 0.0065$), followed by an inverse correlation between vitamin D and CRP ($\tau = -0.172$, $p = 0.0071$)
	Castellano-Castillo et al. (2018)[53]	Colorectal cancer patients	Division into 2 groups; those who underwent colorectal surgery and control subjects who	Serum CRP levels were negatively correlated with serum 25(OH)D levels and positively correlated with both VDR

Type of Study	Author (Year)	Types of Cancer	Intervention	Related Findings
			underwent hiatal hernia surgery or cholecystectomy	and NFκB1 gene expression in adipose tissue.
	Xie et al. (2017)[54]	Prostate cancer	-	An inverse association was found between serum 25(OH)D and prostate cancer (adjusted OR: 0.785; 95% CI: 0.718–0.858). In prostate cancer patients, serum 25(OH)D was negatively correlated with CRP ($r = -0.286$, $p < 0.05$) and IL-8 levels ($r = -0.376$, $p < 0.01$), while no such correlation was seen in controls.
	Skender et al. (2017)[55]	Colorectal cancer	-	Accelerometry-based vigorous and moderate-to-vigorous physical activity were positively associated with 25(OH)D3 levels ($p = 0.04$; $p = 0.006$).

VAS, visual analog scale; Q-DASH, Quick Disabilities of the Arm, Shoulder, and Hand Questionnaire

CAC involves complex interactions between the tumor, systemic inflammation, and metabolic alteration. Vitamin D deficiency is considered a potential like factor or marker for CAC, particularly due to its association with muscle mass and strength loss. Vitamin D may also contribute to reducing pain, muscle wasting, anorexia, and pro-inflammatory responses. However, the direct therapeutic effect of vitamin D supplementation in reversing or preventing established CAC remains unclear, and current evidence is lacking to conclude its role in improving immune function for supporting therapy of cachexia.

Conclusion

Cachexia is complex and multi-factorial. It's not just a nutritional deficiency. This review hightlights critical gaps of understanding the effects of calcitriol ($1,25(OH)_2D_3$) and its role in immune function in CAC. However, limited evidence exists on immunomodulatory effects of vitamin D in cancer. It is emphasizing the need for robust clinical research across various cancer types to enhance cachexia outcome.

Conflict of interest

The authors declared no conflict of interest regarding this article.

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Author's contribution

NRMM, A, IAP: Conceptualization, data acquisition, formal analysis, interpretation of results, drafting the manuscript, and final approval of the version to be published; A,FW,FN: Supervision, critical revision of the manuscript, interpretation of data, and final approval of the version to be published; NRMM, IAP, FN: Conception and design of the study, critical revision of the manuscript for important intellectual content, and final approval of the version to be published.

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NARRATIVE REVIEW

The role of maltodextrin in iron nanoparticle formulations for food fortification and pharmaceutical applications : A scoping review

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Abstract

Background: Iron nanoparticle formulation is an innovative approach to enhance the stability and bioavailability of iron, which is crucial in addressing global iron deficiency. However, conventional iron supplementation strategies, like oral ferrous sulfate, face limitations in absorption and bioavailability. Specifically, dietary inhibitors and gastrointestinal conditions can impede iron uptake. Moreover, oral iron supplements often cause side effects such as nausea, constipation, and abdominal discomfort, affecting patient compliance. These challenges highlight the need for innovative approaches to enhance iron delivery. In this context, nanotechnology offers a promising solution to conventional iron supplementation limitations. Iron nanoparticles provide improved solubility, targeted delivery, and controlled release, thereby enhancing therapeutic effectiveness. Both in vitro and in vivo bioavailability studies have demonstrated that nanoparticle-based formulations improve iron absorption and reduce side effects. By improving iron absorption and reducing side effects, nanoparticle-based formulations represent a significant advancement in IDA management. Maltodextrin, a water-soluble and neutral starch-derived polysaccharide, serves as an effective encapsulating agent in nanoparticle formulation, enhancing stability, solubility, and controlled release, thereby overcoming limitations of traditional iron supplementation. Both in vitro and in vivo studies have demonstrated the potential of maltodextrin-based iron nanoparticles to improve bioavailability and therapeutic outcomes.

Objective: This scoping review aims to explore the role of maltodextrin in iron nanoparticle formulations based on the latest scientific evidence.

Methods : A systematic literature search was conducted across four databases: PubMed, ScienceDirect, Scopus, and SpringerLink, using structured keywords. Inclusion criteria consisted of original English language articles published between 2019 and 2024 that discussed the use of maltodextrin in iron nanoparticle systems. Exclusion criteria The selection and data synthesis process followed PRISMA-ScR guidelines.

Results : Out of 8620 articles identified, three met the inclusion criteria: Arazo-Rusindo et al. (2023), Kumari et al. (2023), and Baldelli et al. (2023). These studies demonstrated that maltodextrin acts as a carrier, stabilizer, and bioavailability enhancer, while also improving encapsulation efficiency and nanoparticle stability.

Conclusions : These findings highlight the potential of maltodextrin in developing functional food products and pharmaceutical formulations based on iron nanoparticles; however, further research is needed to optimize formulations and evaluate long-term safety.

Keywords: bioavailability, encapsulation, iron, maltodextrin, nanoparticles

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Introduction

One of the main nutritional problems commonly found among adolescent girls is anemia. According to the World Health Organization (WHO), the global prevalence of anemia among adolescents ranges from 40% to 88%. In developing countries, adolescent girls account for up to 53.7% of the total population affected by anemia.[1] This condition arises primarily from insufficient iron availability, leading to diminished hemoglobin synthesis and compromised oxygen transport.[2,3] The health ramifications of IDA (iron deficiency anemia) are profound, encompassing impaired cognitive and motor development in children, increased susceptibility to infections, and elevated risks of maternal and neonatal complications, including preterm birth and low birth weight.[4,5] Despite concerted public health efforts, IDA continues to impose significant morbidity and mortality burdens, particularly in low and middle income countries.[6]

Conventional iron supplementation strategies, such as oral ferrous sulfate administration, often encounter limitations related to suboptimal absorption and bioavailability.[7,8] Factors such as dietary inhibitors (e.g., phytates, polyphenols) and gastrointestinal conditions can impede iron uptake.[2] Moreover, oral iron supplements are frequently associated with gastrointestinal side effects, including nausea, constipation, and abdominal discomfort, which can adversely affect patient compliance.[9] These challenges underscore the necessity for innovative approaches to enhance iron delivery and efficacy.[10]

Nanotechnology has emerged as a promising avenue to address the shortcomings of traditional iron supplementation.[11,12] Iron nanoparticles offer several advantages, including improved solubility, targeted delivery, and controlled release profiles, which collectively enhance therapeutic effectiveness.[12] Both in vitro and in vivo studies have provided evidence supporting the enhanced bioavailability and reduced side effects of nanoparticle-based iron formulations.[13] By facilitating more efficient iron absorption and reducing systemic side effects, nanoparticle-based formulations represent a significant advancement in the management of IDA.[14,15]

Within the realm of nanoparticle engineering, excipients play a crucial role in determining the stability, bioavailability, and overall performance of the formulation.[16,17] Maltodextrin, a polysaccharide derived from starch, has garnered attention for its functional properties in nanoparticle systems.[18] Its inclusion can enhance the stability of iron nanoparticles, improve encapsulation efficiency, and facilitate sustained release, thereby potentially augmenting iron bioavailability.[12] Despite these promising attributes, the specific role and efficacy of maltodextrin in iron nanoparticle formulations remain underexplored in the current literature.[19] Given the existing knowledge gaps, a comprehensive scoping review is warranted to systematically examine the role of maltodextrin in iron nanoparticle formulations. This review aims to collate and analyze peer-reviewed studies published between 2019 and 2024, focusing on the impact of maltodextrin on iron bioavailability, nanoparticle stability and encapsulation efficiency in the pharmaceuticals product. Both in vitro and in vivo evidence will be considered to inform future research directions and contribute to the development of more effective iron supplementation strategies.

Maltodextrin nanoparticles serve as effective carriers with considerable encapsulation efficiency, especially when combined with lipids to improve bioactive loading and stability. Encapsulation efficiency in such systems is a product of optimal formulation strategies that leverage maltodextrin's biocompatible and biodegradable properties enhanced by synergistic components, positioning maltodextrin as a promising matrix for nanoparticle-mediated delivery applications.[20] Encapsulation techniques enhance bioavailability by protecting iron nanoparticles from degradation in the gastrointestinal tract and enabling controlled release, thereby improving absorption and therapeutic efficacy.[21] By elucidating these aspects, the review seeks to inform future research directions and contribute to the development of more effective iron supplementation strategies.

Methods

Scoping Review Framework

This scoping review was conducted following the methodological framework established by Arksey and O'Malley, which provides a systematic approach for mapping key concepts and identifying gaps within existing literature. To enhance methodological rigor, we incorporated refinements suggested by Levac, including the clarification of research questions, application of an iterative team-based approach, and integration of stakeholder consultation throughout the review process. The reporting of this study adheres to the PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews) guidelines, ensuring transparency and completeness in the description of methods and presentation of findings.[22]

Research Questions

The review was guided by three central research questions designed to comprehensively explore the role of maltodextrin in iron nanoparticle formulations. The first question was to investigates the functional role of maltodextrin within these formulations. The second was to examines how nanoparticles formulated with maltodextrin are characterized in terms of their physicochemical properties. The third was to addresses the formulation methods employed and the excipient combinations used alongside maltodextrin in developing iron nanoparticles.

PCC Eligibility Framework

Inclusion criteria were developed based on the Population-Concept-Context (PCC) framework, which is widely recommended for scoping reviews.[23] The population of interest includes studies focusing on iron nanoparticle formulations. The concept involves the use of maltodextrin in these formulations. The context encompasses experimental or formulation-based studies investigating nano iron systems. This framework allowed for targeted yet comprehensive inclusion of relevant studies that provide insight into the application of maltodextrin in iron nanoparticle research.

Eligibility Criteria

Studies were included if they met specific criteria: articles published between 2019 and 2024; peer-reviewed and written in English; explicitly using maltodextrin in iron nanoparticle formulations; experimental in nature, including in vitro, in vivo, stability, or characterization studies; full-text available; and reporting at least one formulation characteristic such as particle size or encapsulation efficiency. Studies were excluded if they were review articles, systematic reviews, or meta-analyses; did not explicitly use maltodextrin; focused on nanoparticles other than iron; were published in languages other than English or lacked full-text availability; or were published prior to 2019. These criteria ensured the inclusion of relevant, high-quality empirical studies.

Literature Search Strategy

A comprehensive literature search was conducted across four major electronic databases: PubMed, Scopus, ScienceDirect, and SpringerLink. The search strategy combined specific keywords with Boolean operators to identify relevant studies. For example, the PubMed search string used was: ("maltodextrin") AND ("iron nanoparticles" OR "nano iron" OR "iron nanoformulation" OR "iron encapsulation"). Search terms and strategies were adapted appropriately for each database to accommodate differences in indexing and search functionalities, thereby maximizing the retrieval of pertinent literature.

Study Selection Process

All identified articles were imported into Mendeley for systematic screening, and duplicate records were removed prior to the selection process. The screening was conducted in two stages: first, titles and abstracts were reviewed to exclude articles that clearly did not meet the predefined inclusion criteria; second, the full texts of the remaining articles were assessed for eligibility. Both stages of screening were conducted independently by two reviewers to ensure objectivity and reduce the risk of individual bias. Any discrepancies or disagreements between reviewers were resolved through discussion, and when consensus could not be reached, a third reviewer was consulted for arbitration. To minimize the risk of selection bias and enhance screening consistency, all reviewers received prior training and calibration using a small sample of studies to harmonize their understanding of the eligibility criteria. A standardized screening form was employed to guide decision making and to systematically document inclusion or exclusion reasons. The use of Mendeley facilitated accurate organization, reference management, and removal of duplicates, while thorough documentation of reviewer decisions ensured transparency, reproducibility, and auditability throughout the review process.

Data Extraction

Data from eligible studies were charted using a structured extraction form capturing key information including article title, authorship and year of publication, country of origin, research objectives, nanoparticle type, the role of maltodextrin, formulation methods applied (e.g., spray drying, freeze drying), characterization data such as particle size, encapsulation efficiency, and stability, as well as main findings. This systematic approach facilitated a comprehensive mapping of existing research on maltodextrin's application in iron nanoparticle formulations.

Data Analysis

Extracted data were analyzed through descriptive narrative synthesis [24]. Findings were organized in tables and figures that highlighted key aspects such as the functional roles of maltodextrin (e.g., stabilizer, cryoprotectant, carrier), types of formulation methods employed, and co-formulants used alongside maltodextrin. This analytical strategy enabled the identification of trends, patterns, and research gaps, providing an integrative overview of the current landscape in iron nanoparticle formulation involving maltodextrin. The synthesis also allowed for the evaluation of how maltodextrin contributes to formulation efficiency, stability, and bioavailability outcomes, thereby offering valuable insights for future research directions and potential improvements in nanoparticle-based iron delivery systems.

Data Mapping

Data mapping was systematically carried out to synthesize and report the characteristics and findings of the eligible studies based on the predefined inclusion criteria. The extracted data were organized and presented in Table 1, which includes detailed information on the article title, authors (year), country of origin, research objective, formulation method, the specific function of maltodextrin within the nanoparticle system, nanoparticle characterization, and the key findings of each study. This structured summary aims to provide a comprehensive overview of the current evidence regarding the role of maltodextrin in iron nanoparticle formulation.

