



# The Effect of Ivermectin Injection on Some Clinicopathological Parameters in Camels Naturally Infested with Scabies

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**Abstract** | Camel mange is a real threat on camel breeding development. This paper aimed to investigate the hematological and biochemical changes in she-camels naturally infested with sarcoptic mange before and after treatment with ivermectin during 28 days and suggest new markers for its diagnosis and treatment monitoring. A total 20 she-camels were used for this purpose; 10 she-camels were apparently-healthy (control group (CG)) and the others (N=10) were naturally infested with sarcoptic mange, confirmed by the mange symptoms and skin scraping microscopic examination (diseased group (DG)). DG was treated with ivermectin 1% S/C (1ml/50 kg) + permethrine 5% topically (treated group (TG)). Blood samples were collected from CG, DG (before treatment) and from TG at 7<sup>th</sup>, 14<sup>th</sup>, 21<sup>st</sup>, 28<sup>th</sup> days post-treatment. Hematological and biochemical parameters were estimated and statistically analyzed. Ivermectin administration succeeded in restoring normal hemogram, leukogram, glucose levels and lipid profile at 14<sup>th</sup> day and total globulin, matrix metalloproteinases (MMPs), iron profile at 21<sup>st</sup> post-treatment. On the other hand, it resulted in a significant elevation ( $P < 0.05$ ) in liver and kidney function tests and a significant ( $P < 0.05$ ) decline in total antioxidant capacity (TAC) in TG at 7<sup>th</sup> day, but at 28<sup>th</sup> day AST, direct bilirubin and creatinine returned to normality and a slight increase in ALT, total and indirect bilirubin and urea concentrations was expressed till the study end. Serum iron (SI), ferritin, TAC, MMP-2 and MMP-9 achieved moderate to high values of area under the curve, cut off points, sensitivity%, specificity%, likelihood ratio, PPV%, NPV% and accuracy rate% in DG and TG. Conclusion: ivermectin administration in camel with scabies, has several adverse effects on liver and kidney functions tests due to oxidative stress. SI, ferritin, TAC, MMP-2 and MMP-9 may be useful indicator for camel mange and for tracking the infested animal response to the treatment proposal.

**Keywords** | Camel mange, Clinicopathological parameters, Ivermectin, Iron profile, Matrix metalloproteinases

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## INTRODUCTION

Mange is a serious problem, negatively affects the Meconomic yield of all animal breeding sections including camel breeding. Although, it is not lethal but the lowered body weights, damaged skin, decreased fertility rates and milk production usually detected in infested camels are economic losses can't be ignored. In addition, the high morbidity and re-infestation rates and subsequent expensive exhausted protocols used for the

disease treatment and control. Furthermore, camel mange has a zoonotic importance (Zahid, 2015; Jarso et al., 2018; Abdel-Saeed, 2020).

Mange is one of the most important parasitic diseases of camels, characterized by scab formation, pruritic dermatitis, thickening and corrugation of skin and hair loss. It caused due to infestation with sarcoptic or choriopic mange mites, but sarcoptic mange is the most common one in camel. Ivermectin is macrocyclic lactone which is

used against many endo and ectoparasites. Injectable, Pour-on and oral formulations of ivermectin are available. For years ivermectin was used for mange treatment and control in camels as well as other animals without sufficient information about its effect on the clinicopathological parameters in the infested camels (Riviere et al., 2009; Awol et al., 2014; Feyera et al., 2015; Abdel-Saeed, 2020).

Hence, this work aimed to study the most important clinicopathological changes associated with camel mange as well as ivermectin administration in infested camels with especial reference to the serum iron (SI), ferritin, total antioxidants capacity (TAC) and matrix metalloproteinases (MMP-2, MMP-9) importance as markers for the disease and treatment monitoring.

## MATERIALS AND METHODS

### ANIMALS

After the ethical approval of Animal and Poultry Health Department, Desert Research Center (DRC), Cairo, Egypt, 20 non-pregnant she-camels (*Camelus dromedarius*, aged 3-4 years), weight 380-400 kg were divided into 2 groups:

Control group (CG): 10 she-camels apparently-healthy (normal skin, no itching or purities).

