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Correlation of endotoxemia from gastrointestinal origin and immune response in patients colonized by *Escherichia coli* in Samarra, Iraq

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Abstract

Background: Gut flora is essential for the maintenance of metabolism and immunity in the host. Gut dysbiosis and infection by pathogens like *Escherichia coli* may lead to inflammation, endotoxemia, and metabolic dysfunction.

Objective: The objective of this study was to find out the relationship between colonisation of *E. coli* and metabolic, inflammatory, oxidative stress, hematological, and biochemical parameters in human participants.

Methods: In total, 150 individuals were recruited for the study, where the participants were assigned to one of two groups, depending on their intestinal colonization with *E. coli* bacteria (Control Group & Colonized Group; n=75). A variety of anthropometric, blood pressure parameters, along with numerous biochemical, inflammatory, oxidative stress, and hematological indices were evaluated and compared.

Results: The colonized group had significantly high BMI, WC, SBP, and DBP than the control subjects ($p<0.05$). Levels of inflammatory mediators such as LPS, LBP, sCD14, TNF-α, IL-6, IL-1β, and hs-CRP were considerably high in the colonized group ($p<0.001$). There was significant increase in oxidative stress markers (MDA, TOS, NO, ROS), whereas antioxidant markers (SOD, CAT, GPx, GSH, TAC) were considerably lower in colonized group subjects ($p<0.001$). The results of hematological analysis showed leukocytosis, neutrophilia, raised NLR, and low lymphocytes percent. Results of biochemical analysis showed hyperlipidemia, hyperglycemia, altered liver and kidney markers, as well as low protein levels in colonized group subjects. There were significant positive correlations between serum LPS and inflammatory and oxidative stress markers, but there were negative correlations with antioxidant markers .

Conclusion: Infection by *Escherichia coli* leads to a number of physiological and biochemical effects including endotoxemia, increased stress burden in the form of inflammation and oxidative stress, and biochemical changes. This implies that there is a relationship between gut flora imbalance and systemic metabolic disorders.

Keywords *Escherichia coli*; Endotoxemia; Lipopolysaccharide (LPS); Oxidative Stress; Insulin Resistance; Dysbiosis; Metabolic Disorders.

1. Introduction

The gastrointestinal system of humans is made up of a diverse microbial ecosystem that is responsible for maintaining metabolic, immune, and physiologic homeostasis of the host[1]. Normally, the gut microbiome helps in processes such as nutrient breakdown, production of biologically active molecules, intestinal permeability control, and regulation of immune functions. In certain circumstances, however, an imbalance within the composition of the gut microorganisms could result in dysbiosis, a condition that has been linked to many metabolic and inflammatory diseases [2].

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Escherichia coli, a Gram-negative, facultative anaerobic bacteria among other gut microflora, is an example of such microorganisms that are normally present in small numbers within the gut [3]. Although most strains are non-pathogenic, some circumstances might promote overcolonization or virulence, resulting in increased synthesis and translocation of lipopolysaccharides (LPS). Lipopolysaccharides, which are part of the outer cell wall in Gram-negative bacteria, are considered powerful endotoxins that can induce inflammation by activating TLR4 (toll-like receptor 4), which is responsible for initiating signaling cascades and cytokine production [4].

New research has brought the idea of "metabolic endotoxemia" into focus, which is described by chronic hyperlipidemia resulting from the high amount of LPS produced by the microbiome[5]. The condition has been linked to the development of insulin resistance, obesity, hypertension, and other components of metabolic syndrome. In this case, the constant presence of endotoxins produced by microorganisms could lead to increased inflammation and metabolic problems [6].

Endotoxemia-induced systemic inflammation is frequently associated with high levels of inflammatory cytokines including TNF-α, IL-6, and IL-1β along with acute phase reactants such as CRP[7]. In addition to being markers of immune activity, they also play an active role in causing endothelial dysfunction and disturbances in glucose and lipid metabolism [8].

On the other hand, oxidative stress serves as another important pathophysiological factor that links inflammation to cellular injury.[9] Overproduction of ROS along with inadequate functions of antioxidants, including superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPx), and glutathione (GSH), contributes to lipid peroxidation, protein damage, and DNA injury. Malondialdehyde (MDA) and total oxidant status (TOS) levels are often considered markers for oxidative damage to tissues in such diseases [10].

While more awareness exists regarding the contribution of the gut microbial community to systemic diseases, it is not known what effect the presence of *E. coli* in the gut lumen may have specifically on inflammatory, oxidative, hematological, and biochemical markers. It is important to determine the effect of such a microbial community on systemic diseases [11].

As such, the current study was designed to explore the link between E. coli colonization in the intestines and several clinical, inflammatory, oxidative stress, hematological, and biochemical variables, in order to determine the possible involvement of this relationship in the induction of systemic metabolic alterations and immunomodulation.

2. Materials and Methods

2.1. Study Design and Participants

The cross-sectional analysis was carried out from January to July 2026 in Samarra, Iraq. The sample population consisted of 150 subjects with age ranging from 18 to 65 years and further categorized into two depending on colonization with Escherichia coli. Subjects who suffered from autoimmune diseases, chronic kidney disease, cancer, hepatitis, systemic infection, or subjects using antibiotics or probiotics within the last month were excluded from this study to eliminate any possible bias.

