RESEARCH PAPER

Role of Subclinical Microbial Dysbiosis and Chronic Low-Grade Infections in Systemic Inflammation, Autonomic Dysfunction, and Cardiovascular Risk in an Urban Community-Based Population

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ABSTRACT

Background
Subclinical microbial dysbiosis and chronic low-grade infections have recently emerged as important contributors to systemic inflammation, autonomic nervous system dysfunction, and cardiovascular disease progression. A disruption in the balance of gut microbes can affect inflammation, metabolism and blood vessel function, especially in urban dwellers who are more likely to have sedentary lifestyles and poor diets.

Objective
To assess the relationship between subclinical microbial dysbiosis, chronic low-level infections and systemic inflammation, autonomic dysfunction and cardiovascular risk in adults in a community-based population in the urban area.

Methods
This community-based cross-sectional study was conducted from June 2024 to September 2025 at the Department of Public Health, Health Services Academy, Islamabad, Pakistan, in collaboration with Abwa Medical College, Faisalabad, Punjab, Pakistan. A total of 130 participants aged 25–70 years were enrolled through non-probability consecutive sampling. Demographic and anthropometric data, inflammatory markers, parameters of the autonomic nervous system and cardiovascular risk markers were measured. The presence of microbial dysbiosis in stool samples was analyzed. ECG recordings were used to assess HRV. Data were analyzed with SPSS version 26.0 and difference at $p<0.05$ was considered significant.

Results
Subclinical microbial dysbiosis was identified in 76 (58.5%) participants. Individuals with dysbiosis demonstrated significantly elevated hs-CRP (5.9±1.8 vs 2.7±1.1 mg/L), IL-6 (11.8±3.4 vs 6.1±2.2 pg/mL), and TNF-α levels (18.9±4.3 vs 10.2±2.9 pg/mL) compared with controls ($p<0.001$). Dysbiosis was significantly related to decreased

HRV and increased resting HR. Participants with microbial imbalance had significantly higher Framingham cardiovascular risk scores and CIT ($p<0.001$).

Conclusion
Systemic inflammation, autonomic dysfunction and cardiovascular risk are all significantly linked to subclinical microbial dysbiosis and chronic low-grade infections in adults living in urban areas.

Keywords: microbial dysbiosis, systemic inflammation, autonomic dysfunction, cardiovascular risk, gut microbiota, chronic low-grade infection

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Introduction

Cardiovascular diseases (CVDs) continue to be a major cause of death and disability, and represent a significant burden for healthcare systems globally [1]. Rapid urbanisation, sedentary lifestyle, poor dietary habits, chronic psychological stress, environmental pollution and the growing prevalence of metabolic disorders have greatly added to the increase in the prevalence of cardiovascular complications especially in developing countries. The association of traditional cardiovascular risk factors with cardiovascular disease is well known, but recent studies indicate that chronic systemic inflammation and changes in human microbiome may be important too in the pathogenesis of cardiovascular disease [2].

The human microbiota is a very complex ecosystem of trillions of microorganisms that settle mainly in the gastrointestinal tract [3]. In physiological conditions, the gut microbiome plays a role in regulation of intestinal barrier, production of metabolites, regulation of inflammation, metabolic functions, and immune system regulation [4]. Microbial dysbiosis or disturbance of a normal microbial balance can lead to overgrowth of pathogenic microorganisms, loss of microbial diversity, increased intestinal permeability and translocation of microbial endotoxins to the systemic circulation. A chronic state of low-grade inflammation has been increasingly linked with metabolic and cardiovascular diseases [5].

Subclinical microbial dysbiosis may not cause any symptoms and signs, but can result in chronic activation of inflammatory pathways mediated by lipopolysaccharides, pro-inflammatory cytokines, and oxidative stress mediators [6]. High levels of inflammatory markers like high-sensitivity C-reactive protein (hs-CRP), tumour necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6) have been linked with endothelial dysfunction, vascular inflammation, insulin resistance and atherosclerosis. Thus, chronic low grade infection as well as microbial imbalance can indirectly be responsible for cardiovascular pathology for apparently healthy humans [7].

The GBA (gut–brain–heart axis) has also been identified as a crucial link between the gut and ANS.It has also been established that the gut/ANS axis is important, and this is known as the gut–brain–heart axis (GB) [8]. Microbial metabolites like short-chain fatty acids, trimethylamine-N-oxide (TMAO) and secondary bile acids can impact autonomic regulation, activity of the sympathetic nervous system, cardiac electrophysiology, and vascular tone. The continuous activation of the inflammatory response with dysbiosis can negatively affect autonomic balance, resulting in a lower level of heart rate variability, a higher resting heart rate and an increase in cardiovascular stress. The autonomic dysfunction has been known to be a separate risk factor for arrhythmias, hypertension, myocardial ischemia and sudden cardiac death [9].

