International Journal of Academic Health and Medical Research (IJAHMR)
ISSN: 2643-9824
Vol. 10 Issue 8 August - 2026, Pages: 20-30

Association of Sedentary Behavior and Systemic Inflammatory Biomarkers with Microvascular and Macrovascular Complications in Type 2 Diabetes

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***Abstract: Background**: Low-grade inflammation plays a crucial role in the pathophysiology of type 2 diabetes mellitus (T2DM) and its complications. Physical activity is recognized as an important modifiable factor associated with improved metabolic control and reduced inflammation. Our study's aim is to determine the impact of physical exercise on systemic inflammatory markers and their association with diabetic complications. **Materials and Methods**: A retrospective analytical study included patients >18 YO with T2DM followed between January 2025 and January 2026. PA was assessed using the Ricci and Gagnon (RG) score. Systemic inflammation-based scores (SIBS) included neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), lymphocyte-to-monocyte ratio (LMR), systemic inflammation index (SII), and us-CRP. Multivariate analysis used with SPSS 26 and $p < 0.05$ as threshold. **Results**: 82 patients were included (mean age 58.6 ± 12.3 years, female predominance). Based on RG score, 68.29% were sedentary (RG<18), 19.5% active (RG 18-35), and 12.19% very active (RG>35). Sedentary cases had the highest levels of inflammatory markers (NLR: 3.6, PLR: 154, SII: 804.8, CRP: 9 mg/L) and complication rates (microvascular: 82.1%, macrovascular: 60.7%), while very active patients had lower levels of inflammatory markers (NLR: 2.6, PLR: 109, SII: 504, CRP: 4 mg/L) and 5% macrovascular complications. Multivariate analysis showed a significant independent association between sedentary behavior and higher odds of diabetic retinopathy (OR = 3.40; 95% CI: 1.50–7.80), neuropathy (OR = 2.90), and ischemic heart disease (OR = 4.10; 95% CI: 1.60–10.50) ($p<0.05$). **Conclusion**: Sedentary lifestyle was independently associated with both increased systemic inflammation and higher odds of diabetic vascular complications, highlighting the importance of incorporating structured PA programs into patient education.*

Keywords: Physical activity, diabetes mellitus, inflammation, diabetic complications, sedentary lifestyle.

Introduction:

Type 2 diabetes mellitus (T2DM) is a global health issue. According to the latest statistics of the International Diabetes Federation (IDF) 2025 Atlas, the global prevalence is increasing, affecting approximately 589 million adults worldwide (1). As mentioned by recent epidemiological studies, a disproportionate distribution of this compounding burden is borne by low- and middle-income regions, with the Middle East and North Africa (MENA) region experiencing steep trajectory of morbidity (2). In Morocco, rapid macroeconomic transitions triggered a sharp spike in diabetes prevalence, reaching 11.9%, and affecting an estimated 2.88 million adults per 24.7 million (3). The true clinical and economic impact of T2DM lies in its progressive microvascular and macrovascular complications, as primary leaders of mortality (4).

Chronic low-grade inflammation (LGI) plays a pathogenic role, linking persistent hyperglycemia to cellular damage and vascular deterioration (5). This phenomenon is derived by an altered secretome, and can be effectively monitored in clinical settings with accessible biochemical biomarkers like high-sensitivity C-reactive protein (hs-CRP) and the neutrophil-to-lymphocyte ratio (NLR) (5,6,7).

Concurrently, physical activity (PA) is universally described as a core therapeutic pillar for optimizing glycemic control and insulin sensitivity (8). Beyond traditional metabolic benefits, regular exercise exerts direct systemic anti-inflammatory actions; the skeletal muscle acts as an active endocrine organ; during contraction, it synthesizes and releases protective signaling peptides, or "myokines," actively countering chronic systemic inflammation and improving endothelial health (9,10).

Despite these clear pathways, real-world data analyzing the triad of physical lifestyle habits, systemic inflammatory markers, and clinical complications remain scarce. Since each biomarker reflects different components of innate and adaptive immunity, their combined evaluation may provide a more comprehensive assessment of systemic inflammation.