2.2. Clinical and Anthropometric Assessment

Demographic and clinical variables such as age, gender, smoker status, diet, exercise, and health background information were obtained through a questionnaire. The anthropometric indices comprised body weight, height, body mass index (BMI), waist circumference, hip circumference, waist-to-hip ratio (WHR), systolic blood pressure (SBP), and diastolic blood pressure (DBP).

2.3. Sample Collection

Venous blood samples of about 5 ml each were collected from all study participants following an overnight fast. The blood samples were distributed into two different types of tubes – those with EDTA for hematological evaluation and those without any anticoagulant for extraction of serum. The serum was isolated through centrifugation at 3000 rpm for 10 minutes and preserved at −20°C for biochemical and immunological investigations.

2.4. Isolation and Identification of *Escherichia coli*

MacConkey and Eosin Methylene Blue (EMB) agars were used to culture stool samples. These cultures were incubated aerobically for 24 hours at 37°C. The suspected colonies of E. coli were determined from colony morphology, Gram staining, and biochemical tests like Indole, Methyl red, Citrate, oxidase, Catalase, Triple Sugar Iron (TSI) and Urea tests. To distinguish between the study groups, quantifiable stool culture was conducted. Subjects with high colonization density of E. coli in their intestines ($\geq 10^6$ CFU/g stool) were classified as colonized, while those with lower colonization density ($<10^4$ CFU/g stool) were categorized as controls.

2.5. Evaluation of Gut-Derived Endotoxemia

The determination of LPS in the serum was performed using an ELISA test. In addition, LBP, sCD14, and EndoCAb were also determined using commercially available ELISA kits following the manufacturers' instructions.

2.6. Assessment of Immune Activation and Inflammatory Biomarkers

The activation of the systemic immune response was evaluated by assessing the levels of TNF-α, IL-6, IL-1β, and hs-CRP in the blood serum. These biomarkers were chosen due to their role in endotoxin-induced inflammation. The assessment was done through the use of commercial ELISA kits for all biomarkers tested.

2.7. Oxidative Stress and Antioxidant Parameters

The oxidative stress status was analyzed with regards to malondialdehyde (MDA), total oxidant status (TOS), nitric oxide (NO), and reactive oxygen species (ROS). The antioxidant defense status was determined by the activities of superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPx), reduced glutathione (GSH), and total antioxidant capacity (TAC). All analyses were done by using standard biochemical and ELISA techniques as per manufacturer guidelines.

2.8. Hematological Parameters

The complete blood count test was conducted through an automated hematology analyzer. Tests included the WBC, RBC, Hb, HCT, platelet count, neutrophils percentage, lymphocytes percentage, monocytes percentage, and neutrophil to lymphocytes ratio. These tests were used to evaluate the systemic inflammatory response and hemodynamic changes due to the presence of endotoxemia.

2.9. Biochemical Parameters

Serum biochemical determinations were done to assess metabolism, liver and kidney functions. Biochemical parameters include fasting blood glucose (FBG), total cholesterol (TC), triglyceride (TG), high density lipoprotein cholesterol (HDL-C), low density lipoprotein cholesterol (LDL-C), alanine aminotransferase (ALT), aspartate aminotransferase (AST), creatinine, urea, albumin, and total protein. Colorimetric technique and diagnostic kits were utilized in accordance to the manufacturer's guidelines.

2.10. Statistical Analysis

SPSS 26.0 version was utilized for data analyses. The findings are presented as mean ± SD. Independent sample t-test and one-way ANOVA were used for comparison among groups. Correlation was performed by Pearson correlation test for association between endotoxemia parameters and inflammatory factors. Multiple linear regression test was done to determine the predictor for immune activation. Significance level is taken at $p < 0.05$.

3. Results

3.1. Demographic and Clinical Characteristics

Demographic and clinical details of the participants have been provided in Table 1. There were no differences in age between the control group and the colonized group ($p > 0.05$). However, the subjects colonized with E. coli had significantly higher BMI, waist circumference, SBP, and DBP compared to the control subjects ($p < 0.001$).

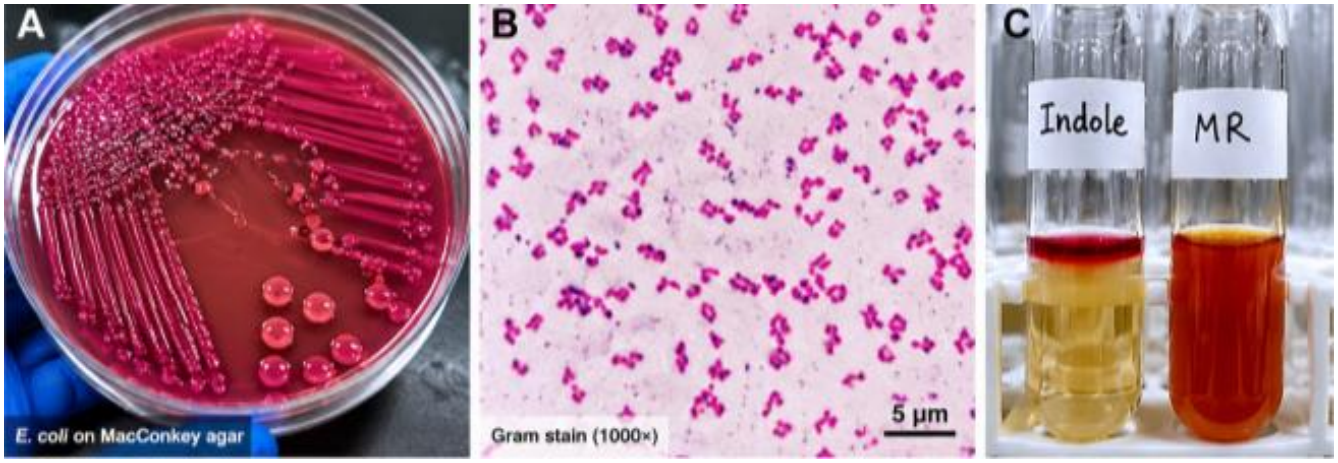

Figure 1 Representative morphology and laboratory characteristics of *Escherichia coli* isolates

