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Elevated White Blood Cell Count Is Associated with an Increased Risk of Insulin Resistance among Non-Diabetic Taxi-Motorbike Drivers Working in Cotonou, Benin

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Abstract

High white blood cell count (WBC) and insulin resistance (IR) are interrelated events that contribute to non-communicable diseases (NCDs), including type-2 diabetes (T2D). However, associations between IR and hematological parameters have never been explored in populations of Benin. The aims of this study were to determine the prevalence of IR and associated hematological parameters in taxi-motorbike drivers (TMDs) working in Cotonou. A total of 133 participants were analyzed in this cross-sectional study. Complete blood count, including WBC and platelet, as well as fasting plasma glucose and insulin, were performed by standard procedures. IR was assessed using the Homeostatic Model Assessment for Insulin Resistance (HOMA-IR). Factors associated with IR, their odds ratios (ORs) and 95% confidence intervals (CIs) were determined by logistic regression analysis. The mean age of the study participants was 39.3 years. The HOMA-IR cut-off (75th percentile) for IR was 5.9. The overall prevalence of IR was 24.1%. IR increased with the increase of exposure duration and WBC levels. Logistic regression analysis revealed that the risk of IR increased significantly with higher total WBC, with adjusted ORs (95% CI) for the second and third tertiles of 3.56 (1.10 - 11.58) and 4.01 (1.21 - 13.31), respectively. Similar patterns of associations were observed in an analysis restricted to non-drinkers, although these estimates lacked statistical significance. BMI > 24.2 kg/m^2 was independently associated with an increased risk of IR (OR = 3.82, 95% CI: 1.33 - 11.03, P = 0.013). In conclusion, the prevalence of IR in TMDs was 24.1%. IR was significantly associated with elevated WBC count and BMI. WBC may serve as a biomarker to identify individuals at the greatest IR risk.

Keywords

Cotonou, Insulin Resistance, Taxi-Motorbike Drivers, White Blood Cells

1. Introduction

Traffic emission is the most important source of air pollution in many developing countries, including Benin. The population in Benin was estimated at 10,008,749 inhabitants in the 2013 census [1]. Cotonou with its suburbs become the most populated area in Benin, with >1 million inhabitants [1]. In the absence of reliable public transport, motorcycles with two-stroke engines become the major means of transportation in Cotonou. As a result, over 160,000 taxi-motorbike drivers (TMDs), which are locally called "Zemidjan" (it means "take me quickly") work in Cotonou and its suburbs. These motorbikes are rather old and poorly maintained. In addition, preference for sub-standard gasoline, illegally imported from neighboring Nigeria, is common in TMDs. Consequently, air quality has worsened in the city over the last two decades. Therefore, we conducted several studies and found that ambient air in Cotonou contains high doses of various carcinogens, including benzene, polycyclic aromatic hydrocarbons (PAHs), and ultrafine particulate matters [2] [3].

Exposure to fine particulate matter (≤2.5 μm in diameter; PM2.5) is an important risk factor for increased type 2 diabetes (T2D) incidence [4]. Importantly, several studies suggested that increased exposure to air pollutants alters key T2D-related pathways, including glucose metabolism [5] and insulin resistance (IR) [6] [7]. Evidence from cross-sectional and longitudinal studies illustrated the strong association of air pollution exposure with a faster decline in insulin sensitivity among the general population of adults and youth [8] [9], as well as in patients with diabetes [10], and individuals at high risk for developing T2D [11] [12]. Consistent experimental evidence of increased IR following exposure to ambient PM2.5 was also demonstrated in animal models [13] [14].

IR, which is defined as a decrease in tissue response to insulin stimulation of target tissues, is thought to precede the development of cardiometabolic diseases, including T2D [15]. Therefore, early IR identification is important for the prevention of associated cardiometabolic diseases. A number of studies have demonstrated that alterations in hematological parameters (e.g. elevation in the levels of white blood cells) and associated markers are related to pathophysiological changes underlying T2D [16] [17] [18]. Furthermore, total white blood cells (WBC) count and the differential WBC counts, even within normal ranges, have been closely related to the presence of metabolic syndrome, a cluster of cardiometabolic risk factors that includes obesity, IR, hypertension, and dyslipidemia [19].

