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Low Plasma Potassium and High Iron Levels Increased the Risk of Dyslipidemia among Non-Diabetic Taxi-Motorbike Drivers Living and Working in Cotonou, Benin

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Abstract

Non-traditional cardiovascular risk factors such as iron and potassium may play a role in lipid metabolism. However, information on this association is lacking in populations of Benin. This study evaluated the associations between plasma iron and potassium levels and risk of dyslipidemia among taxi-motorbike drivers (TMDs) in Cotonou. We conducted a cross-sectional study on 134 males TMDs aged ≥20 years old, of whom 39 (29.1%) had dyslipidemia. Plasma biochemistry including measurements of total cholesterol (TC), triglycerides (TG), low-density lipoprotein cholesterol (LDL-C), and high-density lipoprotein cholesterol (HDL-C), iron, and potassium were performed. Dyslipidemia was defined as any or combinations of the following: TC > 5.2 mmol/L, LDL-C > 3.4 mmol/L, TG > 1.7 mmol/L, and HDL-C < 0.9 mmol/L. Participants were segregated into tertiles based on plasma iron and potassium levels. The associations of plasma iron and potassium levels with dyslipidemia were evaluated through multivariate logistic regression to calculate the odd ratios (ORs) and 95% confidence intervals (CIs). Logistic regression showed that plasma iron level was independently and positively correlated with the risk of dyslipidemia, in a dose-dependent manner. The OR for developing dyslipidemia comparing the 3rd tertile (>18.8 µmol/L) to the 1st tertile of plasma iron (<13.6 µmol/L) was 3.85, (95% CI: 1.20 - 12.35, p = 0.023). We observed similar patterns of association in a subgroup analysis restricted to normotensive patients, although the estimates lacked statistical significance. Our findings also revealed that the risk of dyslipidemia decreased when plasma

potassium levels increased. The OR (95% CI) for dyslipidemia comparing the 2nd tertile (4.4 - 4.8 μmol/L) to the 1st tertile (<4.3 μmol/L) of potassium was 0.31 (0.11 - 0.86, p = 0.025). Interestingly, the risk of dyslipidemia decreased progressively (81% to 86%) and significantly across plasma potassium tertiles when restricting analysis to normotensive patients. The ORs (95% CI) for dyslipidemia comparing the 2nd and 3rd tertiles to the 1st tertile of plasma potassium were 0.19 (0.04 - 0.87, p = 0.032) and 0.14 (0.02 - 0.93, p = 0.043). In conclusion, our study shows that higher plasma iron and low potassium levels are significant predictors of dyslipidemia in TMDs. As such, the findings have public health implications for predicting and preventing dyslipidemia and associated cardiometabolic diseases. However, longitudinal studies are needed to determine if disturbances in iron and potassium levels, even within the normal range, are precursors or consequences of dyslipidemia.

Keywords

Cotonou, Dyslipidemia, Iron, Potassium, Taxi-Motorbike Drivers

1. Introduction

Worldwide, cardiovascular diseases (CVDs) are the most common non-communicable diseases (NCDs), accounting for an estimated 17.9 million deaths in 2019 [1]. More than three quarters of CVDs deaths occur in low-income and middle-income countries [2]. A significant proportion of mortality ascribed to CVDs could be prevented through early detection of cardiovascular risk factors (CVRFs) such as hypertension, dyslipidemia, and diabetes. The association of dyslipidemia with CVDs is well established [3]. As such, early screening for dyslipidemia and effective lipid control strategies could substantially reduce the burden of CVDs in high-risk patients.

However, previous studies revealed that traditional CVRFs such as hypertension and hypercholesterolemia have largely underestimated the true risk for cardiovascular events [4]. Furthermore, accumulating epidemiological evidences have shown that a significant proportion of individuals at risk for dyslipidemia was undiagnosed and untreated, even in developed countries [5] [6]. Both the proportions of undiagnosed individuals and diagnosed and treated vary widely across countries of the globe [7]. Taken together, these data suggest that biomarkers with sufficiently proven sensitivity and specificity for early detection of individuals at high risk for CVDs and more effective strategies to control the global epidemic of chronic NCDs are still needed.

The proportion of undiagnosed dyslipidemia is currently unknown within Benin. A recent study conducted in Parakou showed that the frequency of blood lipid testing in primary care setting was only 8.4% [8]. Recently, we have shown that dyslipidemia was prevalent in 29.1% of taxi-motorbike drivers (TMDs) in Cotonou [9]. However, no reliable statistics are available for treatments of dysli-

pidemia with lipid-lowering medications in Benin. Therefore, it is unclear whether the currently available lipid-lowering therapies, although being highly effective in clinical trials, are sufficient or even suitable in clinical practice to control dyslipidemia in populations of Benin. We anticipated that screening for both traditional and non-traditional CVRFs could help prevent dyslipidemia and reduce the burden of associated cardiometabolic diseases such as type 2 diabetes (T2D) and CVDs.

