EFFECT OF DIFFERENT DURATIONS OF *SCHISTOSOMA MANSONI* INFECTION ON THE LEVELS OF SOME ANTIOXIDANTS IN MICE

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SUMMARY: The levels of lipid peroxides, glutathione, vitamin C, vitamin E catalase and superoxide dismutase enzymes were measured in the livers of Schistosoma mansoni infected mice (CD strain weighing 20-25g) at different durations post infection (1,2,4,6 and 8 weeks). Moreover, the liver weight, body weight, liver to body weight and total protein were studied in the same animal groups. Control non-infected groups were run simultaneously with each infected mice group. The data obtained showed that lipid peroxides were elevated throughout the different durations of infection while glutathione decreased with infection. On the other hand, both vitamins C and E showed a reduction in the livers of mice during the different durations of infection. The activity of catalase showed an insignificant change after one and two weeks and a high significant decrease in the livers of four, six and eight weeks S.mansoni infected mice, while, superoxide dismutase significantly decreased one and two weeks post infection with a significant elevation four, six and eight weeks post infection. Moreover, a significant reduction was observed in body weight after four, six and eight weeks of infection accompanied with an elevation in liver weight only after six and eight weeks. Consequently, liver weight/body weight showed an elevation after four, six and eight weeks of infection. Finally, the protein content was significantly lower at one, six and eight weeks post infection with S.mansoni.

It could thus be concluded that host-parasite association results in production of free radicals as a result of an oxidative stress where the parasites struggle to overcome the immune response of the host and changes in host liver antioxidants occur as a means to scavenge these radicals.

Key words: Antioxidants, Schistosomiasis, Free radicals.

INTRODUCTION

Free radicals influence the secretory functions of the vascular endothelium and are able to cause damage to cells by interacting with plasma membranes, nuclear components and various metabolites. A rational defense against oxygen toxicity should, therefore, include enzymatic scavenging of both O_2 and H_2O_2 (1).

Free radicals have been previously implicated in a number of diseases such as cardiovascular and neurodegenerative diseases, cancer, aging, viral infections (AIDS) and Parasitic infections (2-4). Several external factors directly affect the levels of free radicals and antioxidants of the body. These may either be due to toxic treatments

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or due to deficiency or supplementation of certain vitamins or elements or as a result of infections with different micro organisms. Oxidative stress may not be the fundamental cause of each disease, but it is nevertheless interesting to speculate that a variety of specific pathological and degenerative processes may render cells more susceptible to oxidative damage, depending on the cellular components affected and their turnover rates (5).

Each free radical formed by the body can initiate a series of chain reactions, which continue until free radicals are removed. Free radicals disappear from the body following reactions with other free radicals, or more importantly, due to the actions of the antioxidant system. Aerobic cells produce many antioxidants and several antioxidant enzymes scavenge the reactive oxygen metabolites. Dismutation of O^{-}_{2} by Cu/Zn and Mn- superoxide dismutase and degradation of hydrogen peroxide (H_2O_2) by glutathione peroxides and catalase limit the cytotoxic effects of these reactive oxygen metabolites (6).

Lipid peroxidation and other free radical reactions play a role in damaging biological structures, especially cellular membranes and perturbing cellular functions (7). Bagchi *et al.* (8) added that the breakdown of membrane phospholipids and lipid peroxidation demonstrated in many diseases may be free radical mediated and if unsaturated fatty acids are released from membrane phospholipids a change in membrane fluidity is expected. Also, abnormalities in the plasma lipid composition have been frequently reported in hepatic disorders including chronic liver disease and cirrhosis. A unique type of cirrhosis is induced by bilharziasis characterized by periportal fibrosis and absence of regeneration (9). In vascular disorders the significant increase of serum lipid peroxide levels has been reported (10) and it has been postulated that blood vessels can be injured if they are attacked by a high concentration of lipid peroxides, that can initiate atherogenesis.

