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Stress response and antioxidant profile in Egyptian cows naturally infected with lumpy skin disease

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Abstract. Lumpy skin disease (LSD) is a severe disease of cattle that causes a broad spectrum of economic losses. The purpose of this study is to shed light on some physiological changes that may occur in the infected Egyptian local cows, including the primary and secondary stress responses besides the antioxidant profile. Two groups of Egyptian adult cows were used in the present study. The first group (control group) consisted of 10 clinically healthy cows, while the other one (infected group) consisted of 7 naturally infected LSD cases subjected to routine clinical examination. The clinical investigation revealed skin lesions passing through different progressive stages, starting from the appearance of nodules until the formation of deep scars. LSD was associated with a well-noted stress response, as exemplified by hyperglycemia, hyperlactatemia, and increases in serum cortisol, urea, and creatinine levels. Marked depletion in serum superoxide dismutase and catalase activities, vitamin E, malondialdehyde, and total peroxide levels were observed in the LSD challenged cows. These findings indicated the ability of LSD to induce stress reactivity and disturb the redox balance, and therefore the application of stress-management strategies and administration of dietary antioxidants is highly recommended to enhance the health status of infected animals. This study paves the road towards other works investigating the differential response of oxidative stress biomarkers to this disease according to its severity and stages and choosing the best antioxidant supplements.

***Keywords**:* Lumpy skin disease, cow, skin lesion, stress reactivity, redox balance

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1. Introduction

Lumpy skin disease (LSD) represents a significant health threat to the bovine livestock in Egypt. It poses a severe threat to the rest of the world, representing an economically devastating problem at the levels of reproduction, milk, beef, draft power, and vaccination cost in smallholder farmers and livestock industries [1]. Stress is a state of threatened homeostasis that produces different physiological and pathological changes depending on its severity, type, and duration [2]. Biological responses, such as the release of cortisol as a front-line hormone to overcome stressful situations after infection, are known as a primary stress response [3]. In the long term, sustained primary stress reactions induce a secondary stress response in which energy allocation and metabolism changes occur [4]. It is of utmost importance to shed light on the animal's reaction against the diseased conditions due to the causal relationship between the physiological stress response and several aspects of animal productivity and well-being [5]. Also, exposure to stress is a major driving force contributing to the development and severity of diseases by impairing cellular immunity [6]. An increment accompanies infections in cows in the stress endpoint reflectors [7]. Therefore, we hypothesized that LSD could change the stress responses in Egyptian cows on both levels of its primary and secondary components.

A broad spectrum of data denoted that viral infection in cow target enzymatic and non-enzymatic antioxidants leaving tissues more susceptible to peroxidative injury [8,9]. Viral infection stimulates the immune defensive mechanism with subsequent generation of reactive free radicals culminating at redox status imbalance, which is implicated in several pathological conditions

[10,11]. Antioxidant deficiency acts as a driving force for the emergence of viral mutation due to host immune dysfunction [12]. From the attack of free radicals to polyunsaturated fatty acids, malondialdehyde (MDA) is a well-established indicator of oxidative damage. It interacts with DNA and proteins to generate mutagenic and atherogenic by-products [13], adding a new dimension to an elevation of this diagnostic marker. Mammalian species possess a collaborative and integrative defensive network against oxidative stress composes of a wide array of antioxidants and enzymes. Superoxide dismutase (SOD) catalyzes superoxide anion into hydrogen peroxide and molecular oxygen [14]. Catalase (CAT) is responsible for the decomposition of hydrogen peroxide to water, a function that is shared with glutathione peroxidase (GPH-Px) [15]. Vitamin C is a powerful reducing agent through its ability to denote electrons, scavenging free radicals, and maintaining the vitamin E redox cycle [16]. Vitamin E suppresses the oxidation mediated by radical and non-radical oxidants and lipid peroxidation by breaking chain propagation [17]. The biological imbalance between reactive oxygen species and antioxidants creates a status of oxidative stress leading to adverse alterations in the biomolecules [18].