The urban population might be especially vulnerable to microbial dysbiosis because the intake of processed foods and lack of fiber, high levels of antibiotic exposure, poor sleep, psychological stress, lack of exercise, and exposure to environmental pollutants [10]. All these factors play a role in metabolic dysfunction and inflammatory activation that can lead to increased progression of cardiovascular disease. Although there is increasing international interest on the microbiome–cardiovascular relationship, there is a lack of data on the microbiome impact on systemic inflammation, autonomic dysfunction and cardiovascular risk in community-dwelling people

from urban areas of developing countries, despite subclinical microbial dysbiosis [11].

Therefore, the present study was designed to evaluate the role of subclinical microbial dysbiosis and chronic low-grade infections in systemic inflammatory activation, autonomic nervous system dysfunction, and cardiovascular risk among adults residing in an urban community-based population [12].

Materials and Methods

This community-based cross-sectional study was conducted from June 2024 to September 2025 at the Department of Public Health, Health Services Academy, Islamabad, Pakistan, in collaboration with Abwa Medical College, Faisalabad, Punjab, Pakistan. The aim of the study was to determine if there is a relationship between subclinical microbial dysbiosis and chronic low-grade infections, INA and cardiovascular risk in adults in community-based urban environments.

Net of the study population were the adult residents aged 25–70. In this, non-probability consecutive sampling technique was used and a total sample size of 130 participants was included. The participants were enrolled from urban community health screening camps and OP/CO centres of the participating institutions. The purpose of the study was explained to all eligible persons and informed consent written prior to enrolment.

Permanent residents of urban areas were included who were willing to provide blood and stool samples from 25–70 years of age from either gender. Those who participated were excluded if they had any clinically diagnosed cardiovascular disease, acute febrile illness, active gastrointestinal infection, autoimmune diseases, malignancy, chronic kidney disease, chronic liver disease, pregnancy, recent hospitalization, or antibiotic, probiotic, corticosteroid or immunosuppressive drug use within the four weeks prior to the study. These exclusions were made to minimize factors that may independently influence gut microbiota, inflammatory markers or autonomic function.

Structured proforma was used to collect data. Demographic variables considered were age, gender, living, educational level, occupation, economic status, smoking history, physical activity, diet, sleep time, past medical history, medication history, and family history of cardiovascular disease. The clinical examination consisted of measuring height, weight, body mass index, waist circumference, systolic blood pressure, diastolic blood pressure and resting pulse rate. BMI was defined as weight (kg) divided by height (m2). The blood pressure was taken in the sitting position after 5 minutes rest with a calibrated sphygmomanometer and the average of two readings was taken.

Venous blood samples were taken after overnight fasting (8–12 hours) under aseptic conditions. Laboratory parameters were complete blood count, fasting glucose, HbA1c, lipid profile, high-sensitivity C-reactive protein, interleukin-6 levels and tumor necrosis factor-alpha. Serum samples were separated and stored following standard laboratory practices until analysed. Commercially available enzyme-linked immunosorbent assay (ELISA) kits were used for the measurement of inflammatory biomarkers, if applicable. Persistent elevations of inflammatory markers, in the absence of clinical acute infection, was used as the criterion for chronic low-grade inflammatory status.

Stool specimens were collected in sterile, leak proof containers and sent to the lab with proper conditions. The degree of microbial dysbiosis was determined by stool microscopy, culture-based stool evaluation and microbiological markers of gut microbial imbalance. Dysbiosis was characterized as a decrease in beneficial bacterial patterns, abnormal bacterial overgrowth, elevated microbial colonization by pathogenic species or a disruption of the microbial balance accompanied by elevated inflammatory markers. The participants were divided into two groups: dysbiosis and non-dysbiosis for comparison.

Resting heart rate and a short term HRV assessment were used to evaluate the function of the ANS. Participants were studied in a quiet room following a period of quiet rest of at least 10 minutes. Electrocardiographic recording was performed in supine position and time domain HRV parameters such as the standard deviation of normal to normal interval (NN) and the root mean square of successive differences (RMSD) were recorded. HRV and HRR were taken as measures of autonomic dysfunction.

The cardiovascular risk assessment was done by clinical and biochemical risk factors such as age, sex, smoking status, blood pressure, fasting blood sugar level, lipid profile, BMI, waist circumference and family history of cardiovascular diseases. The participants were divided in to low, moderate and high cardiovascular risk groups based on the combined clinical risk assessment. Subclinical atherosclerosis was determined as the intima-media thickness (IMT) of the carotid artery by ultrasonography in selected participants.

