Original Article from Thesis

Acute phase reactants in Sudanese children with severe protein-energy malnutrition*

Omer S. M. Suliman (1),** Mustafa A. M. Salih (1),** Zein A. Karrar (1), Abdelrahim O. Mohammed (2), Chrestover Helsing (3)

(1) Department of Paediatrics and Child Health, Faculty of Medicine, University of Khartoum, Sudan
(2) Department of Biochemistry, Faculty of Medicine, University of Khartoum, Sudan
(3) The Central Laboratory, Uppsala University, Sweden

**The first two authors contributed equally.

ABSTRACT

The pre-dietary rehabilitation levels of acute phase proteins (APP) namely, alpha-1-antitrypsin (AAT), orosomucoid (ORO), haptoglobin (HAP), fibrinogen (FIB) and C-reactive protein (CRP) in the plasma of Sudanese children with severe protein energy malnutrition (PEM) were compared with those of normal controls, and with the levels after dietary rehabilitation. Eighty one children were included in the study; 49 with severe PEM (23 with marasmus, 17 with marasmic-kwashiorkor and 9 with kwashiorkor), 13 with tuberculosis (TB) and 19 healthy children as controls. The study showed a high incidence of infections, especially acute respiratory infection (ARI), diarrhoeal diseases and intestinal parasites in the malnourished children. The mean plasma level of albumin was significantly lower in the malnourished children compared to controls (P<0.001), with kwashiorkor children showing the lowest mean level. This hypoalbuminaemia was significantly associated with the presence of ARI and intestinal parasites. The mean plasma levels of the APP, except FIB, were significantly higher in malnourished children than in controls, with higher levels associated with ARI and the presence of fever. Malnourished children with TB had significantly higher mean levels of the APP (AAT, HAP, FIB, CRP) compared to those without TB. The mean levels of HAP and AAT were significantly lower in the presence of diarrhoea, suggesting their loss in the stool. The mean levels of the APP after two weeks dietary rehabilitation and antimicrobial treatment showed a significant drop in only two of the APP, namely CRP, ORO, while FIB showed a significant rise.

Key words: Acute phase proteins; Protein-energy malnutrition; Sudanese children; Acute respiratory infection; Tuberculosis.

Correspondence to: Dr. Omer S. M. Suliman, Department of Pediatrics, Al Rass General Hospital, Al Qassim, Saudi Arabia E-mail: omersuli@yahoo.co.uk

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INTRODUCTION

Malnutrition is a major contributor to mortality and is increasingly recognized as a cause of potentially life-long functional disability [1]. The severely malnourished child has dysfunction of the immune response that may increase the risk of morbidity or mortality due to infectious diseases [2]. The synergistic malnutrition–infection complex has significant effects on child health [3-5]. With the superimposition of infection on the metabolic states in malnutrition, essential amino acids are diverted to the production of acute phase proteins (APP) rather than the visceral proteins [6]. The APP response is regulated by cytokines such as interleukin-6 (IL-6), interleukin-1 (IL-1) and tumor necrosis factor (TNF), but may also be influenced by malnutrition [7]. Data by Ling et al [8] showed that malnutrition induces a low-grade inflammatory state in rats, as evidenced by elevated serum levels of TNF, IL-1, IL-6, alpha acid glycoprotein and reduced level of albumin.

An APP has been defined as one whose plasma concentration increases (positive APP) or decreases (negative APP) by at least 25% during inflammatory disorders [9]. IL-6 is the chief stimulator of the production of the positive APP [9], while the negative APP is decreased by another cytokine-mediated mechanism, as well. The cytokine, TNF and secondary eicosanoid metabolites cause capillary membrane leak causing hypoalbuminemia [10]. The extent and quality of the APP response are dependent on the host nutritional state and the severity of the infection [11]. Severe PEM may affect the APP response by reducing the availability of precursors for APP synthesis or by reducing the synthesis of modulating pro-inflammatory factors such as IL-1 and IL-6 [12].

