THE INFLUENCE OF DIETARY PATTERNS ON GALLSTONE FORMATION: A CASE-CONTROL STUDY OF RISK AND PROTECTIVE FACTORS

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Abstract
Gallstone disease (GSD) is a rising global health concern, affecting around 11.7% of Pakistan's population and approximately 10% of adults in Western countries, with a higher prevalence among women. Gallstones are solid formations in the biliary tree, primarily composed of cholesterol, bilirubin, and calcium. This case-control study, conducted in Mardan with 200 participants (100 cases and 100 controls). The recruitment and data collection were carried out over a six-month period, from January 2024 to May 2024. A structured questionnaire was administered to all participants to gather comprehensive data aimed to assess the influence of dietary patterns and lifestyle behaviors on gallstone formation and prevention. Results indicated that females and individuals aged 20–40 were more frequently affected. Major risk factors included higher BMI, sedentary lifestyle, lower education levels, and family history of GSD. Dietary risk factors among cases were frequent consumption of red meat, refined grains, vanaspati ghee, fried and processed foods, artificial juices, and added sugars. In contrast, protective dietary habits observed in controls included higher intake of vegetables, fruits, seafood, eggs, dried fruits/nuts, and the use of vegetable oil. The study concludes that gallstone disease is significantly associated with modifiable factors, particularly unhealthy diets and lifestyle habits. It recommends public health strategies that promote plant-based diets, regular physical activity, the use of healthy fats like vegetable oil, and a reduction in the consumption of processed and high-fat foods, especially among high-risk populations such as women in reproductive age groups.

INTRODUCTION

Gallstone disease represents a significant global health issue, affecting an estimated 11.7% of the population in Pakistan and 10% of adults in the United States and Europe (Humaira et al., 2023). Prevalence is on the rise, with one study in Germany showing an increase from 3.8% in 2002 to 10.8% in 2013, with a higher burden in women (15.1%) compared to men (7.2%) (Kratzer et al., 2021). Gallstones are solid clusters of varying sizes that form within the biliary tree (Portincasa et al., 2023). Their

primary constituents are cholesterol, bilirubin, and calcium, with cholesterol often accounting for over 70% of a stone's mass (Saied et al., 2020).

The clinical impact of gallstone disease ranges from simple biliary colic—a sharp pain in the right hypochondrium that is a strong indicator of the disease—to a myriad of severe complications (Gabash et al., 2021). These complications can include acute cholecystitis, gallbladder wall perforations, choledocholithiasis, gallstone pancreatitis, and even gallbladder malignancies, underscoring the importance of understanding its etiology (Gandhi et al., 2020).

The pathogenesis of gallstones is multifactorial, involving a complex interplay of genetic and environmental influences. Risk factors can be categorized as non-modifiable (age, sex, race, and genetics) and modifiable. Among the key modifiable factors are metabolic syndrome, impaired gallbladder motility, and, notably, dietary habits (Anjum et al., 2023).

Diet is understood to influence gallstone formation by altering biliary lipid composition and modifying gallbladder motility. For instance, Western-type diets—characterized by high caloric intake, saturated fat, and refined sugars with limited fiber—are reported to increase the likelihood of gallstone formation (Del Pozo et al., 2023). Reducing total dietary fat, particularly saturated fat, can lead to lower plasma and biliary cholesterol concentrations, thereby decreasing the risk of cholesterol precipitation in the bile (Madden et al., 2021).

Conversely, certain dietary patterns appear to offer protection. A Mediterranean diet, rich in vegetables, fruits, whole grains, nuts, and fish, has been associated with a lower risk of gallstone disease (Nie et al., 2023). Specific consumption habits, such as high coffee intake, have also been linked to a significantly lower risk (Nordestgaard et al., 2020). This evidence suggests that dietary choices are a critical and modifiable component of gallstone risk.

