

## Investigation of serum insulin and cortisol concentrations in and mouth disease- infected cattle in relation to changes in sero biochemical variables and protein electrophoretic fractionation profile.

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### Abstract

The present study was conducted to monitor serum levels of insulin and cortisol in mouth disease-infected cattle (FMD) in relation to possible alterations in biochemical variables and protein electrophoretic fractionation. The study was carried out on two groups of cattle one group of 15 naturally infected FMD cattle and another group of 8 healthy cattle were used as control. Evaluating parameters included levels of insulin and cortisol, biochemical variables [total protein (TP), albumin, glucose, serum calcium (Ca), serum phosphorus (P), blood urea (BUN), creatinine (Cr) and serum enzymatic activities of alanine amino transferase (ALT) and aspartate amino transferase (AST)] as well as serum protein electrophoresis results showed a significant increase in serum levels of glucose, cholesterol, phosphorus, AST and cortisol and a significant decrease in serum concentrations of total protein, calcium and insulin. Serum protein electrophoretic fractionation showed a significant decrease in albumin and gamma globulins. There was a significant negative correlation between insulin and serum levels of glucose, cholesterol, phosphorus and cortisol and significant positive correlation with serum levels of calcium and total proteins. Serum cortisol concentration was positively correlated with serum levels of glucose, phosphorus and AST and negatively correlated with albumin, calcium and insulin. Our results indicate that FMD infection in cattle results in pancreatic dysfunction and hypoinsulinemia as well as a pronounced stress response as detected by the significant increase in cortisol levels. Further, alterations in biochemical variables and protein electrophoresis seen in FMD group are likely to be related to changes in serum concentrations of these two hormones providing further understanding of the disease process and clinical pathology of FMD in cattle.

### Introduction

Animals undergoing any challenge to their state of health as infection, inflammation, trauma and systemic body illness react by a wide range of non-specific pathophysiological responses collectively known as the acute phase response to illness (Eckersall, 2000). The acute phase response is considered to be a dynamic process involving systemic and metabolic changes providing an early non-specific defence mechanism against insult before specific immunity is achieved (Petersen et al., 2004). This response encompasses diverse countermeasures combining together to minimize tissue damage while enhancing the repair process including physiological changes clinically characterized by fever, anorexia and negative nitrogen balance (Moshage, 1997 and Gruys et al., 2005). In addition, a series of changes in blood chemistry can be measured in the laboratory such as changes in leukocyte numbers and changes in host's metabolic responses as indicated by disturbances in concentrations of proteins, lipids and carbohydrates, hormonal alterations, inc

values of adrenocorticotrophic hormone (ACTH) and glucocorticoids and the concentration in a number of serum proteins known as the acute phase proteins (Ramaekers et al., 1975; Baumann and Gaudie, 1994; Kushibiki et al., Ganheim et al., 2003; Ametaj et al., 2005; Gruys et al., 2005 and Fagliari et al., 2007). The magnitude of this response varies with type and severity of illness which depends on the severity of insult, the type and strain of infectious agent, pathology inside the body, infective dose and status of host (Ramaekers et al., 1975).

Foot and mouth disease (FMD) also known as apthous fever is a communicable disease and one of the most serious livestock diseases that affect cloven-footed domestic and wild animals including cattle, buffalo, camels, sheep, goats, deer and pigs (Blancou, 2002 and Radostits et al., 2007). It is caused by the smallest disease producing viruses known as Aphthovirus or foot and mouth disease virus (FMDV) which is a member of the Family Picornovirus (Radostits et al., 2007). The disease is characterized by blister-like lesions on the tongue, nose, lips, the mouth, on the teats and between the toes which then burst, leaving painful ulcers. Affected animals usually have high fevers, stop eating, give less milk and become lame (Barnett and Cox, 1999 and Remond et al., 2002). On most continents, cattle are usually the most important maintenance hosts for FMDV, but some virus strains are primarily found in pigs, sheep or goats (Lubroth, 2002 and Radostits et al., 2007). While FMD is not a concern for human health, it can cause severe problems for animals with cloven hooves with the potential of causing severe economic losses through trade disruptions in animals and animal products (Lubroth, 2002). Many studies have addressed the cellular and humoral basis of immunity to FMDV or the influence of infection on the regulation of the immune response (Knudsen et al., 1979; McCullough et al., 1986; McCullough et al., 1992 and Baxt and Mason, 1995).

