DOI: https://doi.org/10.17816/brmma677239 EDN: XRLYKG

# Changes in Insulin Resistance and Gastrointestinal Microbiology in Patients With Traumatic Syndrome

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## ABSTRACT

***BACKGROUND:*** It is known that one of the basic processes developing in response to injury is insulin resistance. The mechanisms of development of insulin resistance at the present stage are not fully disclosed. There is an increasing amount of evidence indicating the role of the gastrointestinal microbiota in the development of insulin resistance.

***AIM:*** Was to evaluate the dynamics of the triglyceride-glucose index in relation to the taxonomic composition of the microbiota of the gastrointestinal tract and blood in patients with combined musculoskeletal injury.

***METHODS:*** 44 wounded with combined injury of the musculoskeletal system who were being treated at the clinic of military field surgery of the Military Medical Academy named after S.M. Kirov were examined. The patients underwent a standard examination with the calculation of an indirect indicator of insulin resistance, the triglyceride-glucose index. The microbiota of feces and blood was studied by sequencing 16S ribosomal ribonucleic acid.

***RESULTS:*** The average value of the triglyceride-glucose index in the victims was 4.61±0.22 units. In 79.5% of patients, the value of the triglyceride-glucose index exceeded 4.49 units, which indicates the presence of signs of insulin resistance. There were direct correlations of the triglyceride-glucose index with the level of total cholesterol, serum amylase, the presence of chronic pancreatitis, and a number of ultrasound parameters of the liver, gallbladder, and pancreas. The most significant direct links of the triglyceride-glucose index were established with the presence of *Pseudoscardovia*, *Pyramidobacter*, and *Pediococcus* in the intestinal microbiota, and with bacteria of the genera *Bacillus* and *Pseudomonas* in the blood serum. Moderate inverse associations of the triglyceride-glucose index with the presence of bacteria of the genera *Scardovia*, *Actinomyces*, and *Allofournierella* (synonym: *Fournierella*) in the feces were revealed, *Butyricicoccaceae* UCG-009, *Lactobacillus crispatus* wiggsiae not *Scardovia species*, In. blood serum — bacteria *Bifidobacterium Rodova*, *Phascolarctobacterium*, *Hydrogenophilus*, the type of *Escherichia* is not *Phascolarctobacterium albertii faecium*.

***CONCLUSION:*** The established trends in the nature of changes in insulin resistance, depending on the timing of combat injury, indicate the dynamics of insulin resistance associated with the course of traumatic illness. Insulin resistance in the early period of traumatic illness, which develops in response to stress, blood loss, and tissue damage, can be considered as a compensatory and adaptive response within the framework of the concept of general adaptation syndrome, aimed primarily at eliminating energy deficiency. Therefore, it is necessary to conduct further research that can expand the understanding of the role of the bacterial microbiota as an important component of the gastrointestinal tract biotech complex in the development of metabolic changes in patients with injuries, as well as methods for their correction.

**Keywords:** triglyceride–glucose index; insulin resistance; gastrointestinal microbiota; blood microbiota; gastrointestinal biota and tissue; traumatic syndrome; wound syndrome; wounded patients.

**To cite this article**

Kryukov EV, Salikova SP, Grinevich VB, Kravchuk YuA, Oreshko LS, Egorov DV, Makarenko JA, Samokhvalov IM, Badalov VI, Sitkin SI, Sorokin AN, Petrukov SN. Changes in Insulin Resistance and Gastrointestinal Microbiology in Patients With Traumatic Syndrome. *Bulletin of the Russian Military Medical Academy.* 2025;27(2):153–164. DOI: 10.17816/brmma677239 EDN: XRLYKG

**Submitted:** 17.03.2025 **Accepted:** 25.03.2025 **Published online:** 20.06.2025

DOI: https://doi.org/10.17816/brmma677239 EDN: XRLYKG

# Динамика инсулинорезистентности и микроэкологический статус желудочно-кишечного тракта при травматической болезни

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## АННОТАЦИЯ

**Обоснование.** Известно, что один из базовых процессов, развивающихся в ответ на травму, — это инсулинорезистентность. Механизмы развития инсулинорезистентности на современном этапе раскрыты не полностью. Появляется все больше данных, указывающих на роль в возникновении инсулинорезистентности микробиоты желудочно-кишечного тракта.

**Цель исследования** — оценить динамику триглицерид-глюкозного индекса во взаимосвязи с таксономическим составом микробиоты желудочно-кишечного тракта и крови у раненых с сочетанной травмой опорно-двигательного аппарата.

**Материалы и методы.** Обследованы 44 раненых с сочетанной травмой опорно-двигательного аппарата, находившихся на лечении в клинике военно-полевой хирургии Военно-медицинской академии им. С.М. Кирова. Пациентам проведено стандартное обследование с расчетом косвенного показателя инсулинорезистентности — триглицерид-глюкозного индекса. Микробиоту кала и крови исследовали способом секвенирования 16S рибосомальной рибонуклеиновой кислоты.

**Результаты и обсуждение.** Среднее значение триглицерид-глюкозного индекса у пострадавших составило 4,61±0,22 усл. ед. У 79,5% пациентов значение триглицерид-глюкозного индекса превышало 4,49 усл. ед., что свидетельствует о наличии у них признаков инсулинорезистентности. Были выявлены прямые связи триглицерид-глюкозного индекса с уровнем общего холестерина, амилазы в сыворотке крови, наличием хронического панкреатита, рядом ультразвуковых параметров печени, желчного пузыря, поджелудочной железы. Наиболее значимые прямые связи триглицерид-глюкозного индекса установлены с наличием в кишечной микробиоте *Pseudoscardovia*, *Pyramidobacter, Pediococcus*, в сыворотке крови — с бактериями родов Bacillus и Pseudomonas. Выявлены умеренной силы обратные связи триглицерид-глюкозного индекса с представленностью в кале бактерий родов *Scardovia, Actinomyces, Allofournierella* (синоним: *Fournierella*), *Butyricicoccaceae UCG-009*, видов *Scardovia wiggsiae* и *Lactobacillus crispatus*, в сыворотке крови — бактерий родов *Bifidobacterium*, *Phascolarctobacterium*, *Hydrogenophilus*, видов *Escherichia albertii* и *Phascolarctobacterium faecium*.