We hypothesized that lower PA levels would be associated with higher inflammatory burden and increased prevalence of diabetic complications. By providing real-world clinical data from a North African population, this study addresses a significant gap in the literature by elucidating how low-grade systemic inflammation acts as a key biological intermediary linking sedentary behavior directly to specific microvascular and macrovascular diabetic outcomes. So, our study aimed to evaluate the association between physical activity, inflammatory markers and diabetic complications in a Moroccan sample of patients with DM.

Materials and Methods:

Study design:

A retrospective analytical study was conducted over a one-year period from January 2025 to January 2026, of patients aged over 18 years followed in the department of Endocrinology, Diabetology and Metabolic Diseases, Hassan II University Hospital, Fez, Morocco, for uncontrolled T2DM (A1c > 7%).

Participant Selection and Ethical Criteria

We included patients who had provided informed consent for participation and had a complete baseline laboratory profile detailing systemic LGI markers. Simultaneously, patients were excluded if they had incomplete medical or laboratory charts, active acute infections at the time of bio-sampling, or documented histories of chronic inflammatory or autoimmune diseases (such as rheumatoid arthritis or systemic lupus erythematosus).
In addition, pregnant women and individuals presenting with absolute contraindications to physical exercise (e.g., unstable angina or uncompensated heart failure) were excluded (Figure 1).

A comprehensive recording of baseline sociodemographic parameters, clinical characteristics, and glycemic control parameters was performed.