Fewer studies have studied the hematological and biochemical changes associated with FMD infection in cattle (Yeotikar et al., 2003; Gokce et al., 2004 and El-Saied et al., 2007) but to the best of our knowledge effect of FMD on serum concentrations of insulin and cortisol as well as serum profile of protein electrophoresis in FMD infected cattle are not well documented. Consequently, the present investigation aims to monitor the possible alterations in serum insulin and cortisol levels in FMD infected cattle in relation to changes in some biochemical variables and serum profile of protein electrophoretic fractionation in these patients.

### Materials and Methods

**Cattle:** Two groups of cattle were used in this study, one consisted of 15 naturally affected FMD cases showed characteristic clinical signs of FMD based on routine clinical examination and observation of the characteristic lesions. Animals with characteristic lesions for FMD were not used in the study. The other group consisted of 8 clinically healthy cattle and were used as controls.

**Blood samples:** Blood samples were collected from the animals of both groups. Serum samples were stored at -20°C until used for different assays described in this study.

### Biochemical parameters:

Serum samples were evaluated for the concentration of total protein (TP), albumin (Alb), glucose, cholesterol (Chol), calcium (Ca), phosphorus (P), blood urea nitrogen (BUN), creatinine (Cr) and serum enzymatic activities of alanine aminotransferase (ALT) and aspartate aminotransferase (AST). All biochemical parameters were determined by spectrophotometric method using commercial kits.

**Hormonal assays:**

Serum levels of insulin and cortisol were determined by enzyme-linked immunosorbent assay (ELISA) using commercially available test kits of Hellabio diagnostics company and following the manufacturer's instructions.

**Serum protein electrophoresis:**

Electrophoretic separation of serum proteins was accomplished by an agarose gel electrophoresis using commercially kits of Cobasintegra company and following the manufacturer's instructions.

**Statistical analysis:**

All the values were presented as mean  $\pm$  standard deviation (SD). Mean value FMD infected group and control group were compared by Student's t-test at 1% level of probability. Differences at  $p < 0.05$  were considered significant. Correlations between monitored variables were determined with Pearson's simple correlation method. A difference was considered significant at  $P < 0.05$ .

**Results****Serum biochemical parameters:**

Results of serum biochemical tests as shown in (table 1) revealed that there was significant decrease in serum total proteins ( $P < 0.05$ ) in FMD-infected group compared to the control one. Comparison of the mean values for blood glucose between the groups showed a significant increase ( $P < 0.001$ ) in glucose level in the FMD-infected cattle. The mean values of serum cholesterol were significantly higher ( $P < 0.001$ ) in FMD-infected group. Serum calcium concentration showed a significant decrease ( $P < 0.05$ ) in the FMD-infected cattle while, serum phosphorus was significantly increased ( $P < 0.05$ ). The mean values of serum BUN and creatinine in FMD-infected and healthy cattle were similar. Comparison of the mean values of serum enzyme activities of ALT and AST demonstrated a significant increase ( $P < 0.01$ ) in serum ALT and no significant changes were seen in serum ALT activity.

**Hormonal assays:**

The mean values of serum insulin levels were significantly lower ( $P < 0.05$ ) in the FMD-infected group while serum cortisol levels showed a significant increase ( $P < 0.01$ ) (Table 2).

There was a significant negative correlation between insulin and serum levels of glucose, cholesterol, phosphorus and cortisol ( $R = 0.887, 0.839, 0.891$  and  $0.923$  respectively) and significant positive correlation with serum levels of calcium and proteins ( $R = 0.834$  and  $0.923$  respectively) (table 4). Serum cortisol concentration positively correlated with serum levels of glucose, phosphorus and AST ( $R = 0.976$  and  $0.957$  respectively) and negatively correlated with albumin, calcium and insulin ( $R = 0.859, 0.911$  and  $0.902$  respectively).

