



# The Relationship Between Malnutrition and Liver Enzymes in Hospitalized Children in Zahedan: A Case-control Study

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Received 2020 April 06; Revised 2020 June 25; Accepted 2020 July 07.

## Abstract

**Background:** Malnutrition causes nutritional, metabolism, and biochemical disorders and finally leads to mortality. Several studies have highlighted that serum liver enzymes are increased in patients with malnutrition.

**Objectives:** This study aimed to evaluate the relationship between malnutrition and liver enzymes in hospitalized children in Zahedan.

**Methods:** This case-control study was conducted among 145 hospitalized children under six years old, including 74 cases and 71 controls. The case group was diagnosed with malnutrition according to weight for age indices (Z-Score < -2SD), and controls were determined based on the following indices (Z-Score > -2SD) of classification of WHO 2006 growth standards. Serum was isolated after taking blood from the samples. Then liver enzymes, including AST, ALP, and ALT, were measured by spectrophotometric method.

**Results:** A total of 145 subjects were enrolled that consisted of 74 cases and 71 controls. No significant difference was observed in serum liver markers, including AST, ALT, and ALP between the two groups, However, the level of AST, ALT, and ALP was higher than the standard level. There was a significant correlation between AST with ALT ( $r = 0.74$ ,  $P < 0.001$ ), and ALP ( $r = 0.27$ ,  $P = 0.03$ ).

**Conclusions:** The findings indicated that there was no significant alteration in enzyme markers in the two groups. However, AST and ALT levels increased, and ALP levels decreased compared with the control. Different degrees of malnutrition, including mild, moderate, and severe, can probably change the levels of hepatic enzymes in under-nourished children. Alteration of these liver enzymes could be due to the metabolic modification, which can be the result of protein deficiency.

**Keywords:** Malnutrition, Enzymes, Alanine Aminotransferase, Aspartate Aminotransferase, Alkaline Phosphatase

## 1. Background

Protein-energy malnutrition (PEM) or malnutrition is a situation that progresses whilst the organism does not intake enough macro and micronutrients (1). It occurs in individuals who are either under-nourished or over-nourished (2). Classically, undernutrition has been well known as the biggest agent in malnutrition. It is the consequence of loss or waste of nutrient stock without being supplied or replaced (3). It underlies 45% of child deaths globally (4). Children who are previously malnourished are hurt from starvation and infection. Therefore, micronutrients such as mineral and trace elements are necessary for nutritional requirements and physiological ac-

tivities (5).

According to the World Health Organization (WHO), underweight, stunting, and wasting are defined as Z-scores less than -2 standard deviations of weight for age, height for age, and weight for height, respectively (6). Worldwide reports show that 21.9%, 13.4%, and 7.3% of those under 5 years of age are stunted, underweight, and wasted, respectively (7). At present, 88% of the countries are at risk of PEM based on 2 or 3 anthropometric malnutrition indicators (8). The last civil study in Iran in 1998 showed that 10.9% and 15.4% of children under five years suffer from underweight and stunting, respectively (9).

There is a close relationship between malnutrition and acute and chronic diseases. It has been proven that the dis-

ease can be the cause of malnutrition, and sometimes malnutrition is the cause of illness. Malnutrition is the main problem, which leads to several disorders in vulnerable groups (10). It has been shown that serum liver enzymes increase in patients with PEM (11). Patients who have been diagnosed with starvation hepatitis can be at risk of malnutrition by numerous mechanisms, including apoptosis, hypoperfusion of the liver, hypoxia, oxidative stress, and nutritional anemia (12, 13).

Hepatic enzymes such as Aspartate Amino Transferase (AST) and Alanine Amino Transferase (ALT) are the enzymes responsible for intracellular amino acid transport, which are abundant in the liver cells. These enzymes are released into the bloodstream after injury or death of liver cells (14). Alkaline Phosphatase (ALP) is a metalloenzyme of the cell membrane. It is responsible for phosphate group transport, and it helps break down proteins. Its activity increases in cases such as pregnancy and intra- and extrahepatic cholestasis. Most ALP levels are in the first six months of life (15). In some studies, decreased ALP activity has been reported in cases such as hypophosphatemia, PEM, zinc, and magnesium deficiency (16, 17). Malnutrition affects liver cells and causes liver enzyme imbalances. Several studies have shown that malnutrition increases the levels of liver enzymes such as ALT and AST in patients. These changes have been reported in different degrees of malnutrition. However, the amount of ALP was lower in malnourished children (18, 19).