In a study of infected children with marasmus, it was shown that the kinetic mechanisms used in mounting an APP response included alterations in both the rates of synthesis and catabolism of the protein [13]. It has also been suggested that specific deficiency of amino acids such as cysteine, glycine, or serine, may limit the production of some of the acute phase proteins (APP) which are proportionally very rich in these amino acids [14]. The increased synthesis of the positive APP in the liver is accompanied by a decrease in the production of the nutritionally important proteins such as albumin and transferrin [10]. From data presented by Fleck [11] and Colley and Fleck [15], a minimum synthesis rate of APP in response to an acute injury was estimated to be 1.2 gm of protein per kg per day, which is six times the normal rate of albumin synthesis in an adult man. This may well constitute a serious drain on the capacity of the liver to synthesize the negative APP.

The aims of this prospective study were to determine the pattern of APP in children with severe protein energy malnutrition (PEM) and to evaluate their behavior during the recovery phase of PEM. Another goal was to examine the effects of infection on APP levels in malnourished children.

MATERIAL AND METHODS

The study was conducted at the University Pediatric Wards of Khartoum Teaching Hospital (KTH) and Soba University Hospital (SUH), and the Pediatric Surgical Ward of the KTH, Khartoum, Sudan, over a six months period (December 1992 – May 1993). The Pediatric wards at KTH and SUH are general pediatric wards to which children with various medical problems are admitted; 25-30 of the bed complement on each ward are assigned to children with severe forms of PEM.

A total of 81 children were included in the study. Forty-nine (60.5%) of them had various forms of severe PEM (marasmus 23 [46.9%], marasmic–kwashiorkor 17 [34.7%] and kwashiorkor 9 [18.4%]); this included eight children who also had pulmonary
tuberculosis (TB). They were newly admitted with severe PEM classified according to the Welcome classification [16], using NCHS charts [17] and were aged between six months and five years. The remaining 32 comprised 13 children with various forms of TB but without severe PEM and 19 well nourished others (aged six months to five years) with minor surgical problems; the latter served as controls. The findings during detailed history and physical examination were entered on to a comprehensive protocol sheet which was completed for each child. The patients and controls were weighed initially and again, two weeks later. The same weighing machine was used throughout and weight was recorded to the nearest 0.1 kg. The mid-arm circumference (MAC) was recorded to the nearest 0.1 cm using a fiberglass tape. Urinalysis, stool examination (for parasites), chest X-ray and Mantoux test were done for every child. Urine cultures and sensitivities were also done in those with significant bacteriuria. Five ml of blood was obtained from each child into citrated tubes; 2.5 ml of this was sent for the estimation of haemoglobin (Hb), packed cell volume (PCV), erythrocyte sedimentation rate (ESR) and white blood count (WBC) in the central laboratory of KTH; the other 2.5 ml was sent for plasma separation, in sterile cryotubes which were stored at -20°C and later transported in dry ice to Sweden for determination of the APP and albumin.

**Analysis of the plasma**

Plasma samples were analyzed at the Central Laboratory, Uppsala University Hospital, Uppsala, Sweden. Each sample was analyzed for plasma albumin, using the dye binding (Bromocresol green) method and also for some of the acute phase proteins (APP) which included alpha-1-antitrypsin (AAT), orosomucoid (ORO), haptoglobin (HAP), fibrinogen (FIB) and C-reactive protein (CRP). The various proteins were separated using the agarose gel electrophoresis. Then the level of each protein was measured using the rate nephelometric method (ArryTM protein system model 7571; Beckam Immunochemistry Systems CA, Palo Alto, USA). Due to some logistical problems, analysis of the CRP was carried out on some plasma samples from malnourished children only, and was not done on samples from the control or tuberculous groups.

Follow up examination and blood sample collections were carried out two weeks later, in 28 of the 49 children with PEM. These samples were obtained and analysed using the same methods as were used for the initial samples. During the intervening period, the children were fed with high calorie milk-based feeds, and any infection was treated with the appropriate antimicrobial drugs.

**Statistical analysis**

The data was analyzed by an IBM computer using Epi Info program and SPSS statistical package. The paired student t-test was used for comparison within the different study groups. A P-value <0.05 was considered significant.