**Serum protein electrophoretic fractionation:**

The major changes observed in the electrophoretic pattern of FMD infected cattle included significant decrease in both albumin and gamma globulins ( $P < 0.05$ ) (table 1). Table 1. Mean values  $\pm$  SD of serum biochemical parameters in the FMD-infected cattle compared to the control group. Values are means  $\pm$  SD.

Variable group	Control group	FMD infected group
Total protein (g/dl)	7.85 $\pm$ 0.11	6.58 $\pm$ 0.07

Glucose (mg/dl)	62.43±5.53	106.37±7
Cholesterol (mg/dl)	125.40±17.09	196.12±21
Calcium (mg/dl)	13.43±2.18	10.95±1.1
Phosphorous (mg/dl)	5.30±0.30	6.39±1.1
ALT (U/l)	58.27±1.32	57.17±3
AST (U/l)	137.00±4.95	153.84±
BUN (mg/dl)	17.57±1.41	18.18±0
Creatinine (mg/dl)	1.39±0.21	1.43±0.30

Significant differences in the values between the FMD and control groups are indicated by \* P < 0.05, \*\* P < 0.01, \*\*\* P < 0.001.

Table 2. Serum insulin and cortisol concentrations in the FMD- infected cattle compared to the control group. Values are means ± SD.

Hormone group	Control group	FMD infe
Insulin (µIU/ml)	15.90±2.50	11.93±1.0
Cortisol (µg/dl)	1.43±0.07	2.65±0.2

Significant differences in the values between the FMD and control groups are indicated by \*P < 0.05, \*\* P < 0.01.

Table 3. Serum profile of protein electrophoretic fractionation in the FMD- infected cattle compared to the control group. Values are means ± SD.

Variable	Control group	FMD infected grou
Total protein (g/dl)		7.8
6.58±0.07		
Albumin (g/dl)		3.4
2.90±0.10		
Alpha 1 globulin (g/dl)		0.50
0.36±0.11		
Alpha 2 globulin (g/dl)		0.70±
0.86±0.03		
Beta globulin (g/dl)		0.80
0.83±0.07		
Gamma globulin (g/dl)		2.40
1.65±0.09		

Significant differences in the values between the FMD and control groups are indicated by \* P < 0.05.

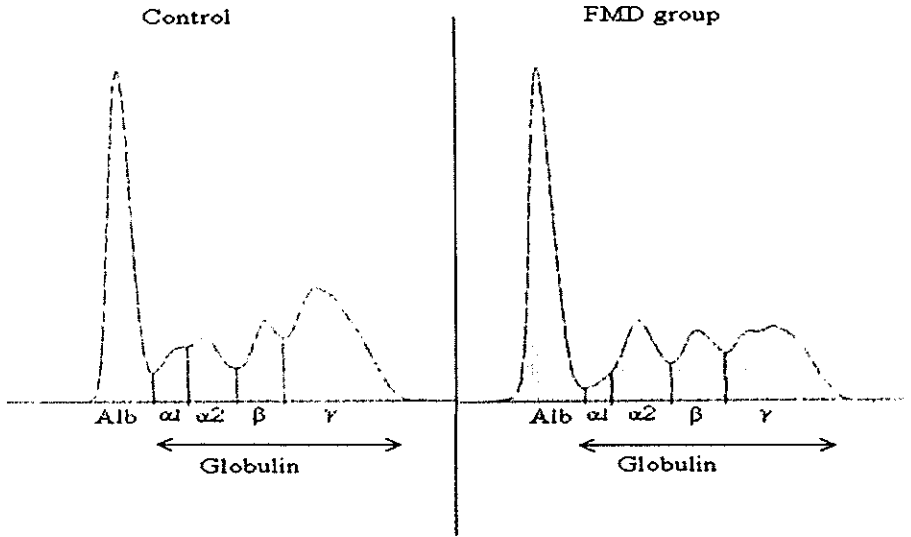


Figure 1. Schematic representation of protein electrophoresis agarose gel in FMD infected cattle compared to control group.