The mission of the current study is to investigate some physiological aspects in Egyptian cows clinically infected with LSD by measuring serum stress and antioxidant parameters.

2.Materials and methods

2.1. Animals

Two groups of Egyptian adult cows feed on concentrate, and grain rations were used in this study. The first group (control group) consisted of 10 clinically healthy cows, while the other one (infected group) consisted of 7 naturally infected LSD cases subjected to routine clinical examination.

2.2. Blood sampling

The blood samples were collected from the jugular vein into plain tubes. Serum was isolated after centrifugation at 3000 rpm for 10 min and stored at -20 °C until analysis for determining the biochemical parameters later on.

2.3. Biochemical measurements

According to the manufacturer's instructions, cortisol was determined by enzyme-linked immunosorbent assay (ELISA) using commercially available kits (Immunospec Corporation, USA). The cortisol concentrations were then calculated using a standard cortisol curve. The ELISA assay has a sensitivity of 91.5 pg, and this is equivalent to a sample containing a concentration of 0.366 µg/dl. Glucose, total cholesterol (TC), triglycerides (TG), and lactate were estimated depending on enzymatic colorimetric methods using commercially available reagent kits (Egyptian Company for Biotechnology, Cairo, Egypt). Albumin was assessed based on its binding to the indicator dye, bromocresol green, at pH 4.3 to form a blue-green colored complex [19]. Urea was measured according to the modified Urease-Berthelot method [20], and creatinine was analyzed through the colorimetric method following deproteinization [21].

SOD measurement relies on its ability to inhibit the phenazine methosulphate-mediated reduction of nitroblue tetrazolium dye [22]. GPH-Px levels were estimated by the UV method [23], and CAT assay was performed according to [24]. MDA levels were measured by the thiobarbituric acid reaction [25]. Total peroxide (TPX) levels were assessed following the protocol of [26] and calculated from the standard curve constructed using standard concentrations. Vitamin C determination is based on its redox reaction with 2,6-dichlorophenol indophenols in acid solution [27]. Vitamin E levels were estimated by a commercially available kit (ABC Diagnostic, Egypt).

2.4. Ethical statement

A research ethics committee approved all Faculty of Veterinary Medicine procedures, Assiut University, Assuit, Egypt.

2.5. Statistical analysis

The data were expressed as means ± standard error of the mean (SEM). Statistical differences between groups were analyzed by independent samples T-test using SPSS program version 16 (SPSS, Richmond, VA, USA).

3. Results and discussion

3.1. Clinical signs

Clinical examination of the infected cows revealed the presence of well-observed skin lesions passing through different progressive stages, as presented in Figures 1-5.

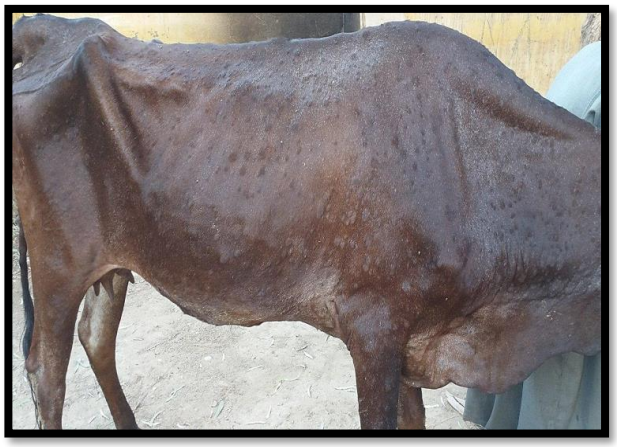

Figure 1. Cow shows the characteristic skin lesions of lumpy skin disease.