Malnutrition and growth failure are the most problems in children leading to half of children's death in developing countries (20). Zahedan is located in the south-east of Iran. It is in neighboring Afghanistan and Pakistan. Although there are many efforts, facilities, and programs to improve the economic and nutritional standards in this area, there are still a lot of nutritional problems and deprivation in this region. Particularly in vulnerable groups such as children that suffered from undernutrition (UN) (21, 22). It should be noted that the burden of malnutrition is unacceptably high, and few studies are available to investigate the serum liver enzymes in children with the UN under six years in Iran, particularly Zahedan. So it is important to investigate this issue in this community.

## 2. Objectives

Therefore, the aim of this study was to determine the relationship between malnutrition and serum enzymes of the liver in hospitalized children under six years.

## 3. Methods

### 3.1. Study Design and Subjects

This case-control study was performed at the Pediatric Ward of the Imam Ali Hospital in Zahedan, south-east of Iran, from September 2017 to December 2017. This study was done among 145 hospitalized children under six years. The study population consisted of 74 cases (39 boys and 35 girls) and 71 controls (46 boys and 25 girls).

### 3.2. Inclusion and Exclusion Criteria

Inclusion criteria were children of either gender under six years who were referred to the pediatrics clinic of the hospital because of malnutrition and also various complaints that consequently required hospitalization. Exclusion criteria were children with congenital malformations, chronic diseases, and any systematic disorders. Both groups were evaluated and selected by a pediatrician. After taking informed consent from the parents or guardians of children in two groups, they were asked questions based on the aim of the study.

### 3.3. Diagnosis of Undernutrition

In this study, weight for age was determined using the nutritional reference standards recommended by the WHO cut-off point. UN was defined as less than -2 standard deviation (-2SD) of weight for age Z-Scores (23). Accordingly, the case group was diagnosed. Moreover, the controls were selected based on weight for age above -2SD of WHO 2006 growth standards.

### 3.4. Blood Sampling and Biochemical Tests

Considering aseptic precautions, 3 ml of blood was drawn from the participants. Centrifuging the blood sample at 2000 for 10 min., the serum was separated. Serum Enzymes were assessed by the kinetic method. Aspartate aminotransferase (AST), Alanine aminotransferase (ALT), and Alkaline Phosphatase (ALP) serum levels were measured by commercial kit and routine laboratory methods.

After recording demographic characteristics of samples in two groups, liver enzymes, including AST, ALP, ALT, were measured by spectrophotometric method, Pars Azmun Kit, Iran, and a Hitachi 902 Automatic Analyzer. The bodyweight of the participants was measured with light clothing and without wearing shoes on a duly calibrated electronic anthropometric scale in the presence of the mother. These measures were performed twice, and the mean was used for the calculation of the indices.

### 3.5. Ethics Statements

The ZAUMS board of ethics approved the study protocol (IR.ZAUMS.REC.1395.39 code). The purpose of the study was explained to the participants and managed as per standard protocol.

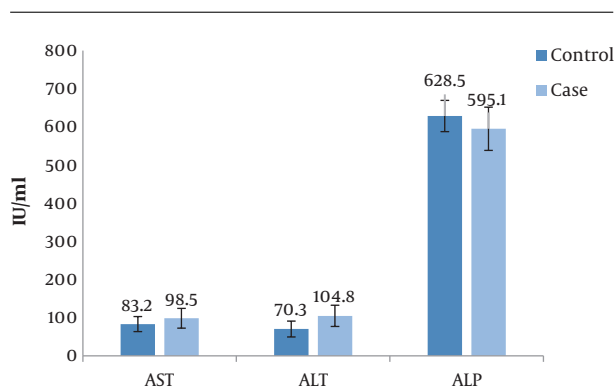
### 3.6. Statistical Analysis

Statistical analysis was done using SPSS, version 21. All data were expressed by mean  $\pm$  SD and frequency distribution. Comparison between two groups was analyzed by independent sample T-test in quantities variables and Chi-square in qualitative. Spearman correlation coefficients were used to find the association between the variables.  $P < 0.05$  was considered statistically significant (Table 1).