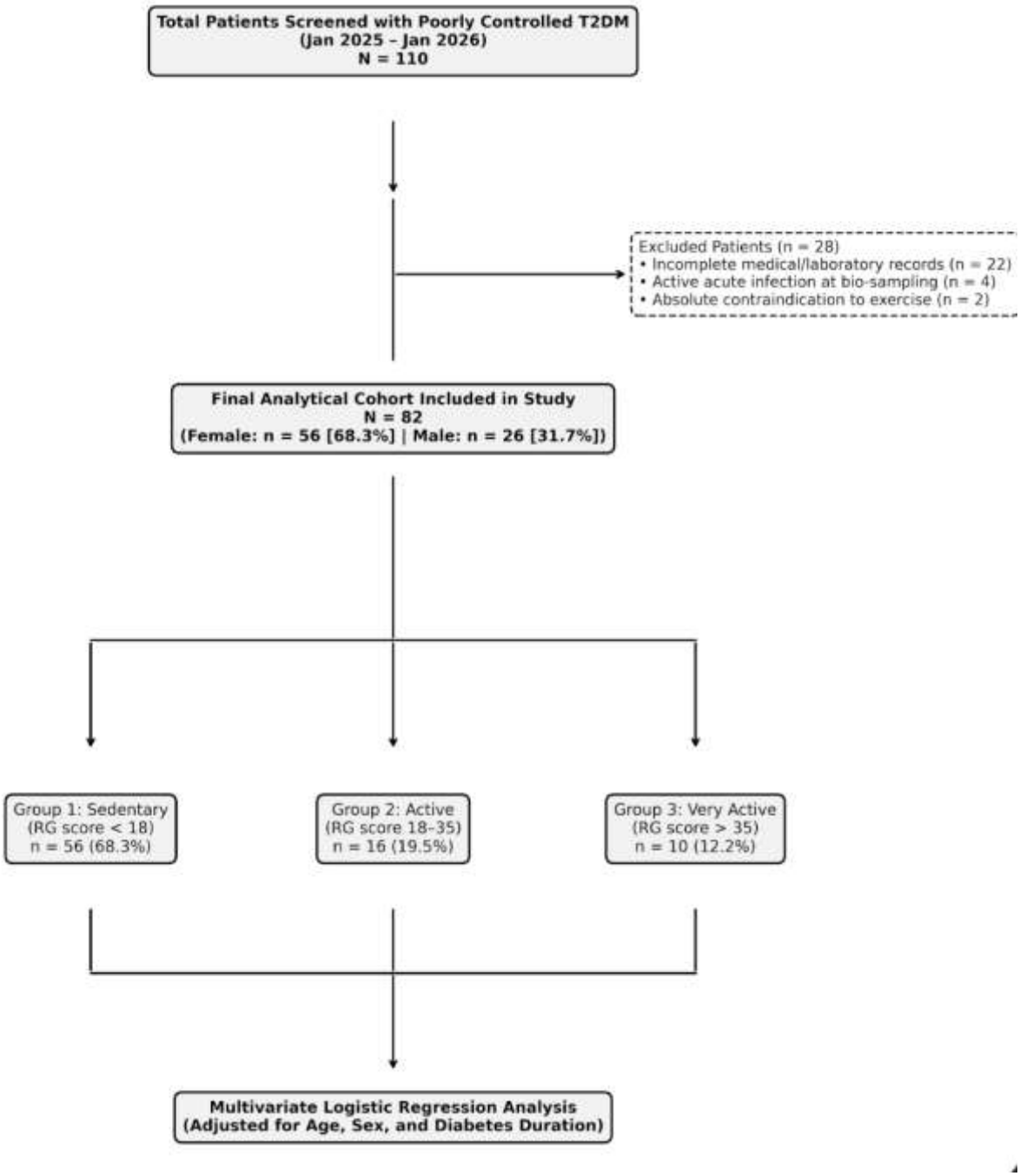


Figure 1: flowchart of the study design

Assessment of Physical Activity

PA levels were evaluated using the validated Ricci and Gagnon (RG) questionnaire, which evaluates the frequency, intensity, and duration of both occupational duties and leisure-time physical exercise. Based on this, participants were stratified into three distinct lifestyle categories:

- **Sedentary:** RG score < 18

- **Active:** RG score between 18 and 35
- **Very Active:** RG score > 35

Inflammatory Biomarkers and Clinical Outcomes

Systemic inflammation-based scores (SIBS) were calculated using absolute values from routine complete blood counts (CBC) :

- **Neutrophil-to-lymphocyte ratio (NLR)**
- **Platelet-to-lymphocyte ratio (PLR)**
- **Lymphocyte-to-monocyte ratio (LMR)**
- **Systemic inflammation index (SII):** Calculated as (Platelet count × Neutrophil count) / Lymphocyte count.
- **High-sensitivity C-reactive protein (hs-CRP)**

Diabetic vascular complications were adjudicated via comprehensive medical record reviews. Microvascular ones included documented retinopathy (via a specialized ophthalmological examination), neuropathy (evaluated by DN4 score and monofilament test), and nephropathy (by calculation of eGFR and ACR), while macrovascular endpoints encompassed ischemic heart disease, cerebrovascular accidents, and peripheral artery disease, all diagnosed via specialized exploration methods.

Statistical Analysis

Clinical and biochemical data were extracted from the institutional database into Microsoft Excel and subsequently analyzed using SPSS software (Version 26.0). Descriptive statistics were expressed as means ± standard deviations for normally distributed continuous variables, medians with interquartile ranges for skewed data, and frequencies/percentages for categorical variables.
Multivariate logistic regression models were performed to evaluate the independent impact of physical activity levels and systemic inflammatory indices on our primary binary outcomes: the risk of developing diabetic retinopathy, neuropathy, and ischemic heart disease. These models were subsequently adjusted for clinical confounders, including age, BMI, and A1c.

Given the limited sample size in the "Very Active" category and to preserve sufficient statistical power while ensuring the numerical stability of the multivariate logistic regression models, "Active" (n = 16) and "Very Active" (n = 10) groups were pooled into a single combined category designated as "Non-sedentary" (n = 26). Consequently, physical activity was evaluated as a binary exposure factor (Sedentary versus Non-sedentary) within all fully adjusted models. Statistical significance was defined a priori at a two-tailed p-value < 0.05.

Results:

Baseline Clinical and Demographic Characteristics

82 patients with poorly controlled T2DM were enrolled in the study. The baseline clinical, metabolic, and demographic markers of the entire cohort are summarized in Table 1. The mean age of the population was 58.6 ±12.3 years (range: 31–82 years), with a notable female predominance with 56 women (68.3%) and 26 men (31.7%), and a female-to-male sex ratio of 2.1:1. The mean diabetes duration was 11.7 ± 6.1 years and mean HbA1c of 8.9 ±1.4%. The mean Body Mass Index (BMI) was 29.2 ± 4.5kg/m, while the comorbidities of hypertension and dyslipidemia were present in 65.9% and 58.5% of the patient collective, respectively.