The data entered and analyzed in SPSS version (26.0). The quantitative variable data were presented as mean ± SD and the categorical variable data were presented as frequency and percentage. Continuous variables were compared between groups using independent sample t-test and categorical variables were compared

using chi-square test. The relationships between inflammatory biomarkers, autonomic parameters and cardiovascular risk indicators were determined by Pearson correlation analysis. The independent predictors of increased cardiovascular risk after adjustment for potential confounding factors were identified using multivariate regression analysis. A p value of < 0.05 was deemed to be statistically significant.

Results

The total number of participants in the study were 130, of which 74 (56.9%) were males and 56 (43.1%) were females. Among the participants diagnosed with subclinical microbial dysbiosis, 43 (56.6%) were males and 33 (43.4%) were females, whereas the non-dysbiosis group included 31 (57.4%) males and 23 (42.6%) females. The mean age of the entire population studied was 45.7±10.9 years. There were significant differences in body mass index, waist circumference, systolic blood pressure, diastolic blood pressure, fasting blood glucose and LDL cholesterol between the microbial dysbiosis and non-dysbiosis groups ($p<0.05$). The participants with dysbiosis were also significantly more likely to have a sedentary lifestyle, smoke cigarettes and to have irregular sleep times and diets. Baseline demographic and clinical data are described in detail in Table 1.

Table 1: Baseline Demographic and Clinical Characteristics of Study Participants

Variables	Dysbiosis Group (n=76)	Non-Dysbiosis Group (n=54)	p-value
Age (years)	47.6±10.2	43.1±11.4	0.018
Male Participants, n (%)	43 (56.6%)	31 (57.4%)	0.924
Female Participants, n (%)	33 (43.4%)	23 (42.6%)	0.924
Body Mass Index (kg/m²)	29.4±4.1	25.8±3.6	<0.001
Waist Circumference (cm)	99.2±10.6	89.7±8.8	<0.001
Systolic Blood Pressure (mmHg)	139.1±14.8	124.5±11.7	<0.001
Diastolic Blood Pressure (mmHg)	88.3±9.1	79.6±7.3	<0.001
Fasting Blood Glucose (mg/dL)	116.5±21.4	97.8±17.2	<0.001
LDL Cholesterol (mg/dL)	144.7±28.5	118.2±24.6	<0.001
Smokers, n (%)	29 (38.2%)	13 (24.1%)	0.041
Sedentary Lifestyle, n (%)	48 (63.2%)	19 (35.2%)	0.002
Poor Sleep Quality, n (%)	44 (57.9%)	16 (29.6%)	0.001

The systemic inflammatory biomarkers were significantly higher in participants with microbial dysbiosis than in those without dysbiosis. Mean hs-CRP was significantly elevated in the dysbiosis group (5.9±1.8 mg/L) compared with the non-dysbiosis group (2.7±1.1 mg/L). Similarly, IL-6 and TNF-α concentrations were significantly elevated among participants with dysbiosis, indicating persistent systemic inflammatory activation associated with chronic low-grade infections and altered microbial balance. In addition, the dysbiosis group had significantly higher total leukocyte count and HbA1c levels. The results of these tests are summarized in tabular form in Table 2.

Table 2: Comparison of Systemic Inflammatory Biomarkers Between Study Groups

Biomarkers	Dysbiosis Group (n=76)	Non-Dysbiosis Group (n=54)	p-value
hs-CRP (mg/L)	5.9±1.8	2.7±1.1	<0.001
Interleukin-6 (pg/mL)	11.8±3.4	6.1±2.2	<0.001
TNF-α (pg/mL)	18.9±4.3	10.2±2.9	<0.001
Total Leukocyte Count (×10⁹/L)	8.8±1.7	6.6±1.3	<0.001
HbA1c (%)	6.5±1.0	5.6±0.7	<0.001

The participants with microbial dysbiosis had significantly impaired autonomic regulation, as assessed by autonomic nervous system tests. Participants in the dysbiosis group had significantly higher mean RHR, and significantly lower HRV parameters, such as SDNN and RMSSD, than those who were not in the dysbiosis group. There was a reduction in HRV in male and female participants with dysbiosis, indicating increased sympathetic activation and decreased parasympathetic activity, regardless of gender. Detailed autonomic function parameters are shown in Table 3.