## 4. Results

A total of 145 subjects were enrolled that consisted of 74 cases (39 males and 35 females) and 71 controls (46 males and 25 females). The age of the participants in the case and control groups are shown in Table 2. No significant difference was observed between the two groups based on age ( $P > 0.05$ ). There was not a significant difference between the two groups based on sex ( $P > 0.05$ ). In other words, two groups were adjusted together.

The levels of liver enzymes, including AST, ALT, and ALP, are shown in Figure 1.



**Figure 1.** The levels of ALT, AST, and ALP serum enzymes in the studied groups

AST, ALT, and ALP are measured in international units per liter (IU/L). Data are presented as mean  $\pm$  SD. The result of this study showed the levels of serum enzymes, including AST and ALT in the case group, were higher than the control group. However, the ALP level was lower in the case group compared with the control. However, these differences were not significant (Figure 1).

A significant correlation was observed between AST and ALT ( $r = 0.735$ ,  $P < 0.0001$ ), AST and ALP ( $r = 0.267$ ,  $P = 0.033$ ), and age and body weight ( $r = 0.946$ ,  $P < 0.0001$ ), while there was only a significant correlation between AST and ALT ( $r = 0.947$ ,  $P < 0.0001$ ), and between age and body weight ( $r = 0.95$ ,  $P < 0.0001$ ) in the control group.

## 5. Discussion

This case-control study revealed that there was no significant difference among the studied groups based on the levels of serum enzymes. However, it was observed a slight increase in the concentration of AST and ALT, and a reduction in the level of ALP levels in the patients. Rao A et al. reported the aminotransferase elevation in children suffering from PEM. They revealed that there was a positive relationship between aminotransferase increase and severity index calculated from height and weight retardation (24). In the present study, a significant correlation was observed between AST and ALT, AST and ALP levels, and between age and body weight, respectively.

According to UNICEF, the prevalence of stunting and underweight in Iranian children below five years of age was 15% and 11%, respectively (25, 26). It has been reported 65% to 90% of malnutrition is related to different forms of liver disease (27-29). Several studies have been done in different areas of Iran around the prevalence of malnutrition in different groups of children (30-33). But based on our knowledge, the studies on the association between liver enzymes and UN status in children are very limited.

The result of this study showed the levels of serum enzymes, including AST and ALT in the case group, were more than controls. On the contrary, the level of ALP was decreased. However, this difference was not significant. It seems different degrees of malnutrition, including mild, moderate, and severe, probably change the levels of hepatic enzymes in the UN children. Similar to the present study, Kumari et al. demonstrated that the mean serum enzymes values such as ALP, cholinesterase, and lactate dehydrogenase in malnutrition were significantly lower than the healthy subjects. But the mean serum concentrations of AST and ALT in malnourished children were significantly higher than the controls, and the maximum raise mentioned enzymes were in patients with PEM Grade I. On the contrary, the level of ALP decreased in malnutrition. Because serum ALP may be reduced due to impairment of protein synthesis in the liver. These findings are suggested that abnormalities in the serum levels of enzymes happen in different forms of PEM, (34). Additionally, in another study, Samantha et al. showed that 25%-50% of patients with cystic fibrosis had elevated liver enzymes that

**Table 1.** Correlation Coefficients Between Different Variables in the Case Group

Variables	Case		Control	
	r	P	r	P
AST and ALT	0.735	< 0.0001	0.67	< 0.0001
AST and ALP	0.267	0.033	0.9	0.43
ALT and ALP	-0.002	0.986	0.27	0.3
AST and BW	0.029	0.804	0.1	0.38
ALT and BW	-0.009	0.939	0.17	0.15
ALP and BW	-0.123	0.334	-0.05	0.7
Age and AST	-0.003	0.978	0.15	0.2
Age and ALT	-0.009	0.939	0.16	0.2
Age and ALP	-0.123	0.334	0.005	0.97
Age and BW	0.95	< 0.0001	0.91	< 0.0001

Abbreviations: ALT, Alanine transaminase; AST, Aspartate transaminase; ALP, Alkaline phosphatase; BW, Body Weigh