**Заключение.** Установленные тренды характера изменений инсулинорезистентности в зависимости от сроков получения боевой травмы свидетельствуют о динамике инсулинорезистентности, ассоциированной с течением травматической болезни. Инсулинорезистентность в ранний период травматической болезни, развивающуюся в ответ на стресс, кровопотерю, повреждение тканей, можно рассматривать как компенсаторно-приспособительную реакцию в рамках концепции общего адаптационного синдрома, направленную прежде всего на ликвидацию энергодефицита. Следовательно, необходимо проведение дальнейших исследований, способных расширить представления о роли бактериальной микробиоты как важного компонента биототканевого комплекса желудочно-кишечного тракта в развитии метаболических сдвигов у пациентов с травмами, а также методиках их коррекции.

**Ключевые слова:** триглицерид-глюкозный индекс; инсулинорезистентность; микробиота желудочно-кишечного тракта; микробиота крови; биототканевой комплекс желудочно-кишечного тракта; травматическая болезнь; раневая болезнь; раненые.

**Как цитировать**

Крюков Е.В., Саликова С.П., Гриневич В.Б., Кравчук Ю.А., Орешко Л.С., Егоров Д.В., Макаренко Ю.А., Самохвалов И.М., Бадалов В.И., Ситкин С.И., Сорокин А.Н., Петруков С.Н. Динамика инсулинорезистентности и микроэкологический статус желудочно-кишечного тракта при травматической болезни // Вестник Российской военно-медицинской академии. 2025. Т. 27, № 2. С. 153–164. DOI: 10.17816/brmma677239 EDN: XRLYKG

**Рукопись получена:** 17.03.2025 **Рукопись одобрена:** 25.03.2025 **Опубликована online:** 20.06.2025

## BACKGROUND

Severe concomitant injuries in humans are associated with various causal biological patterns of injury response [1]. These include endocrine, metabolic, and immune changes that result in adaptive and pathogenic complex responses [2]. Insulin resistance is a known injury response [3]. According to Belik and Gruzdeva [4], insulin resistance is a crucial adaptive mechanism for survival during injury, malnutrition, or inflammation by maintaining required glucose levels for various biosynthetic processes. However, persistent hyperglycemia and hypermetabolism in patients with injuries cause infectious complications, delayed wound healing, and overall unfavorable outcomes [5].

In this context, the underlying mechanisms of insulin resistance remain unclear. Physical activity, diet, stress, estrogen levels, nocturnal sleep duration, age, and other factors affect tissue insulin sensitivity [6]. Growing evidence reveals the role of the gut microbiota in insulin resistance [7].

In recent years, the triglyceride–glucose (TyG) index has been used to assess insulin resistance, along with conventional techniques such as clamp test, fasting plasma insulin test, and Homeostasis Model Assessment of Insulin Resistance (HOMA-IR) [8, 9]. Several studies [10–13] indicated that the TyG index can be an independent marker of cardiovascular risk and cardiovascular disease prognosis. Avagimyan et al. [14] reported that the TyG index outperforms conventional markers such as HOMA-IR in predicting cardiometabolic outcomes. The association between the TyG index and injury or surgical prognosis is poorly understood [15].

**This study aimed** to assess TyG index changes and its relationship with the gut and blood microbiota composition in patients with multiple musculoskeletal injuries.

## METHODS

Forty-four male patients with multiple musculoskeletal injuries aged 19–51 years (mean age: 31.5 ± 8.89 years) who were treated at the Military Surgery Hospital of the Kirov Military Medical Academy were included. The patients provided written informed consent to participate in the study. The study was part of the university support program Priority 2030.

Patients with abdominal, spinal, or open traumatic brain injuries, diabetes mellitus, tuberculosis, or cancer were excluded. The patients underwent conventional surgical and conservative treatment. Anthropometric, clinical, laboratory, and imaging examinations were performed at baseline. Moreover, family and allergy history, nutrition status, sleep quality, unhealthy habits (i.e., smoking, alcohol consumption, and drug abuse), and comorbidities were assessed. Alcohol consumption was evaluated using the Alcohol Use Disorders Identification Test. Using the calculator available at https://www.mdapp.co/tyg-index-calculator-359/ [8], the TyG index was calculated as follows:

$$\ln [\text{fasting triglycerides (mg/dL)} \times \text{fasting glucose (mg/dL)}]/2$$

The gut and blood microbiota was assessed using 16S ribosomal ribonucleic acid (16S rRNA) sequencing. Metagenomic testing was performed at Cerbalab LLC (Russia). Stool ($n$ = 44) and serum ($n$ = 18) samples were collected using sterile single-use containers, frozen, and stored at –80°C for 1 month to 1 year. Stool and blood samples were thawed and then homogenized in a lysis solution; total deoxyribonucleic acid (DNA) was isolated. Bead mill homogenization and subsequent DNA extraction were performed using a Qiagen column (Germantown, MD, USA) according to manufacturer guidelines. Furthermore, 16*S* metagenomic libraries were prepared according to the Illumina protocol (part #15044223 Rev.B). The target 16S rRNA gene fragment was amplified using recommended primers for the *V*3–*V*4 region, with 5 ng of total DNA per sample. Twenty-five polymerase chain reaction cycles were carried out using KAPA HiFi HotStart ReadyMix (2×) (Roche Diagnostics, Switzerland). Then, the Illumina MGIEasy Universal Library Conversion Kit (App-A) was used to start sequencing on a BGI platform.

Bioinformatic processing of the 16S rRNA database was conducted using R v.3.6- and Python3-based bioinformatic software developed by the authors of this study. Bacterial species were identified using a DADA2 exact matching algorithm, with user scripts for SILVA v138 sequence preprocessing.

Clinical, laboratory, and imaging examination findings and metagenomic testing results were analyzed considering the time from injury.