Results

Article Characteristics

Figure 1 presents the systematic selection process of studies included in this scoping review. An initial total of 8,260 records were retrieved from four electronic databases: ScienceDirect (n = 84), Scopus (n = 1), PubMed (n = 8,153), and SpringerLink (n = 22). Following the removal of seven duplicate entries, 8,253 records were subjected to title and abstract screening. During this phase, 8,241 records were excluded for not meeting the predefined inclusion criteria. Specifically, 4,433 articles were published outside the designated timeframe of 2019–2024, 2,330 articles lacked accessible full-text, and 1,478 employed study designs that did not align with the eligibility criteria for experimental research. Subsequently, 12 full-text articles were assessed for eligibility. Of these, nine articles were excluded due to the absence of maltodextrin in the nanoparticle formulation or a focus on non-iron nanoparticles. Ultimately, three studies met all inclusion criteria and were included in the final synthesis.

Study Characteristics and Objectives

Table 1 summarizes the key characteristics of the three studies included in this scoping review, all of which were published in 2023 by Arazo-Rusindo et al.[25], Kumari et al.[26], and Baldelli et al.[27]. These studies reflect a growing global interest in the application of maltodextrin in iron nanoparticle formulations. The studies employed diverse methodologies, ranging from in vitro models, combined in vitro/in vivo approaches, to formulation and characterization studies. Their shared objective was to improve the bioavailability, stability, and functional properties of iron in food or pharmaceutical products, with each study focusing respectively on legume soup reformulation, millet-based pasta enrichment, and anemia recovery in animal models. The legume soup reformulation targets older adults by enhancing micronutrient bioaccessibility, particularly iron, through stable iron nanoparticles. The millet-based pasta enrichment focuses on incorporating encapsulated ferrous gluconate to improve solubility and stability, producing a nutrient-fortified functional food. Both demonstrate the use of maltodextrin as an effective encapsulating agent to improve iron delivery and nutritional value.[25.28]

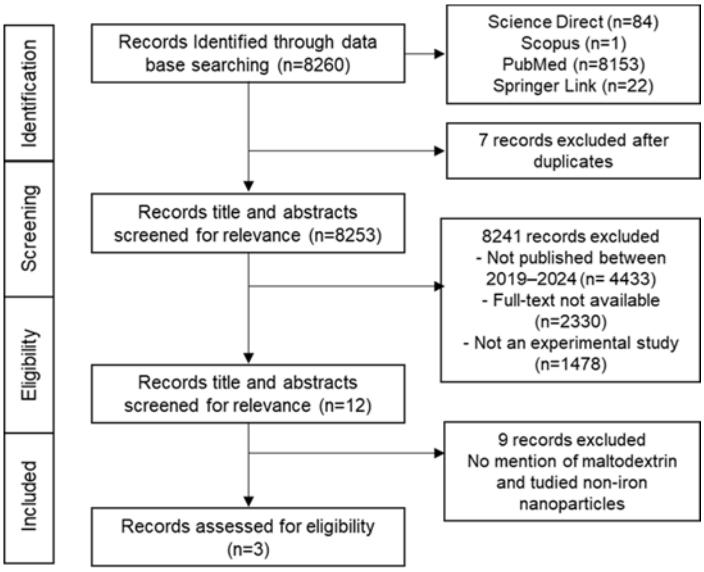

Figure 1. PRISMA-ScR Flow Diagram

Maltodextrin consistently functioned as an effective encapsulating agent across all studies. It acted as a water-soluble carrier, improving iron solubility, controlled release, and particle stability.[29] Technologically, maltodextrin enhanced bioaccessibility, reduced moisture content, promoted uniform particle morphology, and improved flowability when combined with excipients like hydroxypropyl methylcellulose (HPMC). These improvements contributed significantly to the stability and efficacy of iron nanoparticle formulations.[30,31]

Spray drying was the common technique for nanoparticle preparation, with maltodextrin paired with various co-excipients tailored to each study's application: inulin and caseinate, HPMC, and iron gluconate with vitamin B12.[25-27] The formulations yielded nanoparticles with favorable size, yield, and iron retention metrics. Notably, in vivo tests showed accelerated anemia recovery using maltodextrin-based dual encapsulation, highlighting its therapeutic potential alongside food fortification applications demonstrated in the other studies.[27]

Table 1. Summary of exploration of the role of maltodextrin in iron nanoparticle formulation

No	Article Title	Authors (Year)	Country	Research Objective	Kind of Products	Formulation Method	Nanoparticle Formulation	Function of Maltodextrin	Nanoparticle Characterization	In-vitro/In-vivo Bioavailability	Key Findings
1	Redesign of an Instant Legume Soup for Older Adults with Increased Micronutrients Bioaccessibility and Adequate Sensory Attributes by Using Encapsulation	Arazo-Rusindo et al. (2023)	Chile	To redesign instant legume soup for older adults with enhanced micronutrient bioaccessibility and sensory attributes using encapsulation technology	Food product	Spray drying of dispersion (iron) and emulsion (calcium and vitamin D3) using maltodextrin-inulin and maltodextrin-caseinate	- Type of iron: ferrous sulfate monohydrate - Formulation: The nanoparticle formulation involved creating iron dispersions and calcium/vitamin D3 emulsions using materials like ferrous sulfate, calcium lactate, vitamin D3, sunflower oil, and Tween-80, which were then encapsulated via spray drying with encapsulants such as maltodextrin (MD), inulin (IN), and calcium caseinate (CA) in various ratios	Used as a water-soluble encapsulating agent to form a protective matrix, enhancing stability and controlled release of micronutrients	Particle size: 200–300 nm; PDI <0.3; Zeta potential: -20 to -30 mV; Yield: 75–85%; Iron retention efficiency: 30–40%;	he proposed encapsulation process significantly increased the in-vitro micronutrient bioaccessibility, with an increase of 41 times for iron, 4.9 times for calcium, and 2.3 times for vitamin D3 at the particle level, as well as an increase of 20%, 29%, and 37% for these respective micronutrients in the developed lentil soup compared to the control product	Maltodextrin formed stable particles and enhanced iron bioaccessibility; potential for food fortification applications

2	Development and Characterization of Apple Pomace and Finger Millet-Based Pasta Enriched with Encapsulated Micronutrient	Kumari et al. (2023)	India	To encapsulate ascorbic acid and ferrous gluconate for enrichment into millet and apple-based pasta	Food product	Spray drying with 2.2–2.8% maltodextrin, 0.2–0.8% HPMC, and 1.5% iron gluconate core; Inlet temp: 120°C, Outlet temp: 80°C, Feed rate: 5 mL/min	- Type of iron: Iron-(II) gluconate (IG) - Formulation: The formulations for microencapsulated iron powder (IGP) consist of a fixed amount of 1.5% ferrous gluconate as the core material, with varying percentages of hydroxypropyl methylcellulose (HPMC) from 0.2% to 0.8% and maltodextrin (MD) from 2.8% to 2.2% as the wall materials	Used as wall material for encapsulation to maintain nutrient stability	Yield: 18.18–26.19%; Iron content: 40–51.5 mg/g; Solubility: >97%; Moisture content: 4.64–5.38%; Hygroscopicity: 16.47–23.57%; Color: bright yellow-green; Morphology: smooth to wrinkled; Uniform iron distribution	does not present in-vitro or in-vivo bioavailability data for its developed compound, it mentions that iron bioavailability can be enhanced by adding ascorbic acid and using HPMC as a wall material, and it references another study that has investigated the in-vitro bioavailability of microencapsulated iron	Maltodextrin improved solubility and reduced moisture content; HPMC reduced flowability and increased hygroscopicity; Encapsulation produced particles with uniform iron distribution and stable nutrients for functional pasta enrichment
3	Dual and Triple Encapsulated Iron Gluconate Speed Up Anemia Recovery in an Animal	Baldelli et al. (2023)	Canada	To investigate the effectiveness of dual and triple encapsulated iron gluconate with vitamin B12 in accelerating anemia recovery in an animal model	Phamaceutical product	Spray drying using HPMC as wall material and maltodextrin as bulk material	- Type of iron: Iron(II) gluconate hydrate - Formulation: consists of bioactive compounds like iron gluconate, vitamin B12, and others, encapsulated using hydroxypropyl methylcellulose (HPMC) as the wall material and maltodextrin as the bulk material, with HPMC and maltodextrin each at	Used as bulk material in combination with HPMC to improve stability and bioavailability	Average particle size: 2–5 µm (SEM); Uniform microspheric morphology; Homogeneous chemical distribution; No chemical structure changes (FTIR)	In-vitro studies showed a 25% increase in Caco-2 cell uptake with dual-encapsulated iron and vitamin B12, while in-vivo studies in anemic rats demonstrated hemoglobin recovery in just five days, significantly	Dual encapsulation (iron gluconate + vitamin B12) increased HepG2 cell viability by 17% and iron uptake by Caco-2 cells by 25%; In vivo, the fastest anemia recovery occurred in 5 days in rats fed with dual encapsulated

		9 wt% and the bioactive components totaling 7 wt%		faster than with encapsulated iron alone (15 days) or pure iron (21 days).	particles, compared to 15 and 21 days in single encapsulated and pure iron groups, respectively

Discussion

The three included studies all used spray-drying of maltodextrin-based formulations but with different co-carriers and conditions. Arazo-Rusindo et al. (2023) spray-dried aqueous and oil emulsions containing iron gluconate with maltodextrin–inulin or maltodextrin–caseinate matrices, while Kumari et al. (2023) used a maltodextrin/HPMC blend (2.2–2.8% MD with 0.2–0.8% HPMC) at an inlet/outlet of 120/80 °C (5 mL/min feed). Baldelli et al. (2023) also spray-dried iron–HPMC formulations with maltodextrin as a bulk carrier. In each case maltodextrin served as a film-forming, water-soluble matrix that stabilizes the mineral core.[32,33] Differences in wall composition and solids loading led to varied outcome, Arazo-Rusindo[25] reported high powder yields (75–85%) but modest iron retention (30–40%), whereas Kumari's[26] formulation gave only ~18–26% yield but retained high iron content (40–51.5 mg/g) in the powder. These contrasts suggest a trade-off between encapsulation environment (liquid soup vs. dry pasta matrix) and product recovery, which has also been noted by others (e.g. high MD levels can boost yield but sometimes at the expense of core retention).[33,34]

Spray drying is an effective, practical, and preferred microencapsulation method for micronutrients in this study, enabling enhanced protection, controlled release, and improved bioaccessibility of iron, calcium, and vitamin D3.[25,28,35] Spray-drying process parameters strongly influenced particle properties.[36,37] For example, increasing the inlet temperature tends to produce larger, drier particles and higher yields, at the risk of thermal degradation.[32,38] Consistent with this, Kumari's[26] relatively mild 120 °C inlet produced a powder with very low moisture (~4.6–5.4%) and excellent solubility (>97%), whereas Arazo-Rusindo[25] (using typical 140–180 °C conditions) achieved similarly low moisture (yielding stable matrices) but could sacrifice some micronutrient. Likewise, higher feed rates enlarge particle size and moisture.[32] Baldelli's[27] dual-encapsulated particles were reported as 2–5 µm spheres (SEM), much larger than Arazo-Rusindo's[25] 200–300 nm nanoparticles, likely reflecting differences in feed solids and atomization. In general, spray-drying at 150–200 °C (as reviewed by Piñón-Balderrama et al.(2025) minimizes water while preserving actives.[32,39] Solids concentration also matters: more concentrated feeds increase viscosity and yield larger, often irregular particles.[32,40] These formulation insights help explain the observed morphologies: Kumari noted smooth-to-wrinkled MD/HPMC particles, whereas Arazo-Rusindo's[25] nanoemulsions (PDI<0.3) formed uniform ~200–300 nm sphere.[32,42] Baldelli's[27] particles, though microscale, were still spherical and uniform by SEM, indicating well-controlled co-spray conditions.[39,42]

The critical nanoparticle characteristics align in part with known benchmarks. Arazo-Rusindo's[25] particles (200–300 nm, PDI <0.3) were well below the 500 nm threshold often cited for enhanced absorption, and their zeta potential (–20 to –30 mV) falls near the commonly cited ±30 mV stability threshold.[41,43-45] In contrast, Churio and Valenzuela

(2018) showed that larger (~0.9–1.0 µm) maltodextrin microparticles can still achieve 83–88% iron retention.[34] Encapsulation efficiency (iron retention) should ideally exceed 50% for effective fortification [(19,46,47)]. Indeed, most literature values are far higher for example, Kaul et al. (2022) reported ~90.7% iron retention in MD–starch spray-dried capsules, and Wang et al. (2017) achieved ~98.6% encapsulation efficiency with MD/CMC/caseinate. Recommended targets thus include size <500 nm for bioaccessibility, zeta potential |≥30 mV| for colloidal stability, and high encapsulation efficiency (often >80%).[41,44] In this review, moisture <6% was generally met (Kumari's[26] 4.6–5.4%), consistent with food-powder norms, while Kumari's[26] >97% solubility and low hygroscopicity (≤6% moisture and moderate hygroscopicity ~16–24%) indicate good reconstitution. Notably, Kumari et al. (2023) and Baldelli et al. (2023) did not report zeta-potential, but Arazo-Rusindo's[25] values (–20 to –30 mV) are on the edge of recommended stability.[44] Overall, the reported values largely fall within desirable ranges, though Arazo-Rusindo's[25] iron retention (30–40%) was lower than expected and suggests incomplete encapsulation or losses during spray drying.