Previous studies have shown that lipid metabolism may be affected by non-traditional CVRFs such as iron and potassium [10] [11] [12] [13]. Iron and potassium are critical elements that perform important cellular functions including transport and storage of oxygen, electron transfer, synthesis of hormones, replication of DNA, and maintenance of fluid balance of cells. Compelling evidences revealed that disturbances in the levels of iron and potassium were strongly associated with many chronic diseases such as T2D and CVDs [12] [14] [15] [16]. For example, lower dietary potassium intake and serum potassium levels were reported to be inversely associated with the risk of incident T2D [17]. Furthermore, potassium intake was inversely correlated with mortality from coronary heart disease and total CVDs [18]. Other investigators have shown that individuals with low serum potassium levels had higher level of triglycerides and uric acid, reduced HDL-C, and a higher prevalence of insulin resistance [11]. Conversely, both epidemiologic studies and animal models have demonstrated that elevated iron levels can contribute to the development of many cardiometabolic disorders, including dyslipidemia, metabolic syndrome (MetS), CVDs, and diabetes [12] [13] [19] [20] [21]. However, the association of plasma iron and potassium levels with the risk of dyslipidemia is lacking in populations of Benin.

Aside from dyslipidemia, other metabolic disorders such as hyperuricemia and insulin resistance (IR), are common among TMDs in Cotonou [22] [23]. Based on this clustering of CVRFs, we hypothesized that plasma iron and potassium levels might be associated with dyslipidemia in TMDs. Therefore, we conducted this cross-sectional study on 134 TMDs living and working in Cotonou to determine whether plasma iron and potassium levels within the normal ranges are independently associated with the risk of dyslipidemia.

2. Patients and Methods

2.1. Study Design and Study Participants

This study was conducted using data from previous investigations of the health impacts of air pollution in TMDs. TMDs are exposed to various environmental carcinogens (e.g., ultrafine particles) and are at-risk for NCDs such as CVDs and T2D. Detailed information on TMDs population has been previously described [24] [25]. TMDs residing and working in Cotonou or its suburbs were recruited in 2009, following communication at a public meeting of the findings of a previous investigation on air pollution.

Anthropometrical measurements were obtained through face-to-face interviews using structured questionnaires. All participants also took part in detailed health examinations and laboratory tests. Patients had received no specific treatments at the time of blood donation.

In brief, inclusion criteria were participants aged over 20 years old, males and non-smokers without any history for chronic diseases (e.g., diabetes or CVDs). In this retrospective cross-sectional study, participants could only be included if they met the above-mentioned criteria and had plasma biochemistry data including blood lipids, iron, and potassium. We assessed 147 TMDs for eligibility, but 13 participants who had a fasting glucose level > 7.0 mmol/L or lacked anthropometrical or biochemical data were excluded, resulting in the inclusion of 134 TMDs in the final analyses. Written informed consent was obtained from each participant prior to enrolment in the study. The study was reviewed and approved by the Benin Environmental Agency.

2.2. Clinical and Biochemical Analyses

Sociodemographic characteristics of each survey participant were collected by trained staffs using a standard questionnaire. Alcohol consumption was classified as "never" and current (drinking regularly). Body height and body weight were recorded using standard protocols. The body mass index (BMI) was calculated by dividing weight in kilograms by the square of height in meters (kg/m^2). Systolic (SBP) and diastolic blood pressure (DBP) measurements were obtained by trained doctors.

Blood samples were collected early in the morning after an overnight fasting of at least 10 h. Detailed information about the blood collection and processing has been previously described [22]. Plasma aliquots (1 ml) were transported on dry ice to Nancy, where they were stored at –20˚C until analyzed. Biochemistry analyses including measurements of total cholesterol (TC), triglycerides (TG), low-density lipoprotein cholesterol (LDL-C), and high-density lipoprotein cholesterol (HDL-C), liver enzyme such as alanine aminotransferase (ALT), aspartate aminotransferase (AST), and alkaline phosphatase (ALP), creatinine, C-reactive protein (CRP), iron, potassium, uric acid, fasting insulin, and glucose were performed for each subject All biological analyses were performed by standardized methods within the research Unit NGERE: "Nutrition-Génétique-Exposition aux risques environnementaux", Faculté de Médecine, Nancy, France.

2.3. Definitions of Hypertension, Insulin Resistance, and Dyslipidemia

Hypertension was defined as SBP ≥ 140 mmHg or DBP ≥ 90 mmHg [26]. Alcohol intake was defined as the average consumption of 1 or more alcoholic drinks per day. The homeostatic model assessment-insulin resistance (HOMA-IR) was assessed as previously described [23]. Dyslipidemia was defined according to the American Heart Association classification, corresponding to

any or combinations of the following: TC > 5.2 mmol/L, LDL-C > 3.4 mmol/L, TG > 1.7 mmol/L, and HDL-C < 0.9 mmol/L [27]. Based on this definition, 39 of the 134 participants analyzed in this study had dyslipidemia for a prevalence of 29.1% [9].