Diseased group (DG): 10 she-camels suffered from clinical signs of mange (emaciation, poor appetite, pale mucous membrane, alopecia, itching, keratinized skin, annoyed and restless). Skin scraping and microscopical examination confirmed the diagnosis (Sarcoptic mites) (Ulutas et al., 2005). A single dose of ivermectin 1% (Promectine®, Invesa) was subcutaneously injected in the diseased group at dose (1ml/50 kg) + permethrin 5% (Ectomethrin®5, Misr Co. For Pharm. Ind.) was applied on the skin lesion daily till the complete cure (treated group (TG)).

### SAMPLE COLLECTION AND ANALYSIS

- Blood samples were collected through jugular vein puncture from CG (one time at the beginning of the study) and from DG before and after treatment at 7<sup>th</sup>, 15<sup>th</sup>, 21<sup>st</sup> and 28<sup>th</sup> day (TG).
- Each blood sample was split into two tubes: 10% dipotassium-EDTA salt solution was added to the 1<sup>st</sup> tube to hinder the coagulation cascade for assessment of the hematological parameters in the studied animals manually following the method described by Feldman et al. (2000). The blood in the 2<sup>nd</sup> tube was centrifuged after its coagulation at 37°C 3000 r.p.m. for 20 minutes to obtain serum for subsequent biochemical examination.
- Following manufacturer's instructions: transferrin (Tf) serum levels were determined in serum by turbidimetric method using Elabscience (USA) kits

and serum ferritin concentrations were evaluated by CLIA method using Abnova (Taipei) kits, MMP-2, MMP-9 serum concentrations were detected by ELISA technique using Cloud-ELISA kits of Clone Corp company®, Huston, USA, While, the rest biochemical parameters were measured in serum spectrophotometrically using commercial kits supplied by Biodiagnostic® company, Egypt.

- Transferrin saturation percent (Tf sat. %) = serum iron (SI) / total iron binding capacity (TIBC)\*100.
- Unsaturated iron binding capacity (UIBC)= TIBC-SI.
- Skin scrapes were collected and microscopically examined from TG at 7<sup>th</sup>, 15<sup>th</sup>, 21<sup>st</sup> and 28<sup>th</sup> day.

### STATISTICAL ANALYSIS

All estimated parameters were expressed as mean ± standard deviation (SD). SPSS program version 20 was used for comparing between the means of the studied groups by one-way ANOVA test and detection of the post hoc differences between means by a multiple comparison Tukey's HSD test. Differences were considered significant when P< 0.05.

- Graph pad prism version 5 program was used to evaluate the area under the curve (AUC), cut off points, sensitivity%, specificity% and likelihood ratio (LR) for the estimated parameters in DG compared to CG and in TG compared to DG.

The positive predictive value (PPV), negative predictive value (NPV) and accuracy rate for them were calculated according the next equations:

$$PPV = \text{True positive} \div \text{Total positive} \times 100$$

$$NPV = \text{True negative} \div \text{Total negative} \times 100$$

$$\text{Accuracy rate} = (\text{True positive} + \text{True negative}) \div \text{Total population} \times 100$$

## RESULTS AND DISCUSSION

The treated she-camels showed a marked improvement of the clinical signs and they gradually obtained normal appetite, mucous membrane color and body weight and become rest. A prominent enhancement of the skin lesion and the skin re-appeared smooth and weber grew again at 21<sup>st</sup> day. Microscopically, the skin scraping by 21<sup>st</sup> day showed no living mites, just few debris completely withdrew at 28<sup>th</sup> day.

### HEMATOLOGICAL PARAMETERS AND IRON PROFILE

Table 1 illustrated a significant (P< 0.05) reduction in all red blood cell parameters and indices (red blood cell count (RBCs), hemoglobin concentration (Hb), packed cell volume (PCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC),

**Table 1:** Comparison between the hematological parameters and iron profile in CG, DG and TG (N=10). Values are means ± SD.