Comparing across studies highlights some inconsistencies and trade-offs. Arazo-Rusindo's[25] high yield but low iron retention contrasts with Kaul (2022) and Churio (2018) who achieved ~80–90% retention.[34,48] This likely reflects Arazo-Rusindo's[25] complex emulsion matrix (soup) versus simpler dry systems; losses of iron in the aqueous phase or during emulsification may account for the modest 30–40% retention. In turn, Kumari's[26] low yield (~20%) but high nutrient load (40–51 mg/g) suggests that the MD/HPMC matrix was efficient at loading but that much feed was not recovered (maybe due to stickiness or cyclone losses). The addition of HPMC (as in Kumari[26] and Baldelli[27]) increased powder hygroscopicity, in line with previous observations that hydrocolloids raise moisture uptake. Zeta potentials, where reported, were moderate: Arazo-Rusindo's[25] –20 to –30 mV is lower than some ideal values but matches other maltodextrin systems (Abbasi *et al*.[41] (2022) found ~–30 mV needed for stability). Particle size outcomes were most divergent: Arazo-Rusindo's[25] 200–300 nm vs. Baldelli's[27] 2–5 µm, underscoring how wall material and method (nanospray vs. conventional) dominate size. These differences reflect known effects adding more polymer (HPMC, alginate, etc.) often yields larger particles, and denser solids give more microspheres.[50,51] No major contradictions appear beyond these expected trade-offs, and all studies noted uniform, spherical particles (smooth surface typical for MD matrice).[33]

These findings have practical implications. Formulators should target the submicron range and stable zeta potenstial to maximize bioavailability.[41,44] Given that maltodextrin enhances solubility and protection of actives, increasing MD proportion (up to its glass transition limit) will improve particle stability and yield, but mixing with other polymers (HPMC, CMC, proteins) can tailor release or protect against oxidation.[33] For instance, Piñón-Balderrama et al (2020). showed that MD-alginate blends produce more stable iron microcapsules. In practice, inlet temperatures of ~150–180 °C (yielding <6% moisture) are recommended, and feeding rates should be optimized to avoid excessive particle growth.[32] Future research should systematically explore MD dextrose equivalent, MD/auxiliary ratios, and nozzle technologies (including nano-spray drying) to control size and EE. Importantly, in vivo bioavailability trials beyond the rat model of Baldelli[27] are needed to link these particle metrics to actual iron absorption. Standardizing measurements (e.g. using unified definitions of yield and retention, or simulating gastrointestinal release as Churio[34] did) will also help reconcile results.

Ultimately, these studies confirm maltodextrin as a versatile matrix for iron micro/nanoparticles, though optimizing parameters is crucial for stability and bioactive retention.[25-27] Iron nanoparticles show superior bioavailability due to their size and surface area, enhancing interaction with intestinal mucos .[52] In rats, absorption occurs via enterocyte endocytosis, bypassing regulatory mechanisms that limit ionic iron uptake, resulting in more efficient systemic absorption. Integrating these insights with microencapsulation advances highlights the potential for iron nanoparticle formulations that maximize bioavailability while reducing side effects.[53,54] Refining maltodextrin-based encapsulation processes with understanding of absorption mechanisms provides a foundation for advancing iron supplementation strategies.[34,48]

Conclusions

In conclusion, maltodextrin plays a crucial role in iron nanoparticle formulation in the some products such as food fortification and pharmaceutical applications by acting as a water-soluble encapsulating agent that enhances particle stability, solubility, and controlled release. Its include for some iron forms such as ferrous sulfate, ferrous fumarate, and ferric pyrophosphate. Its application through spray-drying techniques, often in combination with co-polymers like HPMC or caseinate, has been shown to produce nanoparticles with favorable characteristics, including particle sizes below 500 nm, zeta potentials within the ±20–40 mV range, and encapsulation efficiencies exceeding 50%. However, differences in formulation methods such as inlet temperature, feed rate, and wall material composition contribute to variability in outcomes like yield, moisture content, and iron retention. These parameters must be carefully optimized to ensure stability, bioavailability, and controlled release of the encapsulated iron, making spray-drying a versatile and scalable approach for iron fortification in food and pharmaceutical applications. While Maltodextrin shows promise for micronutrient delivery, limitations include insufficient in vivo studies and non-standardized metrics across food matrices. Current evidence lacks data on long-term safety. For anemia treatment, maltodextrin-encapsulated iron supplementation can enhance bioavailability and reduce side effects by improving stability and controlled release. Programs should combine this system with dietary diversification to target iron absorption. Implementation requires evidence-based dosing based on age, physiological status, and anemia severity. Clinical trials are needed to validate this approach. evidence-based interventions.

Conflict of interest

The authors declare no conflict of interests regarding the publication of this article.

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Author's contribution

R.A.: Conceptualization, literature search, study screening and selection, data extraction, formal analysis, interpretation of findings, drafting of the manuscript, and final approval of the version to be published;
D.I.: Conceptualization, methodological supervision, interpretation of findings, critical revision of the manuscript for important intellectual content, correspondence, and final approval of the version to be published;
Y.H.S.: Supervision, interpretation of findings, critical revision of the manuscript, and final approval of the version to be published.

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NARRATIVE REVIEW

Nutrition strategies for obesity management

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Abstract

Introduction: Obesity is a chronic disease that requires a nutritional strategy for effective weight management. Behavioral modifications related to nutrient intake, food selection, and dietary patterns are essential for maintaining long-term results. Many diet interventions have been developed to help facilitate weight loss among obese patients.
Objective: This review aims to provide an in-depth exploration of nutrition-based strategies that can effectively address the obesity epidemic and their applicability in the Indonesian context.
Methods: This narrative review was conducted by searching electronic databases, including Google Scholar, PubMed, and ScienceDirect, for relevant papers published between 2004 and 2025. The search strategy included the terms 'obesity,' 'diet,' 'strategies,' and 'weight loss.'
Results: Several diet approaches are utilized in weight-control programs, including calorie restriction, intermittent fasting, low-carbohydrate and low-fat diets, high-protein diets, the Mediterranean diet, and a vegetarian diet. These diets differ in the quantity and type of food consumed, timing of food intake, and other influencing factors.
Conclusion: The optimal dietary approach for weight loss depends on individual preferences, metabolic factors, and health considerations. Therefore, a locally food-appropriate and professionally guided dietary approach is essential to achieve sustainable and effective weight-management outcomes.

Keywords: diet, obesity, weight loss

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Obesity has emerged as a significant global public health challenge, with its prevalence continuing to rise across populations and regions. According to the World Health Organization (WHO), in 2022, 43% of adults were overweight, and 16% were obese.[1] This trend is similarly evident at the national level. In Indonesia, data from the 2023 Indonesian Health Survey indicate that the prevalence of obesity—defined as a body mass index (BMI) of 27 kg/m² or higher—reached 23.4%, up from 21.8% in 2018.[2,3] The prevalence of obesity among females (31.2%) is higher than that among males (15.7%).[2] These findings highlight the escalating burden of obesity at both global and national levels, reinforcing the urgent need for context-specific, nutrition-based interventions.

Obesity is a significant risk factor for various chronic diseases, including type 2 diabetes, cardiovascular disease, hypertension, and malignancies. Based on several studies, obesity can increase the mortality risk by up to 1.8-fold in individuals with heart failure, and by as much as 108% for all-cause mortality.[4,5] Moreover, central obesity is closely linked to chronic low-grade inflammation, which plays a critical role in the pathogenesis of many obesity-related diseases.[6]

Nutrition and obesity are closely related.[7,8] Unbalanced nutrient intake can lead to obesity, while obesity can affect nutrient intake and increase the risk of developing chronic diseases.[9] Although numerous nutritional strategies have been created to reduce obesity rates, each strategy presents distinct strengths and limitations.[10] Therefore, this literature review aims to provide an in-depth exploration of nutrition-based strategies that can effectively address the obesity epidemic and their applicability in the Indonesian context.

Methods

This narrative review emphasizes the interaction between satiety and hormonal responses, dietary risk factors in obesity, and nutrition-based strategies to address obesity. This review was conducted by searching for relevant papers published in electronic databases, including Google Scholar, PubMed, and ScienceDirect, between 2004 and 2025. The search strategy included the terms 'obesity,' 'diet,' 'strategies,' and 'weight loss.' Additional studies published in English or Indonesian were identified through manual screening of reference lists from relevant review articles.

Discussion

Individual variability and physiological interactions between satiety and hormones in obesity

Sex-based biological differences and gender-related factors significantly shape obesity prevalence, adipose tissue distribution, metabolic profiles, and treatment responses. In women, estrogen facilitates greater subcutaneous fat storage.[11] It enhances brown adipose tissue (BAT) thermogenic activity, whereas men are more susceptible to visceral fat accumulation and exhibit diminished BAT thermogenic capacity.[11,12] Although women generally demonstrate higher overall obesity prevalence and increased susceptibility to obesity-related cancers and mental health conditions, men tend to accumulate more visceral fat, which is associated with heightened risk of cardiovascular disease, type 2 diabetes, and other cardiometabolic disorders.[11]

Individuals with obesity may have greater gastric capacity, potentially allowing higher energy intake before gastric distension–mediated satiation.[13] Ghrelin stimulates appetite and is suppressed after eating. It is generally lower in individuals with obesity than in lean individuals, possibly reflecting maximum suppression due to excess adiposity.[13,14] Additionally, gut-derived satiety hormones seem to be dysregulated in obesity. Postprandial secretion of peptide YY (PYY), which promotes satiety, is reduced in obese individuals and is linked to a diminished satiety response.[14] Similarly, secretion of glucagon-like peptide-1 (GLP-1) is decreased in obesity.[15] Weight loss partially restores GLP-1 secretion, and that impaired GLP-1 response may be a result of excess adiposity rather than an inherent defect.[14]

Dietary risk factor in obesity

The leading cause of obesity is an imbalance between energy intake and expenditure, whereby increased consumption combined with reduced activity can result in significant weight gain.[16] Modifiable diet-related risk factors—including nutrient intake, food choices, dietary patterns, and eating behaviors—play an essential role in the development of obesity.[17] Limited access to healthy food options contributes to poor diet quality and greater consumption of junk food.[18] The Western dietary pattern, typical in modern lifestyles, is characterized by high consumption of ultra-processed foods, fast foods, and high-fat snacks, along with low intake of fruits, vegetables, whole grains, fiber, and unsaturated fats, and high intake of calories, added sugars, sodium, and trans fats—factors that are strongly associated with non-communicable diseases.[18,19]

Dietary patterns commonly practiced in Indonesia

Traditional dietary patterns in Indonesia include a high consumption of fish, vegetables, and fruits such as bananas, leafy greens, papaya, carrots, and sweet potatoes.[20] Rice often functions as the primary carbohydrate source.[21] Plant-based proteins like tofu and tempeh are commonly used to replace dairy products.[22] In the broader Asian dietary context, especially in Indonesia, red meat consumption is often limited, with a preference for lean cuts and alternative protein sources such as tofu. A variety of locally sourced fruits and vegetables are typically included, as these foods generally have a low glycemic index and provide significant amounts of dietary fiber, vitamins, minerals, and antioxidants.[21]

Obesity-related dietary guidelines commonly used in other countries may not fully apply to the Indonesian context due to unique cultural and dietary patterns. A study in Indonesia reveals that consumption data indicate ongoing deficiencies in intake of cereals and tubers (285 g/day versus 300 g/day), vegetables (111 g/day versus 250 g/day), and fruits (46 g/day versus 100–150 g/day), emphasizing a persistent gap in meeting recommended dietary targets.[23] While average protein intake from both animal and plant sources (87.46 g/day) falls within the recommended range (70–140 g/day), the excessive consumption of added sugar (40.58 g/day versus ≤40 g/day) and salt (10 g/day versus 6 g/day) remains a significant concern.[23] These dietary imbalances reflect poor diet quality and could elevate the risk of non-communicable diseases. Overall, these findings support the need for culturally appropriate, context-specific dietary strategies to improve nutritional quality and health outcomes in Indonesia.

Result

Nutrition strategy

Weight loss, far beyond aesthetics, is a cornerstone of disease prevention and management.[24] According to the American Heart Association's 2013 guidelines on obesity management, lifestyle intervention constitutes the initial step and involves both nutrition and physical activity. This intervention includes recommendations for aerobic exercise and resistance training performed at moderate to high intensity, typically involving more than 14 sessions over six months. Pharmacological therapy, including fat blockers, GLP-1 receptor agonists, and combinations of sympathomimetic agents, may be indicated when lifestyle modification is insufficient to prevent weight gain or in patients with a BMI ≥27 kg/m².[25,26]

Several dietary methods are utilized in weight-control programs, each aiming for long-term effectiveness while minimizing side effects.[27,28] Dietary approaches include traditional calorie restriction, low-carbohydrate and low-fat diets, intermittent fasting, plant-based diets, the Mediterranean diet, and personalized or mindful eating.[28] These diets differ in the quantity and type of foods consumed, the timing of food intake, and various other factors.