Characteristic	Study Population (N = 82)
Age (years, mean ± SD)	58.6 ± 12.3
Age Range (years)	31 – 82
Gender: Female (n, %)	56 (68.3%)
Gender: Male (n, %)	26 (31.7%)
Sex Ratio (F/M)	2.1 / 1
Duration of Diabetes (years, mean ± SD)	11.7 ± 6.1
Mean HbA1c (%, mean ± SD)	8.9 ± 1.4
BMI (kg/m², mean ± SD)	29.2 ± 4.5
Hypertension (n, %)	54 (65.9%)
Dyslipidemia (n, %)	48 (58.5%)

Table 1: Baseline Characteristics (Publication-Grade Image)

Distribution of Physical Activity Levels

Stratification of the cohort according to individual Ricci and Gagnon (RG) score metrics revealed that a vast majority of the patients led a sedentary lifestyle (Figure 1): 56 cases (68.3%) were sedentary (Group 1: RG score < 18),16 cases (19.5%) were classified as active (Group 2: RG score 18–35), and only 10 cases (12.2%) were categorized as very active (Group 3: RG score > 35).

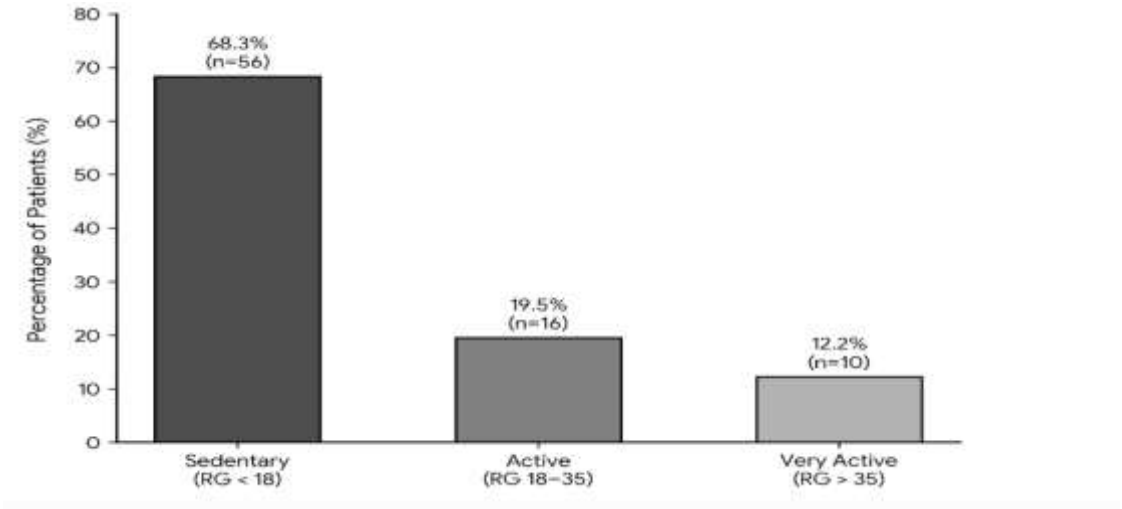


Figure 1: Physical Activity groups

Inflammatory Profile by Physical Activity Group:

Mean values of SIBS highlighted a statistically significant inverse relationship with PA intensity across the three groups (Table 2). Group-wise univariate comparisons showed that sedentary patients (Group 1) exhibited the highest absolute baseline values for all calculated systemic inflammatory biomarkers. Notably, the mean hs-CRP level within the sedentary subgroup reached 9.0 mg/L, whereas both active and very active patient groups demonstrated significantly lower concentrations 4.0mg/L ($p < 0.001$).

Similarly, the systemic inflammation index (SII) peaked sharply in the sedentary patients (804.8) and fell progressively to its lowest tier within the very active cohort (504.0; $p < 0.001$). Strong intergroup variations were also confirmed for the rest of the ratios as mentioned in the table.

Biomarker	Sedentary (RG < 18, n=56)	Active (RG 18–35, n=16)	Very Active (RG > 35, n=10)	p-value
NLR (Neutrophil-to-Lymphocyte Ratio)	3.6 ± 0.8	3.0 ± 0.6	2.6 ± 0.4	<0.001
PLR (Platelet-to-Lymphocyte Ratio)	154.0 ± 32.5	130.5 ± 24.1	109.0 ± 18.5	0.002
SII (Systemic Inflammation Index)	804.8 ± 145.2	652.4 ± 110.8	504.0 ± 85.6	<0.001
us-CRP (mg/L)	9.0 ± 2.4	6.5 ± 1.8	4.0 ± 1.1	<0.001