Table 1 Demographic and Clinical Characteristics of Study Participants

Parameter	Control Group (n=75)	*E. coli* Colonized Group (n=75)	p-value
Age (years)	38.4 ± 7.2	39.8 ± 6.9	0.28
BMI (kg/m^2)	24.6 ± 2.3	28.1 ± 3.1	<0.001
Waist Circumference (cm)	84.5 ± 5.4	93.7 ± 6.8	<0.001
SBP (mmHg)	118.2 ± 8.6	129.4 ± 10.2	<0.001
DBP (mmHg)	76.5 ± 6.1	84.8 ± 7.5	<0.001

Based on Table 1, increased adiposity measures along with high blood pressure levels were related to intestinal colonization by *E. coli*, indicating a possible relationship between gastrointestinal dysbiosis and cardiometabolic disease risk factors.

Table 2 shows the distribution of demographic and lifestyle variables among study participants.

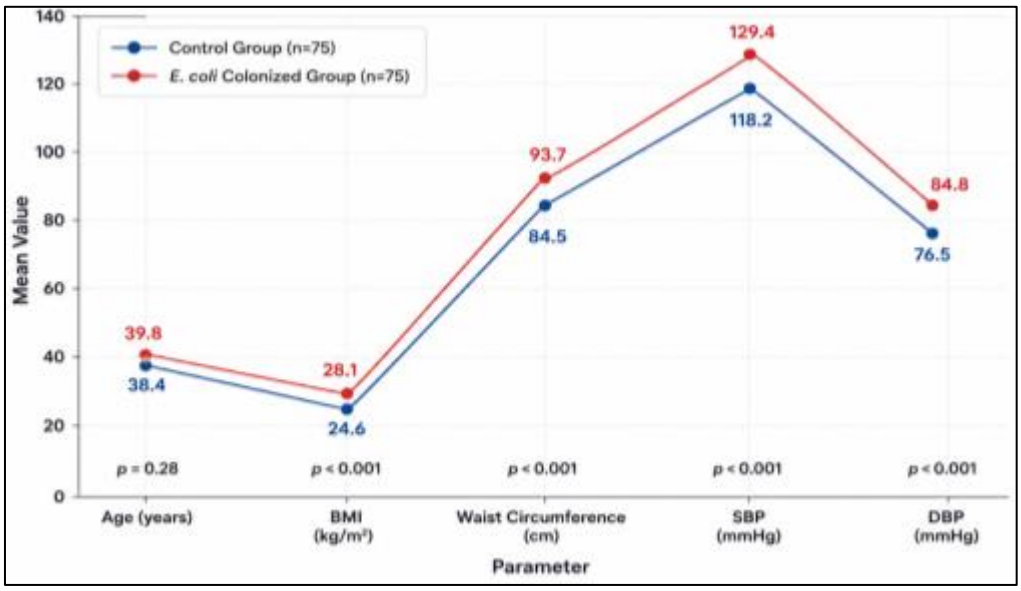

Figure 2 Comparison of body mass index and blood pressure parameters between control and *E. coli* colonized participants.

Table 2 Baseline Lifestyle Characteristics of Study Participants

Variable	Control Group (n=75)	Colonized Group (n=75)	p-value
Male, n (%)	42 (56.0)	45 (60.0)	0.71
Female, n (%)	33 (44.0)	30 (40.0)	0.71
Smokers, n (%)	18 (24.0)	20 (26.7)	0.64
Physical Activity, n (%)	54 (72.0)	49 (65.3)	0.52
High-fat Diet, n (%)	28 (37.3)	47 (62.7)	0.02

From Table 2, it can be seen that sex, smoking, and level of exercise had no significant difference between the two groups. However, there was a significant higher prevalence of consumption of high fat diet among those that were colonized compared to the other group (P = 0.02).