In parasitic diseases, there is a complex and dynamic physiological relationship between the parasite and the antioxidant defense components of the main host (11). It was previously reported that during schistosome infestation, the parasite tends to switch from Krebs cycle to lactate production in the host. This results in a surplus supply of O_2 which subjects the infected host to a state of oxidative stress or increased free radical formation (12,13). In another study, Sayed and Williams (14) reported that schistosomes use alternative electron donors and their variable resistance to overoxidation may reflect their presence in different cellular sites and emphasizes the significant differences in overall redox balance mechanisms between the parasite and the mammalian host.

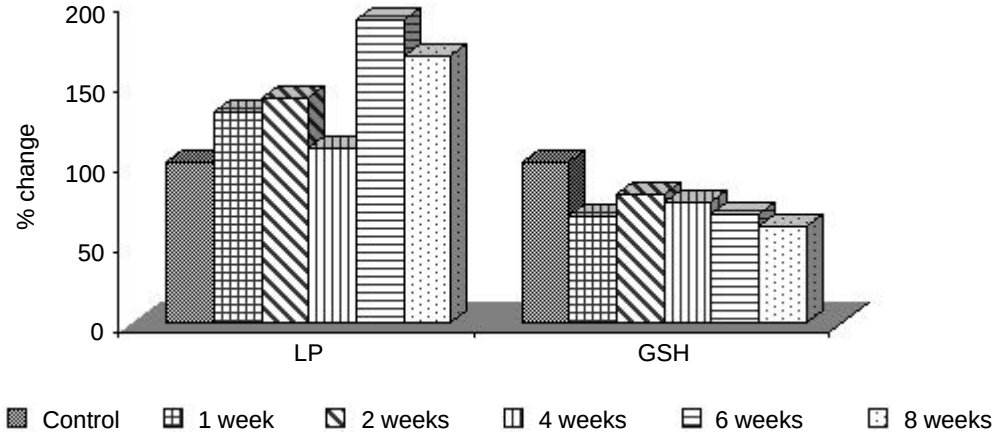
In some reports concerning *Schistosoma mansoni*, Sheweita *et al.* (15,16) pointed out that levels of reduced glutathione and glutathione reductase were increased, while the activity of glutathione-S-transferase was decreased in human and mice infected with *Schistosoma mansoni*. The same authors (17) added that high levels of free radicals provide new evidence for organ damage since glutathione is decreased and lipid peroxides increased in different organs of hamsters infected with *S.hematobium.* In this manner *S. mansoni* infection alters the hepatic levels of glutathione and activities of glutathione metabolizing enzymes and alterations may affect the capacity of the liver to detoxify or neutralize the toxic effects of endogenous and exogenous compounds.

Moreover, Farrag and Faddah (18) studied the effect of *Schistosoma* infection on some antioxidant enzymes in mice liver. Liver glucose-6- phosphate dehydrogenase, glutathione peroxidase and glutathione -5- transferase activities were found to be decreased in infected mice compared to non infected animals, whereas superoxide dismutase was not affected by *Schistosoma mansoni* infection.

Gharib *et al.* (3) confirmed that superoxide dismutase, catalase and glutathione peroxidase activities were decreased in livers of mice infected with *S. mansoni*. In contrast, glutathione-S- transferase was unaffected. Reduced glutathione concentrations also dropped as a result of infection. Lastly, a two-fold increase in the levels of hepatic products generated by lipid peroxidation was observed. Recent reports by Pascal *et al.* (19) and Soliman *et al.* (20) postulated that lipid peroxidation was elevated in both serum and liver of man and mice infected with *Schistosoma mansoni*.

From the previous information, it was of interest in the present study to investigate the levels of glutathione (GSH) Vitamin E, Vitamin C, superoxide dismutase (SOD), catalase and lipid peroxides, in infected mice groups at different stages of infection with *Schistosoma mansoni* in order to trace the changes that occur in these antioxidants throughout the infection period.