**RESULTS**

Nine (11.1%) of the 81 were aged below 12 months, 60 (74.1%) were 13-36 months and 12 (14.8%) were older than 36 months. The groups were comparable with regard to age, except those with TB who were significantly older than the other groups (mean age 18.7 months; P < 0.001). The male: female ratio for the study population was 1.9:1; the ratio among the groups were 1.9:1 for marasmus, 1.1:1 for marasmic-kwashiorkor, 1.2 :1 for kwashiorkor, 2:1 for the controls and 5.5:1 for TB.

The mean plasma albumin levels were significantly lower in the malnourished groups compared to controls (p<0.01)
while the APP (AAT, ORO, HAP) were significantly higher (P<0.01, P<0.001, P<0.05, respectively). However, the plasma FIB level showed no significant difference between the two groups (Table I).

Table 1 - Plasma acute phase protein (APP) levels in malnourished and control groups

<table>
<thead>
<tr>
<th>Acute phase protein</th>
<th>Malnourished (n = 49)</th>
<th>Controls (n=19)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Albumin [g/L]</td>
<td>28.4(4.06)</td>
<td>33.7(5.1)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>AAT [g/L]</td>
<td>2.4(1.1)</td>
<td>1.52(0.6)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>ORO [g/L]</td>
<td>2.47(1.1)</td>
<td>0.78(0.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HAP [g/L]</td>
<td>1.7(0.6)</td>
<td>1.02(0.6)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>FIB [g/L]</td>
<td>2.6(1.4)</td>
<td>2.56(0.7)</td>
<td>&gt;0.05</td>
</tr>
</tbody>
</table>

Values are given as mean (SD)

The Kwashiorkor group had the lowest albumin level compared to other groups (P<0.001). The marasmic group had the highest AAT level compared to the marasmic-kwashiorkor and kwashiorkor groups. ORO level was significantly higher in the three PEM groups, with the oedematous group (kwashiorkor and marasmic-kwashiorkor) having significantly higher levels than the marasmic group (P<0.001, P<0.001, P<0.005, respectively). While the HAP level was only significantly high in the marasmic group (P<0.05), the FIB level was significantly lower in the kwashiorkor and marasmic-kwashiorkor groups compared to controls (p<0.05; Table 2).

Table 2 - Acute phase protein (APP) levels according to types of malnutrition and in controls

<table>
<thead>
<tr>
<th>Acute phase protein</th>
<th>Marasmus (n = 23)</th>
<th>Marasmic-kwashiorkor (n = 17)</th>
<th>Kwashiorkor (n = 9)</th>
<th>Controls (n = 19)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Albumin [g/L]</td>
<td>26.7(7) **</td>
<td>26.8(6.8) **</td>
<td>16.5(4.2) ****</td>
<td>33.7(5)</td>
</tr>
<tr>
<td>AAT [g/L]</td>
<td>2.8(1.2) ***</td>
<td>2.05(0.95) **</td>
<td>1.9(0.5) **</td>
<td>1.52(0.6)</td>
</tr>
<tr>
<td>ORO [g/L]</td>
<td>2.4(1.5) ***</td>
<td>2.6 (0.7) ****</td>
<td>2.4 (0.5) ****</td>
<td>0.78 (0.4)</td>
</tr>
<tr>
<td>HAP [g/L]</td>
<td>2.3(1.8) **</td>
<td>1.3(1.4) *</td>
<td>0.87(0.9) *</td>
<td>1.02(0.7)</td>
</tr>
<tr>
<td>FIB [g/L]</td>
<td>3.8(1.5) *</td>
<td>2.1(1.2) **</td>
<td>2.1(1.2) *</td>
<td>2.56(0.7)</td>
</tr>
</tbody>
</table>

AAP - alpha-1-antitrypsin, FIB – fibrinogen, HAP - haptoglobin, ORO - orosomucoid.
Values are given as mean (SD)
* P > 0.05 (NS)
** P < 0.05
*** P < 0.005
**** P < 0.001

After two weeks of dietary rehabilitation, the plasma albumin showed no significant change in the malnourished and the oedematous groups, while its level had increased significantly in the marasmic group (P<0.01). The level of AAT and HAP showed no significant change, while ORO and CRP levels had decreased significantly in all malnourished groups, with the oedematous group showing the most significant drop in ORO (P < 0.001) and the marasmic group showing the most significant drop in CRP (P < 0.001) [Table 3].