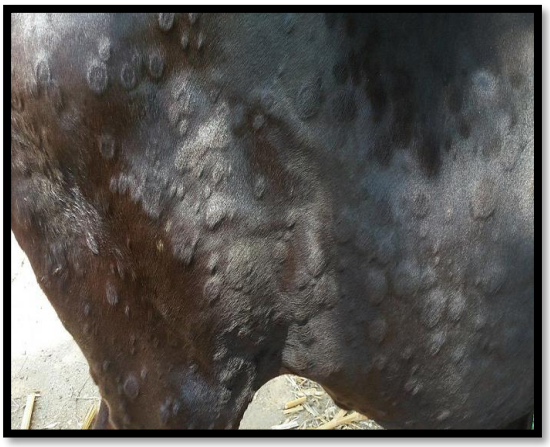

Figure 2. Firstly the lesion starts as small nodules with erected hair all over the body.

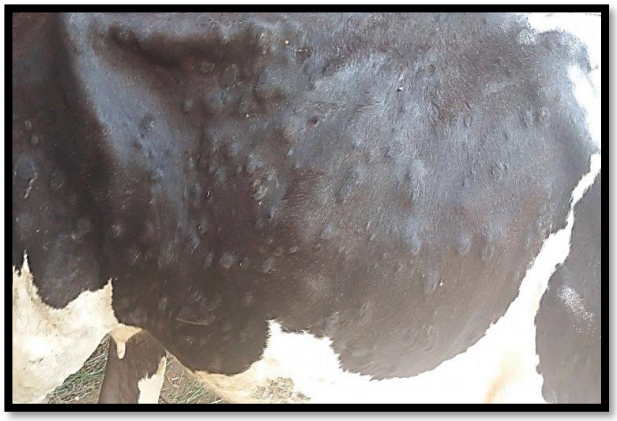

Figure 3. Secondly, those nodules become very prominent hard lumps.

Figure 4. Lastly, the lumpy skin areas become necrotic and separated from the surrounding healthy skin.

Figure 5. The necrotic separated skin starts to fall down leaving large ulcers called "Setfast".

3.2. Egyptian cows naturally infected with lumpy skin disease are characterized by a marked increase in primary and secondary stress biomarkers

As shown in Table 1, serum cortisol levels of infected cows were significantly (P≤0.001) higher than that of healthy ones. LSD group was characterized by marked hyperglycemia and hyperlactatemia (P≤0.001). Compared with the control group, serum urea and creatinine levels were significantly (P≤0.05) higher in the LSD group. Slight decreases were also observed in serum albumin, TC, and TG levels of LSD challenged cows, but the differences with the healthy ones were not statistically significant.

Based on the findings of this study, LSD represented a significant challenge to Egyptian cows from the stress point of view, as manifested by the exhaustion of energy stores. The infected animals tried to cope with this stressful condition by hyperglycemia and increased cortisol secretion. LSD shifted the antioxidant profile of diseased cows towards the pro-oxidant side. These outcomes open new windows for further researches exploring the potential changes in the stress and redox defense system and perhaps other physiological features according to the severity and stages of the disease.

The recorded clinical signs in this study agree with the results of previous authors [28,29], who observed that LSD infected animals showed pyrexia due to release and rapid clearance of pyrogens and skin nodules which ranged from a few to several hundred sometimes coalesced together. Later, these nodules contained clear serous or purulent exudates with ulcer formation. Once these skin lesions heal, they leave scars that permanently damage the hide. The significant increase in serum cortisol levels of LSD-challenged cows is in the same line as other bovine infectious diseases [7]. It is well known that stress and viral infections stimulate the adrenal glands through the hypothalamic-pituitary-adrenal axis to release the cortisol in the bloodstream [30].

Prolonged distress renders the animals more vulnerable to disease due to immune suppression and compromises their ability to reproduce and develop properly [31]. Profound hyperglycemia in infected cows is in harmony because viral infections are most frequently associated with hyperglycemia [32]. Viral infections may cause diabetes mellitus in cattle by direct destruction of β cells, the auto-immune response in the host, or as a consequence of hypocalcemia [32,33].