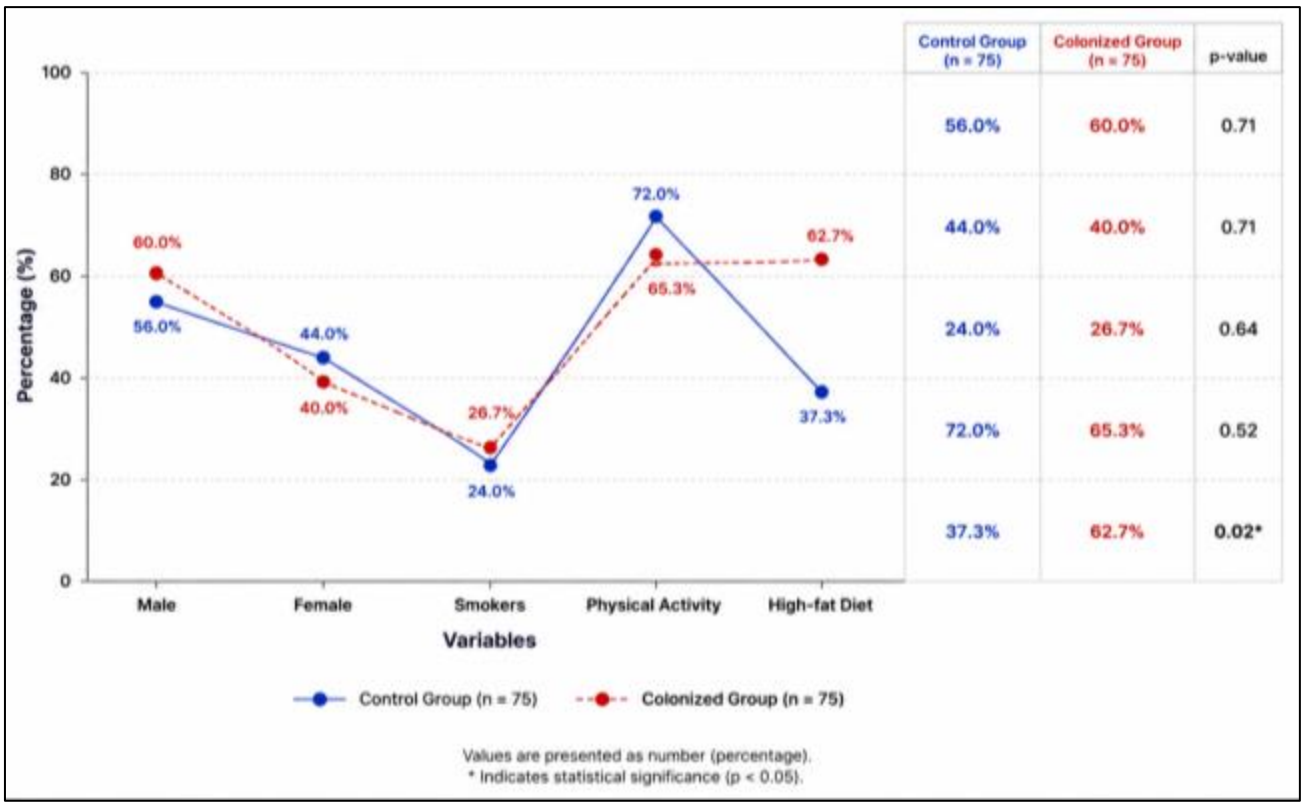

Figure 3 Comparison of body mass index and blood pressure parameters between control and *E. coli* colonized participants

3.2. Endotoxemia and Immune Activation Biomarkers

Serum markers indicative of endotoxemia and systemic immune response associated with gut endotoxemia were assessed for both patient groups. As evident from Table 3 below, those harboring *E. coli* had significantly higher amounts of LPS, LBP, sCD14, TNF-α, IL-6, IL-1β, and hs-CRP than those in the control group ($p < 0.001$). Conversely, the levels of EndoCAbs were significantly lower in colonized subjects.

Table 3 Endotoxemia and Inflammatory Biomarkers in Study Participants

Parameter	Control Group (n=75)	Colonized Group (n=75)	p-value
LPS (EU/mL)	0.38 ± 0.07	0.94 ± 0.15	<0.001
LBP (µg/mL)	12.5 ± 2.1	26.4 ± 4.3	<0.001
sCD14 (ng/mL)	1245 ± 145	1986 ± 210	<0.001
EndoCAb (MU/mL)	68.4 ± 7.8	42.3 ± 6.5	<0.001
TNF-α (pg/mL)	14.2 ± 2.8	31.5 ± 4.6	<0.001
IL-6 (pg/mL)	8.4 ± 1.6	22.7 ± 3.9	<0.001
IL-1β (pg/mL)	6.2 ± 1.3	18.6 ± 2.7	<0.001
hs-CRP (mg/L)	2.1 ± 0.5	7.9 ± 1.4	<0.001

The presence of increased markers of endotoxemia in colonized subjects suggests an increased permeability for passage of bacterial products into the blood stream. In addition, the increased levels of pro-inflammatory cytokines and acute phase proteins suggest systemic inflammation pathways have been activated in response to the microbial imbalance in the intestine. Decreased EndoCAb levels suggest the continued intake of anti-endotoxin antibodies due to continuous endotoxin production.

The elevated inflammatory biomarkers observed in the colonized group are shown in Figure 4.