Parameters	CG	DG	TG			
			7 <sup>th</sup> day	14 <sup>th</sup> day	21 <sup>st</sup> day	28 <sup>th</sup> day
RBCs(×10 <sup>6</sup> /μl)	10.79±0.34 <sup>d</sup>	9.06±0.41 <sup>c</sup>	10.01±0.09 <sup>c</sup>	10.66±0.21	10.79±0.34	10.79±0.34
Hb (g/dl)	12.16±0.35 <sup>d</sup>	8.76±0.11 <sup>c</sup>	11.48±0.37 <sup>c</sup>	12.15±0.35	12.16±0.35	12.23±0.37
PCV (%)	36.40±0.52 <sup>d</sup>	27.80±0.46 <sup>c</sup>	30.13±0.30 <sup>c</sup>	36.40±0.52	36.40±0.52	36.40±0.52
MCV (fl)	33.80±0.75 <sup>d</sup>	30.73±1.57 <sup>c</sup>	30.13±0.30 <sup>c</sup>	34.15±0.53	33.76±0.94	33.76±0.94
MCH (pg)	11.28±0.38 <sup>d</sup>	9.68±0.46 <sup>c</sup>	11.48±0.40	11.40±0.42	11.28±0.38	11.34±0.47
MCHC (%)	33.42±1.19 <sup>d</sup>	31.52±0.52 <sup>c</sup>	38.10±1.25 <sup>c</sup>	33.39±1.20	33.42±1.19	33.60±1.31
TLC(×10 <sup>3</sup> /μl)	8.43±0.30 <sup>d</sup>	10.37±0.23 <sup>c</sup>	9.38±0.12 <sup>c</sup>	8.19±0.44	8.40±0.28	8.40±0.28
N(×10 <sup>3</sup> /μl)	5.08±0.23 <sup>d</sup>	7.09±0.19 <sup>c</sup>	6.01±0.05 <sup>c</sup>	4.81±0.42	5.05±0.23	5.05±0.23
L(×10 <sup>3</sup> /μl)	2.56±0.16 <sup>d</sup>	1.97±0.05 <sup>c</sup>	2.31±0.10 <sup>c</sup>	2.53±0.87	2.56±0.16	2.56±0.16
E(×10 <sup>3</sup> /μl)	0.36±0.04 <sup>d</sup>	0.89±0.01 <sup>c</sup>	0.63±0.02 <sup>c</sup>	0.40±0.01	0.36±0.04	0.36±0.04
M(×10 <sup>3</sup> /μl)	0.41±0.04	0.50±0.04	0.50±0.04	0.50±0.04	0.41±0.04	0.41±0.04
B(×10 <sup>3</sup> /μl)	0.39±0.05	0.38±0.04	0.39±0.06	0.39±0.06	0.39±0.06	0.39±0.06
SI (μg/dl)	164.11±6.30 <sup>d</sup>	123.61±2.45 <sup>c</sup>	135.61±3.81 <sup>c</sup>	150.81±0.98 <sup>c</sup>	160.42±4.02	162.58±6.51
TIBC (μg/dl)	475.54±11.58 <sup>d</sup>	634.40±39.67 <sup>c</sup>	587.01±8.39 <sup>c</sup>	499.20±6.12 <sup>c</sup>	489.70±3.54	478.49±11.06
UIBC (μg/dl)	311.43±12.77 <sup>d</sup>	510.78±38.71 <sup>c</sup>	451.39±9.41 <sup>c</sup>	348.39±6.39 <sup>c</sup>	329.28±5.21	315.92±8.19
Tf sat. %	34.53±1.52 <sup>d</sup>	19.55±1.13 <sup>c</sup>	23.11±0.74 <sup>c</sup>	30.21±0.45 <sup>c</sup>	32.76±0.85 <sup>c</sup>	33.97±0.99
Ferritin (ng/ml)	124.50±4.82 <sup>d</sup>	167.14±6.29 <sup>c</sup>	156.18±2.63 <sup>c</sup>	133.68±1.96 <sup>c</sup>	128.33±3.71	124.90±5.40
Tf (mg/dl)	15.62±0.69 <sup>d</sup>	24.28±2.02 <sup>c</sup>	20.81±0.11 <sup>c</sup>	18.40±0.12 <sup>c</sup>	16.01±0.99	15.86±0.79