Low-calorie and very low-calorie diets represent structured dietary interventions aimed at reducing total daily calorie intake.[29] Low-calorie diets (1,000–1,500 kcal/day) are recommended by many obesity societies and clinical guidelines, compared with very low-calorie diets (800 kcal/day).[28,30] Food replacements offer a practical way to reduce daily caloric intake, including fixed-energy, portion-controlled, or prepackaged foods.[31] Food replacement is effective for weight loss and improving various clinical parameters, but it is not suitable for long-term use due to the severe energy restriction.[32]

Nutrition strategies categorized by food composition include low-fat, low-carbohydrate, ketogenic, high-protein, and Mediterranean dietary patterns.[28] A low-fat diet involves reducing fat intake 10%-30% of total calories and limiting saturated fatty acids consumption to below 7-10%.[33] Reducing total fat intake impacts overall calorie consumption, given that fat provides 9 kcal/g, more than double the energy density of carbohydrates or protein (4 kcal/g each).[34] Low-carbohydrate and ketogenic dietary approaches restrict carbohydrate intake to varying degrees; low-carbohydrate diets typically provide 150 g/day, while ketogenic diets restrict non-fibre carbohydrates to approximately 20–50 g/day.[35] A high-protein diet—increasing protein consumption to about 30% of total calories per day—improves satiety, decreases fat mass, and serves as a valuable tool for weight loss.[28] The Mediterranean diet is a predominantly plant-based dietary pattern characterized by high consumption of vegetables, dairy products, fish, and poultry, while limiting red meat intake.[36]

Meal timing diet prioritizes the temporal distribution of food intake rather than specific food selection, macronutrient composition, or caloric targets.[28,37] Intermittent fasting is a dietary pattern characterized by alternating periods of fasting and eating.[38] The benefits include reduced calorie intake, subsequent metabolic switching to reverse insulin resistance, enhanced immune system, and improved physical and cognitive performance.[39]

A low-glycemic index diet affects postprandial glycemia, resulting in a more stable blood glucose level.[40] The effect of a low-glycemic index is to promote rapid weight loss and lower fasting glucose and insulin concentrations.[41] The Nordic diet, adapted from the Nordic countries, emphasizes whole grains, fish, root vegetables, and berries.[42]

Vegetarian diets tend to contain more carbohydrates and fiber, while excluding meat and other animal-derived products.[43] Table 1 summarizes all the diets listed above. We also provide the perks and pitfalls of each diet.

Table 1. Overview of dietary approaches and their benefits and limitations

Diet	Definition	Composition or characteristics	Feasibility and effectiveness	Perks	Pitfalls
Low-calorie diet	Consumption of 1000 – 1500 kcal per day or deficits of 500-750 kcal per day[28]	Fundamental principle of energy restriction, usually restricts carbohydrate or fat, and enhances the consumption of fiber[28]	Around 2 kg per month weight loss[44]	Modest weight loss without severe adverse effects[44]	Weight loss rate is slowing down due to the hormonal mechanism[45]
Very low-calorie diet	Consumption of less than 800 kcal a day[28]	Extreme caloric restriction[46]	Limited to patients with a BMI greater than 25 with complications of overweight[47]	Rapid weight loss[48]	Complications such as loss of lean body mass, increased serum uric acid, ketosis, and cholelithiasis.[49] Need intensive monitoring.
Food replacement	Substitution of one or more daily meals with specially formulated and portion-controlled products[50]	Shakes, bars, soups to create a caloric deficit[32]	Replacing regular meals with controlled calorie alternatives, an individual can create a consistent and predictable diet[32]	Simple and convenient, structured meal plan, eliminates the need for calorie counting[31]	Can cause boredom if done in the long term[31]
Low-fat diet	Reducing total fat intake for weight loss	Divided into a wide range of fats: very low (contains less than 10% calories from fat) to moderate (less than or equal to 30% calories from fat)[33]	Influenced by the recognition that not all dietary fats are detrimental. Certain fats, such as those from sources like nuts and fish, can be consumed in moderation[51]	Significant weight loss in normal and overweight patients compared to diet[34]	Can not be used in the long term[34]
Low-carbohydrate diet	Carbohydrate consumption lower than 45-65% of total daily energy in adults[28]	Limiting or eliminating high-carbohydrate meals like bread, pasta, and sugary snacks while increasing intake of foods rich in protein and healthy fats[35,52]	Rapid weight loss. Lifelong maintenance can continue according to patients' preferences. Therefore, it is more flexible[53]	Help to control appetite, which contributes to weight loss, can be used to manage type 2 diabetes, other than losing weight[54,55]	Elevating the risk of mortality due to increased Low-Density Lipoprotein (LDL) cholesterol level if the low-carbohydrate diet is combined with high-fat intake[56]

Diet	Definition	Composition or characteristics	Feasibility and effectiveness	Perks	Pitfalls
Ketogenic diet	Restricting carbohydrates to induce nutritional ketosis. Carbohydrate consumption was limited to around 20-50 grams[53]	Significant reduction of carbohydrate consumption. Consumption of a wide range of low-carbohydrate, high-fat foods, including meats, fish, eggs, dairy products, non-starchy vegetables, and nuts[57]	Some individuals find success and sustainability with this dietary pattern because it reduces feelings of hunger and enhances satiety associated with high-fat intake. Effectivity varies among individuals and depends on various factors, including metabolic status, activity level, and health goals[58]	Weight loss and improvement of metabolic markers such as blood glucose and insulin sensitivity[58,59]	Others may have problems with strict carbohydrate restrictions and miss the variety offered by a balanced diet[58]
High-protein diet	Protein consumption over 0.8 g/kg/day, or increased protein consumption to 30% of total calories per day[28]	High-protein foods include lean meat, fish, poultry, dairy products, legumes, and plant-based protein sources such as tempeh and tofu[60]	The satiating nature of protein can reduce feelings of hunger and promote a sense of fullness. It contributes to its feasibility[61]	Effective for weight loss and muscle development[62]	Strain on kidneys due to higher nitrogen load, dehydration if water intake is inadequate, excessive calorie intake, which can hinder weight loss effort[61]
Mediterranean Diet	Limiting red meat intake while increasing consumption of vegetables, dairy products, and fish, as well as poultry[28]	Fruits and vegetables such as tomatoes, cucumbers, olives, regular consumption of nuts, whole grains such as couscous and quinoa, olive oil, fish like salmon and mackerel (fatty fish), moderate consumption of dairy products and wine, limited consumption of meat[36,63]	To ensure long-term sustainability, it is crucial to encourage the cultivation and consumption of Mediterranean-inspired foods that can be locally grown[64,65]	Superior to low-fat diet in case of long-term weight management, can reduce mortality in cause-specific mortality cases, reducing cardiovascular disease risk[66,67]	No evidence on long-term weight management effect[68]

Diet	Definition	Composition or characteristics	Feasibility and effectiveness	Perks	Pitfalls
Intermittent fasting	a dietary regimen that alternates between periods of fasting and eating[28]	During fasting periods, consumption of water, herbal tea, and black coffee is usually allowed, which can help curb hunger and enhance feasibility[69]	The flexibility in choosing fasting and eating windows allows individuals to tailor Intermittent fasting to their schedules and preferences. The dietary choices during intermittent fasting windows play a crucial role in the effectiveness of intermittent fasting. While there are no strict rules about which foods to eat, it is advisable to prioritize nutrient-dense, balanced meals. Whole foods, including lean proteins, vegetables, fruits, whole grains, and healthy fats, are encouraged[69]	Flexible and can be tailored according to personal preferences, promoting weight loss[69,70]	Increased feelings of hunger, irritability, fatigue, and difficulty concentrating. Dehydration can also occur if individuals ignore their fluid intake during fasting periods[69]
Meal timing diet	Focusing on when to eat the food instead of what to eat[28]	Lean proteins, fruits, vegetables, whole grains, and healthy fats. Meals should provide essential nutrients and be well-rounded to ensure nutritional adequacy[71]	For many individuals, meal timing diets are feasible and adaptable to their daily routines. The flexibility in choosing eating windows allows individuals to adjust their meal timing according to their schedules[72]	Improved weight management, better blood sugar control, and potential benefits for metabolic health. By aligning eating patterns with the body's circadian rhythm, meal timing diets may optimize the utilization of nutrients and energy, potentially leading to better health outcomes[73,74]	Skipping meals or fasting for extended periods can lead to nutrient deficiencies if not carefully planned. Moreover, the emphasis on when to eat can sometimes overshadow the importance of what to eat[73]

Diet	Definition	Composition or characteristics	Feasibility and effectiveness	Perks	Pitfalls
Low glycemic index diet	Consuming food which can cause a low to moderate increase in postprandial blood glucose[40,75]	Foods like oats, barley, quinoa, and whole wheat, and Legumes such as beans, lentils, and chickpeas, which are rich in fiber and protein and have a low glycemic index. Most non-starchy vegetables and many fruits, particularly those with high fiber content, are suitable for a low glycemic index diet. Furthermore, incorporating lean proteins, such as poultry, fish, and tofu, alongside low glycemic index carbohydrates can create balanced meals[76]	Does not require strict portion control or calorie counting, making it accessible to many individuals. Additionally, the satiating nature of low glycemic index foods can contribute to overall dietary satisfaction, potentially enhancing adherence[41]	Blood sugar management, especially for those with type 2 diabetes, reduces the risk of insulin resistance, promoting a feeling of fullness due to its slower digestion and absorption[41]	The glycemic index of a food can vary depending on various factors. An overly restrictive diet may overlook the essential aspects of nutrition[41]
Nordic diet	Diet inspired by traditional eating habits in Nordic countries[42]	Emphasize whole grains, fish, root vegetables, and berries[42]	Feasibility may be limited in other countries outside the Nordic area because several foods may be less accessible[77]	The diet may lead to neuroprotective effects due to the nature of antioxidant activity in the meal[78]	The benefit of this diet has been observed, but it is generally inconsistent[42]
Vegetarian diet	Exclusion of meat and, in some cases, animal-derived products[79]	Vegetables, fruits, legumes, nuts, and whole grains, which are rich in essential fiber, nutrients, and antioxidants[43]	Access to plant-based food makes it feasible. Vegetarians may also be influenced by certain beliefs, culture, or religion[80]	Potential health benefits and reduced environmental impact, lower risk of chronic disease[56]	Nutrient deficiency such as vitamin B12, iron, calcium, and omega-3[43]

Conclusions

It is important to recognize that no single diet is universally the "best." The optimal dietary approach for weight loss depends on individual preferences, metabolic factors, and health considerations. While numerous diets have been studied and found effective in specific contexts, it is crucial to emphasize that long-term success often depends on an individual's ability to sustain and adhere to a chosen dietary pattern. Although several dietary patterns have been shown to promote weight loss, their long-term sustainability remains challenging for many individuals. For instance, diets like low-calorie, very low-calorie, and ketogenic diets may yield rapid weight loss but often require close medical supervision and might not be sustainable in the long run. In contrast, diets such as the Mediterranean, Nordic diet, and vegetarian diets prioritize overall health and offer a balanced, sustainable approach to weight management. The Mediterranean diet, supported by substantial evidence of its benefits for cardiovascular health and physical outcomes, stands out as a highly advantageous approach, particularly given its potential compatibility with traditional Indonesian foods.

Dietary interventions should be personalized, with weight-management strategies based on locally available Indonesian foods to encourage long-term adherence. However, because individual preferences and physiological needs vary, professional guidance from healthcare providers or nutritionists is crucial for creating dietary plans that align with personal health goals and requirements.

Conflict of interest

The authors declared no conflict of interest regarding this article.

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Author Contributions

DEA: Conceptualization, made the first draft of the manuscript, and final approval of the version to be published; VAN: Critical revision of the manuscript and final approval of the version to be published; F and DS: Supervision and final approval of the version to be published.

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ORIGINAL PAPER

The relationship between diet patterns and physical activity with the incidence of overweight in adolescents at SMAN 8 Maros

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Abstract

Background: Adolescents are a vulnerable age group prone to nutritional problems, particularly overweight and obesity, which often result from an imbalance between energy intake and energy expenditure. Dietary patterns high in energy and fat but low in fiber, combined with insufficient physical activity, contribute to the rising prevalence of overweight and obesity. Preliminary data at SMAN 8 Maros showed that 10.13% of students were overweight and 9.03% were obese.
Objective: This study aimed to examine the relationship between dietary patterns and physical activity with the incidence of overweight among adolescents at SMAN 8 Maros.
Methods: This research employed a quantitative design with a case-control approach. A total of 82 students from grades X and XI were selected using simple random sampling, with a 1:1 ratio between the case group (41 students with overweight/obesity) and the control group (41 students with normal nutritional status). Dietary data were collected using 2x24-hour food recall and Food Frequency Questionnaire (FFQ), while physical activity was measured using the Global Physical Activity Questionnaire (GPAQ). Data were analyzed using the Spearman rank correlation test.
Results: Statistical analysis revealed a significant relationship between dietary intake including energy (p=0.000), protein (p=0.006), fat (p=0.008), and carbohydrate (p=0.002)—and the incidence of being overweight. In contrast, no significant association was found between the frequency of main meal and processed food consumption (p=0.828 & p=0.824) and overweight incidence. Physical activity demonstrated a significant correlation (p=0.002) with being overweight.
Conclusion: Dietary intake (energy, protein, fat, carbohydrates) and physical activity are significantly associated with being overweight among adolescents. However, no significant relationship was observed between meal frequency and overweight incidence among adolescents at SMAN 8 Maros.