The growing body of evidence on gallstone disease (GSD) underscores a complex relationship between diet, lifestyle, and metabolic health, offering critical insights for prevention. The influence of broad dietary patterns is a central theme, with a hospital-based case-control study by Naseri et al. (2022) identifying a "Healthy" pattern (high in fruits,

vegetables, fish) and an "Unhealthy" pattern (high in sweets, processed meats). Notably, participants adhering to the healthy pattern had a significantly lower risk of GSD (OR 0.33, 95% CI = 0.12–0.89). However, the definition of a "healthy" diet may be context-dependent, as a large-scale cohort study in China by Nie et al. (2023) found that an alternative Mediterranean diet (aMED) was unexpectedly associated with an increased GSD risk, whereas a traditional "rice" dietary pattern was protective.

Beyond general patterns, specific nutrients and dietary choices play a crucial role. A case-control study by Tehrani et al. (2023) demonstrated that higher dietary fiber intake was associated with a reduced risk of GSD, particularly for individuals with an elevated BMI. The role of specific diets, such as vegetarianism, presents a more complex picture. An analysis of the EPIC-Oxford cohort by McConnell et al. (2017) observed a small but significant increase in GSD risk among vegetarians after adjusting for BMI. In contrast, Chang et al. (2019) found that vegetarian women in Taiwan had a lower risk of symptomatic GSD, especially those with normal cholesterol levels, emphasizing the modifying role of metabolic factors.

This highlights the importance of underlying metabolic health, a point reinforced by multiple studies. A Mendelian randomization study by Yuan et al. (2022) established causal links between obesity, type 2 diabetes, and increased GSD susceptibility. Similarly, a hospital-based study by Khan et al. (2023) identified age, BMI, diabetes mellitus, and cholesterol levels as independent predictors of GSD, noting that women had a twofold higher risk. This multi-faceted etiology is further captured by Wirth et al. (2020), who found that a comprehensive Healthy Lifestyle Score (HLS)—incorporating diet, physical activity, non-smoking, and coffee and moderate alcohol intake—was associated with a 62% and 74% lower risk in women and men, respectively.

Among specific lifestyle components, coffee consumption has been singled out for its protective effects. Using genetic and observational data, Nordestgaard et al. (2020) demonstrated that consuming more than six cups of coffee daily was causally linked to a 23% lower risk of symptomatic GSD. Summarizing the breadth of evidence, an umbrella review by Wang et al. (2022) concluded

that while consumption of fruits, vegetables, tea, and coffee is protective, high intake of alcohol, raw fish, and nitrate-rich foods elevates risk. Collectively, these studies indicate that while dietary patterns rich in fiber, fruits, and vegetables are generally protective, GSD risk is significantly modulated by BMI, metabolic health, genetic predispositions, and specific lifestyle behaviors. The objective of this research study is to investigate the impact of specific dietary patterns on the formation and prevention of gallstones, identifying key dietary components and lifestyle factors that contribute to gallstone risk and protection among affected individuals and healthy controls.

METHODOLOGY

This case-control study was conducted to investigate the association between various risk factors and gallstone disease (GSD). The study population comprised two groups: "cases" and "controls". The case group consisted of 100 patients with a confirmed diagnosis of GSD, recruited from the Mardan Medical Complex. The control group included 100 individuals from the general population of Mardan who had no clinical evidence of gallstone disease.A total of 200 participants were enrolled in the study using a purposive (judgmental) sampling technique. The recruitment and data collection were carried out over a seven-month period, from October 2024 to May 2025. A structured questionnaire was administered to all participants to gather comprehensive data. The questionnaire was divided into several sections to collect the following information: Age, gender, socioeconomic status, and other relevant background information, personal history of comorbidities (e.g., diabetes) and a family history of gallstone disease. Anthropometric measurements were performed following standard procedures. Body weight was measured in kilograms (kg) using a calibrated digital scale, and height was measured in meters (m) using a stadiometer. Body Mass Index (BMI) was subsequently calculated for each participant using the standard formula: BMI=height $(m)^2$/weight(kg).

Dietary patterns and behaviors of the participants were assessed using a custom-designed Food Frequency Questionnaire (FFQ). The FFQ was developed specifically for this study to capture the typical dietary intake of the local population. The data collected from the questionnaires were entered and organized in Microsoft Excel. A descriptive statistical analysis was performed to calculate frequencies and percentages for the variables of interest. The results were subsequently summarized and presented in tabular and graphical formats for interpretation.