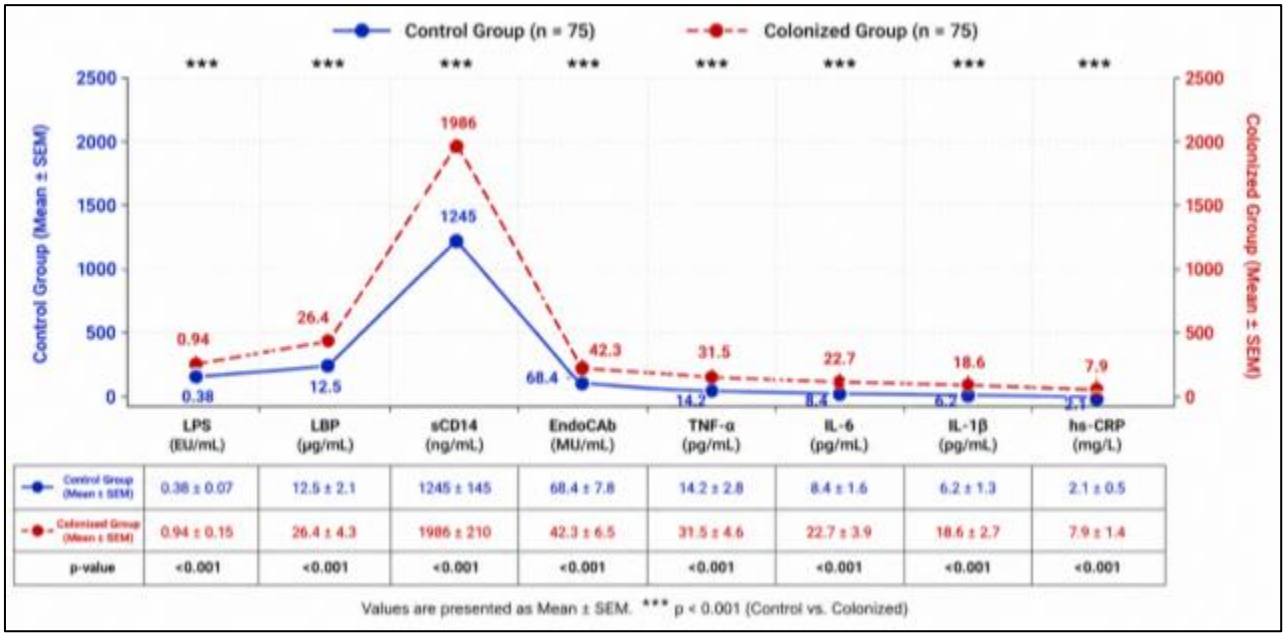

Figure 4 Serum concentrations of endotoxemia and inflammatory biomarkers in control and *E. coli* colonized groups

3.3. Oxidative Stress and Antioxidant Status

Increased levels of oxidative stress biomarkers such as MDA, TOS, NO, and ROS were observed in the colonized group compared to controls ($p < 0.001$), while reduced levels of antioxidant biomarkers such as SOD, CAT, GPx, GSH, and TAC were noted ($p < 0.001$).

Table 4 Oxidative Stress and Antioxidant Biomarkers

Parameter	Control Group	Colonized Group	p-value
MDA (nmol/mL)	2.8 ± 0.4	6.9 ± 0.8	<0.001
TOS (µmol H2O2 Eq/L)	8.4 ± 1.2	18.7 ± 2.4	<0.001
NO (µmol/L)	24.1 ± 3.5	46.3 ± 5.1	<0.001
ROS (U/mL)	92.4 ± 10.3	168.5 ± 15.7	<0.001
SOD (U/mL)	11.8 ± 1.4	6.1 ± 0.9	<0.001
CAT (U/L)	62.5 ± 5.8	38.6 ± 4.3	<0.001
GPx (U/mL)	48.7 ± 4.5	27.9 ± 3.1	<0.001
GSH (µmol/L)	7.2 ± 0.8	3.9 ± 0.5	<0.001
TAC (mmol/L)	1.86 ± 0.21	0.98 ± 0.14	<0.001

The alterations in oxidative stress and antioxidant defense markers are illustrated in Figure 5