Recently, we reported the coexistence of multiple cardiometabolic risk factors, including IR, hypertension, and dyslipidemia in TMDs working in Cotonou

[20]. Furthermore, we have also demonstrated that higher circulating total calcium and low phosphate levels are significant predictors of IR in TMDs [21]. However, the relationship between IR and hematologic parameters, including red blood cells (RBC), hemoglobin, hematocrit, WBC, and platelet has never been explored in this population. Our aims in the present study were to determine the prevalence of IR and associated hematologic parameters in nondiabetic TMDs of Cotonou. We hypothesized that hematological parameters may be associated with IR in TMDs and tested this hypothesis in a cross-sectional study.

2. Patients and Methods

2.1. Study Design and Population

This retrospective cross-sectional study utilized data from the 2009 survey that investigated the impact of air pollution on exposed populations in Cotonou, including TMDs. We recruited 147 TMDs working in Cotonou and its suburbs, between April and July 2009, following communication at a public meeting of the findings of a previous investigation on air pollution. The study population has been described previously [20] [22]. Briefly, TMDs who drive 8 h/day with at least two years of taxi-motorbike driving experience were selected from taxi stations. Inclusion criteria were predefined as volunteers of 18 years of age or older. Prior to inclusion, participants underwent a complete routine physical examination by a trained physician. They were excluded if they are smokers or had a prior diagnosis of diabetes, cardiovascular diseases, history of acute infection, anemia or taking any drug that could affect hematological parameters. We applied a pragmatic approach to determine the sample size rather than a formal power calculation as this is an exploratory study.

Participants could be included in the study if they had complete blood count, glucose, and insulin data available. Thus, those missing insulin data and hematological parameters (n = 12) or having a fasting blood glucose level of ≥7.0 mmol/L (n = 2) were excluded. Finally, 133 TMDs were analyzed in this study (**Figure 1**). TMDs included in this study were considered as nondiabetic because they had no prior diagnosis of diabetes and had a fasting glucose < 7 mmol/L [23]. All participants signed informed consent forms prior to enrolment in the study. Survey participants who could not write indicated consent with a thumb print. The whole study protocol was evaluated and approved by the Benin Environmental Agency.

2.2. Anthropometric and Biochemical Data

We used a structured questionnaire and face-to-face interviews to collect information on duration of exposure, sociodemographic data (age, height and weight, smoking or drinking status), and health-related data (medical history and medications of participants). The body mass index (BMI) was calculated as follows: BMI = weight (kg)/height squared (m^2). Systolic blood pressure (SBP) and diastolic blood pressure (DBP) were measured by standard mercury sphygmomanometers on the right arm of subjects while they were seated.

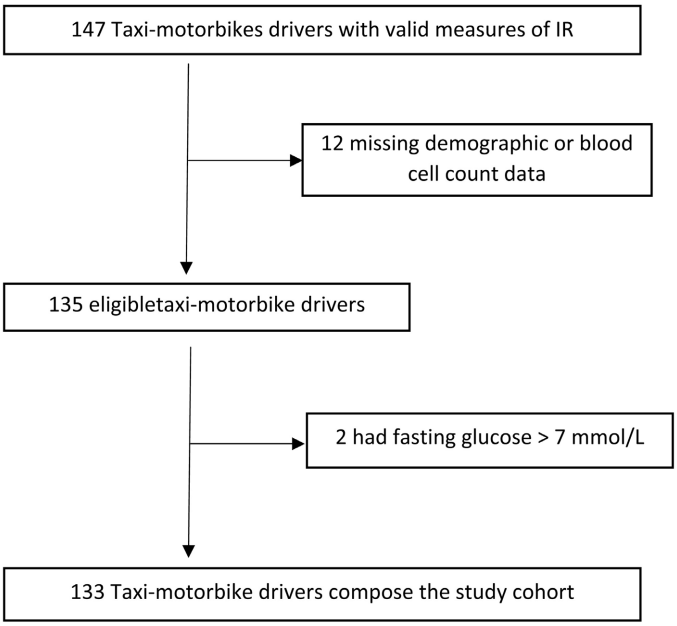

Figure 1. The flow chart of sample selection.