RESULTS AND DISCUSSIONS

In this case-control study involving 200 participants from Mardan (100 cases and 100 controls), females were predominant in both groups, constituting 82% of the cases and 74% of the controls. Age distribution revealed that gallstone cases skewed younger, with 42% falling between 20–40 years, compared to 53% in the control group. These findings align with Morris-Stiff et al. (2023), who identified female gender and younger age as strong predictors for symptomatic gallstone development. Similarly, Gutt and Lammert (2020) reported that while gallstones typically form between 20 and 40 years of age, they often become symptomatic much later. Regarding marital status, a higher proportion of married individuals were observed among cases (84%) compared to controls (69%), while single individuals were more prevalent in the control group (31% vs. 16% in cases). Educational attainment varied significantly; 35% of the cases were uneducated, in contrast to only 11% of controls. A large majority of controls (78%) had attained higher education.

Lifestyle factors also differed markedly. Sedentary behavior was more common in cases (53%) compared to controls (67%). BMI differences were particularly striking: 66% of cases were overweight, compared to just 12% of controls. These observations support findings by Krawczyk et al. (2023) and Qamar Kiani et al. (2020), both of whom noted a strong association between elevated BMI and gallstone disease. A significant proportion of the case group (57%) reported a family history of gallstone disease. Additionally, comorbid conditions such as hepatitis B or C were more prevalent among cases (20%) than controls (13%). While cirrhosis and chronic kidney disease were observed only among cases (2% and 4%, respectively), their rare occurrence may still indicate potential contributory

roles. Ileostomy or colostomy was also exclusively found in 2% of the cases, suggesting these conditions might be associated risk factors for gallstone formation.Medication and supplement use for gallstone disease was reported by 80% of the case group. Furthermore, 24% of cases had a history of hyperlipidemia, compared to none in the control group, highlighting a possible link between lipid abnormalities and gallstone disease.

Dietary fat usage patterns diverged significantly. Among the cases, 28% used vegetable oil, 1% used animal fat, 37% consumed banaspati ghee, and 34% used multiple fat sources. In contrast, 77% of controls used vegetable oil, while 4% used banaspati ghee and 19% used multiple fats. This indicates that higher usage of banaspati ghee and mixed fats, as opposed to vegetable oil, may be associated with increased gallstone risk (Figure 1).

Whole grain consumption was similar in both groups (56% daily consumption). However, refined grain intake was higher among cases, with 19% consuming them daily versus only 7% among controls, suggesting a potential link with gallstone formation (Table 3). Fruit and vegetable consumption also varied; daily fruit intake was slightly higher in controls (34% vs. 26%), and vegetable intake was significantly higher (85% vs. 71%). These dietary trends support the protective role of a plant-based diet in reducing gallstone risk. Regarding beverages, daily tea/coffee consumption was more frequent in cases (81%) than controls (56%), though weekly consumption was higher in controls (24% vs. 10%). Interestingly, Yuan et al. (2022) found an inverse association between coffee consumption and gallstone disease in a Mendelian randomization study, suggesting potential protective effects despite the higher frequency among cases in this cohort. Artificial juice consumption showed different patterns. Only 1% of cases consumed these beverages daily, with 43% consuming them monthly, substantially more than the 24% among controls. In contrast, 55% of controls rarely consumed artificial juices, compared to only 33% of cases. This trend may suggest a connection between artificial juice intake and gallstone risk.