Keywords: dietary pattern, physical activity, overweight, adolescents

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Introduction

Adolescence is a transitional period between childhood and adulthood characterized by rapid biological, psychological, and social changes. According to the World Health Organization (WHO), adolescence refers to individuals aged 10–19 Years.[1] During this period, nutritional requirements increase to support growth and development; however, adolescents often adopt unhealthy eating behaviors influenced by peers, family, and media exposure.[2]

Overweight and obesity among adolescents have become major global public health concerns. WHO defines overweight and obesity as excessive fat accumulation that may impair health and increase the risk of non-communicable diseases, including type 2 diabetes, cardiovascular disease, musculoskeletal disorders, and certain cancers.[3] In 2022, more than 390 million children and adolescents aged 5–19 years were classified as overweight or obese, an increase from 8% in 1990 to 20% in 2022.[4] This trend was observed in both sexes, with a prevalence of 19% among adolescent girls and 21% among boys.[4]

In Indonesia, the prevalence of overweight and obesity among adolescents has also shown an upward trend. The Indonesia Health Survey (SKI) in 2023 reported that 8.8% of adolescents aged 16–18 years were overweight, and 3.3% were obese.[5] In South Sulawesi Province, the prevalence of overweight reached 8.8% and obesity 4.1%.[5] Similarly, the 2018 South Sulawesi Basic Health Research (Riskesdas) revealed that in Maros Regency, the prevalence of overweight among adolescents was 7.93%, and obesity 2.72%.[6] Moreover, 30.05% of residents aged ≥10 years were categorized as having low physical activity, accompanied by high consumption of sugary foods (41.51%), sweetened beverages (59.40%), and fatty foods (36.08%), with low intake of fruits and vegetables (15.92%).[6]

The causes of overweight in adolescents are multifactorial, involving an imbalance between energy intake and expenditure, poor dietary habits, and low physical activity levels.[7] According to the energy balance theory, body weight increases when energy intake exceeds energy expenditure through metabolism and physical activity.[8] Other contributing factors include stress, insufficient sleep, and environmental influences from school and family.[9]

Adolescents tend to consume high-calorie foods such as fast food, sweetened beverages, and snacks due to accessibility, peer influence, and modern lifestyle patterns.[10] Such dietary habits are associated with an increased risk of overweight and obesity.[11] Studies have reported that high intake of fat and sugar, coupled with low consumption of fiber, fruits, and vegetables, is positively correlated with higher body mass index (BMI).[12] Physical activity plays a crucial role in maintaining energy balance by enhancing energy expenditure and improving fat metabolism.[8]

Several studies have confirmed the relationship between dietary habits, physical activity, and overweight among adolescents. Pajriyah and Sulaeman, [13] found a significant association between nutrition knowledge, dietary patterns, and physical activity with overweight incidence among adolescents. Similarly, Wahyuningsih and Pratiwi, [14] reported that adolescents with low physical activity levels were more likely to experience overweight compared to those with moderate or high activity levels. Roring[15] also demonstrated that physical activity contributes to maintaining ideal body weight by increasing metabolism and promoting fat utilization.

Overweight not only affects physical health but also has psychological consequences such as decreased self-esteem, increased anxiety, and negative body image perception.[16] Therefore, preventive measures focusing on healthy eating behaviors and regular physical activity are essential to reduce the risk of overweight and obesity among adolescents.
Preliminary data from SMAN 8 Maros revealed that 10.13% of students were overweight and 9.03% were obese out of a total of 454 students.[17] These findings indicate that overweight remains a significant public health concern among high school adolescents in the region.

Based on the above considerations, it is necessary to investigate factors associated with overweight among adolescents, particularly focusing on dietary habits and physical activity.

The objective of this study is to determine the relationship between dietary habits and physical activity with the incidence of overweight among adolescents at SMAN 8 Maros.

Methods

This research is case control study was conducted between January and July 2025 at SMAN 8 Maros, a public senior high school located in Maros Regency, South Sulawesi, Indonesia. The study aimed to examine the relationship between dietary habits and physical activity with overweight among adolescents. A quantitative analytic approach was applied using a case–control design, which retrospectively investigates determinants of a specific health outcome.[17,18] The case group consisted of students from grades X and XI classified as overweight or obese, while the control group comprised students with normal nutritional status. The independent variables were dietary habits and physical activity, and the dependent variable was overweight status. The total school population included 454 students enrolled in grades X and XI. The sample size was determined using the Lemeshow formula, yielding a minimum of 82 participants, divided equally between case (n=41) and control (n=41) groups. A simple random sampling method was employed using Microsoft Excel (RAND function) to ensure random and representative selection. This study uses the Spearman Rank test. Participants were included if they (1) were actively enrolled in grades X or XI, (2) were aged 15–17 years, and (3) had anthropometric measurements recorded during the initial screening. Students classified as overweight or obese were assigned to the case group, while those with normal nutritional status formed the control group. Exclusion criteria included (1) withdrawal from the study before completion and (2) failure to meet inclusion requirements. Data collection was conducted using structured interviews and validated questionnaires.

Anthropometric measurements include body weight and height. Body weight is measured using a calibrated digital scale, Onemed EB 9312-10097, with participants wearing light clothing and no shoes. Height is measured using a portable Seca 213 stadiometer, with participants standing upright, without shoes, and with the head positioned in the Frankfurt plane. All measurements were conducted following standard anthropometric procedures recommended by WHO. Body Mass Index (BMI) was calculated as weight (kg) divided by height squared (m^2) and classified according to WHO standards for adolescents. Measurements were carried out by the researcher to minimize measurement bias. Nutritional status was assessed using BMI-for-age Z-scores (BAZ) according to the Indonesian Ministry of Health Regulation No. 2 of 2020.[19] Classifications were defined as: normal (–2 SD to +1 SD), overweight (>+1 to +2 SD), and obese (>+2 SD). Dietary habits were assessed using two complementary methods: 2

x 24-hour recalls (weekday and weekend) to find out the respondents' food intake, to estimate daily energy and nutrient intake (carbohydrates, protein, and fat). Insufficient if intake is <80%, adequate if intake is 80-110%, excessive if intake is >110%. To minimize recall bias in the 24-hour recalls, the researchers conducted interviews with guiding questions such as meal times and types of food with the participants. The researchers used household measurements and a food photo book aid to help participants estimate portion sizes more accurately.

Food Frequency Questionnaire (FFQ) was used to find out the respondents' eating frequency, adapted from the Indonesian Ministry of Health, evaluated food type, portion, and consumption frequency. Scores ≥408 for staple foods, ≥50 for processed foods.[20-22] Physical activity was measured using the Global Physical Activity Questionnaire (GPAQ) developed by WHO. MET (Metabolic Equivalent of Task) values were calculated to categorize activity levels as light (<600 MET), moderate (600–3000 MET), or vigorous (>3000 MET). [8,23] Sociodemographic characteristic such as age, gender, parental education, occupation, and household income were obtained using a structured background form completed by students. All completed questionnaires were checked for completeness and accuracy prior to data entry. Data were coded, cleaned, and analyzed using IBM SPSS Statistics version 26. Descriptive statistics were used to summarize participant characteristics. Univariate analysis was performed to present frequency and percentage distributions of each variable.[24] Bivariate analysis employed the Spearman Rank correlation test to assess the association between dietary habits, physical activity, and overweight status.[25] A *p*-value <0.05 was considered statistically significant. This study was reviewed and approved by the Health Research Ethics Committee of Universitas Muslim Indonesia (Approval No.410/A.1/KEP-UMI/VII/2025). All participants and their guardians received verbal and written explanations about the study objectives and procedures. Written informed consent was obtained prior to participation. Confidentiality and anonymity were strictly maintained throughout data collection and analysis.

Results

The sociodemographic characteristics of the subjects are shown in **Table 1** below. This study involved 82 respondents, consisting of 41 students in the case group (overweight/obese) and 41 students in the control group (normal nutritional status).

Most respondents were 16 years old (58.5%), with a balanced gender distribution between males and females. Most respondents brought pocket money <IDR 16,000 (56.1%). Most respondents came from families with incomes <UMK (regional minimum wage) (54.9%). Most respondents' fathers were employed (91.5%), while most respondents' mothers were unemployed (80.5%). The education levels of respondents' fathers and mothers were predominantly higher (68.3%) and higher (59.8%).

Table 1. Sociodemographic characteristics of the respondents (n = 82)

Respondent Characteristics	Case		Control		Total	
	n	%	n	%	n	%
Age						
15 years	0	0	1	1.2	1	1.2
16 years	24	29.3	24	29.3	48	58.5
17 years	17	20.7	16	19.5	33	40.2
Gender						
Man	16	19.5	16	19.5	32	39
Woman	25	30.5	25	30.5	50	62.2
Pocket money						
< IDR 16,000	22	26.8	24	29.3	46	56.1
≥ IDR 16,000	19	23.2	17	20.7	36	43.9
Parents' Income						
< Regional Minimum Wage (UMK)	17	20.7	28	34.1	45	54.9
≥ Regional Minimum Wage (UMK)	24	29.3	13	15.9	37	45.1
Father's Occupation						
Doesn't work	5	6.1	2	2.4	7	8.5
Work	36	43.9	39	47.6	75	91.5
Mother's Occupation						
Doesn't work	32	39	34	41.5	66	80.5
Work	9	11	7	8.5	16	19.5
Father's Education						
Low (no formal education, incomplete PS, JHS, and SHS)	8	9.8	18	22	26	31.7
High (completion of SHS or equivalent and higher education)	33	40.2	23	28	56	68.3
Mother's Education						
Low (no formal education, incomplete PS, JHS, and SHS)	13	15.9	20	24.4	33	40.2
High (completion of SHS or equivalent and higher education)	28	34.1	21	26.6	49	59.8

Notes: PS: Primary School, JHS: Junior High School, SHS: Senior High School

Table 2 shows that the control group (48.8%) was dominated by low energy intake. Meanwhile, respondents with high energy intake were dominated by the case group (2.4%). Respondents with low protein intake were dominated by the control group (28%). Meanwhile, respondents with high protein intake were dominated by the case group (12.2%). Respondents with low fat intake were dominated by the control group (34.1%). Meanwhile, respondents with high fat intake were dominated by the case group (9.8%). Low carbohydrate intake was dominated by the control group (48.8%), and there were no respondents with high carbohydrate intake. Respondents with low frequency of main meal consumption were dominated by the case group (24.4%), while high frequency of main meal consumption was dominated by the control group (26.8%). Respondents with low frequency of processed product consumption were dominated by the case group (20.7%), while high frequency of processed product consumption was dominated by the control group (30.5%).

Table 2. Relationship between eating patterns and the incidence of being overweight

Dietary habit	Case		Control		p-value	r value
	n	%	n	%		
Energy Intake						
Not enough	19	23.2	40	48.8	0.000*	0.569
Enough	20	24.4	1	1.2		
Over	2	2.4	0	0		
Protein Intake						
Not enough	13	15.9	23	28	0.006*	0.300
Enough	18	22	16	19.5		
Over	10	12.2	2	2.4		
Fat Intake						
Not enough	17	20.7	28	34.1	0.008*	0.293
Enough	16	19.5	11	13.4		
Over	8	9.8	2	2.4		
Carbohydrate Intake						
Not enough	30	36.6	40	48.8	0.002*	0.345
Enough	11	13.4	1	1.2		
FFQ Main Food						
Not enough	20	24.4	19	23.2	0.828	-.024
Over	21	25.6	22	26.8		
FFQ Processed Products						
Not enough	17	20.7	16	19.5	0.824	-.025
Over	24	29.3	25	30.5		

Notes: *p < 0.05 indicates statistical significance

Based on the results of the study, **Table 3** shows the results of the highest and lowest FFQ respondents, the highest consumption of staple foods with a daily frequency was rice, in the case group (46.3%), in the control group (50%). While the lowest consumption of staple foods with a frequency of 3-6 times per week in the case group was sweet potatoes (2.4%), while in the control group it was cassava and sweet potatoes (1.2%). The highest consumption of side dishes with a frequency of 3-6 times per week in the case group and the control group was chicken (30.5%) and (29.3%). The lowest frequency of side dish consumption in the case group was squid, beef, green beans and red beans (1.2%) and the control group was snapper and beef (1.2%). The highest consumption of vegetables with a frequency of 3-6 times per week in the case group was carrots (17.1%), while in the control group it was kale (19.5%). The lowest vegetable consumption in the case group was eggplant and bean sprouts (1.2%), while in the control group it was moringa leaves and long beans (1.2%). The highest fruit consumption with a frequency of 3-6 times per week in the case group was papaya (13.4%), while in the control group it was banana (17.1%). The lowest fruit consumption frequency in the case group was guava (1.2%), while in the control group it was avocado (3.7%). The highest consumption of processed products with a frequency of 3-6 times per week was meatballs, UHT milk, and sweetened condensed milk. In the case group, meatball consumption was 9.8%), UHT milk (12.2%), and sweetened condensed milk (11%). In the control group Meatball consumption (9.8%), UHT milk (20.7%), and sweetened condensed milk (11%). Meanwhile, the lowest consumption of processed products was nuggets, in the case group (1.2%) and the control group (3.7%).

Table 4 shows that light physical activity was dominated by the case group (3.7%). Meanwhile, respondents with vigorous physical activity were dominated by the control group (11%).

Discussion

Energy intake is the result of the metabolism of carbohydrates, fats, and proteins, which serve as energy sources for metabolism, body temperature regulation, growth, and physical activity. Weight loss and other nutritional deficiencies will occur if energy intake is low over a prolonged period.[28] The results of the study in Table 2 indicate that most respondents had a daily energy intake that was classified as insufficient or sufficient, as found in overweight adolescents or in the case group. This condition is caused by respondents tending to have irregular eating patterns. This study using the Spearman Rank test obtained a value of $p = 0.000 < 0.05$, which means that there is a significant relationship between energy intake and the occurrence of being overweight. The interpretation of the correlation coefficient $r = 0.569$ that there is a positive correlation shows the result of a one-way relationship. It means that the higher the energy intake, the greater the possibility of being overweight in adolescents. Based on interviews, respondents stated that they often skipped breakfast or main meals, but replaced them with snacks high in sugar, salt, and fat. In a study by Rokhmah,[27] it was stated that energy intake from food should be in line with the body's needs. If there is an imbalance between energy consumed and energy used over a long period of time, it can cause problems with nutritional status.