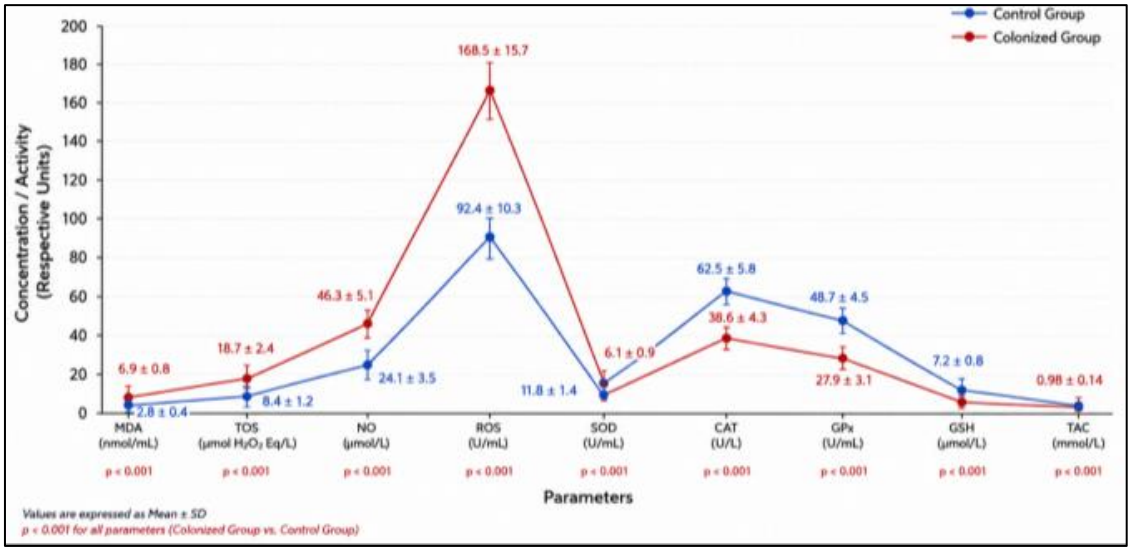

Figure 5 Oxidative stress and antioxidant biomarker levels in study groups

3.4. Hematological Findings

Table 5 Hematological Parameters in the Study Groups

Parameter	Control Group	Colonized Group	p-value
WBC ($\times 10^9$/L)	6.4 ± 1.1	12.9 ± 2.2	<0.001
RBC ($\times 10^{12}$/L)	4.82 ± 0.34	4.41 ± 0.29	0.002
Hb (g/dL)	13.9 ± 1.1	12.2 ± 1.0	<0.001
HCT (%)	41.8 ± 3.2	37.4 ± 2.8	<0.001
Platelets ($\times 10^9$/L)	245 ± 28	318 ± 35	<0.001
Neutrophils (%)	56.7 ± 4.6	78.9 ± 5.1	<0.001
Lymphocytes (%)	34.2 ± 3.7	16.8 ± 2.9	<0.001
Monocytes (%)	5.6 ± 1.1	9.8 ± 1.5	<0.001
NLR	1.65 ± 0.32	4.72 ± 0.61	<0.001

The results of the complete blood count analysis revealed highly significant increases in the counts of WBCs, neutrophils, monocytes, platelets, and the neutrophil to lymphocyte ratio (NLR). On the other hand, there were highly significant decreases observed in the percentage of lymphocytes and hemoglobin concentration.

The hematological alterations associated with *E. coli* colonization are presented in Figure 6.

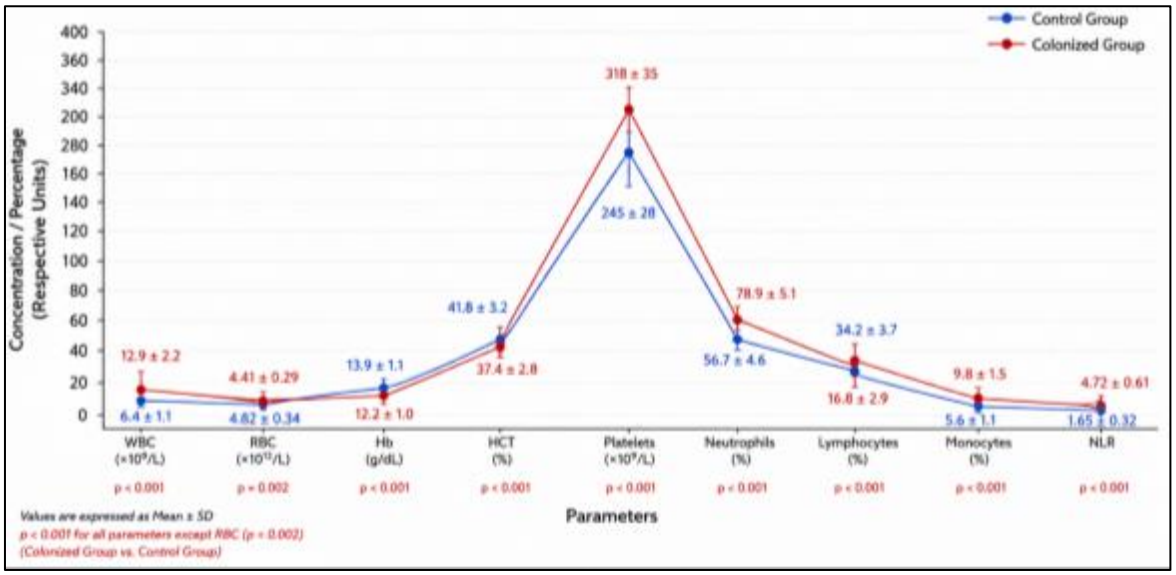

Figure 6 Comparison of hematological parameters between study groups.

3.5. Biochemical Findings

Significant increases in FBG, TC, TG, LDL-C, ALT, AST, creatinine, and urea levels were found in the colonized group as compared to control ($p < 0.05$). On the other hand, HDL-C, albumin, and total protein levels were significantly reduced.

Table 5 Serum Biochemical Parameters

Parameter	Control Group	Colonized Group	p-value
FBG (mg/dL)	92.4 ± 8.7	128.6 ± 14.2	<0.001
TC (mg/dL)	168.5 ± 15.6	226.3 ± 21.4	<0.001
TG (mg/dL)	121.4 ± 18.2	198.7 ± 24.9	<0.001
HDL-C (mg/dL)	49.8 ± 5.1	36.4 ± 4.7	<0.001
LDL-C (mg/dL)	98.6 ± 11.5	149.7 ± 17.3	<0.001
ALT (U/L)	24.7 ± 4.3	48.2 ± 6.1	<0.001
AST (U/L)	21.5 ± 3.6	42.9 ± 5.4	<0.001
Creatinine (mg/dL)	0.82 ± 0.11	1.26 ± 0.18	<0.001
Urea (mg/dL)	28.5 ± 4.7	44.8 ± 6.2	<0.001
Albumin (g/dL)	4.5 ± 0.4	3.6 ± 0.3	<0.001
Total Protein (g/dL)	7.2 ± 0.5	6.1 ± 0.4	<0.001

The biochemical alterations between the two groups are illustrated in Figure 7.