2.4. Statistical Analysis

Data are presented as a mean (standard deviation, SD) for continuous variables and as a percentage for categorical variables. The study population was divided into three groups based on plasma iron and potassium levels: 1st tertile, 2nd tertile, and 3rd tertile. The tertiles for potassium and iron were <4.3, 4.4 - 4.8, >4.8 mmol/L and <13.6, 13.7 - 18.8, >18.8 μmol/L, respectively. Demographic and biological characteristics of survey participants were compared by tertiles of iron and potassium using one-way analysis of variance (ANOVA) or chi-square tests as appropriate for the variable. The associations of plasma iron and potassium levels with dyslipidemia were assessed by logistic regression models, using backward selection procedure. The logistic regression models mutually adjusted for plasma iron and potassium along with 13 independent variables (e.g., age, BMI, alcohol, uric acid, SBP, DBP, ALP, ALT, AST, creatinine, insulin, glucose, and CRP). These covariates were selected and controlled for based on previously published studies [22]. The 1st tertiles of iron and potassium were set as the reference groups to calculate the odds ratios (ORs) for dyslipidemia with the corresponding 95% confidence intervals (CIs) in the 2nd and 3rd tertiles. Additionally, we segregated patients according to hypertension status and performed subgroup analyses to evaluate the impact of blood pressure on the relationship between plasma iron and potassium and dyslipidemia. P-values < 0.05 were considered to indicate a statistical significance. All analyses were performed using IBM SPSS Statistics 20.0 software.

3. Results

3.1. Demographic and Biological Characteristics of Study Participants

The general characteristics of the 134 participants included in the current study are summarized in **Table 1**. The means (SD) of age, BMI, plasma iron, and potassium for the whole study cohort were 39.4 (7.8) years, 23.5 (3.9) kg/m^2, 16.7 (6.4) μmol/L, and 5.6 (4.1) mmol/L, respectively.

We also compared demographic and biological characteristics by tertiles of iron and potassium (**Table 1**). ALP and ALT levels decreased progressively and significantly when plasma potassium levels increased (**Figure 1(a)** and **Table 1**). Dyslipidemic patients had elevated iron levels compared with those without dyslipidemia (18.3 vs. 16.1 μmol/L, p = 0.053, **Figure 1(b)**). Overall, an increasing trend in the prevalence of dyslipidemia across plasma iron tertiles was observed (**Table 1**). Patients with elevated plasma iron levels had increased SBP (p = 0.049) and elevated TG levels (p = 0.031). In addition, the prevalence

Table 1. Demographic and biological parameters according to plasma iron and potassium tertiles.

Variables	Whole study cohort	Potassium levels, mmol/L				Iron levels, µmol/L			
		1st tertile (<4.3)	2nd tertile (4.4 - 4.8)	3rd tertile (>4.8)	p-value	1st tertile (<13.6)	2nd tertile (13.7 - 18.8)	3rd tertile (>18.8)	p-value
n (%)	134 (100.0)	47 (35.1)	48 (35.8)	39 (29.1)	-	45 (33.6)	43 (32.1)	46 (34.3)	-
Age, years	39.4 (7.8)	41.0 (7.3)	39.0 (8.0)	37.9 (7.9	0.171	39.3 (7.1)	39.3 (8.3)	39.4 (7.8)	0.986
BMI, kg/m^2	23.5 (3.9)	23.6 (4.2)	23.8 (3.6)	23.2 (3.8)	0.738	22.7 (3.4)	24.2 (3.9)	23.8 (4.2)	0.164
SBP, mmHg	134.2 (18.8)	136.4 (21.1)	133.4 (17.2)	132.5 (17.9)	0.601	129.3 (15.4)	134.3 (17.7)	138.9 (21.7)	0.049
DBP, mmHg	84.7 (13.2)	85.2 (15.7)	84.2 (11.8)	84.9 (11.7)	0.925	83.2 (11.7)	84.7 (13.0)	86.3 (14.7)	0.539
Creatinine, mg/L	11.5 (1.3)	11.2 (1.3)	11.6 (1.3)	12.0 (1.2)	0.015	11.5 (1.3)	11.6 (1.3)	11.7 (1.5)	0.746
CRP, mg/L	3.3 (5.2)	4.5 (5.0)	3.0 (4.6)	2.2 (1.8)	0.117	4.2 (6.7)	2.9 (2.8)	2.9 (4.8)	0.374
ALP, UI/L	66.5 (20.6)	73.4 (21.2)	63.8 (19.7)	61.1 (18.8)	0.012	70.0 (23.6)	63.7 (18.7)	66.0 (19.2)	0.362
ALT, UI/L	12.7 (6.1)	15.0 (7.6)	12.0 (4.5)	10.9 (4.9)	0.050	12.8 (6.0)	11.9 (5.3)	13.5 (6.9)	0.450
AST, UI/L	33.3 (14.4)	36.5 (19.8)	31.8 (11.2)	31.4 (11.2)	0.175	33.0 (18.1)	31.7 (9.3)	35.2 (14.4)	0.499
Glucose, mmol/L	4.2 (0.6)	4.2 (0.7)	4.2 (0.6)	4.1 (0.6)	0.492	4.2 (0.6)	4.2 (0.6)	4.2 (0.7)	0.879
Insulin, µU/mL	26.6 (20.9)	27.9 (22.2)	22.8 (13.6)	26.6 (25.8)	0.250	30.2 (23.6)	24.9 (16.7)	24.8 (21.5)	0.378
HOMA-IR	5.1 (4.6)	5.6 (5.7)	4.5 (3.3)	5.5 (4.6)	0.451	5.6 (4.4)	4.8 (3.4)	5.0 (5.57)	0.667
Insulin resistance, n (%)	33 (24.6)	13 (39.4)	9 (27.3)	11 (33.3)	0.498	13 (39.4)	10 (30.3)	10 (30.3)	0.708
TC, mmol/L	4.3 (0.9)	4.2 (1.0)	4.2 (0.8)	4.6 (1.0)	0.142	4.2 (0.8)	4.3 (0.9)	4.4 (1.1)	0.551
TG, mmol/L	0.8 (0.4)	0.9 (0.5)	0.8 (0.3)	0.8 (0.3)	0.241	0.7 (0.3)	0.8 (0.4)	0.9 (0.5)	0.031
HDL-C, mmol/L	1.3 (0.4)	1.3 (0.5)	1.3 (0.3)	1.4 (0.3)	0.296	1.3 (0.3)	1.3 (0.3)	1.4 (0.5)	0.466
LDL-C, mmol/L	2.6 (0.8)	2.5 (0.8)	2.5 (0.7)	2.8 (0.8)	0.136	2.6 (0.6)	2.6 (0.8)	2.6 (0.9)	0.992
TC > 5.2 mmol/L, n (%)	23 (17.2)	8 (34.8)	6 (26.1)	9 (39.1)	0.429	4 (17.4)	6 (26.1)	13 (56.5)	0.039
HDL-C < 0.9 mmol/L, n (%)	12 (9.0)	10 (83.3)	2 (16.7)	0 (0.0)	0.001	5 (41.7)	3 (25.0)	4 (33.3)	0.792
Dyslipidemia*, n (%)	39 (29.1)	20 (51.3)	9 (23.1)	10 (25.6)	0.033	11 (28.2)	9 (23.1)	19 (48.7)	0.075
Uric acid, µmol/L	350.9 (68.2)	342.2 (63.1)	362.2 (70.1)	347.4 (71.5)	0.337	338.1 (60.3)	360.6 (68.3)	354.3 (74.6)	0.278
Iron, µmol/L	16.7 (6.4)	17.2 (6.8)	16.7 (5.4)	16.2 (7.0)	0.785	10.4 (3.4)	16.2 (1.4)	23.3 (4.6)	<0.001
Potassium, mmol/L	5.6 (4.1)	4.0 (0.3)	4.6 (0.2)	8.8 (6.6)	<0.001	6.5 (6.4)	5.0 (2.1)	5.2 (2.0)	0.173
Alcohol intake, n (%)	51 (38.1)	20 (39.2)	20 (39.2)	11 (21.6)	0.321	12 (23.5)	20 (39.2)	19 (37.3)	0.136