<sup>d</sup>(significant between the studied groups); <sup>c</sup>(significant with CG); considered statistically significant at P<0.05. CG: Control group; DG: Diseased group before treatment; TG: Diseased group after treatment; RBCs: Red blood cell count; Hb: Hemoglobin concentration; PCV: Packed cell volume; MCV: Mean corpuscular volume; MCH: Mean corpuscular hemoglobin; MCHC: Mean corpuscular hemoglobin concentration; TLC: Total leukocytic count; N: Neutrophils; L: Lymphocytes; E: Eosinophils; M: Monocytes; B: Basophils; SI: Serum iron; TIBC: Total iron binding capacity; UIBC: Unsaturated iron binding capacity; Tf sat. %: Transferrin saturation percentage; Tf: Transferrin.

lymphocytes, SI, Tf sat. % in DG compared to CG. On the contrary, a significant (P< 0.05) increment in total leukocytic counts (TLC), neutrophils, eosinophils, TIBC, UIBC, ferritin and Tf in DG in relation to CG.

### BIOCHEMICAL PARAMETERS

Table 2 exhibited a significant (P< 0.05) elevation in serum concentration of total protein (TP), total globulin (Glob), liver function tests (aspartate aminotransferase (AST), Alanine aminotransferase (ALT), total bilirubin (T-bilirubin), direct bilirubin (D-bilirubin), indirect bilirubin (I-bilirubin)), kidney function tests (urea, creatinine (Cr)), total lipids, triglycerides, cholesterol, LDL/HDL-cholesterol, MMP-2, MMP-9 in DG compared to CG. On the contrary, the serum levels of albumin (Alb), albumin/globulin ratio (A/G), glucose and TAC significantly (P< 0.05) declined in DG in relation to CG.

### AFTER TREATMENT

Most of the previous parameters levels significantly (P< 0.05) increased or decreased in TG (in relation to DG) towards CG levels. CG levels were achieved in TG (non-significantly (P> 0.05) changed with CG) at 7<sup>th</sup> day for

MCH, at 14<sup>th</sup> for RBCs, Hb, PCV, MCV, MCHC, TLC, neutrophils, lymphocytes, eosinophils, glucose, total lipids, triglycerides, cholesterol, LDL/HDL-cholesterol, at 21<sup>st</sup> days for SI, ferritin, TIBC, UIBC, Tf, Glob, MMP-2, MMP-9 and at 28<sup>th</sup> day for Tf sat. %, A/G, AST, D-bilirubin, Cr, TAC. While, till the end of the experiment TG (compared to CG) showed a significant (P< 0.05) decrease in TP, Alb as well as a significant (P< 0.05) increase in ALT, T/I-bilirubin and urea. Interestingly, TG compared to DG revealed a significant (P< 0.05) increment in MCHC, AST, ALT, T/D-bilirubin and a significant (P< 0.05) decline in Alb, TAC at 7<sup>th</sup> day (Tables 1, 2).

Regarding the value of SI, ferritin, TAC, MMP-2 and MMP-9 importance as diagnostic and prognostic markers for the disease and its treatment evaluation, Table 3 demonstrated that all of them yielded excellent numbers of AUC, sensitivity%, specificity%, LR, PPV%, NPV%, accuracy rate% in both DG and TG except TAC displayed moderate values of AUC and LR in TG.

Sarcoptic mange is still an obstacle facing camel breeding expansion. Clinically, the diseased animals appear weak,