We collected venous blood samples (5 ml in EDTA-containing tubes) from each participant after an overnight fasting of at least 10 h. Complete blood count, including RBC, hemoglobin, hematocrit, WBC count and platelets were measured by automated blood cell counter (Beckman Coulters Inc. USA). Next, plasma was separated and divided into aliquots of 1 ml in our laboratory in Cotonou, and transported on dry ice to the research Unit NGERE: "Nutrition-Génétique-Exposition aux risques environnementaux", Faculté de Médecine, Nancy (France), where they were stored at −20˚C until analyzed. Plasma insulin was determined by radioimmunoassay using a commercial kit (BI INSULIN IRMA, Biorad, Mames la Coquette, France). Glucose was measured through an automated biochemistry analyzer (Siemens, Germany).

2.3. Definitions of Hypertension, Insulin Resistance and Prevalence of Insulin Resistance

Fasting insulin level ≥ 15 μU/ml was considered elevated [24]. Hypertension was defined as SBP ≥ 140 mmHg or DBP ≥ 90 mmHg [25]. Alcohol consumption was defined as the average consumption of 1 or more alcoholic drinks per day. The homeostatic model assessment-insulin resistance (HOMA-IR) was calculated using the formula described by Matthews *et al.* [26]. HOMA-IR = Fasting plasma insulin (μU/ml) × Fasting plasma glucose (mmol/L)/22.5. The 75th percentile of HOMA-IR values was considered as the cut-off point for IR [26]. The prevalence of IR was determined as the proportion of study participants meeting the criteria for IR.

2.4. Statistical Analysis

Quantitative variables are shown as means (standard deviation, SD). Categorical

variables are shown as percentages. Univariate analyses were performed using the chi-squared test for categorical variables and the Mann-Whitney U-test for continuous variables. We divided the study population into three groups based on WBC count: 1st tertile (<4.3 × 10^6 cells/L), 2nd tertile ((4.4 - 5.6) × 10^6 cells/L), and 3rd tertile (>5.6 × 10^6 cells/L). Binary logistic regression analysis was used to examine the associations of WBC levels with IR. The 1st tertile of WBC was set as the reference group to calculate the odds ratios (ORs) for IR with the corresponding 95% confidence intervals (CIs) in the 2nd and 3rd tertiles. Confounders adjusted included age, BMI (<21.3, 21.4 - 24.2, and >24.2 kg/m^2) exposure duration, SBP, DBP, and alcohol consumption (yes or no). Additionally, a subgroup analysis was performed to examine the effects of alcohol consumption on the relationship between WBC and IR. Results were expressed as adjusted ORs with the corresponding 95% CIs. P-values < 0.05 were considered to indicate a statistical significance. Data analysis was performed using IBM SPSS Statistics 20.0 software.

3. Results

Clinicodemographic and metabolic characteristics of the study population are summarized in Table 1. The mean (SD) age of the study subjects and the length of time for which subjects had held the job of taxi-motorbike driving, which we consider as exposure duration, were 39.3 (7.7) years and 11.5 (5.9) years, respectively. The means (SD) of RBC (10^9 cells/L), hemoglobin (g/dL), and WBC (10^6 cells/L) were 5.2 (0.6), 14.0 (1.9), and 5.0 (1.2), respectively. Of the 133 participants, 51 (38.3%) were defined as alcohol consumers. Table 1 also summarizes the characteristics of the study participants according to alcohol consumption. SBP (P = 0.015), DBP (P = 0.020), hematocrit, (P = 0.001), and mean corpuscular volume (P = 0.037) were significantly higher in alcohol consumers in comparison with non-drinkers. There were no significant inter-group differences in age, BMI, glucose, insulin, HOMA-IR, prevalence of IR, RBC, and WBC.