Figure 1: Percentage changes in lipid peroxides (LP) and glutathione (GSH) during different durations of *S.mansoni* infection.



MATERIALS AND METHODS

All chemicals used were of high analytical grade, products of Sigma (USA), Merck and Reidel (Germany), BDH (England), and Fluka (Switzerland) Chemical Co. Praziquantel used as a product of Egyptian International Pharmaceutical Industries Company (E.I.P.I.Co.).

The animals used were healthy male swiss albino mice of CD strain, obtained from Theodor Bilharz Institute, ranging in weight from 20-25 grams. They received fresh, deionized water and standard diet (El-Tkamol-Co.) *ad libitum.* Mice were divided into two main groups, and each was divided into five subgroups.

The first main infected group was sacrificed one, two, four, six and eight weeks post infection with 100 cercariae of Egyptian *Schistosoma mansoni* strain.

The second main group served as control and was run simultaneously with each duration of the infected subgroups. The number of animals ranged from 6 to 10 mice in each subdivision.

To obtain cercariae, 10-20 shedding *Biomphalaria alexandrina* snails were used to ensure bisexual infection and placed in a beaker containing 200 ml dechlorinated water. Then, the snails were exposed to sunlight at 8-9 am. Each mouse was infected subcutaneously by 100 cercariae.

Experimental procedures

The liver was removed from the mouse, plotted with filter paper and weighted. The liver was homogenized in bidistilled water (5%, 10% and 20% w/v) according to the parameter measured, using potter-Elvehjem homogenizer with Teflon pestle.

Estimation of protein

Protein was estimated by the method of Bradford (21). Bradford solution was added to of 5% homogenate and the developed blue colour was measured after 5 minutes at 595 nm in spectrometer (Novaspec, LKB, Sweden) against a blank containing water instead of the homogenate. The amount of protein was calculated from a standard curve using serial concentration of bovine serum albumin (1-10 ug).

Estimation of lipid peroxides

Lipid peroxides were estimated by thiobarbituric acid reaction as described by Ohkawa *et al.* (22) using saturated thiobarbituric acid (A) and trichloroacetic acid (20%) (B) solutions. The working solution was prepared by mixing one volume of solution A with 3 volumes of solution B. 20% tissue homogenate was added to the working solution and mixed. The tubes were boiled, cooled and centrifuged at 3.000 r.p.m for 10 minutes. The developed colour was read against the blank at 532 nm in spectrometer and calculated as μmole malonaldehyde per gram tissue.

Estimation of glutathione

Glutathione was estimated by the method of Moron *et al.* (23) using sodium phosphate buffer and dithiobisnitrobenzoic acid (DTNB). The developed colour was read against blank at 412 nm within 5 minutes in spectrometer. The amount of glutathione was calculated as mg glutathione per gram tissue used from a standard curve plotted for serial concentrations of glutathione (5-100 μg).

Estimation of vitamin C

Vitamin C was estimated by the method of Jagota and Dani (24) using Folin-ciocalteu reagent (2.0 M concentration diluted 3-fold with double - distilled water) and TCA. The developed blue colour was read at 760 nm after 10 minutes in spectrometer against a blank. The amount of ascorbic acid was calculated from a standard curve of vitamin C using 5-70 μg serial concentrations of the vitamin.

Table 1: Estimation of lipid peroxides and glutathione in the liver of mice during different durations of *Schistosoma mansoni* infection.