Protein source consumption patterns further emphasized dietary influences. Weekly and monthly chicken consumption was higher among cases (35%

and 48%) compared to controls (17% and 55%). Seafood intake differed significantly, with 17% of cases consuming it weekly compared to only 1% of controls, though monthly intake was higher in controls (51% vs. 25%). Red meat was consumed daily by 5% and weekly by 45% of cases, while none of the controls reported daily consumption, and only 6% consumed it weekly. Egg consumption was higher in the control group, with 64% consuming eggs daily compared to only 24% of cases. Dried fruits and nuts were consumed daily by 12% of controls but only 1% of cases; weekly intake was also higher in controls (50% vs. 17%). These trends suggest that increased red meat intake and lower intake of seafood, eggs, and dried fruits/nuts may contribute to gallstone risk, while the latter may provide protective effects. Daily legume consumption was slightly higher in cases (6%) than in controls (0%), indicating a complex role possibly influenced by preparation methods or associated dietary patterns.

Fried and processed food consumption was substantially higher among cases: daily (6% and 1%), weekly (24% and 19%), and monthly (60% and 44%), respectively. Conversely, a majority of controls reported rare consumption of fried (77%) and processed (73%) foods. This suggests a strong association between frequent intake of these food types and gallstone disease (Figure 3). Interestingly, pickle consumption was higher among controls, which may suggest that moderate to low intake could be protective. Added sugar intake was higher among cases, with daily and weekly consumption at 29% and 19%, compared to 18% and 12% among controls, respectively. This supports the hypothesis that frequent sugar intake may contribute to gallstone formation. Salt consumption was similar in both groups and may not be a distinguishing risk factor. Spice consumption, however, was higher in controls (83%) than cases (68%), possibly indicating a minor protective effect. Daily ghee consumption was reported by 48% of cases and only 2% of controls. Weekly ghee consumption was also higher in cases (26% vs. 2%). Conversely, daily vegetable oil usage was dominant among controls (97%) compared to 44% of cases. These patterns suggest that ghee consumption may elevate gallstone risk,

while the use of vegetable oil appears protective (Table 3).

Overall, the findings suggest that frequent consumption of refined grains, artificial juices, chicken, red meat, legumes, fried and processed foods, added sugars, and ghee or other unhealthy fats is associated with an increased risk of gallstone disease (Cholelithiasis). Conversely, high intake of whole grains, fruits, vegetables, seafood, eggs, dried fruits/nuts, and substitution of ghee with vegetable oil is associated with a reduced risk. A diet lower in high-fat, high-energy, and cholesterol-rich foods appears to offer protection against gallstone formation.

These findings align with those of Naseri et al. (2022), who identified two major dietary patterns: a "Healthy" pattern, characterized by high intake of vegetable oils, vegetables, fruits, fish, legumes, and nuts, and low intake of hydrogenated fats and salt and an "Unhealthy" pattern, marked by high consumption of artificial juices, processed meats, refined grains, sweets, pickles, and red meats. The unhealthy dietary pattern was found to significantly increase the likelihood of gallstone disease, reinforcing the importance of dietary modification in prevention strategies.

Table 1 Gender, Age, Marital Status, Education, Physical Activity Level and BMI of Participants

Traits	Categories	Percentages	
		Cases	Controls
Gender	Male	18%	26%
	Female	82%	74%
Age	Below 20	3%	8%
	20 to 40	42%	53%
	41 to 60	41%	36%
	More than 60	14%	3%
Marital status	Single	16%	31%
	Married	84%	69%
Education	Uneducated	35%	11%
	Primary	7%	7%
	Secondary	14%	4%
	Higher	44%	78%
Physical Activity Level	Sedentary	53%	67%
	Lightly active	32%	27%
	Moderately active	15%	6%
BMI	Underweight	0%	4%
	Normal weight	34%	84%
	Overweight	66%	12%

Table 2. Familial history of GSD and Disease status of respondents

Traits	Categories	Percentages	
		Cases	Controls
Familial history of GSD	Yes	57%	7%
	No	43%	93%
Diabetes Mellitus	Yes	35%	13%

	No	65%	87%
Hepatitis B or C	Yes	20%	13%
	No	80%	87%
Cirrhosis	Yes	2%	0%
	No	98%	100%
Chronic Kidney Disease	Yes	4%	0%
	No	96%	100%
Ileostomy or Colostomy	Yes	2%	0%
	No	98%	100%
History of hyperlipidemia	Yes	24%	0%
	No	76%	100%
Medications taken for GSD	Yes	80%	0%
	No	20%	100%