Values are presented as means (Standard deviation) or percentages. ALP: alkaline phosphatase, ALT: alanine aminotransferase, AST: aspartate aminotransferase, BMI: body mass index, SBP: systolic blood pressure, DBP: diastolic blood pressure, CRP: C-reactive protein, HDL-C: high-density lipoprotein cholesterol, LDL-C: low-density lipoprotein cholesterol, HOMA-IR: homeostatic model assessment-insulin resistance, TC: total cholesterol, TG: triglycerides. *Dyslipidemia was defined as any or combinations of the following: TC > 5.2 mmol/L, LDL-C > 3.4 mmol/L, TG > 1.7 mmol/L, and HDL-C < 0.9 mmol/L.

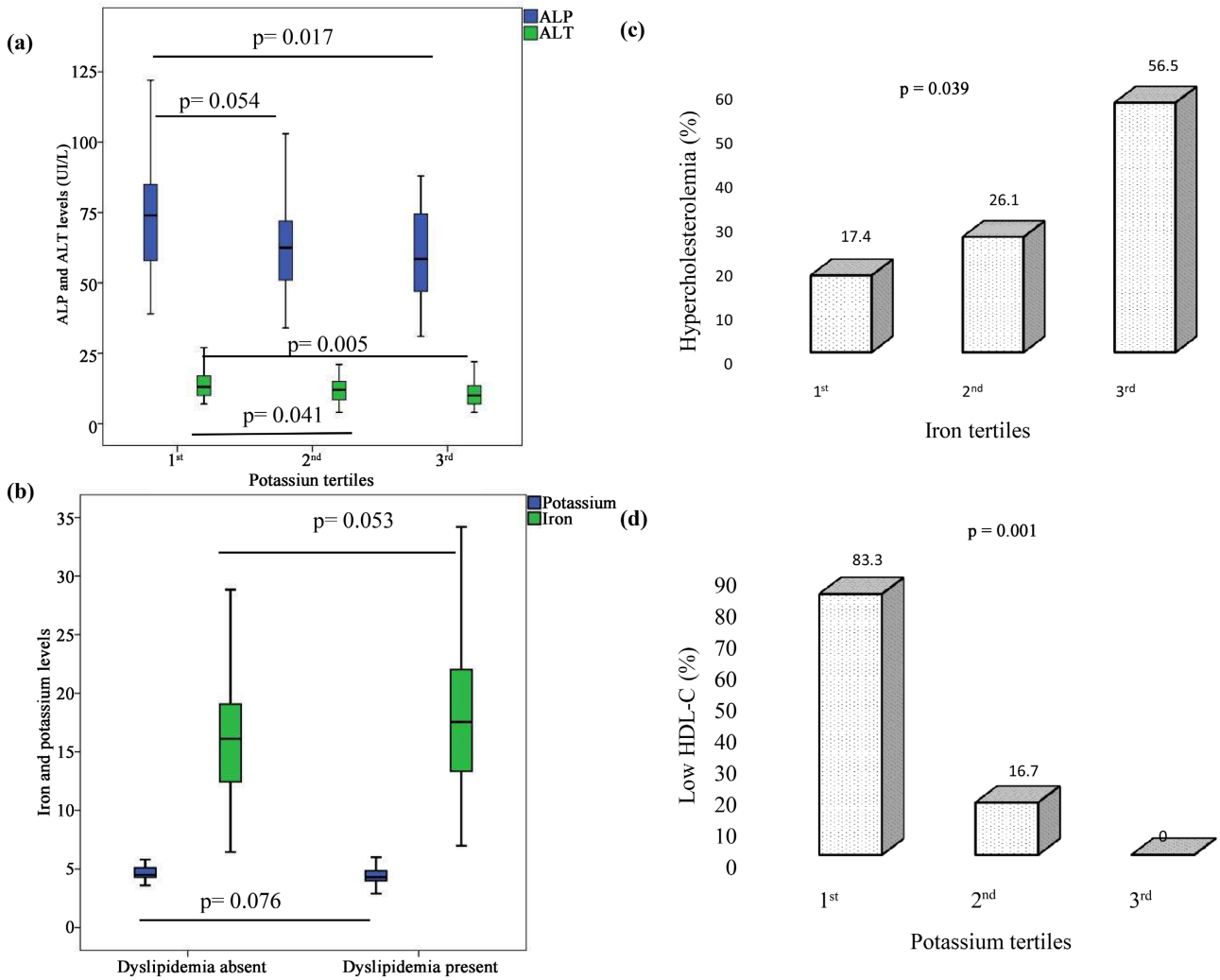

Figure 1. Influence of plasma iron and potassium on liver enzymes and the prevalence of dyslipidemia. (a) Box-plot distribution of ALP and ALT levels according to plasma potassium levels; (b) Box-plot distribution of plasma iron and potassium levels according to dyslipidemia status; (c) Prevalence of hypercholesterolemia according to iron tertiles; (d) Prevalence of low HDL-C according to potassium tertiles. ALP: alkaline phosphatase, ALT: alanine aminotransferase, HDL-C: high-density lipoprotein cholesterol.

of hypercholesterolemia (TC > 5.2 mmol/L) increased with the increase in plasma iron levels (Table 1 and Figure 1(c)). There was a significant decrease in the overall prevalence of dyslipidemia when plasma potassium levels increased (p = 0.033). Furthermore, the prevalence of low HDL-C decreased when plasma potassium level increased (p = 0.001, Table 1 and Figure 1(d)). Plasma potassium or iron levels showed no significant association with age, BMI, uric acid, glucose, fasting insulin, and IR.