The hyperglycemia may be secondary to augmented cortisol secretion during stress. Cortisol inhibits insulin secretion through a genomic action in β cells, activates the critical enzymes involved in hepatic gluconeogenesis, inhibits glucose uptake in peripheral tissues, and increases the glucogenic precursors as amino acids through muscle proteolysis [34-38]. It must keep in mind that stress hyperglycemia is an essential survival response by providing a source of fuel for the immune system and brain at a time of distress [39].

Considering that the organs capable of removing lactate from blood are adversely affected by LSD [28], the elevation in serum lactate concentration in the LSD group may result from an imbalance between production and clearance rates [40]. The decrease in serum albumin level in the infected cows corresponds to the findings of [28] and could be attributed to decreased synthesis and elevated catabolic rate, and damaged liver parenchyma [1]. Elevated serum creatinine and urea levels under LSD stress are similar to the results of [28,29], and most are due to anorexia, loss of muscle mass, the direct effect of LSD virus on the kidneys, increased protein breakdown, and decreased renal blood flow during the viraemic stage of LSD [41].

The reduction in serum TC and TG levels in the LSD infected cows is consistent with that present in other viral infectious diseases and stressful situations in the ruminant animals [42]. Hypocholesterolemia may be due to impaired intestinal absorption of cholesterol, increased macrophage-specific reverse cholesterol transport rate, increased transit through the large intestine, and enhanced fecal bile acid excretion [43,44]. Decreased serum TG level in the current investigation may result from reduced feed intake, and expression levels of jejunal fatty-acid-binding protein 1, and the cluster of differentiation 36 by the viral infection [45].

Mounting evidence suggested the relationship between antioxidant imbalance and stress exposure. Chronic stress increases susceptibility to peroxidative damage through activation of the hypothalamic-pituitary-adrenal axis [46]. Glucocorticoids down-regulate gene expression of antioxidants and transcript levels of rate-limiting enzymes involved in the synthesis of non-enzymatic antioxidants, inhibit key transcription factors related to the regulation of antioxidant genes, and induce reactive oxygen species overproduction [47]. This implies that the redox homeostasis of LSD-affected cows may distribute in concomitant with the increase in stress markers. Our findings reinforced this assumption.

Table 1. The indicators of primary and secondary stress responses in the control and infected groups

Parameters	Control	Infected
Cortisol (µg/dl)	4.565 ± 0.728	18.288 ± 4.723***
Glucose (mg/dl)	24.75 ± 3.351	72.95 ± 3.132***
Lactate (mg/dl)	17.825 ± 2.564	59.525 ± 2.673***
Urea (mg/dl)	29.7 ± 3.9	41.2 ± 0.635*
Creatinine (mg/dl)	0.733 ± 0.033	0.85 ± 0.029*
Albumin (g/dl)	3.712 ± 0.210	2.93 ± 0.030
TC (mg/dl)	160 ± 1.5	157 ± 3
TG (mg/dl)	72.75 ± 9.304	51.5 ± 5.545

TC, total cholesterol; TG, triglycerides.Results are expressed as means ± SEM of 10 cows in the control group and 7 cows in the infected group. *P≤0.05; ***P≤0.001 (independent samples T test).

3.3. Lumpy skin disease shifts the redox potential towards the pro-oxidant side in naturally infected Egyptian cows

As shown in Table 2, the infected group was characterized by a high significant (P≤0.001) inhibition of SOD and CAT activities and depletion of vitamin E levels. Surprisingly, MDA and TPX levels in the LSD challenged cows were significantly (P≤0.05 and P≤0.01, respectively) lower than those of the healthy ones. There were no significant changes in GSH-Px activities and vitamin C levels between the two groups.