Durations post infection	Lipid peroxides (μmol malonaldehyde/g tissue)			Glutathione mg/g tissue		
	Control $\overline{X} \pm$ S.E	Infected $\overline{X} \pm$ S.E.	p <	Control $\overline{X} \pm$ S.E	Infected $\overline{X} \pm$ S.E.	p <
One week	22.85 ± 0.10	30.0 ± 0.133	0.001	1.925 ± 0.045	1.075 ± 0.05	0.001
Two weeks	20.0 ± 0.07	28.0 ± 0.07	0.001	2.108 ± 0.02	1.688 ± 0.017	0.001
Four weeks	23.0 ± 0.10	25.0 ± 0.09	0.01	1.975 ± 0.038	1.488 ± 0.02	0.001
Six weeks	20.6 ± 0.066	39.0 ± 0.07	0.001	1.625 ± 0.037	1.097 ± 0.02	0.001
Eight weeks	28.3 ± 0.06	47.2 ± 0.095	0.001	1.662 ± 0.03	0.997 ± 0.025	0.001

- Data are means (± S.E.) of lipid peroxides and glutathione determinations.
- Significant change as compared to control (p< 0.001 : highly significant and p< 0.01: significant).

Estimation of vitamin E

Vitamin E was estimated by the method of Baker and Frank (25) using 7.7 m M α, α-Dipyridyl and 7.4 m M ferric chloride solution. The absorbance of colour was read for the test and standard against the blank at 460 nm.

Estimation of superoxide dismutase activity

The activity of superoxide dismutase was estimated by the method of Nishikimi *et al.* (26) using nitroblue tetrazolium, NADH and sodium pyrophosphate buffer. Increase in absorbance with time during the reaction was read in spectrometer at 560 nm.

Estimation of catalase enzyme

Catalase activity was assayed according to Lubinsky and Bewley (27). The reaction for assaying catalase activity was initiated by adding 20 μl 5% liver homogenate of concentration to 2.53 ml of the reaction mixture (sodium potassium phosphate buffer containing H_2O_2. The disappearance of hydrogen peroxide was monitored by following the decease in absorbance at 230 nm by spectrometer using molar extinction coefficient for hydrogen peroxide of 62.4.

Statistical Analyses

The analyses included the calculation of the mean value, standard deviation, standard error and "t" values at level is $P \leq 0.05$. These determinations were calculated for both control and treated animals.

RESULTS

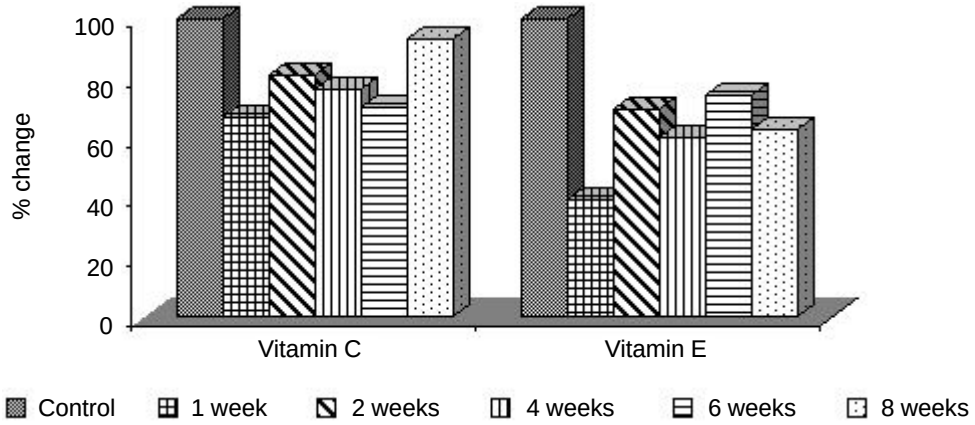
Table 1 demonstrates the levels of lipid peroxides and glutathione in the liver of mice infected with *Schistosoma mansoni* during different durations as compared with control-non infected mice. It is obvious that infected mice showed a highly significant increase in the levels of lipid peroxides with 31.29, 40.0, 89.0 and 66.78% after

Table 2: Determination of vitamin C and vitamin E in the liver of mice during different durations of *Schistosoma mansoni* infection.