Hypertensive patients had higher TC (4.5 vs 4.1 mmol/L, p = 0.014), TG (0.9 vs. 0.7 mmol/L, p = 0.005), HDL-C (1.4 vs. 1.3 mmol/L, p = 0.033), uric acid (360.4 vs. 324.4 μmol/L, p = 0.043), and iron (17.8 vs. 15.7 μmol/L, p = 0.046) levels compared with normotensive patients (Table 2). There was no significant difference in plasma potassium levels between hypertensive and normotensive patients (5.2 vs. 5.9 mmol/L, p = 0.288).

Table 2. Demographic and biological characteristic of the study participants according to hypertension status.

Variables	Hypertensive	Normotensive	P-value
n (%)	63 (47.0)	71 (53.0)	-
Age, years	40.2 (8.1)	38.6 (7.4)	0.236
BMI, kg/m^2	24.3 (3.9)	22.9 (3.7)	0.035
SBP, mmHg	149.8 (14.9)	120.4 (7.9)	<0.001
DBP, mmHg	94.6 (11.7)	76.0 (6.6)	<0.001
Creatinine, mg/L	11.6 (1.4)	11.6 (1.3)	0.977
CRP, mg/L	3.0 (5.0)	3.6 (5.4)	0.529
ALP, UI/L	64.0 (18.5)	68,8 (22.1)	0.188
ALT, UI/L	13.0 (5.1)	12.5 (6.9)	0.601
AST, UI/L	33.4 (11.4)	33.3 (16.8)	0.987
Glucose, mmol/L	4.2 (0.6)	4.2 (0.7)	0.478
Insulin, µU/mL	26.8 (22.5)	26.5 (19.4)	0.916
HOMA-IR	5.1 (4.3)	5.2 (4.9)	0.969
Insulin resistance, n %)	13 (39.4)	20 (60.6)	0.312
TC, mmol/L	4.5 (0.9)	4.1 (1.0)	0.014
TG, mmol/L	0.9 (0.5)	0.7 (0.3)	0.005
HDL-C, mmol/L	1.4 (0.4)	1.3 (0.4)	0.033
LDL-C, mmol/L	2.7 (0.8)	2.5 (0.7)	0.191
TC > 5.2 mmol/L, n (%)	13 (56.5)	10 (43.5)	0.316
HDL-C < 0.9 mmol/L, n (%)	2 (16.7)	10 (83.3)	0.027
Dyslipidemia*, n (%)	19 (48.7)	20 (51.3)	0.800
Uric acid, µmol/L	360.4 (69.5)	324.4 (66.4)	0.043
Iron, µmol/L	17.8 (6.2)	15.7 (6.3)	0.046
Potassium, mmol/L	5.2 (3.2)	5.9 (4.7)	0.288
Alcohol intake, n (%)	22 (43.1)	29 (56.9)	0.072