Elevated insulin level was found in 66.9% (89/133) of participants (Table 1). The mean (SD) of HOMA-IR was 4.9 (3.8) and the cut-off value (75th percentile) for IR was 5.9. Of the 133 participants assessed in this study, 32 met the criteria of IR for an overall prevalence of 24.1% (Table 1). The prevalence of IR increased with the increase of exposure duration and WBC count (Figure 2). For example, participants with exposure duration > 10 years had significantly higher prevalence of IR than those who held the taxi-motorbike driving job < 7 years (62.5% vs. 12.5%, respectively, P = 0.032, Figure 2(a)). Similarly, participants having a WBC > 4.9 × 10^6 cells/L had had significantly higher prevalence of IR than those who did not (16.5% vs. 7.5%, respectively, Figure 2(b)).

The characteristics of the study participants dichotomized into IR and non-IR, based on HOMA-IR are presented in Table 2. Fasting glucose and insulin, along with BMI, exposure duration and WBC were significantly higher in insulin resistant patients in comparison with non-IR patients.

Table 1. Characteristics of participants according to alcohol consumption.

Variable	All participants	Non-drinker	Drinker	P-value[##]
n (%)	133 (100.0)	82 (61.7)	51 (38.3)	-
Age (years)	39.3 (7.7)	38.5 (7.4)	40.5 (8.0)	0.160
BMI (kg/m²)	23.5 (3.9)	23.5 (4.0)	23.5 (3.7)	0.976
Exposure duration (years)	11.5 (5.9)	11.2 (6.0)	11.9 (5.8)	0.558
SBP (mmHg)	134.3 (18.8)	131.0 (16.8)	139.6 (20.8)	0.015
DBP (mmHg)	84.8 (13.2)	82.7 (12.6)	88.2 (13.5)	0.020
Glucose (mM)	4.2 (0.6)	4.2 (0.5)	4.1 (0.6)	0.402
Insulin (µUI/mL)	26.0 (19.5)	27.9 (21.8)	23.9 (14.9)	0.150
HOMA–IR	4.9 (3.8)	5.3 (4.3)	4.3 (2.9)	0.137
RBC (10^9/L)	5.2 (0.6)	5.1 (0.6)	5.2 (0.6)	0.098
Hemoglobin (g/dL)	14.0 (1.9)	13.8 (1.3)	14.3 (2.6)	0.085
Hematocrit (%)	44.7 (4.3)	43.7 (3.9)	46.2 (4.5)	0.001
MCV (fl)	86.9 (5.3)	86.1 (5.0)	88.1 (5.7)	0.037
MCH (pg)	27.4 (2.4)	27.1 (2.3)	27.9 (2.5°	0.069
MCHC	31.5 (1.3)	31.4 (1.4)	31.6 (1.2)	0.496
WBC (10^6/L)	5.0 (1.2)	5.0 (1.2)	5.1 (1.3)	0.559
Neutrophil count (10^6/L)	2.9 (0.8)	2.8 (0.8)	3.0 (0.9)	0.421
Monocyte count (10^6/L)	0.3 (0.1)	0.3 (0.1)	0.4 (0.1)	0.190
Lymphocyte count (10^6/L)	1.6 (0.5)	1.6 (0.4)	1.7 (0.5)	0.273
Eosinophile count (10^6/L)	0.1 (0.1)	0.1 (0.1)	0.1 (0.1)	0.647
Platelet (10^9/L)	2.0 (0.5)	1.9 (0.5)	2.1 (0.5)	0.172
High insulin, n (%)	89 (66.9)	23 (28.0)	59 (72.0)	0.118
Prevalence of IR[#], n (%)	32 (24.1)	21 (25.6)	11 (21.6)	0.596

Data are expressed as means (standard deviation) or percentages. BMI: body mass index; HOMA-IR: homeostatic model assessment for insulin resistance; IR: insulin resistance; SBP: systolic blood pressure; DBP: diastolic blood pressure; RBC: red blood cells; MCV: mean corpuscular volume; fl: femtoliter; MCH: mean corpuscular hemoglobin; pg: picograms; MCHC: mean corpuscular hemoglobin concentration; WBC: white blood cells; BP: blood pressure; IR: insulin resistance. [#]IR was defined as the 75th percentile of HOMA-IR index in the study population (cut-off value: 5.9). [##]Differences between drinkers and non-drinkers were analyzed by chi-square test or Mann-Whitney U-test.