Durations post infection	Vitamin C (μg/g tissue)			Vitamin E mg/g tissue		
	Control $\overline{X} \pm$ S.E	Infected $\overline{X} \pm$ S.E.	p <	Control $\overline{X} \pm$ S.E	Infected $\overline{X} \pm$ S.E.	p <
One week	269.45 ± 7.0	182.29 ± 6.58	0.001	10.50 ± 1.36	4.08 ± 0.50	0.001
Two weeks	269.6 ± 3.0	218.66 ± 3.97	0.001	12.95 ± 1.60	9.0 ± 0.80	0.01
Four weeks	253.75 ± 7.50	193.4 ± 6.0	0.001	6.04 ± 0.56	3.68 ± 0.22	0.001
Six weeks	234.8 ± 5.0	164.95 ± 3.26	0.001	3.218 ± 0.30	2.395 ± 0.16	0.01
Eight weeks	186.35 ± 2.0	173.6 ± 4.28	0.001	2.966 ± 0.44	1.87 ± 0.26	0.01

- Data are means (± S.E.) of vitamin C and vitamin E determinations.
- Significant change as compared to control (p< 0.001 : highly significant and p< 0.01: significant).

Figure 2: Percentage changes in Vitamin C and Vitamin E during different durations of *S.mansoni* infection.



one, two, six and eight weeks of infection respectively, while a significant elevation was detected in the lipid peroxides after four weeks of infection with change 8.69%. On the oher hand *Schistosoma mansoni* infection showed a highly significant decrease in liver glutathione of mice, with 44.0, 19.88, 24.60, 32.46 and 40.0% after one, two, four, six and eight weeks of infection respectively.

Table 2 shows the effect of different periods of infection with *S. mansoni* on vitamins C and E of mice liver. It is obvious that liver vitamin C of infected mice showed a highly significant decrease after one, two, four, six and eight weeks post infection, with 32.34, 18.90, 23.78, 29.70 and 6.80% respectively. Also, vitamin E showed a highly significant decrease after one and four weeks of infection with 61.0 and 39.0% respectively and a significant reduction after two, six and eight weeks of infection with 30.50, 25.57 and 36.95% respectively as compared with clean control mice.

Table 3 reveals the activity of catalase and superoxide dismutase enzymes in the liver of mice infected with *S. mansoni* during different periods. It is obvious that, an insignificant decrease of the catalase activity was detected after one and two weeks of infection, while a highly significant decrease of the liver enzyme activity was detected after four, six and eight weeks of the infection with 18.42, 19.93 and 25.0% respectively, as compared with normal control mice. On the other hand superoxide dismutase enzyme showed a significant

Table 3: Estimation of catalase and superoxide dismutase enzyme activities in the liver of mice during different durations of *Schistosoma mansoni* infection.

Durations post infection	Catalase μmol/mg patients			Superoxide dismutase activity/mg protein		
	Control $\overline{X} \pm$ S.E	Infected $\overline{X} \pm$ S.E.	p <	Control $\overline{X} \pm$ S.E	Infected $\overline{X} \pm$ S.E.	p <
One week	90.04 ± 1.79	87.50 ± 4.60	n.s	331.896 ± 6.60	296.466 ± 6.10	0.001
Two weeks	103.349 ± 2.55	98.39 ± 4.58	n.s	338.14 ± 6.77	319.305 ± 6.50	0.01
Four weeks	99.97 ± 3.40	81.554 ± 3.777	0.001	211.666 ± 4.60	236.747 ± 4.75	0.001
Six weeks	89.195 ± 3.58	71.418 ± 3.15	0.001	178.59 ± 5.0	203.08 ± 5.20	0.001
Eight weeks	85.535 ± 4.59	64.077 ± 2.60	0.001	156.269 ± 5.70	183.04 ± 6.94	0.001

- Data are means (± S.E.) of catalase and superoxide dismutase determinations.
- Significant change as compared to control (p< 0.001 : highly significant, p< 0.01: significant and n.s : insignificant).