Values are presented as means (Standard deviation). ALP: alkaline phosphatase, ALT: alanine aminotransferase, AST: aspartate aminotransferase, BMI: body mass index, SBP: systolic blood pressure, DBP: diastolic blood pressure, CRP: C-reactive protein, HDL-C: high-density lipoprotein cholesterol, HOMA-IR: homeostatic model assessment-insulin resistance, LDL-C: low-density lipoprotein cholesterol, TC: total cholesterol, TG: triglycerides.

3.2. Factors Associated with Risk of Dyslipidemia in the Study Participants

Results of the multivariate analysis are presented in **Table 3**. Plasma iron level > 18.8 µmol/L was independently associated with an increased risk of dyslipidemia in our study population. The multivariable-adjusted ORs (95% CI) for the 2nd and 3rd tertiles of plasma iron were 1.35 (0.43 - 4.28, p = 0.608) and 3.85 (1.20 -

12.35, p = 0.023), respectively. We observed similar patterns of association when restricting the analysis to the subgroup of normotensive patients, although the estimates lacked statistical significance. The OR (95% CI) for dyslipidemia comparing the 3rd tertile to the 1st tertile of plasma iron was 4.93 (0.96 - 25.30, p = 0.056, Table 3). Our study findings also showed that plasma potassium levels > 4.4 mmol/L were associated with a reduced risk of dyslipidemia. The ORs (95% CI) for dyslipidemia comparing the 2nd and 3rd tertiles to the 1st tertile of plasma potassium were 0.31 (0.11 - 0.86, p = 0.025) and 0.47 (0.14 - 1.63, p = 0.235). The lipid-lowering effect of higher plasma potassium levels was further confirmed when the analysis was restricted to normotensive patients. In this subgroup, the ORs (95% CI) for dyslipidemia comparing the 2nd and 3rd tertiles to the 1st tertile of plasma potassium were 0.19 (0.04 - 0.87, p = 0.032) and 0.14 (0.02 - 0.93, p = 0.043), respectively (Table 3). Our findings also showed that ALT was positively and independently associated with dyslipidemia; OR in normotensive patients was 1.20 (95% CI: 1.04 - 1.36, p = 0.014, Table 3). Furthermore, we found that ALP was associated with a small decrease in the risk of dyslipidemia (i.e., 5%), which was confined to normotensive patients (OR = 0.95, 0.91 - 0.99, p = 0.029, Table 3).

4. Discussion

This study investigated the relationship between plasma iron and potassium levels

Table 3. Factors significantly associated with dyslipidemia on logistic regression analysis.

Residual determinants	All study participants (n = 134)			Normotensive patients (n = 71)		
	Fully adjusted OR*	95% CI	p-value	Fully adjusted OR*	95% CI	p-value
Iron levels, µmol/L						
1st tertile (<13.6)	1.00 (Reference)	-	-	1.00 (Reference)	-	-
2nd tertile (13.7 - 18.8)	1.35	0.43 - 4.28	0.608	1.29	0.25 - 7.12	0.789
3rd tertile (>18.8)	3.85	1.20 - 12.35	0.023	4.93	0.96 - 25.30	0.056
p for trend	-	0.052	-	-	-	0.114
Potassium levels, mmol/L						
1st tertile (<4.3)	1.00 (Reference)	-	-	1.00 (Reference)	-	-
2nd tertile (4.4 - 4.8)	0.31	0.11 - 0.86	0.025	0.19	0.04 - 0.87	0.032
3rd tertile (>4.8)	0.47	0.14 - 1.63	0.235	0.14	0.02 - 0.93	0.043
p for trend	-	0.071	-	-	-	0.051
Liver enzymes, UI/L						
ALP	0.99	0.96 - 1.01	0.295	0.95	0.91 - 0.99	0.029
ALT	1.11	1.03 - 1.19	0.006	1.20	1.04 - 1.36	0.014

ALP: alkaline phosphatase, ALT: alanine aminotransferase, CI: confidence interval, OR: odd ratio. *Backward selection procedure was used on logistic regression analysis. The models were adjusted for covariates such as age, BMI (categorical), blood pressure, glucose, creatinine, ALP, ALT, AST, insulin, uric acid, iron, and potassium.