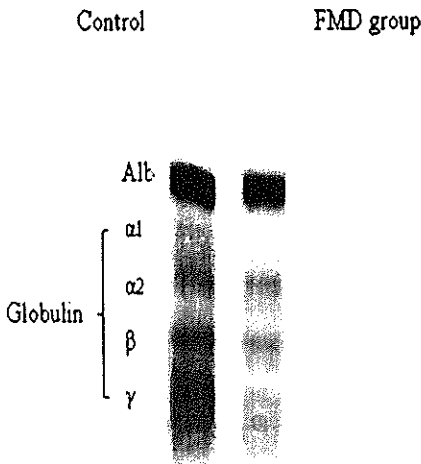


Figure 2. Autoradiogram of protein electrophoresis agarose gel in FMD infected cattle compared to control group

### Discussion

FMD is a severe, highly contagious viral disease which is most important in domesticated and wild cloven-hoofed animals, notably cattle, pigs, goats, buffalo, sheep (Radostits et al., 2007).

The disease is characterized by fever and vesicles (blisters) on the feet, in and around the mouth, and on the mammary gland. Vesicles often rupture rapidly, becoming erosions. Pain and discomfort from the lesions leads to a variety of symptoms including depression, anorexia, excessive salivation, lameness and reluctance to move or stand (Radostits et al., 2007). Where it is endemic, this disease is a major constraint to international livestock trade because it has grave economic losses in the production of meat and milk as well as clinical consequences (Lubroth, 2002). In our study the characteristic clinical signs seen in the FMD-infected cattle comply with those first recorded in previous reports (Yang et al., 1999; Blancou, 2002; Paarlberg et al., 2002; and Remond et al., 2002).

The results of the present investigation revealed that in the FMD group, serum concentrations of glucose significantly increased ( $P < 0.001$ ). Hyperglycemia is a common finding and well documented in cattle affected with FMD (Szopa et al., 1999; Elitok et al., 1999; Yeotikar et al., 2003; Gokce et al., 2004 and El-Saied et al., 2004). Sustained increases in glucose can be seen with insulin deficiency due to pancreatic beta cell ( $\beta$  cells) dysfunction (type I diabetes mellitus) or insulin resistance (type II diabetes mellitus) (Jun and Yoon, 2001 and Clark, 2003). Like some other viruses, both naturally occurring and experimental infections, FMDV has been implicated in the development of type 1 diabetes by 2 different mechanisms. First the virus can directly destroy insulin-producing pancreatic  $\beta$  cells in the pancreas due to viral replication (Barbani et al., 1966 and Jun and Yoon, 2001). Second, an immune response against the virus infection may induce an autoimmune response in the host leading to the destruction of the remaining  $\beta$  cells (Craighead and Steinke, 1971; Boucher and Notkins, 1973 and Jun and Yoon, 2001). Both mechanisms will result in decreased insulin synthesis and thus hyperglycemia (Jun and Yoon, 2001). Therefore, to determine whether hyperglycemia might be attributed to decreased insulin synthesis, serum levels of insulin were determined. The demonstration of significant lower levels of insulin in the serum of FMD infected cattle than in appropriate controls ( $P < 0.05$ ) and the significant negative correlation ( $R = -0.887$ ,  $P < 0.05$ ) between serum level of insulin and serum glucose concentration (table 4) supports the contention that FMD-induced hyperglycemia is, at least in part, secondary to insulin deficiency (Jun and Yoon, 2001).

Insulin resistance can be a result of increased cortisol concentration that opposes the action of insulin on peripheral tissues resulting in hyperglycemia (Coles, 1986; Rousselle et al., 1997; Meyer and Harvey, 1998 and Lassen, 2004). Because cattle tend to produce marked stress hyperglycemia (Kaneko et al., 1997), the significant increase in serum cortisol levels seen in the present work may provide another reason for the significantly higher glucose levels in FMD-infected group. This explanation is further supported by the significant negative correlation between cortisol and insulin levels ( $R = -0.902$ ,  $P < 0.05$ ) and the significant positive correlation between cortisol and glucose levels ( $R = 0.970$ ,  $P < 0.05$ ) (table 4). There is also a hypothesis that the increase in blood glucose concentration in FMD-infected cattle may be a response to hypocalcemia because an adequate amount of calcium ions in extracellular fluid is essential for insulin secretion in response to blood glucose so, hypocalcemia interferes with the secretion of insulin from the pancreas (Kaneko et al., 1997).