Table 3. Distribution of respondents' consumption frequency of staple foods and processed products

Food material	FREQUENCY																							
	A				B				C				D				E				F			
	Case		Control		Case		Control		Case		Control		Case		Control		Case		Control		Case		Control	
	n	%	n	%	n	%	n	%	n	%	n	%	N	%	n	%	n	%	n	%	n	%	n	%
The main food																								
Rice	38	46.3	41	50	3	3.7	0	0	0	0	0	3.7	0	0	0	0	0	0	0	0	0	0	0	0
Cassava	0	0	0	0	0	0	0	0	3	3.7	1	1.2	11	13.4	16	19.5	17	20.7	16	19.5	10	12.2	8	9.8
Sweet potato	0	0	0	0	0	0	0	0	2	2.4	1	1.2	13	15.9	13	15.9	17	20.7	14	17.1	9	11	13	15.9
Chicken meat	0	0	0	0	6	7.3	4	4.9	25	30.5	24	29.3	10	12.2	13	15.9	0	0	0	0	0	0	0	0
Squid	0	0	0	0	0	0	0	0	1	1.2	0	0	10	12.2	11	13.4	19	23.2	15	18.3	11	13.4	15	18.3
Beef	0	0	0	0	0	0	0	0	1	1.2	1	1.2	19	23.2	17	20.7	19	23.2	22	26.8	2	2.4	1	1.2
Snapper	0	0	0	0	0	0	0	0	0	0	1	1.2	7	8.5	9	11	7	8.5	7	8.5	27	32.9	24	29.3
Mung beans	0	0	0	0	0	0	0	0	1	1.2	0	0	8	9.8	18	22	13	15.9	8	9.8	19	23.2	15	18.3
Red beans	0	0	0	0	0	0	0	0	1	1.2	0	0	1	1.2	4	4.9	6	7.3	14	17.1	33	40.2	23	28
Spinach	0	0	0	0	0	0	0	0	12	14.6	16	19.5	25	30.5	23	28	3	3.7	2	2.4	1	1.2	0	0
Carrot	0	0	0	0	1	1.2	0	0	14	17.1	14	17.1	23	28	22	26.8	1	1.2	1	1.2	2	2.4	4	4.9
Eggplant	0	0	0	0	0	0	0	0	1	1.2	0	0	13	15.9	9	11	9	11	13	15.9	18	22	19	23.2
Bean sprouts	0	0	0	0	0	0	0	0	1	1.2	6	7.3	9	11	16	19.5	13	15.9	7	8.5	18	22	12	14.6
Moringa Leaves	0	0	0	0	0	0	1	1.2	3	3.7	1	1.2	6	7.3	11	13.4	15	18.3	11	13.4	17	20.7	17	20.7
Long beans	0	0	0	0	0	0	0	0	4	4.9	1	1.2	15	18.3	19	23.2	7	8.5	10	12.2	15	18.3	11	13.4
Papaya	0	0	0	0	1	1.2	0	0	11	13.4	10	12.2	18	22	20	24.4	6	7.3	6	7.3	5	6.1	5	6.1
Banana	0	0	0	0	1	1.2	0	0	11	13.4	14	17.1	21	25.6	23	28	4	4.9	4	4.9	4	4.9	0	0
Avocado	0	0	0	0	0	0	0	0	0	0	3	3.7	15	18.3	10	12.2	13	15.9	13	15.9	13	15.9	15	18.3
Guava	0	0	0	0	0	0	0	0	1	1.2	0	0	3	3.7	2	2.4	22	26.8	24	29.3	15	18.3	15	18.3
Processed Products																								
Meatball	0	0	0	0	0	0	0	0	8	9.8	8	9.8	31	37.8	30	36.6	2	2.4	2	2.4	0	0	1	1.2
UHT milk	0	0	0	0	2	2.4	0	0	10	12.2	17	20.7	23	28	20	24.4	2	2.4	4	4.9	4	4.9	0	0
Sweetened condensed milk	0	0	0	0	0	0	0	0	9	11	9	11	27	32.9	26	31.7	3	3.7	5	6.1	2	2.4	1	1.2
Nuggets	0	0	0	0	0	0	0	0	1	1.2	3	3.7	16	19.5	10	12.2	13	15.9	18	22	11	13.4	10	12.2

Information : A: Every day (>1 time a day), B: 1 time a day, C: 3-6 times/week, D: 1-2 times/week, E: Twice a month, F: Never

Table 4. Relationship between physical activity and the incidence of overweight

Physical Activity	Case		Control		p-value	r value
	n	%	n	%		
Light	3	3.7	1	1.2	0.002*	-.344
Moderate	38	46.3	31	37.8		
Vigorous	0	0	9	11		

Notes:*p < 0.05 indicates statistical significance

This study is also in line with Wijayanti's study[28] related to nutritional status, namely energy intake, carbohydrate intake, and protein intake ($p < 0.05$). The relationship is negative, meaning that the lower the energy, carbohydrate, and protein intake, the higher the BMI. The relationship between energy, carbohydrate, and protein intake and BMI has a sufficient/moderate correlation because the r value is >0.25 and <0.5. Based on the research data, it was found that respondents in the control group had a significantly lower energy intake than respondents in the case group. Furthermore, respondents in the case group tended to have a higher proportion of energy intake than respondents in the control group. This clearly indicates a relationship between energy intake and the incidence of overweight in respondents. Thus, excess energy intake is a major factor in the occurrence of overweight in respondents.

Protein is an essential macronutrient that functions in the growth, repair, and maintenance of various body tissues such as muscles, skin, hair, and organs. Its role is crucial in improving the nutritional status of adolescents, particularly in supporting growth, the formation and development of muscle mass, and maintaining bone health.[31] The result of the Spearman Rank test shows that $p = 0.006 < 0.05$, which means there is a significant relationship between protein intake and the occurrence of excess bodyweight. As for the interpretation of the correlation coefficient $r = 0.300$, that there is a positive correlation but weak and shows a one-way relationship, which means that the higher the protein intake, the greater the possibility of being overweight in adolescents. Regarding the respondents' protein intake, it can be concluded that the control group had a lower protein intake than the case group. Conversely, the case group had a higher proportion of protein intake than the control group. This indicates that high protein intake has the potential to contribute to weight gain in respondents. Based on the results of interviews with respondents, processing methods and consumption portions varied and were not always in the same portion. Some respondents also admitted to reducing food intake or on a diet, and some even deliberately skipped food at certain meal times. However, adolescents' protein needs increase during the growth period, due to the growth process. If energy intake is insufficient, protein will be used to meet energy needs, so there is not enough available to build or repair damaged tissue. This can lead to a decrease in the amount of growing muscle mass. This also shows that high consumption frequency does not guarantee adequate protein intake.[26] This research is in line with the research of Sari which stated that there is a relationship between protein intake and nutritional status, proven by a p-value of 0.006.[30] This research is also in line with the research conducted by Ristanti[31] with the results of statistical tests using the *Spearman correlation test* of protein intake and nutritional status of adolescent girls, obtained a p-value of 0.000 so that there is a significant relationship between protein intake and nutritional status.

Fat is the body's largest source of energy reserves, formed from a combination of energy-producing nutrients such as carbohydrates and proteins. In addition to storing energy, fat also functions to help transport vitamins and minerals, maintain stable body temperature, serve as a primary energy source, and protect vital organs.[33] Excessive fat consumption can lead to obesity because the energy content of fat is twice as high as the energy content of carbohydrates. Foods containing fat are generally tasty, leading people to overconsume them. Obesity can lead to various long-term diseases such as heart disease, blood vessel disease, and diabetes mellitus.[34] Based on the results of the Spearman Rank test showing $p = 0.008 < 0.05$ which means that there is a significant relationship between fat intake and the occurrence of overweight. As for the interpretation of the correlation coefficient $r = 0.293$ that there is a positive but weak correlation which shows the result of a one-way relationship. It means that the higher the fat intake, the greater the possibility of being overweight in adolescents. In the interview results in this study, some respondents stated that they frequently consume fried foods, such as fried chicken, *tempe mendoan* (thin-sliced battered and lightly fried tempeh), *risoles* (fried pastry filled with vegetables and/or meat), *martabak* (stuffed pan-fried pancake, sweet or savory), fried eggs, or other fried snacks. Sari's study[30] also aligns with this research, stating that there is a relationship between fat intake and nutritional status, as evidenced by a p value of <0.001. Consumption of processed products can contribute significantly to high fat intake in some adolescents. This means that high consumption frequency, especially if fried, can contribute to excess fat intake. Optimal nutritional status is influenced by the consumption of fats containing balanced nutrients. If fat intake is excessive, this can lead to overweight or obesity and increased cholesterol levels. Conversely, a lack of fat in the diet can lead to low calorie intake, deficiencies in fat-soluble vitamins, and the risk of causing the body to become thin.[32] Therefore, it can be concluded that the control group had a lower fat intake than the case group. Conversely, the case group had a higher proportion of excess fat intake than the control group. This condition indicates that high fat intake can contribute to overweight in respondents.

Carbohydrate intake is the primary source of energy, and if consumed in excess, the body will store it as glycogen. Nutritional status can be affected by several factors, one of which is the type of food consumed, especially those containing carbohydrates. Carbohydrates are converted into glucose in the blood and become an energy reserve for the body. If carbohydrate intake is not balanced with the body's needs, it can cause nutritional health problems.[35] The results of the Spearman Rank test show that $p = 0.002 < 0.05$ which means there is a significant relationship between carbohydrate intake and the occurrence of being overweight. As for the interpretation of the correlation coefficient $r = 0.345$ that there is a positive correlation that shows a one-way relationship. It means that the higher the carbohydrate intake, the greater the possibility of being overweight in adolescents. In the interview results, some respondents stated that they often consume fried rice, and some consume instant noodles. Some respondents also buy snacks such as meatballs, *batagor (fried meatball and tofu)*, and chicken noodles. The types and amounts of carbohydrate sources frequently consumed by respondents are simple carbohydrates such as sweetened drinks and sweet bread. Excessive carbohydrate intake can trigger fat formation in the body, while carbohydrate deficiency has the potential to cause weight loss. An unbalanced carbohydrate consumption pattern will have a negative impact on health. If excess carbohydrates occur continuously, it can cause nutritional deficiencies and increase the risk of diabetes.[32] Excess carbohydrate intake does not always cause obesity if the carbohydrate source consumed comes from high-fiber foods, such as vegetables, fruits, and grains. This type of carbohydrate has a different effect compared to simple carbohydrates, such as sugar.[33] This study is in line with research conducted by

Fauziah[34] that the p value on carbohydrate intake ($p = 0.000$) which means $p < 0.05$ indicates a significant relationship between macronutrient intake and the nutritional status of adolescents in Wiyung District, Surabaya. Based on the research results, it can be concluded that the control group had a higher proportion of insufficient carbohydrate intake than the case group. Meanwhile, the case group had a higher proportion of adequate carbohydrate intake. This indicates that respondents with higher nutritional status tended to have more adequate carbohydrate consumption patterns.

Consumption frequency can be defined as how often a person consumes a type of food within a specific period, as evaluated based on weekly consumption scores for different food groups. Eating frequency is an indicator of food consumption patterns, showing how often an individual consumes a particular type of food within a specific time period.[36] Based on the results of the Spearman Rank test showing that the value of $p > 0.05 = 0.828$ and 0.824 shows that there is no significant relationship between the frequency of the main food and processed products with the occurrence of overweight. The results of this study produce an interpretation of the correlation coefficient $r = (-0.024)$ and (-0.025), which means that there is a negative correlation and is very weak, showing the opposite relationship, but the strength is very weak (close to 0), which means that it has no statistical meaning. Thus, the frequency of consumption is not related to the occurrence of being overweight, and the frequency of eating alone may not be the main factor in the occurrence of being overweight. In this study, some respondents were recorded as consuming several processed products, such as meatballs, UHT milk, and sweetened condensed milk, which were used as food supplements and brewed as additional drinks. Theoretically, the consumption of *ultra-processed foods* (UPF) is often associated with increased Body Mass Index due to their high calorie, low fiber, and high sugar content.[38] Although there was no significant relationship between consumption frequency and the incidence of overweight, the results of this study indicate that respondents had a high consumption frequency, both in the control and case groups. This means that some control respondents are at risk of becoming overweight, and caution is needed. If increased nutritional needs are not accompanied by a balance between energy intake and expenditure, adolescents are at risk of overnutrition. Overnutrition during adolescence can lead to various health problems, such as cardiovascular disease, dyslipidemia, joint disorders, and other chronic diseases that have the potential to reduce life expectancy.[39] Improved nutritional status can be influenced by unhealthy eating patterns, for example the habit of consuming foods high in saturated fat and sugar excessively.[40] Nutritional status is not solely influenced by eating patterns, but also by various other factors, such as parental support, food availability at home, amount of pocket money, knowledge about nutrition, perception of body image, and habits in choosing food.[41] Research by Sativa[37] also aligns with this study, stating that there is no relationship between the frequency of fast food consumption and the incidence of overnutrition in adolescents, with a p-value of 0.879 and an r-value of 0.023, respectively. Therefore, this study can be concluded that the control group with normal nutritional status consumed more types of food, especially vegetables and fruit as the main foods, compared to the overweight case group. This may be caused by differences in the quality and nutritional composition of the food consumed by respondents. In other words, overweight respondents have an unbalanced consumption pattern, namely high energy and fat intake but low fiber or micronutrients from fruits and vegetables. The frequency of consumption of liquid dairy products was higher in the control group. Therefore, this indicates that liquid milk consumption is not always related to weight gain. This indicates that the type and quality of milk, as well as the balance of overall energy intake, play a greater role in determining the nutritional status of respondents.