and risk of dyslipidemia among TMDs residing and working in Cotonou. Our findings revealed that subjects with low plasma potassium had significantly higher prevalence of dyslipidemia, with low HDL-C being the most significant individual lipid abnormalities. On logistic regression analysis, the inverse association between plasma potassium and risk of dyslipidemia remained robust after further adjustments for relevant covariates that might influence the prevalence of dyslipidemia. Indeed, we observed that TMDs with plasma potassium levels > 4.4 mmol/L had a 69% decrease in the risk of dyslipidemia (OR = 0.31, 95% CI: 0.11 - 0.86) compared to those with lower potassium levels. Because hypertension is a major risk factor for dyslipidemia [9] [28], we further evaluated the effect of hypertension on the association between plasma potassium and dyslipidemia, restricting the logistic regression analysis to the subgroup of normotensive. This analysis showed that the risk of dyslipidemia decreased progressively and significantly across plasma potassium tertiles. The risk of dyslipidemia in normotensive patients decreased further and ranged between 81% and 86%. The ORs (95% CI) for dyslipidemia in the 2nd and 3rd tertiles of plasma potassium were 0.19 (0.04 - 0.87) and 0.14 (0.02 - 0.93), respectively. This shows that the reduction in the risk of dyslipidemia occurs more significantly with higher plasma potassium levels. These findings are consistent with a systematic review and meta-analyses by Aburto *et al.* who demonstrated that increased potassium intake had no adverse effect on blood lipid concentrations [29]. The lipid-lowering effect associated with higher potassium intake was further confirmed in reports by Bu *et al.* [10]. These authors addressed the consumption ratio of sodium-to-potassium and its association with serum lipid levels in healthy Korean adults. They showed that the ratio of sodium-to-potassium was positively and significantly associated with total cholesterol, and LDL-cholesterol levels [10]. Furthermore, our findings of higher frequencies of dyslipidemia observed among TMDs with low plasma potassium levels are consistent with reports by Sun *et al.* in a cross-sectional study on 10,341 participants [11]. In our study, plasma potassium was not associated with age, uric acid, glucose, fasting insulin, TG, and IR levels. However, these factors were found to be significantly elevated in subjects with low potassium levels [11]. This discrepancy with previous findings could result from different ethnicities, the study sample size, and study design.

The molecular mechanism of the lipid-lowering effect of high potassium levels remains unknown. However, potassium-mediated lipoprotein lipase (LPL) and hepatic triglyceride lipase (HTGL) activities have been demonstrated [30] [31]. Using genetically obese hyperlipemic rats, Matzno *et al.* showed that AL0671, a potassium channel opener, increased LPL activities 4-fold and HTGL activities 3-fold, with a significant decrease in lipid profiles including triglyceride and VLDL, and increased HDL-C levels, following serial administrations of AL0671 [30]. Similarly, treatment of fructose-fed rats with KRN4884, which is another potassium channel opener, resulted in a significant increase in LPL activity while

HTGL was unaffected [31].

The liver performs critical roles in lipid metabolism and liver enzymes including ALP and ALT were positively associated with several lipid profiles (e.g., TC, TG, TC/HDL-C, and LDL-C/HDL-C) [32]. In our study, ALT was positively and independently associated with dyslipidemia; the OR in normotensive patients was 1.20 (95% CI: 1.04 - 1.36, p = 0.014). Consistently, both ALP and ALT levels were found to be significantly elevated among TMDs in the 1st tertile compared to those in the 2nd and 3rd tertiles of plasma potassium. This may partly explain why patients with lower plasma potassium are prone to develop dyslipidemia.

Our study findings also showed that hypertensive patients had lower plasma potassium levels than did normotensive patients, although there was no significant inter-group difference. The relationship between high potassium intake and a decrease in hypertension, CVDs (e.g., stroke and coronary heart disease), and kidney disease (chronic renal failure) is well documented [14]. Several studies have indicated that increased potassium intake has a blood pressure lowering effect in hypertensive patients and reduced the risk of incident stroke [29]. The impact of potassium depletion in blood pressure regulation or CVDs is thought to be mediated by several molecular mechanisms including improper renal sodium handling, increased oxidative stress, impaired endothelium function and decrease of nitric oxide [14]. Potassium depletion induces sodium retention, and sodium-to-potassium intake ratio was suggested as a better predictor of cardiovascular outcomes [18] [33]. Furthermore, animal studies have shown that potassium supplementation causes vasodilatation, whereas low potassium levels produced vasoconstriction [14] [34]. In addition, several lines of evidences clearly have shown that potassium could block formation of reactive oxygen species in endothelial or white blood cells, and may protect against salt-induced cardiac dysfunction through its antioxidant activity [14].