Moore,1997 and Gokce et al., 2004). We reported a significant positive correlation between calcium and insulin levels ( $R= 0.834, P < 0.05$ ) that may support hypothesis (table 4).

A significant reduction in serum TP ( $P<0.05$ ) and albumin ( $P<0.05$ ) was recorded in FMD group. Protein requirement as well as protein catabolism increase in presence of infection or any lesions on the body (Roussel et al.,1997 and Meyer Harvey,1998). Anorexia and off food due to mouth lesions that characterize cattle FMD may be in part a possible cause (Lubroth, 2002 and Gokce et al., 2004). It is well known that glucocorticoids are closely involved in the protein metabolism either their antianabolic effect reducing protein synthesis or catabolic action increase breakdown (Kaneko et al., 1997). Albumin degradation also is increased in presence of increased glucocorticoids and may exceed synthesis which will lead to decrease in serum total protein and albumin concentrations (Coles, 1986 and Kaneko et al., 1997).

Consumption of protein has also been found to be associated with hypoinsulinemia and diabetes mellitus (Moore,1997; Roussel et al.,1997 and Meyer Harvey,1998).Therefore, hypoinsulinemia may in part explain the decrease in protein concentrations observed in this study as detected by the significant positive correlation between serum TP and insulin levels ( $R= 0.923, P < 0.01$ ).

Despite the fact that liver disease is one of the most important causes of decreased serum total proteins, liver dysfunction was not recorded in this study as detected by normal serum activity of ALT a specific marker for liver disease. Serum activity of ALT was significantly increased ( $P<0.01$ ). Elevation in serum AST may be associated with stressful conditions and glucocorticoid excess (Kaneko et al., 1997) so increased serum AST activity can be attributed to increased serum cortisol levels (Correlation between cortisol and AST was indicated as  $R= 0.957, P<0.01$ ).

A significantly high level of cholesterol, ( $P<0.01$ ) was detected in serum samples obtained from cattle with FMD. Abnormalities in lipid metabolism may be secondary to insulin deficiency (Coles, 1986 and Kaneko et al., 1997). In the absence of insulin, lipolysis is enhanced and plasma free fatty acids concentrations rise (Kaneko et al., 1997). Very low density lipoproteins (VLDLs) accumulate in plasma because their catabolism requires insulin for optimal activity which are converted in the blood to low density lipoproteins (LDLs). The rate of cholesterol synthesis is increased by an associated increase in plasma LDLs concentration (Kaneko et al., 1997).

Significant negative correlation between insulin and cholesterol ( $R= 0.839, P < 0.05$ ) was detected in the present study.

Serum calcium values were significantly decreased in FMD group compared to the control group. Hypoproteinemia and hypoalbuminemia resulting in decreased protein bound calcium and may contribute to the hypocalcemia (Moore, 1997; Roussel et al.,1997 and Gokce et al., 2004). Significant positive correlation between albumin and TP was reported as  $R= 0.870, P<0.05$ .

Cortisol also has been found to produce marked depression of Ca uptake from bone due to inhibition of vitamin D (Kaneko et al., 1997). Significant negative correlation between serum cortisol and Ca was indicated as  $R= -0.911, P<0.05$ .

Serum phosphorous was significantly increased in the FMD group may be due to hypocalcemia based on the mass law of interaction between calcium and phosphorous. Hypocalcemia leads to a reciprocal increase in the serum phosphorous concentration (Meyer and Harvey 1998). Significant negative correlation between Ca and phosphorous was indicated as  $R= -0.911, P<0.05$ .