Statistica 13.0 for Windows, IBM SPSS, and Statgraphics were used for statistical analysis and Statistica 13.0 for Windows for descriptive statistics. Categorical data are presented as numbers and percentages. Normality testing involved comparing the mean and median and using Gaussian distribution curves, coefficients of deviation and excess, normal probability plots, and the Kolmogorov–Smirnov and Shapiro–Wilk tests. Normally distributed quantitative variables were described using arithmetic means ($M$), standard deviations, and 95% confidence intervals. Non-normally distributed quantitative variables were expressed as median ($Me$) and upper and lower quartiles [$Q_1$–$Q_3$]. The direction and strength of correlation between two quantitative variables were assessed using Spearman's rank correlation coefficient. A correlation coefficient ($r$) <0.3, of 0.3–0.7, and >0.7 indicated a weak, moderate, and strong

correlation, respectively. The association between the TyG index and non-normally distributed anamnestic and clinical variables was determined using polynomial regression. Significant differences were indicated at $p < 0.05$. The relative prevalence of gut microbiota phyla was assessed using RStudio 2023.06.1 and heat maps [16].

The Local Ethics Committee of the Kirov Military Medical Academy approved the study (minutes no. 260; April 22, 2025).

## RESULTS AND DISCUSSION

At baseline, the patients had multiple musculoskeletal injuries, with above-the-elbow or above-the-knee amputations in 29.5% of cases. The patients underwent several surgeries ($n$ = 4 [1; 12]) and antibiotic therapies ($n$ = 3.29 ± 1.32). Risk factors included smoking (54.5%) and varying alcohol consumption levels (77.2%). In this study, the mean TyG index was 4.61 ± 0.22 conventional units. In 79.5% of patients with injuries, the TyG index was >4.49 conventional units. Ultrasound (US) revealed hepatomegaly in 29.54% of patients, signs of thick bile in 11.36%, and pancreatic hyperechogenicity in 11.36%. The patients exhibited increased systemic inflammatory marker levels (Table 1).

Polynomial regression revealed no significant changes in serum glucose levels ($p$ = 0.555) and TyG index ($p$ = 0.448), depending on the time from combat surgical trauma (Fig. 1, *a*). However, the TyG index increased up to >4.49 conventional units on days 1–8 after injury, plateaued on day 11, and decreased on day 22 (Fig. 1, *b*). Moreover, complex associations were observed between the TyG index and number of surgeries. The TyG index increased as the number of surgeries increased to four. An increase in the number of surgeries to eight did not cause an increase in the TyG index (Fig. 1, *c*); however, it increased later. A direct linear correlation was found between the TyG index and number of antibiotic therapy courses (Fig. 1, *d*).

Fig. 2 shows the gut microbiota composition in study participants, with different phyla represented by different colors on heat maps.

Based on 16S rRNA gene sequencing, the most prevalent phyla in fecal microbiota were *Bacillota* (synonym: *Firmicutes*) (52%), *Pseudomonadota* (synonym: *Proteobacteria*) (16%), and *Bacteroidota* (synonym: *Bacteroidetes*) (15%) (Fig. 3). The most prevalent phyla in serum were *Pseudomonadota* (synonym: *Proteobacteria*) (32%), *Actinomycetota* (synonym: *Actinobacteriota*) (29%), and *Bacillota* (synonym: *Firmicutes*) (18%) (Fig. 4).

Correlation analysis revealed associations between the TyG index and several clinical, laboratory, and imaging examination parameters in patients with multiple musculoskeletal injuries. Moderate direct correlations were found between the TyG index and total serum cholesterol ($r$ = 0.39; $p$ = 0.007) and US parameters of the gallbladder

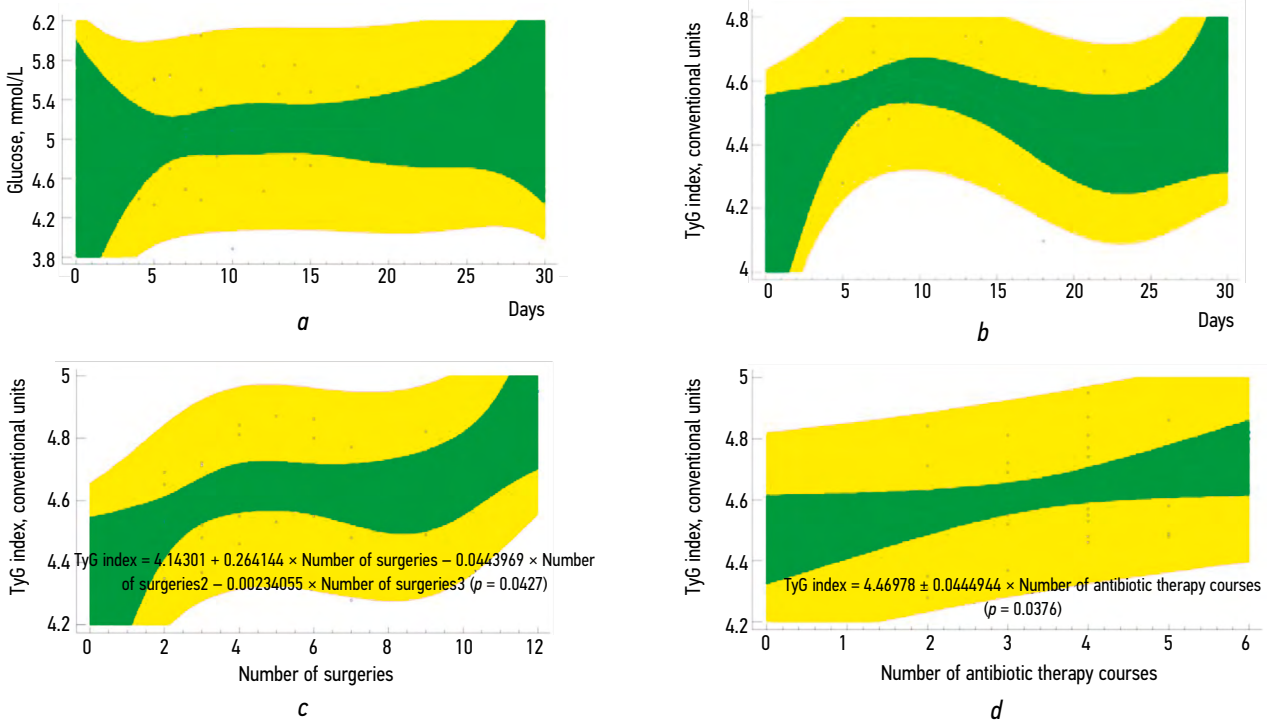


**Fig. 1.** Associations between the triglyceride–glucose (TyG) index and glucose level (*a*), time from injury (*b*), number of surgeries (*c*), and antibiotic therapy courses (*d*).