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Table 3 - Acute phase proteins according to types of malnutrition, on admission and after dietary rehabilitation

<table>
<thead>
<tr>
<th>Acute phase proteins</th>
<th>All malnourished</th>
<th>Marasmus</th>
<th>The oedematous group*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Sample 1 (n = 49)</td>
<td>Sample 2 (n = 28)</td>
<td>Sample 1 (n = 23)</td>
</tr>
<tr>
<td>Albumin [g/L]</td>
<td>35.49 (5.07)</td>
<td>33.18 (7.05)*</td>
<td>25.8 (8.3)</td>
</tr>
<tr>
<td>AAT [g/L]</td>
<td>2.38 (0.94)</td>
<td>2.07 (0.53) *</td>
<td>2.67 (1.30)</td>
</tr>
<tr>
<td>ORO [g/L]</td>
<td>2.18 (0.91)</td>
<td>1.55 (0.91)**</td>
<td>2.5 (2.8)</td>
</tr>
<tr>
<td>HAP [g/L]</td>
<td>1.71 (1.58)*</td>
<td>1.75 (1.26)</td>
<td>1.9 (0.9)*</td>
</tr>
<tr>
<td>FIB [g/L]</td>
<td>2.57 (1.2)</td>
<td>3.3 (1.3)**</td>
<td>2.9 (1.9)</td>
</tr>
<tr>
<td>CRP [g/L]</td>
<td>31.8 (41.1)</td>
<td>19.2 (19.4)**</td>
<td>45.8 (5.2)</td>
</tr>
</tbody>
</table>

AAP - alpha-1-antitrypsin, FIB – fibrinogen, HAP - haptoglobin, ORO - orosomucoid

*The oedematous group includes those with kwashiorkor and others with marasmic-kwashiorkor

Values are given as mean (SD)

Sample 1 was obtained on admission
Sample 2 was obtained two weeks after dietary rehabilitation

*   P > 0.05 (NS)
**  P < 0.05
*** P < 0.01
**** P < 0.001

The malnourished children had significantly lower levels of Hb and PCV compared to controls, and significantly higher ESR and WBC. After two weeks of treatment, these haematological indices including the ESR showed no significant changes. Thirty-two (78%) of 41 malnourished children without pulmonary TB, had acute respiratory tract infections (ARI); 18 (43.9%) had pneumonia, eight (19.5%) had otitis media and six (14.6%) had other upper respiratory tract infections (URTI). Forty-three (87.8%) of all the 49 malnourished children had diarrhoea, and half of them had parasites in the stool, mainly *Giardia lamblia* and *Entamoeba histolytica*. The urine was cultured in 13 malnourished children (28.5%) who had significant pyuria; nine had positive cultures of which 6 were E.coli , 2 were Proteus and one Klebsiella spp. The mean plasma albumin was significantly lower in the presence of ARI (P<0.001) while the other APP showed significantly high levels in the presence of ARI with the highest level attained by ATT (P<0.001; Table 4). In those with fever, all APP except ORO, showed significantly higher levels (P<0.05). In the presence of diarrhoea, the levels of HAP and AAT, were significantly low.
### Table 4 - Acute phase proteins in relation to fever, infections and diarrhoea