In the present study a significant high serum concentration of cortisol was recorded. Stress due to febrile conditions, systemic infection and general body illness associated with increase in adrenal activity resulting in increased glucocorticoid levels (Chase et al., 1995; Adcock Torpy and Ho, 2007). Cortisol is the major glucocorticoid known as the critical stress hormone whose levels are increased in response to stressful conditions and is considered a part of the host's response to abnormal events particularly in the acute phase of the illness (Ramaekers et al., 1975; Roman 1995; Gruys et al., 2005 and Moolchandani et al., 2008).

The current findings of protein electrophoresis in FMD infected cattle reveal a significant decrease in gamma globulins (fig.1, 2). Cortisol is known to weakly suppress the activity of the immune system by inhibiting lymphoid mitosis and reducing immune cell number and function (Ramaekers et al., 1975; Campbell and Coles, and Meyer and Harvey, 1998.) In the present study, significant negative correlation (results not shown) between serum levels of cortisol and gammaglobulin was recorded ( $R = -0.851, P < 0.05$ ) which indicates that excess cortisol may inhibit antibody production and can result in decreased gammaglobulin concentrations an effect which usually occurs before specific immunity is achieved (Roman, 1995 and Catcott 2007).

In conclusion, infection of cattle with FMDV results in hypoinsulinemia which indicates the development of pancreatic dysfunction in these patients. In addition, FMDV infection induces a prominent stress response as indicated by the significant increase in serum cortisol levels. Further, it seems likely that the alterations that take place in biochemical variables and protein electrophoresis in FMD-infected groups can be closely connected with changing in serum insulin and cortisol concentrations. It appeared to be related to the magnitude of this alteration obviating the importance of considering or even the need for measurement of these two hormones in FMD control. Finally, the present findings may provide a better understanding of the disease process and clinical pathology of FMD in cattle.

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## ركيزات الانسولين والكورتيزول في الابقار المصابه بالحمي القلاعيه وعلاقتها بالتغيرات في المتغيرات البيوكيميائيه والفصل الكهربائي للبروتين

هذه الدراسة لتقييم تركيز الانسولين والكورتيزول في مصل الابقار المصابه بالحمي القلاعيه وعلاقته بالتغيرات في بعض المتغيرات البيوكيميائيه والفصل الكهربائي للبروتين وقد تم اجراء الدراسه علي مجموعتين من الابقار داهما من ١٥ بقرة مصابه بالحمي القلاعيه بينما تكونت الاخرى من ٨ بقرات سليمة وقد شملت الاختبارات ميين نسب كل من الانسولين ، الكورتيزول ، البروتين الكلي ، الاليومين ، الجلوكوز ، الكالسيوم ، الفسفور ، الكرياتينين ، خمائر الالاتين والاسبرتات امينوترانسفيريز بالاضافه الي الفصل الكهربائي للبروتين .

ت النتائج حدوث نقصا معنويا في كل من الانسولين ، البروتين الكلي ، الكالسيوم في الحيوانات المصابه مقارنة ، السليمه وحدثت زياده معنويه في كل من الكورتيزول ، الجلوكوز ، الكوليستيرول ، الفسفور ، خمائر الاسبرتات

ت نتائج الفصل الكهربائي للبروتين حدوث نقصا معنويا في كل من الاليومين وجلوبولينات جاما وعن علاقه رات بنسب الانسولين والكورتيزول فقد اظهرت الدراسه وجود علاقه معنويه ايجابيه بين هرمون الانسولين وبين كالسيوم والبروتين الكلي واخري معنويه سلبيه بين الانسولين ومستويات الجلوكوز ، الكوليستيرول ، الفوسفات ول وبالنسبه لهرمون الكورتيزول اظهرت النتائج وجود علاقه معنويه ايجابيه بين الكورتيزول وكل من الفوسفات وخمائر الاسبرتات بينما وجدت علاقه معنويه سلبيه بين الكورتيزول وكل من الاليومين والكالسيوم

ه ان هذه الدراسه تبين ان اصابه الابقار بمرض الحمي القلاعيه ينتج عنه خلل في وظائف البنكرياس وانخفاض ات الانسولين بالاضافه الي زياده معنويه في هرمون الكورتيزول وان معظم التغيرات الحادته في بيوكيمياء الدم بطه بالتغير المرأي في هذه الهرمونات مما يتطلب وضع هذه الهرمونات بعين الاعتبار عند تقييم الاختبارات في الابقار المصابه بالحمي القلاعيه وهذه النتائج قد تساعد علي فهم اكبر لطبيعه المرض في الابقار .