(thick, nonhomogeneous bile [$r$ = 0.40; $p$ = 0.021]) and left lobe of the liver (size, mm [$r$ = 0.42; $p$ = 0.014]) (Table 2).

Moreover, moderate direct correlations were noted between the TyG index and prevalence of *Pseudoscardovia* ($r$ = 0.40; $p$ = 0.007), *Pyramidobacter* ($r$ = 0.37; $p$ = 0.014), and *Pediococcus* ($r$ = 0.33; $p$ = 0.029) in the gut microbiota (Table 3) and *Bacillus* ($r$ = 0.51; $p$ = 0.031) and *Pseudomonas* ($r$ = 0.47; $p$ = 0.045) in serum (Table 4).

The other correlations between the TyG index and microbiota were significantly negative. A moderate

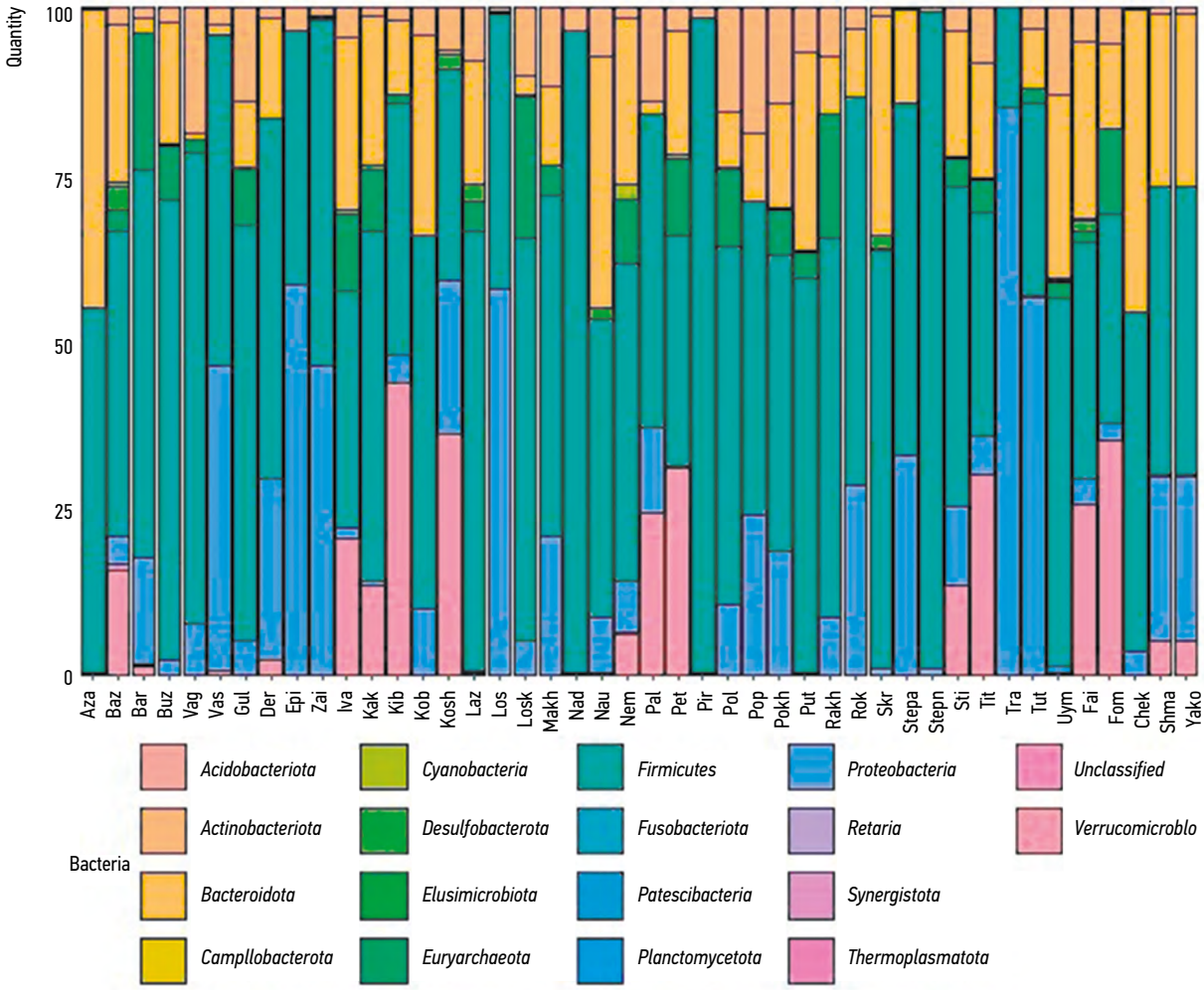


**Fig. 2.** Heat map of the prevalence of bacterial phyla in stool samples of patients with multiple musculoskeletal injuries.

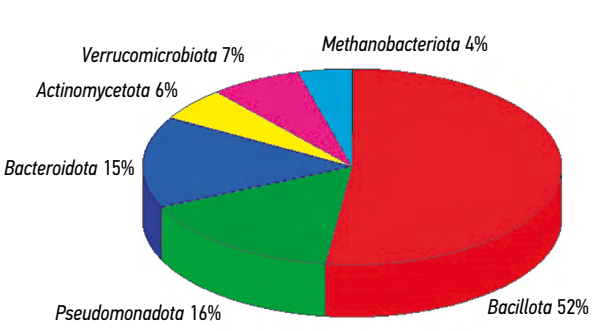


**Fig. 3.** Relative prevalence of main microbiota phyla in stool samples of patients with multiple musculoskeletal injuries.