Table 4: Body weight, liver weight and liver weight/ body weight ratio of control and infected mice during different durations post infection with *S. mansoni.*

Durations post infection	Control			Infected			P<	P_1<	P_2<
	Body wt.	Liver wt.	L.wt/B.wtx 100%	Body wt.	Liver wt.	L.wt/B.wtx 100%			
One week	21.28 ± 0.68	1.20 ± 0.10	5.66 ± 0.337	20.50 ± 0.44	1.20 ± 0.06	5.81 ± 0.22	n.s	-	n.s
Two weeks	25.0 ± 0.365	1.50 ± 0.03	6.07 ± 0.15	25.0 ± 0.30	1.56 ± 0.03	6.195 ± 0.11	-	0.05	n.s
Four weeks	28.16 ± 0.20	1.66 ± 0.03	5.90 ± 0.11	26.0 ± 0.70	1.60 ± 0.08	6.19 ± 0.16	0.001	n.s	0.05
Six weeks	30.0 ± 0.258	1.6 ± 0.03	5.30 ± 0.06	28.60 ± 0.50	2.01 ± 0.06	7.0 ± 0.11	0.01	0.001	0.001
Eight weeks	31.66 ± 0.66	2.0 ± 0.049	6.40 ± 0.07	26.65 ± 0.55	2.44 ± 0.04	8.857 ± 0.29	0.001	0.001	0.001

- Data are means (± SE) of body wt, liver wt and liver wt /body wt ratio.
- Significant change as compared to control (p< 0.001 : highly significant, p< 0.01: significant, 0.05: slightly significant and n.s: insignificant).

decrease in the liver of infected mice with 10.67 and 5.57%, respectively, after one and two weeks of the infection with *S. mansoni.* Also, the enzyme activity showed a highly significant increase after four, six and eight weeks of the infection giving 11.85, 13.70 and 17.13% respectively, as compared with normal control mice.

Table 4 illustrates the body weight, liver weight and liver weight/body weight ratio in normal and schistosoma infected mice during different periods. It is obvious that an insignificant change is observed in the body weight after one and two weeks of infection, while a significant decrease was recorded with 7.67, 4.66 and 15.80% after four, six and eight weeks of infection with *S. mansoni*, respectively. Liver weight showed an insignificant change after one and four weeks of infection and a significant increase after two weeks of infection with 4.0% while, a highly significant increase is recorded in liver weight after six and eight weeks of infection with 25.60 and 22.0%, respectively. Liver weight/body weight ratio showed an insignificant change after one and two weeks, while a slightly significant increase with 4.9% was shown after four weeks of infection and highly significant increases after six and eight weeks of infection with 32.0 and 38.39% as compared with normal control.

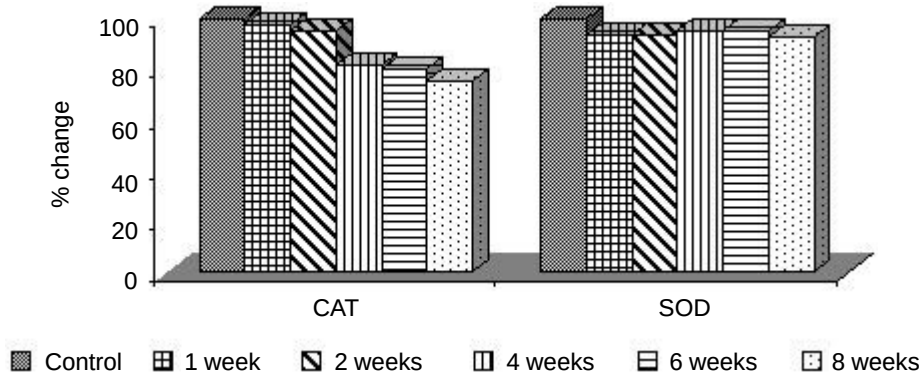
Table 5 shows the levels of total proteins in control and infected mice during different periods of infection with *S. mansoni*. It is observed that the level of total protein showed a significant decrease after one week of infection