<table>
<thead>
<tr>
<th>Acute phase proteins</th>
<th>Fever</th>
<th>ARI</th>
<th>Diarrhoea</th>
<th>Parasites in stool</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Present</td>
<td>Absent</td>
<td>Present</td>
<td>Absent</td>
</tr>
<tr>
<td>(n = 23)</td>
<td>(n = 26)</td>
<td>(n = 32)</td>
<td>(n = 9)</td>
<td>(n = 43)</td>
</tr>
<tr>
<td>Albumin [g/L]</td>
<td>33.9(5.7)***</td>
<td>33.1(8.4)***</td>
<td>33.3(8.3)***</td>
<td>35.8(6.2)***</td>
</tr>
<tr>
<td>AAT [g/L]</td>
<td>2.59(1.1)***</td>
<td>2.2(1.1)***</td>
<td>2.83(1.2)***</td>
<td>1.77(0.5)***</td>
</tr>
<tr>
<td>ORO [g/L]</td>
<td>2.45(0.8)***</td>
<td>2.51(1.4)***</td>
<td>2.75(1.3)***</td>
<td>2.1(0.7)***</td>
</tr>
<tr>
<td>HAP [g/L]</td>
<td>2.1(1.1)***</td>
<td>1.33(1.5)***</td>
<td>2.17(1.7)***</td>
<td>1.02(1.2)***</td>
</tr>
<tr>
<td>FIB [g/L]</td>
<td>2.9(1.5)***</td>
<td>2.35(1.3)***</td>
<td>3.08(1.6)***</td>
<td>1.99(0.93)***</td>
</tr>
<tr>
<td>CRP [g/L]</td>
<td>47.8(52)***</td>
<td>28.4(32)***</td>
<td>49(49)***</td>
<td>14.9(17.7)***</td>
</tr>
</tbody>
</table>

AAP - alpha-1-antitrypsin, ARI – acute respiratory infection, CRP, C-reactive protein, FIB – fibrinogen, HAP - haptoglobin, ORO - orosomucoid

Values are given as mean (SD)

* P > 0.05 (NS)

** P < 0.05

*** P < 0.01

**** P < 0.001

Eight (16.3%) of the 49 malnourished children had pulmonary TB (Table 5). No significant differences in the ESR and other haematological indices were found in the malnourished children with TB and those without. By contrast, the APP (AAT, HAP, FIB and CRP) showed significantly higher levels in the malnourished group with TB than in those without TB (P<0.01, P<0.01, P<0.01, P<0.001 respectively).
Table 5 - The acute phase proteins and the haematological indices in the malnourished children with tuberculosis (TB) compared to those without tuberculosis and controls

<table>
<thead>
<tr>
<th>Acute phase protein</th>
<th>Malnourished with TB (n=8)</th>
<th>Malnourished without TB (n=8)</th>
<th>Controls (n=19)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Albumin [g/L]</td>
<td>28.6 (7.1)</td>
<td>28.3 (4.4) *</td>
<td>33.7 (5.1) **</td>
</tr>
<tr>
<td>AAT [g/L]</td>
<td>3.19 (0.8)</td>
<td>2.24 (1.1) ***</td>
<td>1.52 (0.65) ****</td>
</tr>
<tr>
<td>ORO [g/L]</td>
<td>2.23 (0.9)</td>
<td>2.53 (1.18) *</td>
<td>0.78 (0.48) ***</td>
</tr>
<tr>
<td>HAP [g/L]</td>
<td>3.03 (1.3)</td>
<td>1.44 (1.6) ***</td>
<td>1.02 (0.66) ****</td>
</tr>
<tr>
<td>FIB [g/L]</td>
<td>3.74 (1.5)</td>
<td>2.4 (1.3) ***</td>
<td>2.56 (0.7) ***</td>
</tr>
<tr>
<td>CRP [g/L]</td>
<td>47 (20)</td>
<td>13.6 (14) ****</td>
<td>-</td>
</tr>
<tr>
<td>ESR [mm/hr]</td>
<td>75.9 (49)</td>
<td>55.3 (44.9)*</td>
<td>25.2 (13.6)***</td>
</tr>
<tr>
<td>WBC [mm3]</td>
<td>4750 (1489)</td>
<td>5756 (1758)*</td>
<td>4668 (1225)*</td>
</tr>
<tr>
<td>Hb [ gm/dl]</td>
<td>7.4 (1.6)</td>
<td>7.5 (1.9)*</td>
<td>9.3 (1.8)**</td>
</tr>
<tr>
<td>PCV (%)</td>
<td>22.5 (5.4)</td>
<td>23.2 (7.4)*</td>
<td>28.1 (4.8)*</td>
</tr>
</tbody>
</table>


Values are given as mean (SD)

*   P > 0.05 (NS)
**  P < 0.01
*** P < 0.001
**** P < 0.0001

Likewise, the mean APP (AAT, ORO, HAP) levels were significantly higher in the malnourished children with TB compared to the well nourished children with TB, while no significant change was observed in the level of ESR and FIB (Table 6).