**Table 2.** Frequency Distribution of Age in the Studied Groups<sup>a</sup>

Groups, Age	Case, No. %	Control, No. %	Total, No. %
< 6 month	26, 74.3	9, 25.7	35, 100
6mon-1 years	13, 52	12, 48	25, 100
1-2 years	16, 45.7	19, 54.3	35, 100
2-3 years	9, 37.5	15, 62.5	24, 100
3-4 years	4, 50	4, 50	8, 100
4-5 years	3, 33.3	6, 66.7	9, 100
5-6 years	3, 33.3	6, 66.7	9, 100

<sup>a</sup>  $\chi^2 = 11.97$ ,  $df = 6$ ,  $P = 0.06$ .

may be caused by malnutrition. They have reported almost all the children with cystic fibrosis had at least one increased liver enzyme, such as abnormality in Gamma-glutamyl transpeptidase (GGT) and ALT activity (35). Elissa Rosen et al. declared that malnutrition was associated with increased liver enzymes in eating disorders, particularly anorexia nervosa (AN) (36). Freijer et al. showed that Disease-related Malnutrition (DRM) is related to a 40% increase in charge of hospital treatment compared to children without DRM, especially in children aged 1-4 years (37). In recent years, evidence has shown that 17-25% of children patients are influenced by malnutrition (38, 39).

Disorders in the function and concentration of liver enzymes can cause inappropriate conditions in the body, which may lead to PEM. It seems the most breakdown of tissue has been done in the initial steps of PEM. It was also observed an increase in serum ALT and AST in Grade 2 more than Grade 3 PEM. The concentration of ALP is reduced in a direct proportion to the severity of PEM. Nevertheless,

these enzymes can be valuable indicators, which apply to diagnosis and predictive clinical evidence (19).

In the present study, it was observed a correlation between AST with ALT and also ALP serum levels in the UN children. The present results represent a significant correlation between these liver enzymes, not the severity of correlation between them. Nevertheless, the correlation between the level of liver enzymes and different degrees of malnutrition needs more studies and precise evaluation of the clinical and nutritional status of patients.

Unfortunately, because of the limitation of samples, we could not determine different grades of PEM. It seems the moderate increase in AST and ALT level in malnutrition is not due to damage of the liver. However, it can be due to increased tissue breakdown. Besides, the progression of the transamination mechanism leads to increased activity of ALT and AST levels in the body. Decrease in ALP could be due to protein deficiency leading to synthesis reduction and failure of bone growth and weight loss in the children (34). Several limitations of the present study are as follows: the cross-sectional nature of the study, limited sample size, and insufficient facilities to accurately measure more liver serum enzymes, and determination of different degrees of malnutrition in the patients. It is difficult to present a fundamental relationship based on this cross-sectional design. Nevertheless, further studies are needed to understand factors affecting these markers during malnutrition, especially, PEM is known to be a chronic disease, not an acute one.

### 5.1. Conclusion

In the present study, it was revealed that there was no significant difference in enzyme markers between the two

groups. Besides, serum enzymes, including AST and ALT levels in the patients, were higher, and ALP level was lower than controls insignificantly. It seems different degrees of malnutrition, including mild, moderate, and severe, can probably change the levels of hepatic enzymes in undernourished children. Besides, in comparison to published data, the changes of serum enzymes probably indicate alteration of these liver enzymes due to metabolic modification, consequent from protein deficiency.

## Acknowledgments

We would like to thank the children for their informed collaboration and gratefully acknowledge their parents and colleagues who willingly cooperate in this study.

## Footnotes

**Authors' Contribution:** Mansour Karajibani and Farzaneh Montazerifar conceived and designed the research. Fatemeh suni, Mahshid Fadaeimokhtarkhanlo, and Razieh Hosseini performed experiments and prepared tools and facilities for field study; Ali Reza Dashipour performed statistical analysis; Mansour Karajibani and Farzaneh Montazerifar drafted and revised the manuscript.

**Conflict of Interests:** No potential conflict of interest relevant to this article was reported.

**Ethical Approval:** ZAUMS Board of Ethics approved the study protocol (IR.ZAUMS.REC.1395.39- 2017 Nov 7).

**Funding/Support:** This research has been approved and supported by the Deputy of Research of Zahedan University of Medical Sciences with financial assistants (registration no. 8391: 2017 June 7).

**Informed Consent:** Informed consent was obtained from parents or keepers of children in two groups.

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