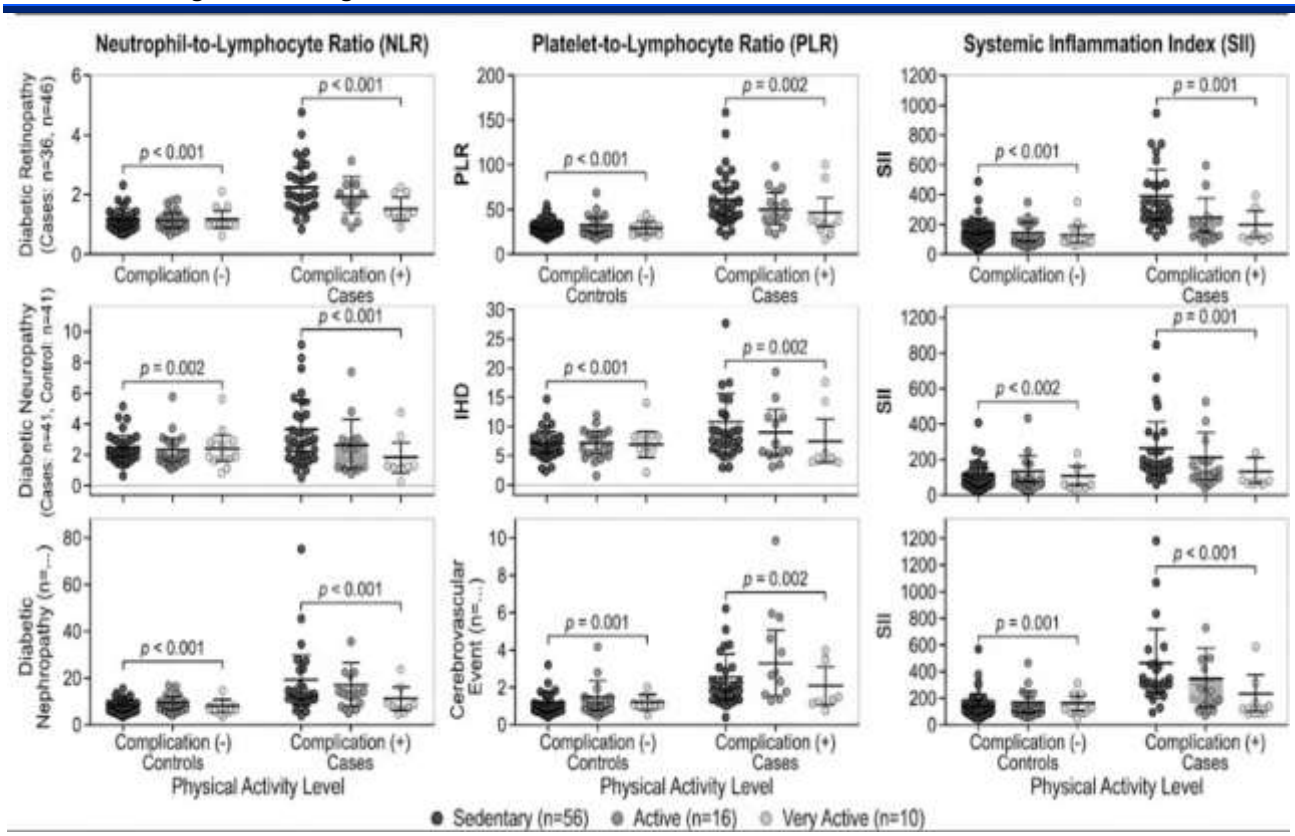
Table 2: Systemic Inflammatory Biomarkers Across Physical Activity Groups

Values are presented as subgroup means. NLR: neutrophil-to-lymphocyte ratio; PLR: platelet-to-lymphocyte ratio; LMR: lymphocyte-to-monocyte ratio; SII: systemic inflammation index; hs-CRP: high-sensitivity C-reactive protein. Statistical significance determined across physical activity strata, with $p < 0.05$ indicating statistical significance.

Complication Rates by Physical Activity Group:

The prevalence of both microvascular and macrovascular complications was markedly higher in sedentary patients and decreased progressively with higher PA levels (Fig 2). In the sedentary group, 46 patients (82.1%) presented at least one microvascular complication, and 34 patients (60.7%) had macrovascular complications. In contrast, in the very active group, only 40% had microvascular complications, and notably, 5% had macrovascular complications.