**Table 2:** Comparison between the biochemical parameters in CG, DG and TG (N=10). Values are means ± SD.

Parameters	CG	DG	TG			
			7 <sup>th</sup> day	14 <sup>th</sup> day	21 <sup>st</sup> day	28 <sup>th</sup> day
TP (g/dl)	5.82±0.40 <sup>d</sup>	7.77±0.26 <sup>c</sup>	4.58±0.08 <sup>c</sup>	5.02±0.05 <sup>c</sup>	4.99±0.05 <sup>c</sup>	5.39±0.11 <sup>c</sup>
Alb (g/dl)	3.83±0.41 <sup>d</sup>	2.37±0.30 <sup>c</sup>	1.43±0.12 <sup>c</sup>	2.25±0.08 <sup>c</sup>	2.93±0.04 <sup>c</sup>	3.41±0.14 <sup>c</sup>
Glob (g/dl)	1.99±0.63 <sup>d</sup>	5.40±5.40 <sup>c</sup>	3.16±0.11 <sup>c</sup>	2.77±0.09 <sup>c</sup>	2.06±0.06	1.98±0.15
A\G	2.18±1.01 <sup>d</sup>	0.45±0.11 <sup>c</sup>	0.46±0.06 <sup>c</sup>	0.82±0.05 <sup>c</sup>	1.42±0.06 <sup>c</sup>	1.73±0.19
MMP-2 (ng/ml)	16.48±1.15 <sup>d</sup>	25.64±0.64 <sup>c</sup>	20.74±0.15 <sup>c</sup>	18.42±0.22 <sup>c</sup>	17.07±0.84	16.80±0.89
MMP-9 (ng/ml)	24.43±2.87 <sup>d</sup>	39.28±0.98 <sup>c</sup>	31.18±0.75 <sup>c</sup>	28.35±0.31 <sup>c</sup>	26.75±2.27	25.55±1.97
Glucose (mg/dl)	100.62±4.36 <sup>d</sup>	81.84±6.12 <sup>c</sup>	90.94±0.04 <sup>c</sup>	97.50±2.26	101.14±1.63	101.14±1.63
Total lipids (mg/dl)	424.73±7.45 <sup>d</sup>	490.81±20.17 <sup>c</sup>	442.90±6.49 <sup>c</sup>	430.57±7.40	431.39±11.02	433.52±9.39
Triglycerides (mg/dl)	75.03±3.45 <sup>d</sup>	90.79±1.74 <sup>c</sup>	80.68±0.33 <sup>c</sup>	77.14±3.10	76.75±5.81	78.16±5.59
Phospholipids (mg/dl)	159.54±5.19	160.82±5.87	161.74±6.58	162.14±7.11	164.89±8.27	164.89±8.27
Cholesterol(mg/dl)	190.16±2.83 <sup>d</sup>	239.20±17.41 <sup>c</sup>	200.48±0.31 <sup>c</sup>	191.29±4.20	189.74±2.80	190.47±3.84
LDL-c (mg/dl)	93.83±1.85 <sup>d</sup>	118.20±5.03 <sup>c</sup>	98.69±0.32 <sup>c</sup>	95.38±1.99	94.43±2.54	94.80±2.78
HDL-c (mg/dl)	96.34±2.70 <sup>d</sup>	121.01±19.65 <sup>c</sup>	101.80±0.54 <sup>c</sup>	95.92±4.46	95.31±3.01	95.67±4.12
TAC (Mm/L)	1.49±0.14 <sup>d</sup>	0.55±0.04 <sup>c</sup>	0.47±0.01 <sup>c</sup>	0.81±0.06 <sup>c</sup>	1.05±0.12 <sup>c</sup>	1.48±0.13
AST (U/L)	20.16±0.50 <sup>d</sup>	33.18±1.93 <sup>c</sup>	38.61±0.27 <sup>c</sup>	34.88±0.04 <sup>c</sup>	25.51±2.47 <sup>c</sup>	20.29±0.28
ALT (U/L)	26.83±2.62 <sup>d</sup>	42.57±1.36 <sup>c</sup>	46.61±0.30 <sup>c</sup>	40.86±0.09 <sup>c</sup>	30.58±0.16 <sup>c</sup>	29.04±0.10 <sup>c</sup>
T-bilirubin (mg/dl)	0.42±0.03 <sup>d</sup>	0.94±0.03 <sup>c</sup>	1.02±0.02 <sup>c</sup>	0.88±0.04 <sup>c</sup>	0.76±0.03 <sup>c</sup>	0.53±0.03 <sup>c</sup>
D-bilirubin (mg/dl)	0.23±0.02 <sup>d</sup>	0.39±0.03 <sup>c</sup>	0.49±0.03 <sup>c</sup>	0.35±0.02 <sup>c</sup>	0.27±0.02 <sup>c</sup>	0.25±0.02
I-bilirubin (mg/dl)	0.20±0.03 <sup>d</sup>	0.54±0.05 <sup>c</sup>	0.52±0.04 <sup>c</sup>	0.53±0.04 <sup>c</sup>	0.49±0.04 <sup>c</sup>	0.28±0.04 <sup>c</sup>
Urea (mg/dl)	24.90±1.56 <sup>d</sup>	38.55±0.70 <sup>c</sup>	42.59±0.38 <sup>c</sup>	36.55±0.36 <sup>c</sup>	28.71±0.27 <sup>c</sup>	26.28±0.12 <sup>c</sup>
Cr (mg/dl)	1.37±0.30 <sup>d</sup>	2.01±0.05 <sup>c</sup>	2.36±0.12 <sup>c</sup>	2.08±0.05 <sup>c</sup>	1.81±0.06 <sup>c</sup>	1.45±0.18