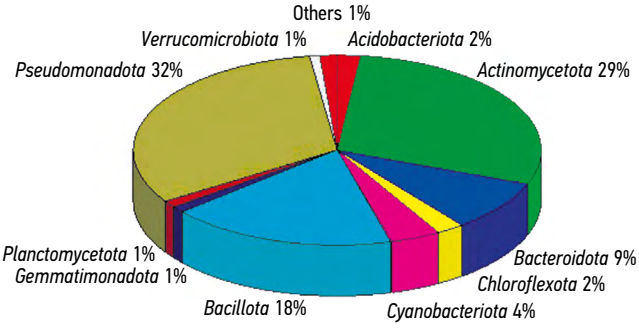


**Fig. 4.** Relative prevalence of main microbiota phyla in serum samples of patients with multiple musculoskeletal injuries.

inverse correlation was found between the TyG index and prevalence of genera *Scardovia* ($r$ = –0.47; $p$ = 0.001) and *Actinomyces* ($r$ = –0.330; $p$ = 0.028), phylum *Allofournierella* (synonym *Fournierella*) ($r$ = –0.322; $p$ = 0.033), and species *Scardovia wiggsiae* ($r$ = –0.49; $p$ = 0.001) and *Lactobacillus crispatus* ($r$ = –0.303; $p$ = 0.046) in stool samples. Moreover, a moderate inverse correlation was observed between the TyG index and prevalence of phylum *Cyanobacteriota* ($r$ = –0.51; $p$ = 0.029); genera *Bifidobacterium* ($r$ = –0.68; $p$ = 0.001), *Phascolarctobacterium* ($r$ = –0.63; $p$ = 0.004), and *Hydrogenophilus* ($r$ = –0.56; $p$ = 0.014); and species *Escherichia albertii* ($r$ = –0.51; $p$ = 0.031) and *Phascolarctobacterium faecium* ($r$ = –0.47; $p$ = 0.048) in serum samples.

Considering the complex pathophysiological mechanisms that determine insulin resistance, the obtained data were comprehensively analyzed. The findings indicate several significant correlations between clinical, laboratory, and imaging examination parameters and the prevalence of various bacteria in gut and serum microbiota and bacterial–bacterial associations (Table 5).

The strongest direct correlations were found between blood amylase levels and the prevalence of *Bacillus* ($r$ = 0.5207) in blood and between cefazolin use and the relative prevalence of *Bifidobacterium* ($r$ = 0.5596) and *Escherichia albertii* ($r$ = 0.7289) in blood.

Moreover, moderate inverse correlations were observed between cefazolin use and the relative prevalence of *Bacillus* ($r$ = –0.5814) in blood. The latter had an inverse correlation with the prevalence of *Bifidobacterium* ($r$ = –0.6121) and *Escherichia albertii* ($r$ = –0.6155) in blood.

The TyG index was >4.49 conventional units in 79.5% of patients early after injury. This phase of research did not focus on the prognostic value of the TyG index in patients with injuries. However, considering that persistent hyperglycemia

**Table 1.** Clinical, laboratory, and imaging examination parameters at baseline, abs. (%), $M \pm SD$, $Me$ [$Q_1$–$Q_3$]

| Parameter | Value |
|---|---|
| Age, years | 31.91±8.89 |
| Smoking, patients | 24 (54.5) |
| Alcohol consumption, patients | 34 (77.2) |
| Low-risk consumption (0–7 points), % | 65.22 |
| Hazardous or harmful consumption (8–15 points), % | 30.43 |
| Moderate–severe alcohol use disorder (16–19 points), % | 4.34 |
| Above-the-elbow or above-the-knee amputations | 13 (29.5) |
| Days from combat surgical trauma | 11 [2; 80] |
| Number of surgeries | 4 [1; 12] |
| Number of antibiotic therapy courses | 3.29 ± 1.32 |
| Body mass index, kg/m$^2$ | 22.17 ± 5.13 |
| Waist circumference, cm | 83.95 ± 10.49 |
| Systolic blood pressure, mmHg | 124.83 ± 16.02 |
| Diastolic blood pressure, mmHg | 70.61 ± 7.21 |
| Glucose, mmol/L | 5.52 ± 1.88 |
| Glycated hemoglobin, % | 5.06 ± 0.73 |
| Total cholesterol, mmol/L | 3.69 ± 1.00 |
| Low-density lipoprotein cholesterol, mmol/L | 2.28 ± 0.88 |
| Very low-density lipoprotein cholesterol, mmol/L | 0.58 [0.19; 1.01] |
| High-density lipoprotein cholesterol, mmol/L | 0.87 ± 0.26 |
| Triglycerides, mmol/L | 1.28 ± 0.43 |
| Triglyceride–glucose index, conventional units | 4.61 ± 0.22 |
| Total amylase, U/L | 60.86 ± 28.58 |
| C-reactive protein, mg/L | 72.78 [2.53; 241.61] |
| Hemoglobin, g/L | 5.28 ± 1.52 |
| Erythrocyte sedimentation rate, mm/h | 53.02 ± 11.91 |
| Hepatomegaly (US), patients | 13 (29.54) |
| Thick bile (US), patients | 5 (11.36) |
| Pancreatic hyperechogenicity (US), patients | 5 (11.36) |

**Table 2.** Correlations between the triglyceride–glucose index and clinical, laboratory, and imaging examination parameters in patients with multiple musculoskeletal injuries

| Parameter | *n* | *r* | *p* |
|---|---|---|---|
| Total cholesterol | 44 | 0.39 | 0.007 |
| Left hepatic lobe size | 33 | 0.42 | 0.014 |
| Chronic pancreatitis | 35 | 0.39 | 0.021 |
| Thick, non-homogeneous bile | 33 | 0.40 | 0.021 |
| Heterogeneous structure of the pancreas | 32 | 0.38 | 0.033 |
| Total amylase | 41 | 0.32 | 0.039 |
| Pancreatic hyperechogenicity | 32 | 0.35 | 0.047 |