Table 5: Determination of total protein in the liver of control and infected mice during different durations post infection with *Schistosoma mansoni.*

	Durations post Infection				
	One week ± S.E.	Two weeks ± S.E.	Four weeks ± S.E.	Six weeks ± S.E.	Eight weeks ± S.E.
Control	147.40 ± 2.90	143.66 ± 3.36	137.26 ± 2.60	143.20 ± 2.30	148.60 ± 1.55
Infected	140.44 ± 1.30	144.20 ± 3.66	172.35 ± 1.38	126.12 ± 1.227	124.80 ± 1.10
p<	0.01	n.s	0.001	0.001	0.001

- Data are means (± S.E.) of total protein level .
- Significant change as compared to control (P< 0.001: highly significant, P < 0.01 : significant and n.s : insignificant)
- Total protein is expressed in mg protein /g tissue used.

Figure 3: Percentage changes in Catalase (CAT) and Superoxide dismutase (SOD) during different durations of *S.mansoni* infection.



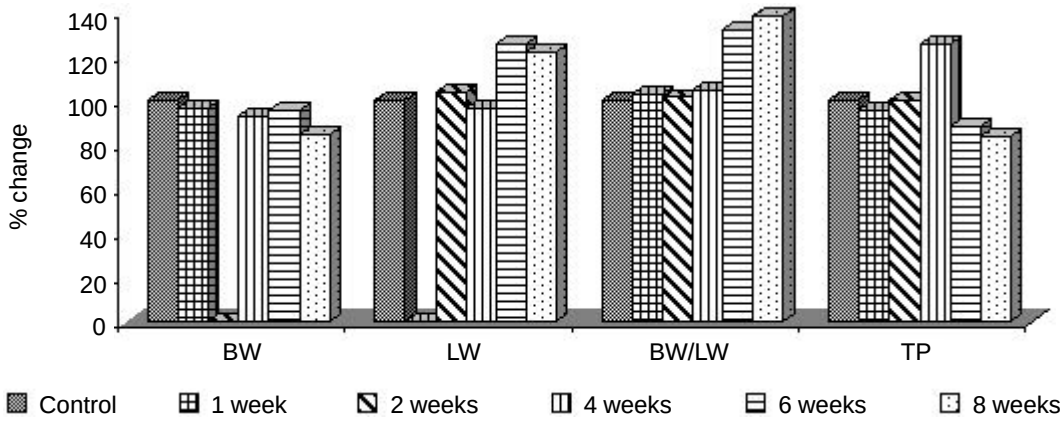
with 4.72% and an insignificant change after two weeks of infection. After four weeks of infection the total protein showed a highly significant increase with 25.5%, while after six and eight weeks of infection the total protein showed a highly significant decrease with 11.90 and 16.0%, respectively.

DISCUSSION

It was previously reported that in parasitic diseases, there is a complex and dynamic physiological relationship between the parasite and the antioxidant defence components of the host (11). In schistosomiasis, granuloma macrophages isolated from hepatic, intestinal and pulmonary lesions were found to release significant amounts of O_2 and H_2O_2 radicals (28). The oxidative processes which occur upon contact with *S. mansoni* eggs trapped in the liver seem to proceed uncontrolled, since the enzymatic activities involved in O_2 and H_2O_2 detoxification decrease drastically. Such events may be, at least in part, responsible for the pathology associated with schistosomiasis (3). The infection with *S. mansoni* not only triggers the production of reactive oxygen species, but it also leads to the alteration of the antioxidant defence mechanism (19).