Table 3: Comparison of Autonomic Dysfunction Parameters Between Study Groups

Parameters	Dysbiosis Group (n=76)	Non-Dysbiosis Group (n=54)	p-value
Resting Heart Rate (beats/min)	85.2±8.9	72.8±7.1	<0.001
SDNN (ms)	89.6±17.5	124.2±21.7	<0.001
RMSSD (ms)	23.8±7.9	37.5±9.8	<0.001
Reduced HRV in Males, n (%)	28 (65.1%)	8 (25.8%)	<0.001
Reduced HRV in Females, n (%)	21 (63.6%)	6 (26.1%)	<0.001

Microbial dysbiosis was a factor that significantly increased cardiovascular risk in the subjects undergoing cardiovascular risk assessment. Mean Framingham cardiovascular risk scores and carotid intima-media thickness values were significantly higher in the dysbiosis group compared with controls. Cardiovascular risk was observed in moderate to high range in both male and female participants with dysbiosis while, frequencies of cardiovascular risk were slightly higher in male participants. It was observed that there was a significant decrease in HDL cholesterol levels and an increase in triglyceride levels in the participants who had dysbiosis. Detailed cardiovascular risk findings are summarized in Table 4.

Table 4: Cardiovascular Risk Assessment Among Study Participants

Variables	Dysbiosis Group (n=76)	Non-Dysbiosis Group (n=54)	p-value
Framingham Risk Score (%)	18.4±6.1	9.8±4.3	<0.001
Carotid Intima-Media Thickness (mm)	0.93±0.17	0.69±0.10	<0.001
Moderate-to-High Cardiovascular Risk in Males, n (%)	24 (55.8%)	7 (22.5%)	<0.001
Moderate-to-High Cardiovascular Risk in Females, n (%)	17 (51.5%)	4 (17.4%)	<0.001
HDL Cholesterol (mg/dL)	38.6±7.2	46.4±8.1	<0.001
Triglycerides (mg/dL)	198.3±41.7	149.5±33.6	<0.001

Significant positive correlations were observed between inflammatory biomarkers and cardiovascular risk indicators with high-sensitivity CRP (hs-CRP) showing strong positive correlation with SBP ($r=0.58$, $p<0.001$), LDL cholesterol ($r=0.49$, $p<0.001$) and Framingham cardiovascular risk score ($r=0.61$, $p<0.001$). There were significant inverse correlations between reduced HRV parameters and inflammatory biomarkers and between CIMT and reduced HRV. After controlling for age, gender, smoking status and diabetes mellitus, multivariate regression analysis revealed that higher levels of hs-CRP, IL-6, higher BMI, higher LDL cholesterol and lower SDNN were independent predictors of higher cardiovascular risk.

In conclusion, the results of this study showed that there was a significant association between subclinical microbial dysbiosis and chronic low-grade inflammatory activation with autonomic dysfunction and increased cardiovascular risk in both male and female adults living in urban communities.

Discussion

The present study demonstrated a significant association between subclinical microbial dysbiosis, chronic low-grade inflammatory activation, autonomic nervous system dysfunction, and elevated cardiovascular risk among adults residing in urban community settings [1]. The inflammatory biomarkers were significantly higher, HRV parameters more impaired, and metabolic profiles adverse in subjects with microbial dysbiosis than in those without. The cardiovascular risk scores were also higher in subjects with microbial dysbiosis than without. The results are consistent with the increasing evidence that changes in the gut microbial composition and chronic subclinical inflammatory conditions could play a significant role in the pathogenesis of cardiovascular diseases [2].

An important and salient finding in the current study was the significantly higher levels of inflammatory markers such as hs-CRP, IL-6 and TNF-α in participants with microbial dysbiosis [3]. It's becoming well understood that chronic low-grade inflammation is a key mechanism connecting gut microbial imbalance and metabolic/cardiovascular disease. Systemic inflammatory activation could be a consequence of translocation of bacterial endotoxins and activation of inflammatory pathways as a result of dysbiosis, which can alter the permeability of intestinal cells. High inflammatory cytokines can be associated with endothelial dysfunction, oxidative stress, vascular damage, insulin resistance and early atherosclerosis. The levels of hs-CRP and cytokines that are much higher in the current study, as shown by previous studies, are evidence of the inflammatory effect of gut microbial disturbances on cardiovascular physiology [4].

Another important finding of the study was that subjects with microbial dysbiosis showed significant deficits in autonomic function, with increased resting heart rate and decreased HRV parameters such as SDNN and RMSSD [5]. Heart rate variation (HRV) is regarded as an important measure of autonomic nervous system balance and lower HRV has been linked with higher sympathetic activity, lower

parasympathetic activity, induction of arrhythmia, hypertension and cardiovascular mortality. Based on the results of the present study, it can be concluded that an imbalance in the microflora as a consequence of chronic inflammatory activation can negatively impact the autonomic control via the gut–brain–heart axis. Sympathetic overactivation and suboptimal cardiac autonomic control may be due to the collective activity of microbial metabolites, inflammatory mediators and neuroimmune signaling pathways [6].