Table 3: Food consumption of respondents

| Food item	Frequency	Percentages	
		Cases	Controls
Whole grains	Daily	56%	56%
	Weekly	31%	31%
	Monthly	6%	3%
	Rarely	3%	1%
	Never	1%	1%
Refined grains	Daily	19%	7%
	Weekly	53%	35%
	Monthly	14%	38%
	Rarely	12%	20%
	Never	2%	0%
Fruits	Daily	26%	34%
	Weekly	58%	61%
	Monthly	16%	5%
	Rarely	0%	0%
Vegetables	Daily	71%	85%
	Weekly	26%	15%
	Monthly	3%	0%
	Rarely	0%	0%
Tea/coffee	Daily	81%	56%
	Weekly	10%	24%
	Monthly	6%	14%
	Rarely	2%	5%
	Never	1%	1%
Artificial juices	Daily	1%	0%
	Weekly	13%	12%
	Monthly	43%	24%
	Rarely	33%	55%
	Never	10%	9%
	Rarely	16%	28%
Added sugars	Daily	29%	18%
	Weekly	19%	12%
	Monthly	24%	29%
	Rarely	27%	41%
	Never	1%	0%
Salt	Daily	93%	99%
	Weekly	1%	0%
	Monthly	1%	1%
	Rarely	5%	0%
Spice	Daily	68%	83%
	Weekly	11%	5%
	Monthly	7%	3%
	Rarely	14%	9%
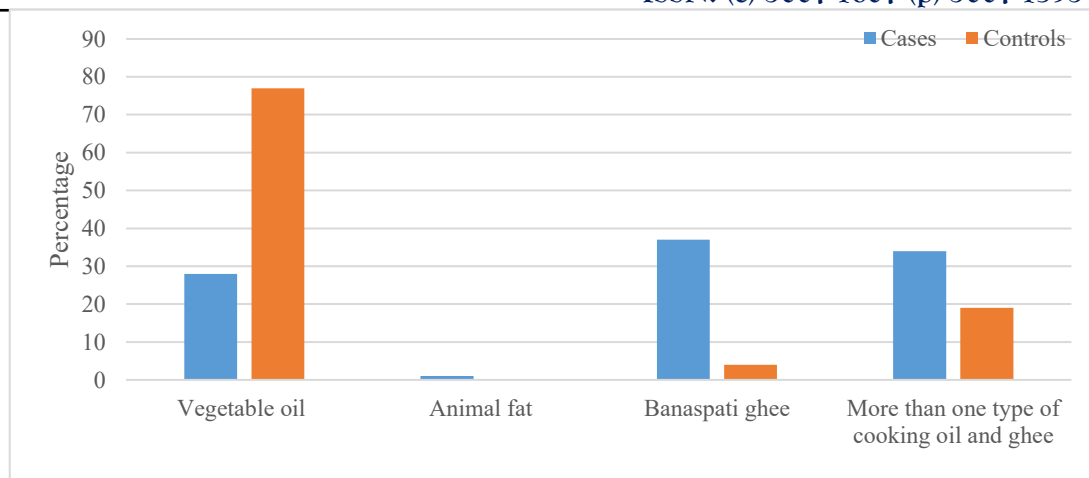
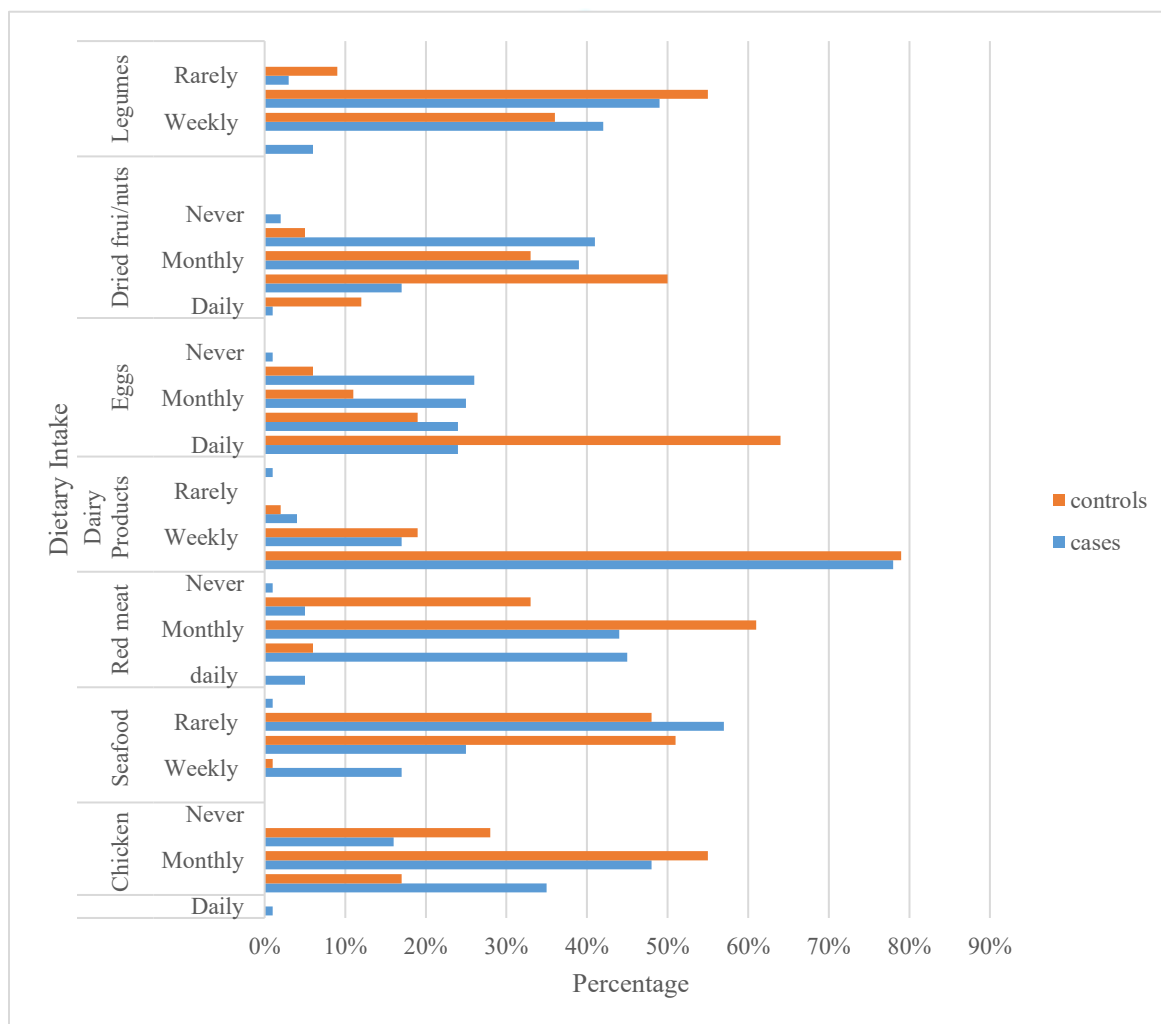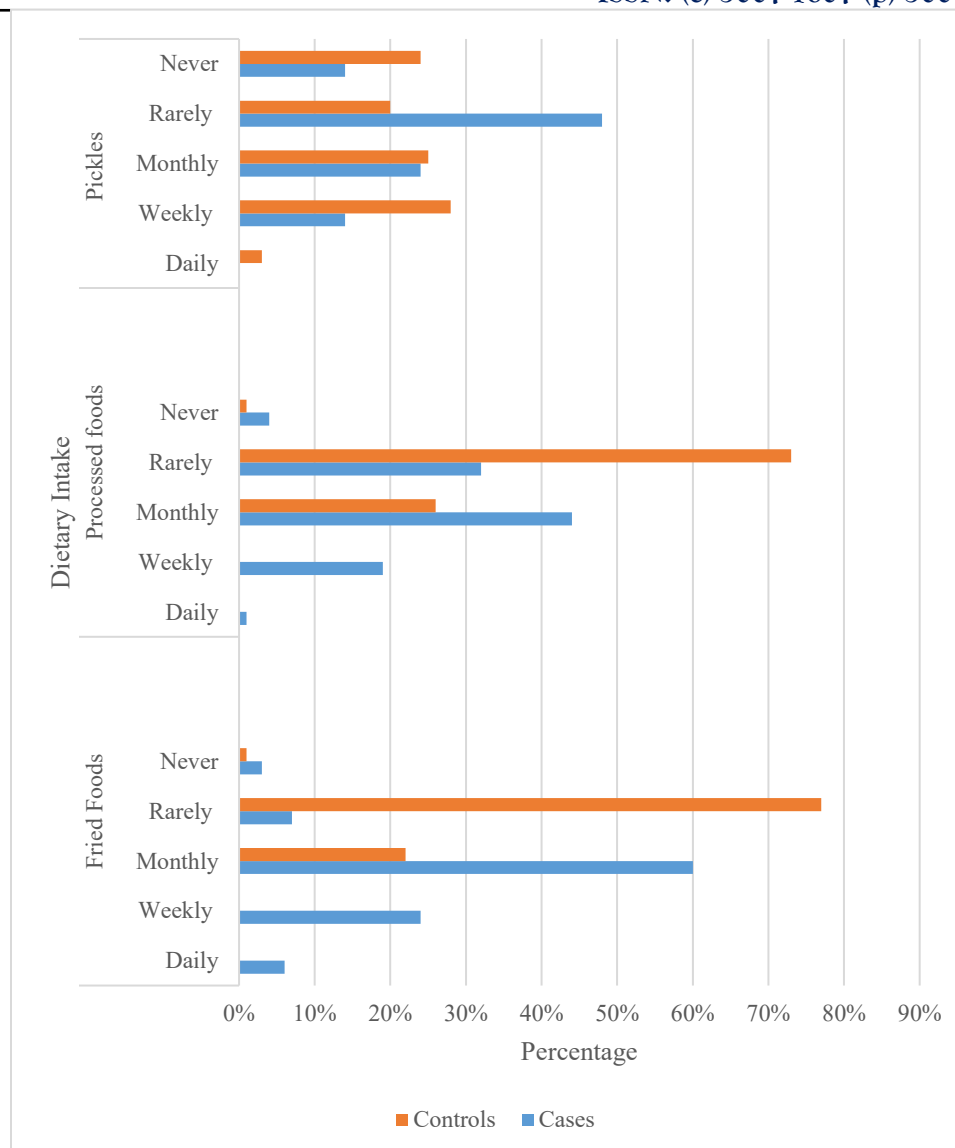**Figure 1: Type of fat used by the respondents for cooking**