Fig 2. Prevalence of diabetic complications according to physical activity level



Multivariate Regression Analysis

To highlight the impact of PA on diabetic vascular complications, multivariate logistic regression models were constructed (Fig 3, Table 3). The models were adjusted for baseline demographic features (age, sex, and total diabetes duration) and clinical parameters, including glycemic control (HbA1c), Body Mass Index, and smoking status.

For microvascular outcomes, the model predicting diabetic retinopathy (total number of events: n = 36) demonstrated high explanatory power and robust discrimination, yielding a Nagelkerke R2 of 0.342 and an Area Under the Curve (AUC) of 0.795 (95% CI: 0.684–0.906, p < 0.001). After adjusting for these major risk factors, membership in the sedentary group (Group 1) remained a highly robust, independent predictor of severe vascular complications when compared directly against the combined non-sedentary reference group (Active and Very Active patients, n = 26). Specifically, sedentary patients exhibited a more than threefold increase in the odds of presenting with diabetic retinopathy (OR = 3.40; 95% CI: 1.50–7.80; p = 0.003), independent of their mean HbA1c profile, which itself was independently significant (OR = 1.52 per 1% increase; p = 0.012). Similarly, the model for diabetic neuropathy (total number of events: n = 41; Nagelkerke R2 = 0.298; AUC = 0.762, 95% CI: 0.648–0.876, p = 0.001) confirmed that sedentary status was independently tied to a nearly threefold inflation in neuropathy risk (OR = 2.90; 95% CI: 1.30–6.50; p = 0.010) compared to the non-sedentary cohort.

Within macrovascular outcomes, the model constructed for ischemic heart disease (IHD) (total number of events: n = 31) exhibited excellent overall fit and discriminatory accuracy (Nagelkerke R2 = 0.415; AUC = 0.841, 95% CI: 0.742–0.940, p < 0.001). In this model, sedentary status showed the strongest adverse effect size on ischemic heart disease, presenting an adjusted odds ratio of 4.10 (95% CI: 1.60–10.50; p = 0.002) relative to non-sedentary control subjects. At the same level, elevated BMI (OR = 1.21; p = 0.001) and active smoking status (OR = 2.38; p = 0.024) also served as significant co-predictors. No independent statistical associations reached the threshold of significance for nephropathy or cerebrovascular events after adjustments.

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Clinical Outcome / Independen	OR	95% CI	p-value
Diabetic Retinopathy Model	—	—	—
• Sedentary Status (vs. Active/	3.40	1.50 – 7.80	0.003
• HbA1c (per 1% increase)	1.52	1.10 – 2.10	0.012
• BMI (per kg/m² increase)	1.05	0.94 – 1.18	0.340
• Smoking Status (Yes vs. No)	1.18	0.68 – 2.05	0.561
Diabetic Neuropathy Model	—	—	—
• Sedentary Status (vs. Active/	2.90	1.30 – 6.50	0.010
• HbA1c (per 1% increase)	1.41	1.02 – 1.95	0.038
• BMI (per kg/m² increase)	1.12	1.01 – 1.25	0.031
• Smoking Status (Yes vs. No)	1.45	0.78 – 2.70	0.245
Ischemic Heart Disease Model	—	—	—
• Sedentary Status (vs. Active/	4.10	1.60 – 10.50	0.002
• HbA1c (per 1% increase)	1.15	0.88 – 1.50	0.312
• BMI (per kg/m² increase)	1.21	1.08 – 1.36	0.001
• Smoking Status (Yes vs. No)	2.38	1.09 – 5.22	0.024

Table 3:

Multivariate Regression Analysis

Each model is simultaneously adjusted for age, sex, and total diabetes duration. OR: Adjusted Odds Ratio; CI: Confidence Interval; BMI: Body Mass Index; HbA1c: Glycated Hemoglobin. Statistical significance is defined as $p < 0.05$.