In the current study, the prevalence of dyslipidemia increased when plasma iron levels increased, with hypercholesterolemia being the most significant individual lipid abnormalities. However, the logistic regression did not suggest any significant association between plasma iron and risk of dyslipidemia when comparing patients in the 2nd tertile (13.7 - 18.8 μmol/L) to those in the 1st tertile (< 13.7 μmol/L) of plasma iron. In contrast, our results revealed that individuals in the 3rd tertile of plasma iron (>18.8 μmol/L) had an increased risk of developing dyslipidemia (OR = 3.85, 95% CI: 1.20 - 12.35). This suggests a dose-response relationship between plasma iron levels and risk of dyslipidemia. Importantly, the positive association between plasma iron and risk of dyslipidemia was independent of relevant confounders, suggesting that plasma iron level might be a potential risk biomarker for dyslipidemia. On the other hand, this observation suggests that dyslipidemia occurs more significantly with higher iron levels. We observed similar patterns of association when restricting logistic regression analyses to the subgroup of normotensive patients. However, our estimates lacked statistical significance, probably because of the low sample size. These findings

strengthened reports by Al Akl *et al.* who demonstrated that the risk of dyslipidemia was linearly related to the levels of circulating ferritin, which is a key marker of iron status [35]. Consistent with this, Li and colleagues also reported in a cross-sectional study of 7109 Chinese adults that the risk of overall dyslipidemia, high TG, high TC, high LDL-C, and low HDL-C levels increased when serum ferritin levels increased [36]. In our investigation, TG level, which is a biomarker of cardiovascular risk, increased progressively across iron tertiles. This result was consistent with findings from both animal models and human studies [12] [13] [37] [38]. However, the molecular mechanisms linking increased iron storage to dyslipidemia are not entirely elucidated. Nonetheless, it is suggested that ferritin could reduce apolipoprotein B secretion, leading to overproduction of cellular TG [39].

In the current study, we found no relationship between plasma iron and HOMA-IR, possibly because of our study design, which excluded numerous sources of inflammation as a prerequisite for inclusion in the study. However, previous studies have shown that increased iron storage was associated with increased insulin and HOMA-IR [40] [41]. Furthermore, increasing evidence of a relationship between higher serum ferritin and risk of developing T2D has been reported in prospective studies [42]. In a cohort study of 2225 Chinese individuals followed up for a median of 20 months, Chen *et al.*, reported that elevated serum ferritin levels were associated with an increased risk of T2D independent of traditional risk factors [16]. These authors found an independent association between baseline ferritin levels and incident T2D risk in men but not in women [16]. Akter and coworkers followed-up 4754 Japanese employees for 5 years and demonstrated an association between elevated serum ferritin levels and increased risk of T2D, which association was confined to non-obese participants [15]. However, the mechanism by which iron storage could lead to T2D is not fully understood. Increased iron storage is known to affect insulin synthesis and secretion in the pancreas [43]. Furthermore, studies have shown that excess free iron can lead to cellular oxidative damage and a decrease of insulin secretion as well as cellular insulin [44]. It is suggested that the ferritin-T2D association is partly dependent on association with oxidative stress and inflammatory processes [45].

Taken together, our data suggest that low plasma potassium and high iron levels increased the risk of developing dyslipidemia among TMDs. This finding should raise concern. Furthermore, the study findings appear to suggest that low plasma potassium levels could lead to liver injury and abnormal lipid metabolism, leading to the onset of dyslipidemia. In view of cardiometabolic disease burden in patients with dyslipidemia, physicians should pay attention to aberrations in biomarkers that are related to liver injury and lipid metabolism, particularly in patients with low potassium or elevated iron levels (even if variations are within the normal ranges). On the other hand, the inverse association between plasma potassium levels and dyslipidemia risk suggests that optimal potassium intake is of critical importance for the prevention of cardiometabolic diseases. Therefore,

diet counselling should encourage sources of potassium in TMDs as well as in other populations.

Our study has several limitations and obtained findings should be interpreted cautiously. The cross-sectional nature and the relatively small sample size are the main limitations of the current study. Only male patients were studied and the participants could only be divided into three groups; this limits generalizability of our findings. Additionally, single measurements are available for plasma iron and potassium. As such, a causal relationship between plasma iron and potassium levels cannot be directly established. A further limitation of this study was the lack of assessments for dietary iron and potassium intake in the studied population. Although covariates of dyslipidemia were carefully controlled for in this study, it is possible that other metabolic diseases may affect the relationship of plasma iron and potassium with the risk of dyslipidemia.

Despite its limitations, our current study has several strengths. To the best of our knowledge, this is the first study to assess the association of iron and potassium with dyslipidemia in TMDs. Our findings strengthened existing literature regarding the relationships between plasma iron and potassium and risk of dyslipidemia. As such the findings provide evidence for future larger studies to assess gender-related differences in the detection rate of dyslipidemia and explore the strengths of this paper in this regard. A further strength of this study was the availability of extensive data on potential confounders of dyslipidemia, which permitted simultaneous statistical adjustment for multiple variables.

5. Conclusion

In summary, we showed that elevated plasma iron level (>18.8 μmol/L) was positively and independently correlated with the risk of dyslipidemia and that plasma potassium was inversely associated with dyslipidemia risk in TMDs. These findings suggest that patients having higher plasma iron or low potassium levels are at greatest risk for developing cardiometabolic diseases and should therefore be more carefully monitored and managed. Prospective studies are needed to investigate the causal relationship between plasma iron and potassium levels and risk of dyslipidemia.

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Author's Contribution

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

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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