Table 6: Acute phase reactants (APR) in tuberculous children with and without malnutrition

<table>
<thead>
<tr>
<th>APR</th>
<th>TB with PEM (n=8)</th>
<th>TB without PEM (n=13)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ESR (mm/hr)</td>
<td>75.9 (43.9)</td>
<td>55.5 (45)</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>AAT (g/L)</td>
<td>3.2 (0.8)</td>
<td>2.4 (0.71)</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>ORO (g/L)</td>
<td>2.22 (0.14)</td>
<td>1.54 (0.9)</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>HAP (g/L)</td>
<td>3.03 (1.5)</td>
<td>1.9 (1.5)</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>FIB (g/L)</td>
<td>3.7 (1.5)</td>
<td>3.43(1.5)</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Albumin (g/L)</td>
<td>22.6 (7.1)</td>
<td>325.02</td>
<td>&lt; 0.01</td>
</tr>
</tbody>
</table>


Values are given as mean (SD)
The malnourished children with hepatomegaly (28.6%) had significantly lower level of albumin (P<0.001), but no significant change in the level of any of the APP compared to those without hepatomegaly.

**DISCUSSION**

The aims of this study were to determine the pattern of the APP in children with severe PEM compared to well-nourished children, and to determine whether severely malnourished children can mount a general APP response to infection that includes different types of APPs and whether there is any difference in this APP response to infection between the edematous and the non-edematous PEM.

The APPs selected (CRP, hapatoglobin, alpha-1-antitrypsin, orosomucoid, also called alpha-1-acid glycoprotein, and fibrinogen) were chosen because they are representative of APPs with widely different functions [9]. In this study, the higher concentration of three of the APPs (AAT, ORO and HAP) in the infected malnourished state compared to those of well-nourished non-infected children confirm that, the severely malnourished children are capable of mounting an APP response. However, the response dose not includes all the APPs, as the plasma concentration of FIB showed no difference between the two groups. How can the severely malnourished child mount this response, remained unclear. As shown by Golden et al [18] and Tomkins et al [19], whole body protein synthesis rate is reduced in the infected malnourished child compared with both infected and uninfected well-nourished children, suggesting that the malnourished may be mounting an APP response through mechanisms other than a stimulation of synthesis rate. A study by Morlese et al [13] suggested that, in severe malnutrition, the increased pool sizes of the APPs are achieved through mechanisms that involved changes in both the rate of synthesis and catabolism of these proteins. It is possible that the ability of the severely malnourished child to increase the availability of APP by reducing its rate of catabolism represents an adaptive mechanism which has the advantage of conserving the limited supply of amino acids. Our finding of higher APP response in the malnourished children is also reported by many other authors [13, 20-22]. However Razban et al [20], surprisingly, reported significantly low levels of AAT in the malnourished children, a finding not reported by any other study. It is interesting that the plasma fibrinogen concentrations in the children with severe PEM were not significantly different from well nourished children. The major role of fibrinogen is in wound healing [23]. Therefore, its limited availability is not likely to affect the capacity of the malnourished child to combat an infection but certainly will interfere with his recovery from surgery or an injury. Limited availability of this APP is likely to be related to the skin excoriation that are characteristic of the edematous malnutrition, as well as, to the documented delay in post-surgical wound healing in the malnourished child [24].