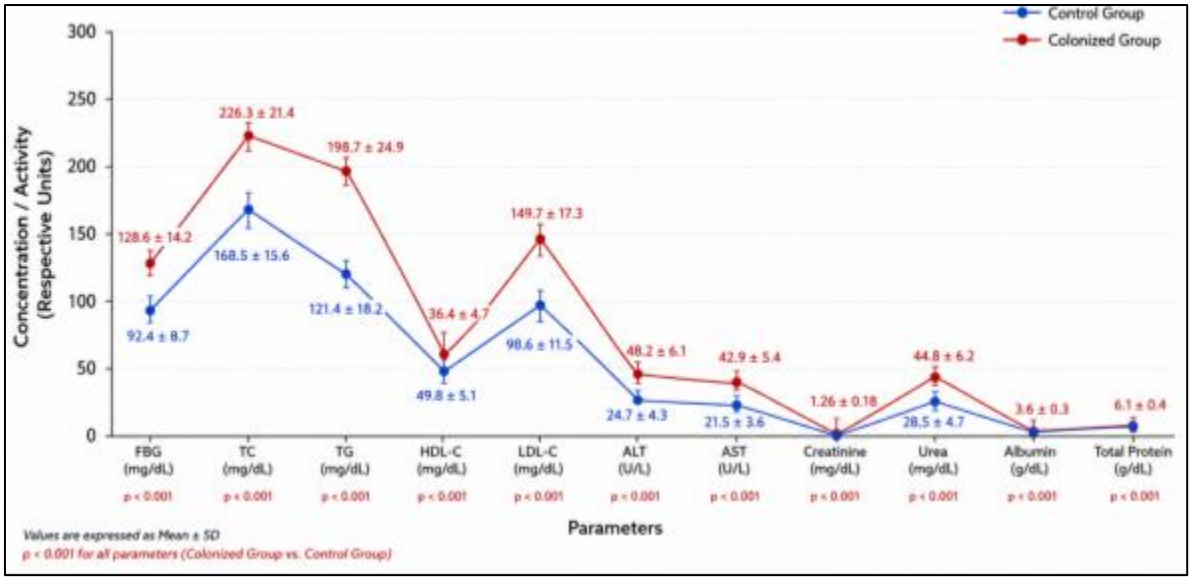

Figure 7 Serum biochemical parameters in control and *E. coli* colonized participants

3.6. Correlation Analysis

Pearson correlation study showed a significant positive correlation between LPS serum levels and markers of inflammation like TNF-α (r = 0.74), IL-6 (r = 0.71), hs-CRP (r = 0.69), and MDA (r = 0.66) (p<0.001). Similarly, LPS had a significant negative correlation with antioxidant markers like TAC (r = -0.62) and GSH (r = -0.58).

Table 7 Correlation Between Serum LPS and Selected Biomarkers

Parameter	Correlation Coefficient (r)	p-value
TNF-α	0.74	<0.001
IL-6	0.71	<0.001
hs-CRP	0.69	<0.001
MDA	0.66	<0.001
TAC	−0.62	<0.001
GSH	−0.58	<0.001

4. Discussion

In this current study, it is shown that gut colonization with *Escherichia coli* is highly associated with deleterious effects on metabolism, inflammation, oxidation, hematology, and biochemistry[12]. Altogether, these observations indicate that gut colonization by E. coli may cause low-grade inflammation and dysmetabolism via endotoxic mechanisms[13].

4.1. Metabolic and Hemodynamic Alterations

Colonized individuals vs. control [14]. These results indicate a possible link between *E. coli* colonization of the intestines and cardiometabolic dysfunction [15]. High body mass index seen among the colonized subjects can be attributed to the chronic inflammatory state triggered by the release of endotoxins from the intestine. The lipopolysaccharides activate TLR4 signaling pathways resulting in insulin resistance, fat tissue dysfunction, and changes in energy metabolism[16,17].

Moreover, increased levels of abdominal girth and high blood pressure could arise due to endothelial dysfunction and inflammation induced by endotoxemia. Studies have shown that circulating endotoxins are capable of causing vascular dysfunction and hypertension [17,18].

4.2. Endotoxemia and Immune Activation

An elevation in LPS, LBP, and sCD14 in the colonized group suggests that there is endotoxemia in their body systems[19]. An elevation in TNF-α, IL-6, IL-1β, and hs-CRP further proves that both innate and adaptive immunity is triggered [20].

This is in line with the theory of "metabolic inflammation" whereby endotoxins from the gut function as chronic inflammation stimuli[21]. The role of LBP and sCD14 in the amplification of LPS signaling demonstrates chronic immune stimulation rather than acute infections[22].

The high correlation found between LPS and inflammatory markers signifies a link between endotoxemia and inflammation [23]. Nevertheless, because of the cross-sectional nature of the current study, it is difficult to establish a definitive causative effect.

4.3. Oxidative Stress Imbalance

Moreover, the current study indicates that colonized individuals suffer from significant oxidative stress, evidenced by increased MDA, TOS, NO, and ROS levels, as well as decreased antioxidant capacity (SOD, CAT, GPx, GSH, TAC)[24].

Such a ratio imbalance may be attributed to increased ROS generation secondary to inflammation signaling pathways[25]. NF-κB activation and cytokine secretion (in particular TNF-α and IL-6) contribute to an increase in oxidative damage and mitochondrial malfunction[26].