Based on the interview results in this study, some respondents engaged in light physical activity, such as walking or sitting for long periods while studying, or lying down while using a mobile phone. Meanwhile, more frequent vigorous physical activity included regular exercise such as running, cycling, playing futsal or soccer, or extracurricular sports. Differences in the type and intensity of these activities affect the amount of energy expended. Therefore, respondents with higher levels of vigorous physical activity tended to have a better energy balance and a lower risk of being overweight. Based on the Spearman Rank test, it produces a significance value with $p = 0.002 < 0.05$ showing that there is a significant relationship between physical activity and the occurrence of overweight. The value of the correlation coefficient $r = (-0.344)$, which means that there is a weak-medium relationship with the negative direction, shows the opposite direction which means that the heavier the level of physical activity, the lower the risk of the possibility of being overweight. People with light physical activity had a higher risk of obesity than those with moderate or vigorous activity. This occurs because calories are not burned optimally, so most of them are stored as fat in the body, leading to weight gain.[42] Based on Table 4 in this study, it can be concluded that respondents in the case group tended to have lower levels of physical activity than respondents in the control group. While there were no respondents with vigorous physical activity in the case group, indicating that lack of physical activity can be a contributing factor to overweight in respondents. Conversely, respondents with vigorous physical activity in the control group demonstrated that adequate and regular physical activity plays an important role in maintaining energy balance and maintaining normal nutritional status. This research aligns with the findings of Purwaningsih and Sumarni[43] who found a relationship between physical activity and the nutritional status of adolescents at Muhammadiyah 7 High School, Sutorejo, Surabaya. The study also stated that low physical activity increases the risk of obesity in adolescents. This research also aligns with the findings of Roring[44] who used the *Spearman test* to determine a relationship between physical activity and nutritional status, with a significant value of 0.003. The strength of the relationship is moderate and positive.

Conclusions

Based on this research, there is a relationship between dietary patterns in terms of energy, protein, fat and carbohydrate intake, and the incidence of being overweight. However, there is no relationship between eating patterns and food frequency and the incidence of being overweight. There is a relationship between physical activity and the incidence of being overweight.

Conflict of interest

The authors declared no conflict of interest regarding this article.

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Author Contributions

Firdhawati: Conceptualization, methodology, data collection and analysis, as well as initial draft writing and manuscript finalization; St. Masithah: Supervision, methodology validation, writing error correction, and critical revision of the manuscript; Siti Uswatun Hasanah: Development of theoretical framework, instrument evaluation, and manuscript editing; Andi Rahmaniar MB: Accompanying data analysis, result verification, and final approval of the published.

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Association of blood glucose levels and body mass index with menstrual cycle patterns among female medical students at Universitas Syiah Kuala

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Abstract

Background: Menstrual cycle disorders are prevalent among women of reproductive age and may be influenced by nutritional and metabolic factors. Body mass index (BMI) and blood glucose levels play important roles in hormonal regulation and reproductive function.
Objective: This study examined the association between blood glucose levels and body mass index with menstrual cycle patterns among female medical students at Universitas Syiah Kuala.
Methods: An analytical cross-sectional study was conducted among 249 female medical students from the 2022–2024 cohorts using quota sampling. Data were collected from 8 - 16 September 2025. Menstrual cycle patterns were assessed using an online menstrual diary based on International Federation of Gynecology and Obstetrics criteria. Blood glucose levels were measured using random blood glucose testing, and BMI was calculated from measured weight and height. Associations were analyzed using Spearman rank correlation and ordinal logistic regression.
Results: Most participants had normal blood glucose levels (61.8%) and normal BMI (44.6%). Normal menstrual cycles were reported by 57% of participants. Blood glucose levels were significantly associated with menstrual cycle patterns ($p = 0.022$; $r_s = 0.145$). BMI was also significantly associated with menstrual cycle patterns ($p = 0.038$; $r_s = 0.132$). The correlation coefficients indicated weak positive relationships between blood glucose levels and BMI with menstrual cycle. Multivariate analysis showed that BMI (OR = 5.06) had a stronger association with menstrual cycle disturbances than blood glucose levels (OR = 4.66).
Conclusion: Blood glucose levels and body mass index are significantly associated with menstrual cycle patterns, with BMI identified as the dominant factor. Maintaining optimal nutritional and metabolic status may support menstrual health in young women.

Keywords: body mass index, blood glucose, menstrual cycle

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Introduction

Puberty is a complex developmental phase involving physiological, morphological, and psychological changes that occur naturally. In adolescent girls, puberty is marked by menarche, which represents the onset of the menstrual cycle and reflects maturation of the reproductive system.[1] However, menstrual cycle disorders remain a common reproductive health problem among women of reproductive age worldwide. The World Health Organization reported that the global prevalence of menstrual cycle irregularities reaches approximately 38.45%, indicating a substantial public health concern.[2] In Indonesia, data from the 2018 National Basic Health Research (Riskesdas) showed that 11.7% of adolescent girls experienced irregular menstruation.[3]

Menstrual cycle irregularities are multifactorial in nature. Hormonal imbalance, psychological stress, unhealthy dietary patterns, and certain medical conditions affecting reproductive function have been identified as contributing factors.[4] In addition, metabolic status and nutritional status commonly assessed through blood glucose levels and body mass index (BMI) play crucial roles in regulating reproductive hormones.[5] Disruption in metabolic homeostasis may interfere with the hypothalamic–pituitary–ovarian (HPO) axis, leading to alterations in ovulation and menstrual regularity.[6]

Abnormal blood glucose levels can be broadly categorized into hyperglycemia and hypoglycemia. Hyperglycemia, defined as elevated blood glucose beyond normal limits, is a hallmark of diabetes mellitus.[7] According to the World Health Organization, the number of individuals with diabetes mellitus in Indonesia is projected to increase from 8.4 million in 2000 to 21.3 million by 2030, with a potential two- to threefold increase by 2035. Data from Riskesdas 2013 reported a diabetes mellitus prevalence of 2.1% among individuals aged 15 years and older, highlighting the growing burden of metabolic disorders in young and productive populations.[8]

Nutritional status, as reflected by BMI, is another important determinant of reproductive health.[9] Riskesdas 2018 reported that among adults aged over 18 years in Indonesia, 9.3% were underweight, 13.6% were overweight, and 21.8% were obese.[3] Furthermore, inadequate dietary intake remains prevalent; approximately 95.7% of individuals aged 20–24 years did not meet recommended fiber intake, while nearly half of the population consumed high-fat foods one to six times per week. These dietary patterns contribute to nutritional imbalance and increase the risk of metabolic disturbances, including abnormal BMI and impaired glucose regulation.[3]

Several studies have demonstrated a potential association between blood glucose levels and menstrual cycle disturbances. Elevated blood glucose may affect ovulatory function and hormonal balance, thereby increasing the risk of menstrual irregularities. Previous research reported that women with abnormal blood glucose levels had a significantly higher risk of experiencing menstrual cycle disorders.[10] Similarly, abnormal BMI both underweight and overweight/obesity has been linked to menstrual irregularities through mechanisms involving altered estrogen production, insulin resistance, and ovarian dysfunction. Nevertheless, findings across studies remain inconsistent, with some reporting no significant association between BMI and menstrual cycle patterns.[11]

Given the increasing prevalence of metabolic disorders and nutritional imbalance among young women, particularly university students, further investigation is warranted. Medical students are particularly vulnerable to metabolic and reproductive health disturbances due to high academic demands, irregular sleep patterns, psychological stress, and inconsistent dietary habits. These factors may contribute to metabolic dysregulation, including impaired glucose metabolism and abnormal body mass index, which in turn can disrupt hormonal balance and menstrual function. Given that menstrual irregularities may reflect underlying endocrine or metabolic disturbances, early identification of these risk factors in medical students is essential to prevent long-term reproductive and metabolic complications.[12] Therefore, this study aimed to examine the association between blood glucose levels and body mass index with menstrual cycle patterns among female medical students at Universitas Syiah Kuala, with the expectation that the findings may contribute to early preventive strategies in reproductive and nutritional health.

Methods

This study employed an analytical observational design with a cross-sectional approach. The research was conducted at the Medical Education Program, Faculty of Medicine, Universitas Syiah Kuala, from 8 to 16 September 2025. The study population consisted of all active female medical students from the 2022, 2023, and 2024 cohorts, totaling 510 students. The sample size was determined using the Slovin formula with a 5% margin of error, resulting in a minimum required sample of 249 participants. Quota sampling was applied to ensure proportional representation from each cohort. The sampling technique employed in this study was quota sampling, selected due to limited access to a comprehensive population sampling frame. In addition, this method enabled the researchers to ensure proportional representation across each academic cohort. Although quota sampling is categorized as a non-probability sampling technique, the determination of quotas was based on the actual population distribution, thereby minimizing the potential for selection bias.

Inclusion criteria were active female medical students from the 2022–2024 cohorts who agreed to participate in the study. Exclusion criteria included participants who were currently using hormonal medications (such as clomiphene, progestin, oral contraceptive pills, metformin, bromocriptine, or gonadotropins), had a physician-diagnosed reproductive system disorder (including cervical cancer, ovarian tumors, polycystic ovary syndrome, or endometriosis), were married, or had moderate to high stress levels based on the Depression Anxiety Stress Scale–42 (DASS-42).

This study was approved by the Ethics Committee of Universitas Syiah Kuala (Ethical Approval No. 175/EA/FK/2025). All participants provided informed consent prior to data collection, and confidentiality of personal data was strictly maintained. Primary data were collected through both questionnaire-based and direct measurements. Menstrual cycle patterns were assessed using an online menstrual diary form based on the International Federation of Gynecology and Obstetrics (FIGO) menstrual cycle parameters. The menstrual cycle was classified as normal, frequent (<24 days), infrequent (>38 days), or amenorrhea (absence of menstruation).[13]

Blood glucose levels were measured directly using random blood glucose testing and classified according to national and international guidelines as normal (<140 mg/dL), prediabetes (140–199 mg/dL), or diabetes (≥200 mg/dL).[14] Body weight and height were measured directly using standardized instruments, and body mass index (BMI) was calculated as weight (kg) divided by height squared (m^2). BMI was categorized according to the Asia-Pacific classification into underweight (<18.5 kg/m^2), normal (18.5–22.9 kg/m^2), overweight (23.0–24.9 kg/m^2), obesity class I (25.0–29.9 kg/m^2), and obesity class II (≥30.0 kg/m^2).[15]

The instrument used to measure and interpret blood glucose levels was the Sinocare Gluco Check device, which has demonstrated validity and reliability in assessing blood glucose concentrations.[16] To ensure measurement validity, the Sinocare Gluco Check device was calibrated according to the manufacturer's standard operating procedures before data collection commenced.

Body weight and height were measured to determine Body Mass Index (BMI) categories using the following instruments:

a. A calibrated GEA digital weighing scale, measured in kilograms (kg).
b. A GEA stature meter for height measurement, with a precision of 0.1 cm.

Menstrual cycle assessment was conducted using the menstrual parameter criteria established by the International Federation of Gynecology and Obstetrics (FIGO). Data were collected through a self-administered Google Form questionnaire. The menstrual cycle was evaluated over the previous three months to determine whether it was normal or abnormal. Assessment was based on several key parameters, including frequency, regularity, duration of bleeding, and volume of bleeding. In this context, cycle frequency was defined as the interval from the first day of the last menstrual period to the first day of the subsequent menstrual period. According to FIGO criteria, a normal menstrual cycle ranges from 24 to 38 days. In the ordinal logistic regression model, menstrual cycle categories were coded numerically in ascending order based on clinical severity (1 = normal, 2 = frequent, 3 = infrequent, and 4 = amenorrhea). Higher category values represented increasing severity of menstrual disturbance.

The Depression Anxiety Stress Scales (DASS-42) questionnaire was administered in the form of a Google Form to measure respondents' stress levels. The instrument was included alongside the informed consent form to ensure appropriate participant selection based on the predefined inclusion and exclusion criteria.

This study was conducted with the assistance of six enumerators, who were 2022 cohort medical students from the Undergraduate Medical Education Program and were not included as research participants. Both the principal investigator and the enumerators had a clear and comprehensive understanding of the procedures for blood glucose testing and anthropometric measurements (body weight and height). This competency was obtained through a structured Training of Trainers (ToT) program conducted as part of a community service initiative organized by the Faculty of Medicine, Universitas Syiah Kuala.

This study has a limitation in that blood glucose levels were measured only once using a random assessment, which may not fully represent the participants' long-term metabolic status.

Data were analyzed using statistical software. Univariate analysis was conducted to describe the distribution of respondent characteristics (age and academic cohort), blood glucose levels, BMI, and menstrual cycle patterns. Bivariate analysis was performed using Spearman rank correlation to assess the association between blood glucose levels and BMI with menstrual cycle patterns. Variables with significant associations were further analyzed using multivariate ordinal logistic regression to determine the dominant factor associated with menstrual cycle disturbances.[16] Statistical significance was set at $p < 0.05$.