In the present study, we could confirm different APP response between the edematous (marasmus – kwashiorkor and kwashiorkor) and non-edematous (marasmus) malnourished children, by showing higher plasma levels of two APP, namely AAT and HAP, in the non-edematous group compared to the edematous group, while ORO showed no significant difference. This has also been shown by other studies [25, 26]. As has also been observed by Reid et al [12], children with edematous PEM can mount an APP response to infection that is similar to the response of children with non-edematous PEM, but the magnitude of the response is less in children with edematous PEM. The weaker response in the edematous group is not surprising, because other aspects of host defense, relating to immune structure and function, are more compromised in children with the edematous PEM than those with non-edematous PEM [25].
In this study, we noticed that while the plasma albumin level was low, the levels of the APP were high in the malnourished children. This has also been observed by Fleck [11], Colley and Fleck [15], and Liao et al [27]. This finding may suggest that, although the synthesis of some of the plasma proteins may decrease because of deficiency of amino acids in the malnourished child, the synthesis of other proteins (APP) may be increased. It is possible that the limiting factor may be the liver, as it is invariably involved in PEM [26]. Although we did not find any significant difference in the plasma levels of the APP in the malnourished children with and without hepatomegaly, further studies are required in this respect. Another explanation for the high levels of the APPs in PEM may be the result of trauma caused by the general wasting effect known to occur in malnutrition [28]. This may simulate the effect of surgical trauma on the level of plasma APPs, as observed by Crokson et al [29] who reported significant elevation of six APPs at varying time intervals following surgical trauma. It is also likely that concomitant infections, which are usually prevalent in PEM, as shown by many studies [30-33] are involved in the causation of the elevated levels of APPs in PEM. In the present study, we confirm this assumption by finding significantly high levels of all the APPs studied in the malnourished children with ARI and a significantly high levels of AAT, HAP, FIB and CRP in the presence of fever. In addition, the mean levels of these APPs were also found to be significantly higher in the malnourished children with TB compared to those without TB. This is in contrast of our findings of a non-significant difference in the ESR between the malnourished children with or without TB. Our finding of significantly low levels of HAP and AAT and no rise in the levels of the other APPs in association with diarrhea may be explained by their loss in stool and may suggest factors other than infections as a cause of diarrhea in PEM [33]. AAT is naturally present in plasma and is not broken down in the gut; indeed, its fecal excretion has been used as a screening test for protein loss [34], and Sarker et al [35] used it to confirm protein-losing enteropathy in post-measles diarrhea.

In the present study, the malnourished children had lower levels of albumin compared to the controls, with the lowest levels being found in children who had kwashiorkor. Similar finding had previously been documented by other workers [36-38]. This hypoalbuminaemia may be explained by the reduced synthesis rate of albumin known to occur in malnutrition [39]. Another factor is the presence of infection, which can lower serum albumin level by reducing the rate of albumin synthesis through reduction of mRNA [27] or by increased loss of albumin from the capillaries [40]. In this regard, we found significantly lower level of plasma albumin (P<0.0001) in malnourished children with ARI compared to those without ARI. Another explanation of the hypoalbuminemia is the toxic effects of free radicals which would be responsible for cell damage leading to the alterations seen in Kwashiorkor such as the hypoalbuminemia [41]. Free radicals are removed via reactions catalyzed by enzymes in which glutathione and trace minerals are important such as selenium-containing glutathione peroxidase [42]. In a study from Sudan, a significant positive correlation between plasma selenium level and albumin was found [38]. A further route of albumin loss is through the gut. In a preliminary study, Cohen et al [43] found a seven-fold increase in the excretion of 131I-PVP in kwashiorkor and considered that this might be significant in the pathogenesis of hypoalbuminaemia. However, in PEM uncomplicated by infection, faecal protein loss appears to be of little importance [43, 44]. In the present study, we found no significant difference in the mean plasma levels of albumin in malnourished children with and without diarrhoea, but we found malnourished children with parasites in the stool to have highly significant hypoalbuminaemia compared
to those without parasites (P < 0.001).

In the present study also, and after two weeks of dietary and antimicrobial treatment, we found significant drops in the plasma levels of CRP and ORO in all malnourished children, a finding that was previously reported by others [12, 13, 20].

In conclusion, the findings in this study suggest that plasma levels of APP constitute a good screening test for the presence of infection in malnourished children and that APP (ORO and CRP) are sensitive indicators of recovery from infection and malnutrition. Significant hypoalbuminaemia was associated with the presence of intestinal parasites; therefore, proper treatment of these parasites would have accelerated the recovery from malnutrition. The study also indicates that FIB like the ESR, is not a good indicator of the presence or absence of infections (acute or chronic) in malnourished children. The fact that the changes in the levels of plasma APP had no correlation with the presence or absence of hepatomegaly in malnourished children indicates the need for further studies to determine the role of the liver, as it has always been implicated in the changes seen in severe malnutrition.

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Co-supervisor: Dr Zein El Abidein A Karrar, MB BS (U of K), FRCP (E), FRCP (L).