<sup>d</sup> (significant between the studied groups); <sup>c</sup> (significant with CG), considered statistically significant at P<0.05. CG: Control group; DG: Diseased group before treatment; TG: Diseased group after treatment; TP: Total protein; Alb: Albumin; Glob: Total globulin; A/G: Albumin/Globulin ratio; TAC: Total antioxidant capacity; AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; T-bilirubin: total bilirubin; D-bilirubin: Direct bilirubin; I-bilirubin: Indirect bilirubin; Cr: Creatinine; HDL-c: HDL-cholesterol; LDL-c: LDL-cholesterol; MMP-2: Matrix metalloproteinase-2; MMP-9: Matrix metalloproteinase-9.

**Table 3:** Area under the curve (AUC), cut off points, sensitivity%, specificity%, Likelihood Ratios (LR), PPV%, NPV%, accuracy rate% of the suggested markers in DG and TG.

Parameters	group	AUC	Cut off points	Sensitivity	Specificity	LR	PPV	NPV	Accuracy rate
SI (µg/dl)	DG	1	155.30	100%	90%	10	90.91%	100%	95%
	TG	1	125.50	100%	80%	5	95.24%	100%	96%
Ferritin (ng/ml)	DG	1	130.20	100%	90%	10	90.91%	100%	95%
	TG	1	159.60	100%	80%	5	95.24%	100%	96%
MMP-2 (ng/ml)	DG	1	18.37	100%	90%	10	90.91%	100%	95%
	TG	1	24.90	100%	90%	10	97.56%	100%	98%
MMP-9 (ng/ml)	DG	1	27.33	100%	80%	5	83.33%	100%	90%
	TG	1	38.24	100%	90%	10	97.56%	100%	98%
TAC (Mm/L)	DG	1	1.30	100%	90%	10	90.91%	100%	95%
	TG	0.75	0.61	75%	90%	7.50	96.77%	47.37%	78%

DG: Diseased group before treatment; TG: Diseased group after treatment; AUC= 0.5–0.65 (useless marker); AUC= 0.7–0.85 (good marker); AUC = 0.86–1 (with satisfactory sensitivity and specificity: excellent marker). LR= 0.5-5: low; LR=5-10: moderate; LR>10: high.

emaciated with pale mucous membranes (Abdally, 2010; Awol et al., 2014; Feyera et al., 2015). Whereas, the irritation and anorexia related to the disease reduce intestinal iron absorption and subsequently decrease iron