Results

The results of this study are presented according to the characteristics and frequency distribution of blood glucose levels, body mass index, and menstrual cycle patterns.

Table 1. Frequency distribution of respondents

Variable	Frequency (n=249)	Percentage (%)
Age (years)		
17	2	1
18	28	11
19	63	25
20	91	37
21	52	21
22	13	5
Cohort Year		
2022	97	39
2023	64	26
2024	88	35
Blood Glucose Level		
Normal (< 140 mg/dL)	154	61.8
Prediabetes (140-199 mg/dL)	63	25.3
Diabetes (≥ 200 mg/dL)	32	12.9
Body Mass Index (BMI)		
Underweight (<18,5)	27	10.8
Normal (18,5-22,9)	111	44.6
Overweight (23-24,9)	34	13.7
Obesity class I (25-29,9)	48	19.3
Obesity class II (≥30)	29	11.6
Menstrual Cycle		
Normal	142	57
Frequent (<24 days)	33	13.3
Infrequent (>38 days)	52	20.9
Amenorrhea (absence of menstruation)	22	8.8

Based on **Table 1**, most respondents were 20 years old, accounting for 91 participants (37%), and the majority were from the 2022 cohort (39%). The number of respondents in each cohort was determined according to sample size calculations and adjusted to the population proportion of each cohort. Based on random blood glucose measurements, most respondents had normal blood glucose levels, totaling 154 participants (61.8%), while 38.2% had abnormal blood glucose levels, classified as prediabetes or diabetes. The largest proportion of participants had a normal body mass index, comprising 111 participants (44.6%). However, 55.4% of respondents had abnormal BMI, including underweight, overweight, and obesity class I–II, indicating that more than half of the study population was at risk of body weight imbalance. Normal menstrual cycle patterns were the most common, reported by 142 participants (57%).

Table 2. Association of blood glucose levels and body mass index with menstrual cycle

Variable	Menstrual Cycle								Total		Spearman rank	
	Normal		Frequent		Infrequent		Amenorrhea				rs	p value
	n	%	n	%	n	%	n	%	n	%		
Blood Glucose												
Normal	110	71.4	13	8.4	23	14.9	8	5.2	154	100	0.145	0.022
Prediabetes	25	39.7	13	20.6	19	30.2	6	9.5	63	100		
Diabetes	7	21.9	7	21.9	10	31.3	8	25.0	32	100		
BMI												
Underweight	15	55.6	3	11.1	6	22.2	3	11.1	27	100		
Normal weight	84	75.7	10	9.0	14	12.6	3	2.7	111	100		
Overweight	17	50.0	4	11.8	10	29.4	3	8.8	34	100	0.132	0.038
Obesity class I	18	37.5	11	22.9	13	27.1	6	12.5	48	100		
Obesity class II	8	27.6	5	17.2	9	31.0	7	24.2	29	100		

Table 2 shows that 110 participants (71.4%) with normal blood glucose levels had normal menstrual cycles. Spearman correlation analysis revealed a statistically significant association between blood glucose levels and menstrual cycle patterns ($p = 0.022$; $r_s = 0.145$), indicating a positive correlation. The correlation coefficient ($r = 0.145$) indicates a weak positive relationship between blood glucose levels and menstrual cycle, although the association was statistically significant ($p < 0.05$). This finding suggests that higher blood glucose levels are associated with an increased likelihood of menstrual cycle irregularities among female students. Menstrual cycle categories were coded numerically in ascending order based on clinical severity (1=normal, 2=frequent, 3=infrequent, and 4=amenorrhea). Higher category values represented increasing severity of menstrual disturbance.

Regarding body mass index, 84 participants (75.7%) with normal BMI had normal menstrual cycles, while 31% of participants with obesity class II experienced infrequent menstrual cycles. Spearman rank correlation analysis demonstrated a statistically significant association between BMI and menstrual cycle patterns ($p = 0.038$; $r_s = 0.132$). The correlation coefficient ($r = 0.132$) indicates a weak positive relationship between BMI and menstrual cycle, although the association was statistically significant ($p < 0.05$). The positive direction of the association indicates that abnormal BMI is associated with a greater tendency toward menstrual cycle disturbances.

Table 3. Multivariable ordinal regression analysis

Variable	Coefficient (B)	OR	95% CI for OR	p value
Blood Glucose Level	1.538	4.66	2.13 – 10.17	<0.001
Body Mass Index	1.621	5.06	2.17 – 11.57	<0.001

Table 3 shows that both blood glucose levels and body mass index were significantly associated with menstrual cycle patterns ($p < 0.05$). The odds ratio (OR) for blood glucose levels was 4.66, indicating that participants with abnormal blood glucose levels had a 4.66-fold greater likelihood of experiencing menstrual cycle disturbances compared with those with normal blood glucose levels. Meanwhile, the OR for BMI was 5.06, suggesting that higher BMI increased the odds of menstrual cycle disturbances by 5.06 times. The confidence interval did not cross 1.0, confirming the statistical significance and suggesting a meaningful strength of association. Both blood glucose level and BMI demonstrated strong positive associations with menstrual cycle disturbances, as reflected

by odds ratios greater than 4.0. Among the two variables, BMI showed a slightly higher odds ratio, indicating a relatively stronger association with menstrual cycle irregularities in this study population.

Discussion

This study investigated the association between blood glucose levels and body mass index with menstrual cycle patterns among female medical students at Universitas Syiah Kuala. The findings demonstrated that both metabolic status, reflected by blood glucose levels, and nutritional status, assessed through BMI, were significantly associated with menstrual cycle disturbances. Notably, body mass index showed a stronger association than blood glucose levels in multivariate analysis.[11]

The majority of participants were aged 17–22 years, with most in late adolescence.[17] At this stage of development, the female reproductive system has generally achieved hormonal maturity, which is expected to support regular menstrual cycles. The relative homogeneity of age in this study reduces potential confounding related to reproductive aging and strengthens the internal validity of the findings. Similar age distributions have been reported in previous studies among female medical students, indicating that menstrual and metabolic health concerns remain relevant even in young, educated populations.[18]

Most participants had normal blood glucose levels; however, more than one-third were classified as having prediabetes or diabetes.[14] This finding highlights an important public health concern, as metabolic disturbances are increasingly observed among young adults.[19] Lifestyle factors commonly encountered in university settings, such as irregular eating patterns, high consumption of energy-dense foods, limited physical activity, and academic stress, may contribute to impaired glucose regulation.[20] The relatively high proportion of abnormal blood glucose levels observed in this study underscores the need for early metabolic screening in young women.[21]

This study found a significant positive association between blood glucose levels and menstrual cycle disturbances. The Spearman correlation test demonstrated a statistically significant association between blood glucose levels and menstrual cycle patterns among female students ($p = 0.022$; $p < 0.05$), with a correlation coefficient of $r_s = 0.145$. This finding indicates a significant yet weak positive relationship between the two variables. Participants with higher blood glucose levels were more likely to experience abnormal menstrual cycles, including infrequent cycles and amenorrhea.[22] This finding is consistent with previous studies reporting that abnormal glucose metabolism increases the risk of menstrual irregularities.[23] From a physiological perspective, hyperglycemia is closely linked to insulin resistance, which plays a key role in reproductive endocrinology. Insulin resistance leads to compensatory hyperinsulinemia, which can stimulate ovarian androgen production and disrupt follicular development, thereby impairing ovulation and menstrual regularity.[24]

Additionally, chronic hyperglycemia may interfere with the hypothalamic–pituitary–ovarian axis by altering gonadotropin secretion and reducing estrogen receptor expression.[25] Oxidative stress induced by elevated glucose levels has been suggested to impair hormonal signaling pathways essential for normal menstrual regulation.[26] These mechanisms provide a plausible biological explanation for the observed association between blood glucose levels and menstrual cycle disturbances in this study.[27]

Body mass index was also significantly associated with menstrual cycle patterns, with abnormal BMI increasing the likelihood of menstrual irregularities.[28] The statistical analysis yielded a p-value of 0.038 and a Spearman correlation coefficient (rs) of 0.132. These results indicate a statistically significant association between the two variables, with the strength of correlation classified as weak. Participants with normal BMI showed the highest proportion of regular menstrual cycles, supporting the role of balanced nutritional status in maintaining reproductive hormonal stability. In contrast, both underweight and overweight/obese participants exhibited higher rates of menstrual disturbances.[29]

In individuals with overweight and obesity, excess adipose tissue increases peripheral aromatization of androgens to estrogens, leading to hormonal imbalance and disrupted feedback mechanisms within the hypothalamic–pituitary–ovarian axis.[15] Obesity is also strongly associated with insulin resistance, further exacerbating hormonal dysregulation and increasing the risk of ovulatory dysfunction. These mechanisms may explain the higher prevalence of infrequent menstrual cycles and amenorrhea observed among participants with obesity in this study.[30]

Conversely, underweight participants also demonstrated a tendency toward menstrual irregularities.[6] Insufficient body fat reduces estrogen production, which may suppress gonadotropin-releasing hormone secretion and subsequently decrease luteinizing hormone and follicle-stimulating hormone levels.[31] This hormonal suppression can impair follicular maturation and ovulation, leading to irregular or absent menstruation. These findings highlight that both extremes of nutritional status can negatively affect menstrual health.[32]

A more critical comparison with previous studies reveals both consistencies and inconsistencies in findings regarding the association between BMI and menstrual cycle patterns. Several studies have reported that elevated BMI is significantly associated with menstrual irregularities, potentially due to altered estrogen production, insulin resistance, and disruption of the hypothalamic–pituitary–ovarian axis. However, other studies have found no significant relationship, suggesting that the association may be influenced by differences in study design, population characteristics, sample size, lifestyle factors, and methods used to classify menstrual abnormalities. These discrepancies highlight the multifactorial nature of menstrual cycle regulation and indicate that BMI alone may not fully explain variations in menstrual patterns across different populations.

Multivariate analysis revealed that BMI had a stronger association with menstrual cycle disturbances than blood glucose levels. This suggests that nutritional status may play a more dominant role in influencing menstrual regularity among young women.[33] While blood glucose levels reflect metabolic function at a given time, BMI represents longer-term nutritional and energy balance, which may exert a more sustained effect on reproductive hormonal regulation.[34]

The findings of this study have important implications for reproductive and nutritional health promotion among female university students.[35] Early identification of abnormal BMI and impaired glucose regulation may allow for timely lifestyle interventions aimed at improving dietary habits, physical activity, and metabolic health.[36] Such interventions may contribute not only to the prevention of metabolic diseases but also to the preservation of normal menstrual function and overall reproductive health.[37]

Several limitations should be considered when interpreting these findings. The cross-sectional design precludes causal inference, and blood glucose levels were assessed using a single random measurement, which may not fully capture long-term glycemic status.[38]

Additionally, other potential confounding factors such as detailed dietary intake, physical activity levels, and sleep patterns were not assessed.[39] Future studies are encouraged to incorporate longitudinal designs, repeated metabolic measurements, and more comprehensive lifestyle assessments to better elucidate causal relationships.[40]

Conclusion

This study demonstrates that both blood glucose levels and body mass index are significantly associated with menstrual cycle patterns among female medical students at Universitas Syiah Kuala with the strength of correlation classified as weak. Participants with elevated blood glucose levels were more likely to experience menstrual cycle disturbances, indicating the role of metabolic dysregulation in reproductive health. Similarly, abnormal body mass index, including both underweight and overweight/obesity, was associated with an increased likelihood of menstrual irregularities.

Multivariate analysis revealed that body mass index had a stronger association with menstrual cycle disturbances compared to blood glucose levels, suggesting that long-term nutritional status plays a dominant role in influencing menstrual regularity. These findings highlight the importance of maintaining balanced nutritional status and metabolic health to support normal reproductive function in young women.

Recommendation

1. For Female Students : Female university students are encouraged to adopt healthy dietary patterns, engage in regular physical activity, and maintain a balanced lifestyle to support normal body mass index and stable blood glucose levels, thereby promoting regular menstrual cycles.
2. For Educational Institutions and Campus Health Services: Universities and campus health providers should implement routine health education programs focusing on reproductive health, nutrition, and metabolic screening, including body mass index assessment and basic glucose monitoring, to enable early detection and prevention of menstrual cycle disturbances.
3. For Healthcare Providers: Healthcare professionals should consider metabolic factors and nutritional status during the initial assessment of menstrual cycle disorders, as early identification may allow for more targeted and effective interventions.
4. For Future Research: Future studies are recommended to include repeated or longitudinal blood glucose measurements, additional metabolic parameters, and more diverse study populations to improve generalizability. Given the relatively high prevalence of prediabetes and diabetes observed in this study, further research is needed to explore metabolic risk factors for diabetes mellitus among young women.

Conflict of interest

There was no conflict of interest related to this research. The authors have no personal or financial relationship that could influence the judgment or action.

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Author's contribution

ASBM contributed to conceptualization, study design, data acquisition, formal analysis, interpretation of the results, and drafting of the manuscript; H contributed to supervision, methodological guidance, and critical revision of the manuscript for important intellectual content; NS contributed to data interpretation, validation of the analysis, and critical manuscript review; DM contributed to supervision, academic guidance, and substantial revision of the manuscript; CRM contributed to overall research supervision, critical intellectual input, and final approval of the version to be published.

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