**Table 3.** Correlations between the triglyceride–glucose index and gut microbiota composition in patients with multiple musculoskeletal injuries

| Bacterial genus/species | *n* | *r* | *p* |
|---|---|---|---|
| *Scardovia* | 44 | –0.47 | 0.001 |
| *Pseudoscardovia* | 44 | 0.40 | 0.007 |
| *Pyramidobacter* | 44 | 0.37 | 0.014 |
| *Actinomyces* | 44 | –0.33 | 0.028 |
| *Pediococcus* | 44 | 0.33 | 0.029 |
| *Allofournierella (Fournierella)* | 44 | –0.32 | 0.033 |
| *Coriobacteriaceae bacterium CHKCI002* | 44 | 0.32 | 0.035 |
| *Butyricicoccaceae UCG-009* | 44 | –0.31 | 0.042 |
| *Cutibacterium* | 44 | 0.30 | 0.046 |
| *Marvinbryantia* | 44 | –0.29 | 0.049 |
| *Peptoniphilus* | 44 | 0.29 | 0.049 |

**Table 4.** Correlations between the triglyceride–glucose index and serum microbiota composition in patients with multiple musculoskeletal injuries

| Taxonomic composition | *n* | *r* | *p* |
|---|---|---|---|
| Genus *Bifidobacterium* | 18 | –0.68 | 0.001 |
| Genus *Phascolarctobacterium* | 18 | –0.63 | 0.004 |
| Genus *Hydrogenophilus* | 18 | –0.56 | 0.014 |
| *Phylum Cyanobacteriota* | 18 | –0.51 | 0.029 |
| Genus *Bacillus* | 18 | 0.51 | 0.031 |
| *Species Escherichia albertii* | 18 | –0.51 | 0.031 |
| Genus *Pseudomonas* | 18 | 0.47 | 0.045 |
| Species *Phascolarctobacterium faecium* | 18 | –0.47 | 0.048 |

and hypermetabolism in these patients are associated with complications, it can be assumed that the TyG index is a valuable marker of unfavorable outcomes. Currently, studies on the association between the TyG index and prognosis in patients with injuries are scarce. Zhang et al. [17] found that the TyG index is an independent predictor of all-cause mortality in patients with sepsis within 28 days after hospitalization. Moreover, TyG index, along with body mass index, visceral fat volume, lipid metabolism parameters, and chronic systemic inflammation, is associated with impaired coronary blood flow in combat veterans after limb amputation compared with wounded patients without amputations and combat veterans without wounds [18].

The liver, adipose tissue, and pancreas, which modulate anabolic and catabolic processes under normal and pathological conditions, play a significant role in regulating metabolic homeostasis in humans. Therefore, in this study, direct correlations between the TyG index and total cholesterol and amylase levels, history of chronic pancreatitis, and US parameters that characterize the morphology and function of the liver, gallbladder, and pancreas were expected.

Liu et al. [19] found that the gut microbiota and its metabolites, such as short-chain fatty acids (SCFAs), trimethylamine-N-oxide, bile acids, branched-chain amino acids, and imidazole, are crucial in insulin resistance.

**Table 5.** Correlations between the triglyceride–glucose index and clinical, laboratory, imaging, and microbiological examination parameters

| Parameter | Total amylase | *Actinomyces* | *Lactobacillus crispatus* | *Escherichia albertii*, blood | *Bacillus*, blood | *Bifidobacterium*, blood |
|---|---|---|---|---|---|---|
| Cefazolin use | –0.2819 | –0.0042 | 0.3056 | 0.7289* | –0.5814* | 0.5596* |
| Triglyceride–glucose index | 0.3230* | –0.3302* | –0.3026* | –0.5073* | 0.5080* | –0.6827* |
| Total amylase | 1 | 0.0964 | –0.1791 | –0.0516 | 0.5207* | –0.3081 |
| *Escherichia albertii,* blood | –0.0516 | 0.0418 | –0.2241 | 1 | –0.6155* | 0.6198* |
| *Bacillus*, blood | 0.5207* | 0.0241 | 0.3337 | –0.6155* | 1 | –0.6121* |
| *Bifidobacterium*, blood | –0.3081 | 0.0979 | –0.3322 | 0.6198* | –0.6121* | 1 |
| *Scardovia wiggsiae* | 0.0529 | 0.3271* | 0.3891* | –0.1401 | 0.1246 | –0.0887 |

* $p < 0.05$.

Insulin resistance may be associated with increased (*Lachnospiraceae* [*Dorea* and *Blautia*], *Prevotella copri* and *Bacteroides vulgatus*, and *Streptococcus mutans*) [20] and decreased (*Akkermansia muciniphila, Blautia hydrogenotrophica, Clostridium spp., Ruminococcus spp., Prevotella spp., and Bifidobacterium spp.*) [21] prevalence and functional activity of certain bacteria in the gut microbiota. Dysbiosis alters intestinal carbohydrate metabolism and increases monosaccharide (fructose, galactose, mannose, and xylose) levels in feces, which may promote ectopic lipid accumulation and immune cell activation, stimulating pro-inflammatory cytokine responses [22].

Our findings confirm the role of gut microbiota in insulin resistance, indicating a direct correlation between the TyG index and number of antibiotic therapy courses, which contribute to dysbiosis. Patangia et al. have reported comparable findings [23].

No studies were found on the impact of gut microbiota on insulin resistance in patients with injuries. However, several experimental and clinical studies have demonstrated microbial composition and intestinal permeability changes in patients with injuries during the acute phase and in the long term [24]. Increased intestinal permeability, accompanied by changes in levels of intestinal permeability biomarkers (e.g., zonulin, lipopolysaccharide-binding protein, claudin 3, and fatty acid-binding protein) and bacterial translocation from the intestine into the bloodstream, was associated with microbial composition changes. The prevalence of *Bacillota* (synonym: *Firmicutes*), *Bacteroidales, Fusobacteriales*, and *Verrucomicrobiales* decreased, whereas the relative prevalence of *Pseudomonadota* (synonym: *Proteobacteria*), *Eubacteriales* (synonym: *Clostridiales*), and *Enterococcus* increased [24–26].