The data obtained in the present study show that lipid peroxides were elevated by *S. mansoni* throughout the different durations of infection. This coincides with the phenomenon of Shaheen *et al.*, (28) that production of

Figure 4: Percentage changes in body weight (BW), liver weight (LW), BW/LW, and total protein (TP) during different durations of *S.mansoni* infection.



free radicals in the chain of biochemical reactions results in an increase in lipid peroxides. It should be pointed out that oxidative stress due to schistosomiasis causes the same effect (3,19, 20) since fibrosis associated with the disease is stimulated by reactive end products of lipid peroxidation (29). In addition, there is a positive correlation between collagen deposition during schistosomal infections and production of malonaldehyde by hepatic cells (30).

Results on glutathione content in infected mice livers revealed a highly significant reduction resulting from an oxidative stress due to schistosomiasis (31-33). Such depletion may be caused by increased cytotoxicity with H_2O_2 which leads to inhibition in glutathione reductase, the latter responsible for keeping glutathione in its reduced state (34). An interesting finding which coincides with the present data was shown by Yegen *et al*., (35) that reduction of cellular GSH is accompanied by increased lipid peroxidation.

The present work was also extended to investigate the level of vitamin C in the different *Schistosoma* infected mice groups. It was found that this vitamin was significantly reduced to scavenge the free radicals produced by the parasite since peroxyl radicals are effectively trapped by ascorbate (36).

Data obtained for vitamin E in infected mice livers revealed a significant reduction in the vitamin since the latter is required to protect biological membranes against oxidative degeneration. The administration of vitamin E in the diet shows a strong antioxidant activity against lipid peroxidation and also it protects hepatocytes against toxic injury (37, 38). Reduction in the vitamin content due to oxidative stress was previously reported by Warren and Reed (39).

In the present study, the activity of superoxide dismutase greatly declined one week post infection while an increase in the enzyme activity started from th 4th week till the end of the infection period. The decrease in SOD may result from production of H_2O_2 during oxidative metabolism as indicated by Pinteaux *et al.*, (40). Moreover the increase in enzyme activity may be an adaptive response to conditions of increased peroxidative stress in the liver. Previously, Shaheen *et al.*, (28) reported an increase in hepatic SOD in mice infected with *S. mansoni*. An interesting finding was reported by Sanz *et al.*, (41) who showed that cell defence mechanisms against oxidative toxicity increase in liver to suppress oxidative imbalance, thus SOD increases and GSH decreases.

Furthermore, the present data reveals a highly significant and progressive reduction in catalase activity which started four weeks post *S. mansoni* infection. In agreement with this, Gharib *et al.*, (3) showed that peroxide dismutation yields H_2O_2 which is detoxified by catalase resulting in decrease in its activity. In a recent study, Hanna *et al.*, (42) added that eosinophil peroxidase and its substrate H_2O_2 are released by inflammatory cells in the immediate vicinity of parasite eggs.

With respect to body and liver weights, it was found that a significant reduction in body weight was recorded after four weeks of infection. These changes may occur due to the presence of the developing parasite worms and the initiation of egg deposition and also due to several metabolites released by the parasite which affect the host hepatic tissue (43). In a good connection to the present results, Ahmed and Gad (44); Magalhaes *et al.*, (45) and Fiore *et al.*, (46) found a reduction in body weight, an increase in liver weight and an increase in liver weight/body weight from the sixth week post-infection with *S. mansoni*, with initiation of schistosomal egg deposition.

On the other hand, data on total proteins recorded an increase after four weeks of infection then a significant decline after six and eight weeks. In hepatic fibrosis as a result of bilharzial infection, protein anabolism decreases while protein catabolism increases. Impairment in protein synthesis was previously supported by Mousa *et al.*, (9) that malabsorption may be a contributing factor in decrease of protein synthesis through a defect in absorption of amino acids.

In conclusion, host-parasite interaction is characterized by the production of free radicals and changes in liver antioxidants and result in fibrosis and other metabolic disorders.

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