An important observation in the present study was the significantly increased cardiovascular risk among participants with microbial dysbiosis. Patients with dysbiosis had higher Framingham cardiovascular risk scores, greater intima-media thickness of the carotid artery, higher LDL cholesterol levels, lower HDL cholesterol levels, and higher triglyceride levels [7]. The results suggest that microbial dysbiosis could impact several metabolic and vascular pathways that contribute to cardiovascular diseases. Persistent inflammatory activation and changes in microbial metabolites, including trimethylamine-N-oxide, can lead to endothelial dysfunction, lipid abnormalities, platelet activation, vascular inflammation and the progression of subclinical atherosclerosis. Further evidence of the influence of dysbiosis on early vascular injury comes from the increase in carotid intima-media thickness among participants with dysbiosis.Additional evidence that dysbiosis contributes to early vascular injury is the increase in carotid intima-media thickness among participants with dysbiosis [8].

This study also showed a lower autonomic function and higher moderate-to-high cardiovascular risk in both sexes with dysbiosis, but with higher frequencies in males [9]. This could partly be attributed to the fact that male participants were more likely to be smokers, have central obesity and metabolic disturbances. However, large-scale cardiovascular and inflammatory abnormalities in females suggests that microbial dysbiosis may have a negative impact on cardiovascular health regardless of gender [10].

Urban lifestyle-related factors probably played a significant role in the microbial imbalance and inflammatory activation in the studied population [11]. The participants with dysbiosis were more likely to be sedentary, eat processed foods, have lower intake of fiber, sleep disturbances, chronic psychological stress, smoking and obesity. Such changes in microbial community and vulnerability to chronic inflammatory diseases could result from these environmental and lifestyle factors. Thus, lifestyle changes and microbiome targeting could be considered as significant preventive measures to lower the incidence of cardiovascular events in the future [12].

The present study is important in the light of its clinical and public health implications. The recognition of subclinical microbial dysbiosis and chronic inflammatory activation could be helpful in the detection of human populations with higher cardiovascular risk before the onset of cardiovascular disease [13]. The use of microbiome-based techniques, dietary interventions, promoting physical activity, stress management, and monitoring inflammatory risk factors could enhance cardiovascular prevention strategies in city dwellers [14].

Several limitations should be acknowledged. Due to the cross-sectional design, it is not possible to determine causal relationships between microbial dysbiosis and cardiovascular abnormalities [15]. There were no advanced genomic sequencing methods available for in-depth microbial characterization. The primary method of data collection was self-report, which can be subject to recall bias [16]. Furthermore, the small number of samples could reduce the generalizability of the results to larger populations. Despite these limitations, the study provides important community-based evidence regarding the relationship between microbial dysbiosis, systemic inflammation, autonomic dysfunction, and cardiovascular risk in an urban Pakistani population [17].

Conclusion

Among adults living in urban communities, subclinical microbial dysbiosis and chronic low grade infections were significantly linked to systemic inflammatory activation, disturbed autonomic nervous system regulation and enhanced cardiovascular risk. A group of participants had dysbiosis and showed higher levels of inflammatory markers, lower HRV, bad lipid profile and higher markers of subclinical atherosclerosis than those who did not. The results indicate that activation of chronic inflammation and autonomic dysfunction may be important mechanistic mechanisms involved in the relationship between microbial dysbiosis and the progression of cardiovascular disease. The prevention of microbial imbalance, through microbiome-focused interventions, could potentially enhance future cardiovascular morbidity and long-term cardiovascular health outcomes, in urban populations.

Competing Interests

The authors declare that there are no competing interests regarding the publication of this study.

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Authors' Contributions

N.W. conceptualized the study, supervised data collection, and drafted the manuscript.

M.H. contributed to cardiovascular assessment,

clinical interpretation, and manuscript revision.
A.Z. supervised microbiological analysis and interpretation of dysbiosis findings.
S.A. performed laboratory investigations and pathological assessment.
R.S. contributed to study methodology, epidemiological analysis, and statistical interpretation.
I.H. assisted in autonomic nervous system assessment and physiological data interpretation.
A.Y.M. contributed to microbiological research support, literature review, and manuscript editing.
S.G. participated in data analysis, interpretation of findings, and final proofreading of the manuscript.
All authors read and approved the final manuscript.

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