Figure 3: Protein Intake of respondents from different sources

Conclusions

The study concluded that gallstone disease is significantly associated with modifiable risk factors, particularly unhealthy dietary patterns and lifestyle behaviors. Female gender, younger age, overweight status, low physical activity, low education, and family history emerged as key demographic and clinical correlates. Consumption of red meat, fried and processed foods, refined grains, banaspati ghee, and added sugars significantly increased the risk of gallstone formation. Conversely, higher intake of whole grains, vegetables, fruits, seafood, eggs, and dried fruits/nuts, as well as the use of vegetable oil instead of ghee, showed a protective effect. These findings reaffirm that gallstone disease is largely preventable through appropriate lifestyle and dietary modifications.

Recommendations

Based on the results, it is recommended to promote public awareness regarding healthy dietary practices to reduce the risk of gallstone disease. Interventions should emphasize the importance of consuming more plant-based foods, whole grains, seafood, and healthy fats such as vegetable oil, while minimizing the intake of refined carbohydrates, red meat, banaspati ghee, and processed foods. Public health programs should also address obesity, physical inactivity, and early screening for high-risk groups, particularly women in the reproductive age group.

Furthermore, integrating nutritional education into primary healthcare and community outreach initiatives can help mitigate gallstone disease burden in high-risk populations like those in Mardan.

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