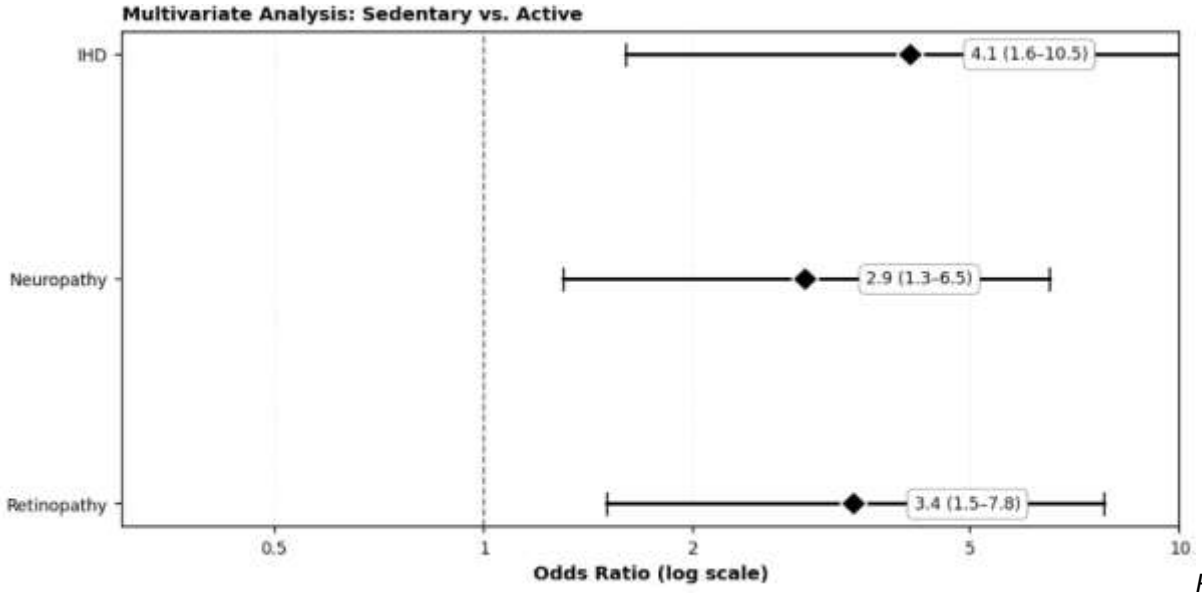

Figure 3:

Multivariate analysis: Sedentary vs. Active

Discussion:

Our study showed an association between PA, LGI, and vascular complications within a Moroccan population with poorly controlled T2DM (1, 2). High (68.3%) prevalence of sedentary behavior was identified and directly correlated with severely elevated SIB (hs-CRP, SII, NLR, and PLR) (7, 11, 12). Multivariate logistic regression showed that sedentary status acts as a powerful, independent predictor of diabetic retinopathy, neuropathy, and ischemic heart disease, even after adjusting for clinical confounders (13).

Highly significant reduction of hematological ratios across PA strata underscores the direct positive effect of exercise on baseline LGI (9). Sedentary patients exhibited highly pathological mean profiles, including an hs-CRP of 9.0 mg/L and a Systemic Inflammation Index (SII) of 804.8, both of which have extreme cardiovascular risk (7, 11). Meanwhile, active and very active patients had low levels of these markers (hs-CRP 4.0 mg/L and SII 504.0) (9).

This aligns with recent multi-centric datasets showing that complete physical stagnation accelerates myeloid lineage expansion, leading to elevated neutrophil and platelet production relative to lymphocytes (11, 14). Our data demonstrates that affordable, routine hemogram-derived profiles like NLR and SII can successfully stratify systemic inflammatory burdens in real-world North African settings (12).

At the molecular level, skeletal muscle functions as an active endocrine organ; during regular, rhythmic muscle contractions, it releases a cascade of myokines, prominently interleukin-6 (IL-6) (9, 10). While chronically elevated circulating IL-6 from adipose tissue is pro-inflammatory (5, 6), muscle-derived IL-6 acts transiently and non-clonally via gp130 signaling to trigger an anti-inflammatory systemic response, upregulating interleukin-1 receptor antagonist (IL-1ra) and interleukin-10 (IL-10) while directly inhibiting tumor necrosis factor-alpha (TNF-alpha) production (9).

Additionally, PA promotes a positive shift in visceral adipose tissue macrophages, leading to a transition from the pro-inflammatory M1 phenotype to the tissue-protective, anti-inflammatory M2 phenotype (15). This switch upregulates endogenous free-radical enzymes, the inflammatory cascade, and systemic oxidative stress (6, 16).