Table 2. Characteristic of study participants according to insulin resistance status.

Variable	Non-IR (n = 101)	IR (n = 32)	P-Value[#]
Age (years)	39.2 (7.5)	40.9 (7.3)	0.234
BMI (kg/m²)	23.0 (3.4)	25.5 (4.5)	0.005
Glucose (mmol/L)	4.0 (0.6)	4.5 (0.5)	<0.001
Insulin (µUI/mL)	17.6 (6.4)	52.4 (23.4)	<0.001
Exposure duration (years)	10.9 (5.7)	13.1 (5.9)	0.042
SBP (mmHg)	136.0 (19.5)	133.4 (18.2)	0.429
DBP (mmHg)	86.2 (14.6)	83.8 (9.6)	0.492

Continued

RBC (10^9/L)	5.2 (0.6)	5.1 (0.5)	0.391
Hemoglobin (g/dL)	14.1 (1.4)	13.6 (2.9)	0.706
Hematocrit (%)	44.7 (4.1)	44.6 (3.6)	0.839
MCV (fl)	86.8 (5.1)	87.2 (6.1)	0.821
MCH (pg)	27.4 (2.3)	27.6 (2.6)	0.69
MCHC	31.5 (1.3)	31.6 (1.4)	0.831
WBC (10^6 cells/L)	4.9 (1.2)	5.4 (1.0)	0.038
Neutrophil count (10^6/L)	2.8 (0.9)	3.1 (0.6)	0.034
Eosinophil count (10^6/L)	0.1 (0.06)	0.1 (0.05)	0.513
Monocyte count (10^6/L)	0.3 (0.1)	0.4 (0.1)	0.196
Lymphocyte count (10^6/L)	1.6 (0.4)	1.7 (0.5)	0.087
Platelet count (10^9 cells/L)	196.6 (46.1)	200.3 (52.5)	0.545

Data are expressed as means (standard deviation). BMI: body mass index; SBP: systolic blood pressure; DBP: diastolic blood pressure; MCV: mean corpuscular volume; fl: femto-liter; MCH: mean corpuscular hemoglobin; pg: pictograms; MCHC: mean corpuscular hemoglobin concentration; WBC: white blood cell. #Differences between IR and non-IR were analyzed by chi-square test or Mann-Whitney U-test.