availability to bone marrow and inhibit erythropoiesis process. Therefore, the blood picture of the infested camels usually clarified a hypochromic microcytic anemia. This anemia was indicated by the obtained decline in the red blood cell parameters and indices values in DG in this research as well as previous researches (Saleh et al., 2011; Momenah, 2014; Zahid, 2015; Abdel-Saeed, 2020). In accordance to this anemia, the iron profile of the infested animals in the current work showed a marked hypoferrinemia and a consequent raised TIBC, UIBC and decreased Tf sat. % (Abdel-Saeed, 2020). Rationally, the transferrin (major iron transport protein) activates in order to correct this hypoferrinemia (Gomme et al., 2005). Thus, a prominent hypertferrinemia was observed in DG. Meanwhile, the spotted hyperferritinemia here, was mainly attributed to the host immune response. Whereas the activated pro-inflammatory cytokines due to presence of the mite and its antigenic products enhance free radicals production which destruct RBCs and hepatic cells leading to a massive iron release (Abd El-Aal et al., 2016; Bhat et al., 2017). This free iron is very harmful to the host body, so these cytokines respond by increasing iron storage as ferritin to protect the host body cells from its oxidative damage. Additionally, this mechanism prevents iron delivery to the parasites, thus it hinders the parasite iron-dependent biological process to destroy it (Kernan and Carcillo, 2017). Unfortunately, this mechanism makes the iron less accessible to the bone marrow and may duplicate the above-mentioned hypoferrinemia and related anemia.

Another outcome for the host immune system activation in this study, is the observed neutrophilic eosinophilic leukocytosis in DG. Whereas, the invigorated pro-inflammatory cytokines maximize circulating the neutrophils (1<sup>st</sup> line of defense) and eosinophils (specific immune cells for parasitic infestation) numbers (Zahid, 2015; El-Aal et al., 2016; Bhat et al., 2017; Abdel-Saeed, 2020). This is commonly acted through two mechanisms: first, encourage their production, proliferation, maturation in bone marrow and release in circulation. Second, rearrangement of the circulatory leukocytes and shifting more neutrophils from marginated pool to circulating pool on expanse of lymphocytes (this caused the noted lymphocytopenia in DG) (Momenah, 2014; Zahid, 2015; Abdel-Saeed, 2020). The stress and hypercortisolism, frequently reported with the disease, may also involve in the depicted eosinophilia in DG (Hallal-Calleros et al., 2013).

Likewise, the obtained hyperglobulinemia in DG, reflected immune proteins formation either  $\alpha$ ,  $\beta$  globulins (acute phase proteins, ferritin, Tf, MMPs), to limit the parasites infestation, growth and multiplication or  $\gamma$  globulins (immunoglobulins) to shatter and remove it (Rahman et al., 2010; Momenah, 2014; El-Aal et al., 2016; Bhat et al., 2017). In turn, a marked hyperproteinemia and decreased

A/G ratio were noted in DG (Zahid, 2015). Parallel to this hyperglobulinemia, MMP-2 and MMP-9 displayed a moderate increase in their activity in DG in the present work. Whereas, the activated pro-inflammatory cytokines due to the infestation stimulate MMPs secretion from different immune cells to intensify the immune response (El-Aal et al., 2016; Bhat et al., 2017). MMPs enhance body defense mechanisms via increasing cellular proliferation, migration, angiogenesis and apoptosis (Tallant et al., 2010).

Contrariwise, the corresponding hypoalbuminemia and hypoglycemia detected in DG in this study, were assigned to amino acids and carbohydrates shortage in infested camels because of the anorexia related to the disease (Momenah, 2014; Zahid, 2015; Abdel-Saeed, 2020). Subsequently, the adipose tissue lysis increases to get energy necessary for host vital processes and a remarkable hypertriglyceridemia and subordinate hyperlipidemia were obtained in DG (Momenah, 2014; Zahid, 2015). While, the hypercholesterolemia (HDL/LDL-hypercholesterolemia) noticed in the infested camels here, referred to an augmented lipid peroxidation due to the oxidative stress recorded in the current data (the decreased TAC in DG) (Saleh et al., 2011; Zahid, 2015).

The oxidative stress is a disproportion between the free radicals generation and their scavengers activity. Free radicals are a basic part of the host innate immunity, but if they accumulate and overcome their scavengers activity they react with body tissue and cause sever organ damages (Saleh et al., 2011; Zahid, 2015). Thus, the oxidative stress had a great contribution to the elevated liver function tests (AST, ALT, T/D/I-bilirubin) and kidney function tests (urea, Cr) in DG (Momenah, 2014; Zahid, 2015). Logically, liver cell destruction hinders I-bilirubin hepatic uptake and decrease its conjugation and prevent D-bilirubin excretion. The oxidative stress may also participate in the described hyperbilirubinemia in DG by another way, as it attacks RBCs and enhances their destruction resulting more I-bilirubin production and dependent hyperbilirubinemia either indirect or total (Momenah, 2014; Zahid, 2015).