The TyG index showed the most significant inverse correlation with the prevalence of the genus *Scardovia* and species *Scardovia wiggsiae* in stool samples. Bacteria of the genus *Scardovia* (phylum *Actinomycetota*, class *Actinomycetes*, and family *Bifidobacteriaceae*) are primarily associated with oral diseases [27]. However, recent studies revealed pathogenetic associations between oral microbiota (*Granulicatella, Veillonella*, *Streptococcus*, and *Scardovia*) and nonalcoholic fatty liver disease, mediated by free sugar metabolism pathways [28]. Unlike oral microbiota, *Scardovia* can have the opposite role in the intestine, preventing metabolic disorders. Moreover, *Scardovia wiggsiae*, such as probiotic bifidobacteria, can produce acetic and lactic acids. These acids can be used for butyrate synthesis, which is inversely correlated with metabolic disorders [27].

Furthermore, our findings indicate an inverse correlation between the TyG index and relative prevalence of SCFA-producing bacteria of the genus *Allofournierella* (synonym: *Fournierella*), family *Oscillospiraceae* (synonym: *Ruminococcaceae*), in the gut microbiota. *Allofournierella massiliensis* (formerly *Fournierella massiliensis*), which is a typical representative of this genus, can produce acetic acid and, to a lesser extent, butyric, isobutyric, and propionic acids. This confirms the crucial role of SCFAs in insulin resistance mechanisms, including insulin secretion, lipogenesis, and pancreatic β-cell proliferation and function [19]. An association was found between the TyG index and relative prevalence of the genus *Butyricicoccaceae UCG-009* (which belongs to the family *Oscillospiraceae, similar to Allofournierella)*. *Butyricicoccaceae UCG-009* are SCFA-producing bacteria with a beneficial effect on human health, including the immune system [29].

Notably, the TyG index is inversely correlated with prevalence of *Lactobacillus crispatus* in fecal microbiota. These bacteria produce hydrogen peroxide and lactic acid, creating an acidic environment, and bacteriocins (crispacin A, crispacin 467, etc.), which prevent the growth of many pathogenic bacteria and fungi. Several studies have shown that a decrease in *Lactobacillus*, *Prevotella*,

*Bacteroides*, *Desulfovibrio*, and *Oxalobacter* in the gut microbiota may change the balance of pro-inflammatory and anti-inflammatory bacterial species, causing metabolic disorders [19]. No data were found on the role of *Lactobacillus crispatus* in insulin resistance; however, several bacteria from this and other genera of the family *Lactobacillaceae* are known to be involved in insulin resistance. For example, *Lactobacillus gasseri* increases GLUT-4 expression and translocation and thus promote insulin-mediated glucose uptake by peripheral tissues. *Lacticaseibacillus rhamnosus* (synonym: *Lactobacillus rhamnosus*) increases adiponectin levels in white adipose tissue, which decreases insulin resistance [30]. Moreover, the use of probiotics containing *Lactobacillus crispatus*, *Limosilactobacillus reuteri* (formerly *Lactobacillus reuteri*), and *Bacillus subtilis* decreased plasma glucose and glycated hemoglobin levels, increased insulin levels, and improved lipid profile in experimental animals with induced diabetes [31].

Sciarra et al. [32] demonstrated the role of the blood microbiota in cardiovascular, endocrine, and gastrointestinal diseases, cancer, and other disorders. Studies on the role of the blood microbiota in patients with injuries are very few. Injuries, which are frequently accompanied by seizure, blood loss, and infectious wound contamination, are associated with increased intestinal permeability, promoting bacterial translocation from the intestinal lumen into the bloodstream [25]. In the present study, genetic material from various microorganisms (*Synergistota*, *Cyanobacteriota*, *Bacillus*, *Bifidobacterium*, *Hydrogenophilus*, *Phascolarctobacterium*, *Pseudomonas*, and others) was found in the serum of patients with multiple musculoskeletal injuries. Bacteria were detected in the serum of patients without clinical or laboratory signs of sepsis. Bacteria in the blood of patients with musculoskeletal injuries may be an adaptive response to stress and traumatic tissue injury. Bacterial translocation through the intestinal wall, bacteremia, and bacterial accumulation in internal organs have been reported in experiments with healthy animals and animals with closed femoral fractures [33]. Our findings indicate that bacterial translocation through the intestinal wall ensures continuous interactions between the immune system and external factors. Specifically, this mechanism may be considered a pathogenetic link in the adaptation to injury in humans. It aims at confining infection to the injury site and promoting wound healing.

Several studies have confirmed this hypothesis [32–35], indicating that healthy people's blood is not sterile. The blood microbiome is dominated by the phyla *Bacillota*, *Actinomycetota*, *Pseudomonadota*, and *Bacteroidota* and the genera *Bacillus*, *Streptococcus*, *Corynebacterium*, *Pseudomonas*, and *Bacteroides* [32]. Some researchers believe that the DNA found in blood belongs to commensal bacteria in the host's body. These bacteria cause no symptoms, and their immunomodulatory properties determine asymptomatic or symptomatic (with sepsis) bacteremia in humans [34]. Recent data on microorganisms found in tissues indicate the significant role of bacterial translocation in cardiometabolic diseases [35].

In the present study, significant correlations were found between the TyG index and numerous circulating bacteria. The identified correlations were predominantly inverse. The present study is the first to determine a direct association between the TyG index and bacteria from the genera *Bacillus* and *Pseudomonas*. The mechanisms behind this association require further research.

The genus *Bacillus* includes pathogenic and nonpathogenic bacteria with complex taxonomic relationships. *B. anthracis*, *B. cereus*, and *B. thuringiensis* are the most well-studied representatives of the genus *Bacillus*, which can cause local and systemic infections [36]. The pathogenetic links between *Bacillus* and the human body and mechanisms of transition from nonpathogenic to pathogenic forms are poorly understood.