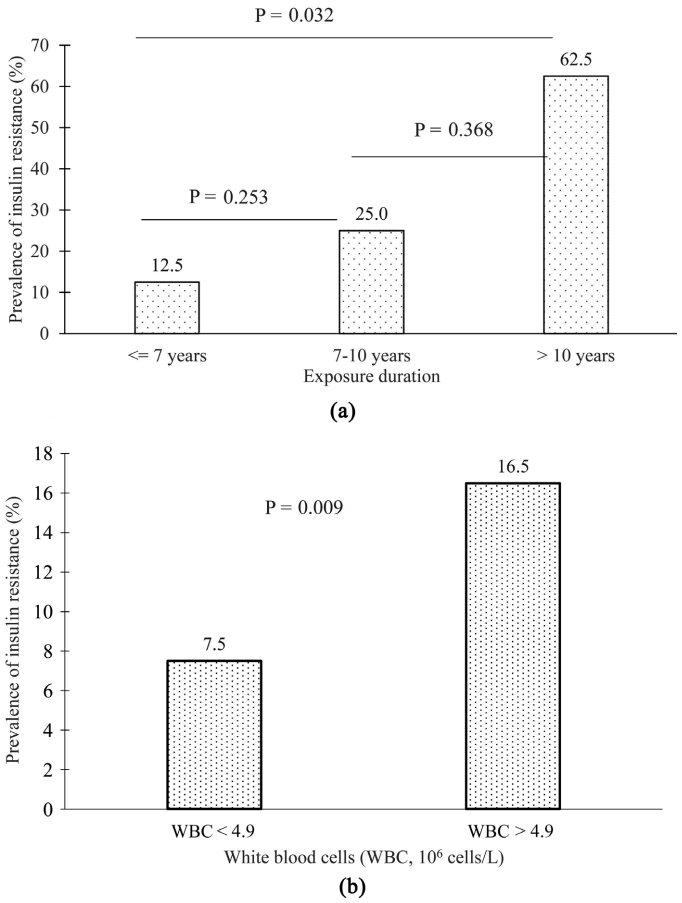

Figure 2. Prevalence of insulin resistance according to exposure duration (a) and white blood cell count (b).

Logistic regression analysis showed that the risk of IR increased significantly with higher total WBC, with adjusted ORs (95% CI) for the second and third tertiles of 3.56 (1.10 - 11.58) and 4.01 (1.21 - 13.31), respectively (Table 3). Similar patterns of association were observed in a subgroup analysis restricted to non-drinkers, although these estimates lacked statistical significance. The OR for IR comparing the first to the third tertile of WBC was 3.16 (95% CI: 0.76 - 13.12). In our study population, BMI > 24.2 kg/m^2 was independently associated with an increased risk of IR (OR = 3.82, 95% CI: 1.33 - 11.03, P = 0.013). This relationship was consistent among non-drinkers (OR = 3.95, 95% CI: 1.07 - 14.65, P = 0.036, Table 3).

4. Discussion

This study found that the overall prevalence of IR according to the HOMA-IR was 24.1% in TMDs of Cotonou. We also documented that IR was significantly associated with BMI. Indeed, there was no significant increase in IR risk between participants in the first (<21.3 kg/m^2) and second tertiles of BMI (21.4 - 24.2 kg/m^2). In contrast, the risk of IR increased significantly between patients in the first and third tertiles of BMI (>24.2 kg/m^2). This shows IR occurs more significantly

Table 3. Risk factors for insulin resistance by logistic regression analyses.

Residual determinants	All participants		P-Value	Non-drinker		P-Value
	OR	95% CI		OR	95% CI	
BMI (kg/m^2)						
1st tertile (<21.3)	Reference	-	-	Reference	-	-
2nd tertile (21.4 - 24.2)	0.75	0.23 - 2.51	0.644	1.57	0.39 - 6.32	0.527
3rd tertile (>24.2)	3.82	1.33 - 11.03	0.013	3.95	1.07 - 14.65	0.036
P for trend	-	-	0.006	-	-	0.087
WBC count (10^6 cells/L)						
1st tertile (<4.3)	Reference	-	-	Reference	-	-
2nd tertile (4.4 - 5.6)	3.56	1.10 - 11.58	0.035	1.48	0.39 - 5.62	0.568
3rd tertile (>5.6)	4.01	1.21 - 13.31	0.023	3.16	0.76 - 13.12	0.103
P for trend	-	-	0.053	-	-	0.272

BMI: body mass index; CI: confidence interval; OR: odds ratio; WBC: white blood cells. Logistic regression analyses were adjusted for age, BMI, blood pressure, and exposure duration.

with higher BMI. These findings are consistent with reports by Jurkovičová *et al.* who demonstrated that the prevalence of IR in adolescents was strongly associated with overweight and obesity [27]. Similarly, Elrayess *et al.* reported a linear relationship between IR and BMI in a cross-sectional study on 150 young healthy females from Qatar [28]. Inflammation is speculated to play a major role in the pathogenesis of obesity-induced IR and subsequent T2D [29] [30]. To the best of our knowledge, only the study by Sossa *et al.* evaluated IR, based on homeostatic model assessment within populations of Benin [31]. Applying a similar cut-off approach for IR in apparently healthy patients, they reported an overall prevalence of 17.8% in males and showed that IR was associated with higher BMI and elevated fasting glucose [31]. Our study findings are consistent with their reports. In our study, the prevalence of IR appears to increase with increasing duration of traffic-related air pollution exposure. Previous studies demonstrated that long-term exposure to air pollutants (e.g. PM2.5) induces IR [8] [9] with subsequent development of T2D [4]. Further, increased T2D-related biomarkers (e.g. higher fasting glucose, HOMA-IR, and LDL-C) with increasing exposure duration and concentration of air pollutants were reported in epidemiologic studies [11] [32] [33], but also in studies involving animal models [34]. However, the mechanisms by which air pollutants induce T2D are not fully understood. Proposed molecular mechanisms include oxidative stress, increased inflammation, and endoplasmic reticulum stress [15] [35].