The ivermectin efficiently controlled the mange infestation and the skin lesions completely recovered at 21<sup>st</sup> day and no living mites were found in the skin scraping. This result is compatible with the previous reports about ivermectin curative action against different types of mites. As, it easily causes parasite death and paralysis through increasing membrane permeability to chloride ions thus inhibiting the electrical activity of nerve cells in nematodes and muscle cells in arthropods. Ivermectin also stimulates the inhibitory neurotransmitter production, GABA at pre-synaptic neurons. Furthermore, it widely distributes in different tissues and lasts in adipose tissue and skin in

huge amounts for long periods. So, it acts against different ectoparasites types and stages (Santoro et al., 2003; Henno et al., 2005; Abdally, 2010; Chhaiya et al., 2012).

Sequentially, ivermectin administration worked on restoring the normal levels of the estimated hematological and biochemical parameters in DG. The fastest parameters returned to their physiological values were, these ones connected with anorexia (anemia, hypoglycemia and hyperlipidemia) (Habeeb, 2014; Falohun and Sadiq, 2015; Zahid, 2015). Whereas, the general clinical signs vanished after ivermectin injection and the infested camels became quiet and started to eat normally and gain weight.

Although the normal leukogram reappeared at 14<sup>th</sup> day due to the death of parasites and absence of its antigenic stimuli as well as the inhibitory effect of ivermectin on the pro-inflammatory cytokines (Zhang et al., 2008), but the immune parameters ranked second. Whereas, the achievement of total globulin, MMP-2 and MMP-9 normal levels delayed to 21<sup>st</sup> day. Logically, they took more time to clean the body from the infestation consequences (remove the parasites debris, eggs and toxic products) (Zahid, 2015). Similarly, hypoferrinemia and hyperferritinemia (and subsequent other iron profile changes) in DG were corrected at 21<sup>st</sup> day (Tf sat. % at 28<sup>th</sup> day), as they have an immune origin as mentioned before in the present work.

Oxidative stress and related alterations (liver and kidney function tests) were the last parameters approached CG levels. Whereas, ivermectin administration usually induces a degree of oxidative stress and subsequent hepatic and renal damages, indicated in this work by the noted decrease in TAC and the prominent increase in liver and kidney function tests in TG compared to DG at 7<sup>th</sup> day (Behera et al., 2011). Therefore, TAC, AST, D-bilirubin and Cr were corrected at 28<sup>th</sup> while, ALT, T/I-bilirubin, urea presented a mild increment till the end of the research (Zahid, 2015). Reasonably, the slight hypoalbuminemia (consequent hypoproteinemia and decreased A/G) noticed in TG at the study end was due to the hepatic damage as liver is the concerned organ with albumin synthesis (Stockham and Scott, 2008). It worth to mention that, the high values of MCHC observed in TG in relation DG at the 7<sup>th</sup> day were also assigned to the oxidative stress associated with ivermectin administration and subordinate hemolytic anemia (Stockham and Scott, 2008).

Concerning the diagnostic and prognostic value of SI, ferritin, TAC, MMP-2 and MMP-9 for the camel mange, Table 3 data suggested them as useful indicators for the disease and confirmed their importance in the disease treatment follow-up and evaluation.

Finally, the study cleared that camel mange treatment with ivermectin has several adverse effects on liver and kidney functions tests (due to oxidative stress) may extend for a while. The study strongly recommended antioxidant administration with ivermectin to reduce its side effects. SI, ferritin, TAC, MMP-2 and MMP-9 may be good markers for camel mange diagnosis and prognosis and for its treatment monitoring.

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## AUTHOR'S CONTRIBUTION

All authors contributed equally.

## CONFLICT OF INTEREST

The authors have declared no conflict of interest.

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