The apparent inhibition of SOD and CAT activities in the current work is in harmony with previous studies on sheep naturally infected with poxvirus [48], but in contrast with that observed in cattle [29]. This controversy may be attributed to the complexity of the case and differences in the stages of the disease. The inhibition of SOD activity by the copper chaperone binding process [49] may be one of the causative factors underlying this outcome.

Poxviruses utilize the de novo fatty acid biosynthesis in the cell, especially the production of palmitates. These molecules undergo β-oxidation in mitochondria and, together with the glutamine catabolism, generate Acetyl-CoA and α-ketoglutarate, respectively [50]. Both molecules enter a tricarboxylic acid cycle in which oxygen plays a key role as a final electron acceptor of oxidative phosphorylation coupled to the electron transfer chain resulting in the production of reactive oxygen species [51]. It could be suggested that the excessive generation of oxidants is incriminated in consuming the antioxidant reserves.

Inconsistent with other researchers [48], a marked depletion in vitamin E was observed in this study. This is another manifestation of the failure of antioxidant-buffering capacity in front of the ability of the viral infection to induce free radical generation secondary to stimulation of respiratory burst and xanthine oxidase activity [52]. Sheep poxvirus triggers host antiviral defense activating innate immune signaling as represented by enhanced expression of pro-inflammatory cytokines [53], which in turn induces endoplasmic reticulum stress [54] associated with increased production of pro-oxidants.

Lipid peroxidation increases the need for lipid-soluble antioxidants, and consequently, consumption of vitamin E [55]. This functional relationship may explain the significant reduction in MDA levels in the LSD infected group relative to the normal one. We must keep in mind that vitamin E deficiency results in increased viral pathogenicity and altered immune responses [12], leaving the animal more vulnerable to infectious diseases.

Differential responses in the antioxidant components to viral infection were found in this study, as evidenced by non-significant changes in vitamin C level and GSH-Px activity, indicating selective inhibition of specific antioxidants. In contrast, others can keep their functionality under LSD stress.

This study's apparent decrease in MDA and TPX levels in the LSD group represents a significant surprise contradicting previous reports [29,48]. One explanation for this outcome pattern is the compensatory protective actions of other antioxidants, such as cysteine, alpha-tocopherol, and ascorbic acid [56], overcoming the suppression SOD and CAT activities and reduces the degree of peroxidative damage. Another explanatory factor is the numerical increase in the activity of GSH-Px, which is involved in the repair of phospholipid hydroperoxide [57].

Table 2. The indicators of antioxidant balance in the control and infected groups

Parameter	Control	Infected
SOD activity (U/mL)	11.07 ± 0.945	4.729 ± 0.762***
CAT activity (U/L)	254.6 ± 9.6	166.71 ± 3.714***
GSH-Px activity (mU/mL)	0.291 ± 0.06	0.439 ± 0.041
Vitamin C level (mg/L)	2.45 ± 0.259	3.071 ± 0.364
Vitamin E level (ng/mL)	10.48 ± 1.328	2.686 ± 0.358***
MDA level (nmol/mL)	7.71 ± 0.635	5.814 ± 0.387*
TPX level (µmol/L)	1315.4 ± 59.847	999.09 ± 61.854**

SOD, superoxide dismutase; CAT, catalase; GSH-Px, glutathione peroxidase; MDA, malondialdhyde; TPX, total peroxide. Results are expressed as means ± SEM of 10 cows in the control group and 7 cows in the infected group. *P≤0.05; ***P≤0.001 (independent samples T test).

4. Conclusion

Primary and secondary stress responses and antioxidant equilibrium were modified in the LSD challenged Egyptian cows. These findings open new thoughts for evaluating the health status of diseased animals based on the modulation in these biomarkers and improving our understanding of the disease's pathophysiological mechanisms. According to these outcomes, the addition of antioxidants to ration formulation and application of stress management protocols could be of significant importance for the animals suffered from LSD.

Conflicts of interest. The authors declare that there is no conflict of interest.

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