Currently, the clinical and prognostic value of the identified associations between the TyG index and blood microbiota cannot be definitively assessed. Amar et al. [37] have demonstrated that individuals at risk of diabetes mellitus have increased blood levels of 16S rRNA. Recent studies have confirmed the role of circulating microbiome and microbial metabolites in type 2 diabetes mellitus onset and progression [38].

Differences in associations between the TyG index and gut and blood microbiota reported in the present study may indicate independent changes in different biotopes in patients with injuries. Moreover, they support the hypothesis of simultaneous existence of gut and blood microbiomes.

## CONCLUSION

Changes in insulin resistance depending on the time from combat surgical trauma indicate changes in insulin resistance associated with response to injury. Early after injury, insulin resistance can be considered a compensatory and adaptive mechanism in response to stress, blood loss, and tissue damage. This corresponds to the concept of general adaptation syndrome and primarily targets low energy availability.

This study is the first to identify complex associations between the TyG index, which is an insulin resistance parameter that has been extensively studied in recent years, and the gut and blood microbiota in patients with multiple musculoskeletal injuries. The study cohort was selected considering two factors. First, as a universal multivariate stress model, injuries enable a comprehensive assessment

from a biological standpoint. Second, there is currently a significant increase in patients with injuries in clinical practice. Our findings show the initial phase of extensive research on the role of gut microbiota and gastrointestinal tissues in impaired homeostasis in patients with injuries; therefore, they should be interpreted with caution. However, numerous associations were demonstrated between the gut and blood microbiota and various clinical, laboratory, and imaging examination parameters that are pathogenetically associated with insulin resistance. This may indicate that the microbiota modulates mechanisms underlying insulin resistance.

This study had several limitations. The gut and blood virome or mycobiome were not assessed. The analysis does not allow for definitive conclusions regarding the causal role of identified associations. However, changes in the gut and blood microbiota composition, intestinal barrier structure and function, and microbiota-dependent metabolite levels are fundamental etiopathogenetic links in the development of various disorders in humans. Further studies are warranted to better understand the overall pathological significance of the microbial–tissue complex and develop optimal treatment strategies.

## ADDITIONAL INFORMATION

**Authors' contribution.** *E.V. Kryukov*: data analysis, final revision; *S.P. Salikova*: general concept development, research design, literature review, chromatographic study, data collection and analysis, article writing; *V.B. Grinevich*: general concept development, research design data analysis; *Yu.A. Kravchuk*: literature review, data analysis, introduction; *L.S. Oreshko*: development of a general concept, research design, collection and processing of materials, writing an article; *D.V. Egorov, Yu.A. Makarenko*: collection and processing of materials; *I.M. Samokhvalov, V.I. Badalov*: data analysis; *S.I. Sitkin*: writing an article; *A.N. Sorokin, S.N. Petrukov*: collection and processing of materials, data analysis. The authors have approved the version for publication and have also agreed to be responsible for all aspects of the work, ensuring that issues relating to the accuracy and integrity of any part of it are properly considered and addressed.

**Ethics approval.** The study was approved by the local Ethical Committee of the Kirov Military Medical Academy (Protocol no. 302 from 22.04.2025).

**Funding source.** The work was carried out under the project «Investigation of the role of the biotech complex of the gastrointestinal tract in the development of homeostatic disorders in patients with polytrauma» within the framework of the «PRIORITY 2030»state university support program.

**Disclosure of interests.** The authors have no relationships, activities or interests for the last three years related with for-profit or not-for-profit third parties whose interests may be affected by the content of the article.

**Statement of originality.** The authors did not use previously published information (text, illustrations, data) to create this paper.

**Data availability statement.** All the data obtained in this study is available in the article.

**Generative AI.** Generative AI technologies were not used for this article creation.

**Provenance and peer review.** This work was submitted to the journal on its own initiative and reviewed according to the usual procedure. Two reviewers: internal and external participated in the review.

## ДОПОЛНИТЕЛЬНАЯ ИНФОРМАЦИЯ

**Вклад авторов.** Е.В. Крюков — анализ данных, внесение окончательной правки; С.П. Саликова — разработка общей концепции, дизайн исследования, обзор литературы, хроматографическое исследование, сбор и анализ данных, написание статьи; В.Б. Гриневич — разработка общей концепции, дизайн исследования, анализ данных; Ю.А. Кравчук — обзор литературы, анализ данных; Л.С. Орешко — разработка общей концепции, дизайн исследования, сбор и обработка материалов, написание статьи; Д.В. Егоров, Ю.А. Макаренко — сбор и обработка материалов; И.М. Самохвалов, В.И. Бадалов — анализ данных; С.И. Ситкин — написание статьи; А.Н. Сорокин, С.Н. Петруков — сбор и обработка материалов, анализ данных. Авторы одобрили версию для публикации, а также согласились нести ответственность за все аспекты работы, гарантируя надлежащее рассмотрение и решение вопросов, связанных с точностью и добросовестностью любой ее части.

**Этическая экспертиза.** Проведение исследования одобрено локальным этическим комитетом Военно-медицинской академии им. С.М. Кирова (протокол № 302 от 22.04.2025).

**Источник финансирования.** Работа выполнена по проекту «Исследование роли биотканевого комплекса желудочно-кишечного тракта в развитии гомеостатических нарушений у пострадавших с политравмой» в рамках государственной программы поддержки университетов «Приоритет-2030».

**Раскрытие интересов.** Авторы заявляют об отсутствии отношений, деятельности и интересов за последние три года, связанных с третьими лицами (коммерческими и некоммерческими), интересы которых могут быть затронуты содержанием статьи.

**Оригинальность.** При создании настоящей работы авторы не использовали ранее опубликованные сведения (текст, иллюстрации, данные).

**Доступ к данным.** Все данные, полученные в настоящем исследовании, доступны в статье.

**Генеративный искусственный интеллект.** При создании настоящей статьи технологии генеративного искусственного интеллекта не использовали.

**Рассмотрение и рецензирование.** Настоящая работа подана в журнал в инициативном порядке и рассмотрена по обычной процедуре. В рецензировании участвовали два рецензента: внутренний и внешний.

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