**Table 4. The correlation between the selected hormones and biochemical variables in the FMD infected group (Pearson's correlation test).**

Parameter	Insulin	Cortisol	Glucose	Cholesterol	TP	Alb	Ca	P	ALT	AST	BUN	Creatinin <sub>e</sub>
Insulin	1	-0.902 <sup>*</sup>	-0.887 <sup>*</sup>	-0.839 <sup>*</sup>	0.923 <sup>**</sup>	0.700	0.834 <sup>*</sup>	-0.891 <sup>*</sup>	0.671	-0.931 <sup>**</sup>	-0.0434	-0.530
Cortisol	-0.902 <sup>*</sup>	1	0.957 <sup>**</sup>	0.788	-0.780	-0.859 <sup>*</sup>	-0.911 <sup>*</sup>	0.976 <sup>*</sup>	-0.350	0.957 <sup>*</sup>	0.654	0.590
Glucose	-0.887 <sup>*</sup>	0.957 <sup>**</sup>	1	0.867 <sup>*</sup>	-0.843 <sup>*</sup>	-0.836 <sup>*</sup>	-0.953 <sup>**</sup>	0.989 <sup>**</sup>	-0.311	0.982 <sup>**</sup>	0.671	0.430
Cholesterol	-0.839 <sup>*</sup>	0.788	0.867 <sup>*</sup>	1	-0.909 <sup>*</sup>	-0.636	-0.848 <sup>*</sup>	0.873 <sup>*</sup>	-0.572	0.923 <sup>**</sup>	0.248	0.082
TP	0.923 <sup>**</sup>	-0.780	-0.843 <sup>*</sup>	-0.909 <sup>*</sup>	1	0.614	0.870 <sup>*</sup>	-0.811	0.624	-0.882 <sup>**</sup>	0.337	-0.329
Alb	0.700	0.859 <sup>*</sup>	-0.836 <sup>*</sup>	-0.636	0.614	1	0.891 <sup>*</sup>	-0.899 <sup>*</sup>	-0.036	-0.843 <sup>*</sup>	-0.855 <sup>*</sup>	-0.540
Ca	0.834 <sup>*</sup>	0.911 <sup>*</sup>	0.953 <sup>**</sup>	-0.848 <sup>*</sup>	0.870 <sup>*</sup>	0.891 <sup>*</sup>	1	-0.911 <sup>*</sup>	0.246	-0.918 <sup>**</sup>	0.620	-0.473
P	-0.891 <sup>*</sup>	0.976 <sup>*</sup>	0.989 <sup>**</sup>	0.873 <sup>*</sup>	-0.811	-0.899 <sup>*</sup>	-0.911 <sup>*</sup>	1	0.369	0.989 <sup>**</sup>	0.614	0.404
ALT	0.671	-0.350	-0.311	-0.572	0.624	-0.036	0.246	-0.369	1	-0.472	0.338	-0.118
AST	-0.931 <sup>**</sup>	0.957 <sup>*</sup>	0.982 <sup>**</sup>	0.923 <sup>**</sup>	-0.882 <sup>**</sup>	-0.843 <sup>*</sup>	-0.918 <sup>**</sup>	0.989 <sup>**</sup>	-0.472	1	0.536	0.372
BUN	-0.0434	0.654	0.671	0.248	0.337	-0.855 <sup>*</sup>	-0.620	0.614	0.338	0.536	1	0.534
Creatinine	-0.530	0.590	0.430	0.082	-0.329	-0.540	-0.473	0.404	-0.118	0.372	0.534	1

Legend: show statistical significance of correlations: \* ( $P < 0.05$ ); \*\* ( $P < 0.01$ ).