A decrease in antioxidant defense could indicate exhaustion of endogenous antioxidant defense mechanisms as a result of oxidative stress that is typical for chronic conditions [27].

4.4. Hematological Changes

The blood profile exhibited leukocytosis, neutrophilia, thrombocytosis, increased neutrophil-to-lymphocyte ratio (NLR), decreased lymphocytes' proportion, and decreased hemoglobin concentration[28].

The above changes point to systemic inflammatory stress and potentially imply immune redistribution. An increased NLR is a known marker for inflammation and has been linked to cardiovascular risk factors[29].

Decreased hemoglobin and hematocrit levels are indicative of inflammation-driven impairment of red blood cell production [30].

4.5. Biochemical Disturbances

Increases in fasting blood glucose, lipids (TC, TG, LDL-C), and liver enzyme levels (ALT, AST) denote that there is a disruption in metabolic regulation[31].

The dyslipidemia and hyperglycemia could be a consequence of inflammation-induced insulin resistance[32]. This condition is brought about by TNF-α and IL-6. These agents interfere with glucose metabolism [33].

Creatinine and urea elevated are indicators of kidney functional stress in the initial stages of the disease process possibly because of system inflammation and oxidative stress[34]. Low serum albumin levels indicate liver insufficiency or higher inflammation [35].

4.6. Correlation Analysis and Mechanistic Insight

The high correlation between LPS and inflammatory markers (TNF-α, IL-6, hs-CRP), and oxidative stress markers (MDA), reiterates the significance of endotoxemia in inducing systemic pathogenesis [36].

Negative correlations with TAC and GSH suggest that an increase in endotoxin load is linked to reduced antioxidant reserves[37].

This suggests a unified pathway:

Colonization by *E. coli* → Increased LPS → Activation of immune response → Cytokine production → Oxidative stress → Metabolic dysfunction[38].

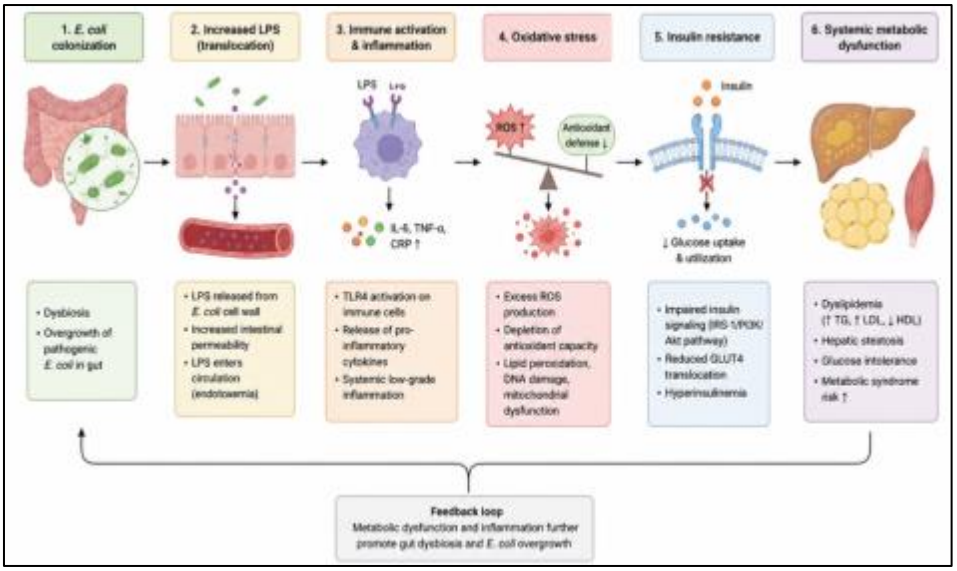

Figure 8 Mechanistic pathway linking *Escherichia coli* colonization to systemic metabolic dysfunction

4.7. Overall Interpretation

In general, it appears that *E. coli* infection within the intestine does not occur without negative effects on the system because this infection can cause systemic metabolic and inflammatory disturbances[39]. These results support the idea of a disruption in the gut/systemic axis regulation, whereby changes in microbial balance affect the host's metabolism and immune function[40].

Gut microbiota manipulation seems to be an important treatment or prevention option for metabolic and inflammatory diseases[41].

5. Conclusion

The current research shows that there is a strong correlation between E. coli colonization and systematic disturbances in metabolism, inflammation, oxidative damage, hematology, and biochemistry. Individuals affected by *E. coli* showed high concentrations of LPS, LBP, and sCD14, indicating the presence of endotoxemia. High levels of these components were associated with high levels of pro-inflammatory cytokines and oxidants.

Thus, the presence of endotoxin-induced immune response may lead to the development of an inflammatory state, which is accompanied by decreased anti-oxidative status, disturbed hematological profile, and negative parameters of metabolism and organ function, such as glucose tolerance impairment, dyslipidemia, and dysfunction of liver and kidneys.

In summary, colonization of the intestines by *E. coli* seems likely to contribute to disruption of intestinal/systemic homeostasis as well as metabolic dysfunction. Consequently, interventions related to gut microbiota manipulation as well as inhibition of endotoxin-associated pathways hold promise for avoiding or minimizing systemic inflammation/metabolic disorders.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed..

Statement of informed consent

Informed consent was obtained from all individual participants included in the study.

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