Our multivariate model revealed that sedentary status more than triples the risk of diabetic retinopathy (OR = 3.40; 95% CI: 1.50–7.80; $p = 0.003$) (17). Chronically elevated inflammatory ratios (NLR and PLR) promote leukostasis within retinal capillaries, accelerating endothelial cell apoptosis and blood-retinal barrier breakdown independent of a patient's exact glycemic level (12, 17, 18). The near tripling of diabetic neuropathy odds (OR = 2.90; $p = 0.010$) reflects the vulnerability of the *vasa nervorum*; low-grade systemic inflammation compromises capillary perfusion to peripheral nerves, causing localized ischemia and structural axonal decay (19).

For macrovascular outcomes, the profound four-fold increase in the odds of ischemic heart disease among sedentary patients (OR = 4.10; 95% CI: 1.60–10.50; $p = 0.002$) represents our most powerful result. High SII and hs-CRP values indicate advanced arterial plaque vulnerability (11, 20). PA works synergistically with this systemic inflammatory state to accelerate atherogenesis, smooth muscle cell proliferation, and coronary remodeling (6, 20). Because this multi-system vascular risk remains highly significant even after forcing HbA1c, BMI, and smoking status into our regression models, PA must be recognized as a mandatory, stand-alone therapeutic target rather than a secondary adjunct to pharmacology (8, 13).

The finding that 68.3% of our study population is completely sedentary is a highly alarming epidemiological indicator that requires contextual interpretation within modern Moroccan society (1, 3, 21). Over the past few decades, Morocco has undergone a rapid, intense demographic and nutritional transition characterized by swift urbanization (2, 3). In urban centers, physically demanding jobs and active transit modes were replaced by mechanized transportation and sedentary administrative roles, reducing daily energy expenditure (21).

In North African urban areas, middle-aged and elderly women have socio-cultural barriers to exercise (22). Outdoor recreational PA is frequently constrained by a lack of safe, culturally adapted, or women-friendly public green spaces (21, 22). Furthermore, traditional domestic role expectations often restrict older female demographics to indoor, sedentary environments, and conventional outdoor attire can make prolonged, brisk aerobic walking physically uncomfortable or socially discouraged (22).

Our real-world data offers a key message: shifting a patient just from the sedentary tier into the moderately "active" tier (RG score 18–35) was accompanied by a dramatic drop in macrovascular complications from 60.7% to 20.0%. This proves that low-to-moderate, achievable volumes of lifestyle modification yield immense cardiovascular protective rewards (13). Consequently, hospital-based therapeutic education programs within Moroccan tertiary centers must design culturally tailored, indoor-accessible exercise protocols—such as home-based resistance loop routines or

structured, low-impact indoor walking programs—specifically engineered to bypass local gender and environmental barriers (22).

Our study provides highly original, real-world clinical evidence from an understudied North African diabetic population where data connecting objective inflammation scores to lifestyle behavior remains scarce. The simultaneous evaluation of multi-line inflammatory biomarkers (SII, NLR, PLR) provides a highly scannable, multi-dimensional window into the immune-metabolic state of these patients (11, 12).

However, several critical methodological biases must be acknowledged:

- Selection Bias: Our data is derived from a tertiary care hospital where we manage the most complex cases.
- Recall and Information Bias: Physical activity levels were captured using the self-reported Ricci & Gagnon questionnaire, which is highly susceptible to recall bias.
- Design Bias: The cross-sectional, retrospective nature of this study is preventing us from establishing temporal causality between the onset of physical inactivity and the development of vascular lesions.

Conclusion:

Our findings suggest that lower physical activity levels are associated with increased systemic inflammation and a higher burden of diabetic complications. Physical activity, through its potent anti-inflammatory effects, appears to be a powerful protective factor. Our real-world data from a Moroccan cohort show that sedentary behavior is prevalent (68%) and is independently associated with higher inflammatory markers and both microvascular and macrovascular complications. Promoting regular physical activity, even at moderate levels, should be elevated to a core priority in the management of type 2 diabetes, with structured implementation in therapeutic education programs to improve long-term prognosis. Future prospective longitudinal studies and randomized controlled trials to evaluate whether structured PA interventions can directly mitigate the long-term burden of microvascular and macrovascular complications in type 2 diabetes cohorts are recommended.

Conflict of Interest

The authors declare that they have no conflict of interest in this work.

Funding: No public or commercial funding.

Disclosures: None declared.

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