The most important finding of this study was the association of IR with WBC, a marker of inflammation. In our study, examination of the relationship between IR and WBC revealed that increased WBC count was strongly associated with an increased risk of developing IR. This association confirmed reports of previous studies that showed alterations of several hematological parameters, including WBC in insulin resistant patients [36] [37]. For example, a cross-sectional study conducted by Di Bonito *et al.* (2016) revealed that children with the highest WBC had an increased risk of high plasma glucose [38]. Additionally, Park *et al.* (2017) demonstrated that elevated WBC count was positively and independently related to HOMA-IR in Korean children and adolescents [39]. Furthermore, a prospective study in nondiabetic Indians demonstrated that having a high WBC at baseline was associated with IR and a subsequent development of T2D [37]. Because alcohol consumption was identified as a major determinant of WBC count [40] and IR [41], we performed subgroup analyses to further examine this feature. In a model restricted to non-drinker, we found that the risk of IR increased as the WBC count increased, but there were no significant inter-group differences between the three levels of WBC, presumably because of low sample size. However, the positive association between BMI and IR remained significant among non-drinkers.

The molecular mechanisms by which a high WBC induces IR are not fully understood. Hypothesized mechanisms include activation of the immune system, leading to overproduction of pro-inflammatory cytokines (e.g. interleukin-6 and TNF-α) that may compromise insulin action, with subsequent pro-

gression of IR [29] [42] [43].

Taken together, elevated WBC count appears to be a good predictor of IR among TMDs. As such, WBC count may serve as a marker to identify individuals at high-risk for developing future noncommunicable diseases (NCDs). Furthermore, a higher WBC count could be an alerting sign for clinicians on the potential to develop NCDs. Therefore, patients with a higher WBC count and without any underlying chronic diseases should be more carefully monitored and managed for prevention of NCDs. On the other hand, this study highlights opportunities to educate TMDs on lifestyle measures (e.g. healthy diet, physical activities, and weight control), which can improve insulin sensitivity and decrease the risk of subsequent cardiometabolic diseases such as T2D and CVDs.

The current study has some limitations. It included only TMDs with relatively small sample size. This is a caveat to the extrapolation of the findings to other population groups. Additionally, variables such as smoking, alcohol use and exposure duration were self-reported and may be prone to social desirability bias. Moreover, no information on exposure to air pollutants was available, which may have biased the observed association. Here, we are unable to disentangle cause and effect because of our cross-sectional design. This can be evaluated in prospective longitudinal studies. Therefore, large-scale studies with comprehensive data are needed to further explore predictors of IR in populations of Benin. Despite these limitations, this study has several strengths. TMDs that have been the target population of this study were an understudied and at-risk population for cardiometabolic diseases. Further, this study adds additional flows to existing medical literature within Benin, as it provides useful epidemiological data on TMDs of Cotonou. In this regard, our findings may help policymakers when planning and implementing evidence-based interventions.

5. Conclusion

In summary, this study showed that IR prevalence was 24.1% in TMDs and was significantly associated with a higher BMI and elevated WBC count. As such, this study confirms the hypothesis that high WBC may play a role in the pathophysiological changes associated with the onset of IR. As a routine laboratory marker that is inexpensive and easy to interpret in clinical practice, WBC count may help identify patients at the greatest risk for developing IR.

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Authors' Contribution

All authors contributed to the study design, and participated in data acquisition. PHA performed laboratory work, analyzed data, and wrote the manuscript. All authors read and approved the final manuscript.

Conflicts of Interest

The authors declare no competing interests regarding this publication.

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