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# Hyperbolic relation between beta-cell function and insulin sensitivity for type 2 diabetes mellitus, malaria, influenza, *Helicobacter pylori*, *Chlamydia pneumoniae*, and hepatitis C virus infection-induced inflammation/oxidative stress and temporary insulin resistance in Central Africans*

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**Background/aim:** We calculated the homeostatic model assessment (HOMA) for estimating insulin sensitivity and beta-cell function in normal, healthy nondiabetics with infections (malaria, influenza, HIV, *Helicobacter pylori*, *Chlamydia pneumoniae*, and hepatitis C virus), type 2 diabetic black patients, and healthy controls from Kinshasa, DR Congo.

**Materials and methods:** A case-control study was carried out between 2006 and 2007 for black Central African participants managed for HOMA.

**Results:** In total, 219 patients and 110 healthy controls were matched for sex and age. The hyperbolic product for 85 infected patients occupied an intermediate position between the hyperbolic product for 110 controls and that of 134 type 2 diabetics. Inflammation/oxidative stress was present in all infected patients, as well as in the type 2 diabetics. Of the patients, 39.3% and 49.8% had insulin resistance and metabolic syndrome, respectively. Insulin resistance was more prevalent in nondiabetics with inflammation/oxidative stress (47.1%; P = 0.041) than in type 2 diabetics (34.3%). Type 2 diabetics had higher insulin sensitivity and lower beta-cell function but a similar HOMA-IR score.

**Conclusion:** We recommend the assessment of insulin resistance in Central African patients with severe infections and type 2 diabetes.

**Key words:** Insulin resistance, type 2 diabetes, inflammation, sub-Saharan Africa, homeostatic model assessment

## 1. Introduction

Homeostasis model assessment (HOMA) is well established as a reliable surrogate and mirror of the glucose clamp technique in the diagnosis of insulin sensitivity (1). The hyperbolic function qualitatively defines the interrelationship between insulin resistance and beta-cell secretion (2–9), while the disposition index quantitatively derives from the nonlinear hyperbola-like curve with an integrated figure of glucose tolerance that includes both insulin sensitivity and secretion (10). Insulin resistance is defined as a state of a cell, tissue, or organism in which it is required to elucidate a quantitatively normal response (11). It can also be the state in which a subnormal glucose-lowering response is observed in the setting of a known concentration of insulin (12–17). Consequently, hyperinsulinemia is not a part of the individual components in which abdominal obesity and innate immunity play key roles in the development of insulin resistance, chronic inflammation, and metabolic syndrome elements through the effects of adipokines (leptin, adiponectin, and resistin) and cytokines (tumor necrosis factor-α, interleukin-6) in liver, skeletal muscle, and immune cells (18).

Clinical and epidemiological data show that inflammatory factors and insulin resistance may be associated with obesity, important risk factors of insulin resistance (7,19,20), type 2 diabetes mellitus (21), and acute phase reactants (22). In this sense, the burden of infection (enteroviruses and *Chlamydia pneumoniae*) and their treatment are associated with chronic low-grade inflammation and oxidative stress, resulting in insulin

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resistance and atherosclerosis (23,24). Interestingly, data from sub-Saharan Africa (25–31) also report a significant association between higher cardiometabolic risk (dyslipidemia, arterial hypertension, type 2 diabetes mellitus, stroke, coronary heart disease, and metabolic syndrome) and infections (HIV, *Helicobacter pylori* infection, malaria, and bacterial pneumonia). This condition may explain the emergence of atherosclerosis (stroke and myocardial infarction) and type 2 diabetes mellitus in sub-Saharan African populations (26,29,32–37).

Neither the Democratic Republic of the Congo (DRC) nor the Central African region has published data to show the critical importance of beta-cell dysfunction for the development of type 2 diabetes mellitus and selected infections. Therefore, the primary objective of this study was to investigate whether insulin secretion and insulin sensitivity are correlated with an inverse, nonlinear function at different positions in Bantu Central Africans with type 2 diabetes mellitus, in a group of patients with infections (malaria, influenza, HIV, *Helicobacter pylori*, *Chlamydia pneumoniae*, and hepatitis C), and in some healthy controls. The secondary objective of the study was to compare metabolic syndrome, pancreatic function, inflammatory, and oxidative stress markers between the type 2 diabetes mellitus and infection groups.

## 2. Materials and methods

### 2.1. Study design, period, and setting

This case-control and comparative study was carried out over a period of 21 months between 2006 and 2007 at the Kinshasa University Teaching Hospital, Kinshasa, DRC. The study protocol was designed according to the Helsinki Declaration II and approved by the local ethics committee.

### 2.2. Participants

Two kinds of participants were eligible: first, newly onset type 2 diabetes mellitus and infected patients admitted to the Emergency Unit of the Department of Internal Medicine, and, second, blood donors for family patients hospitalized within the same study period and setting. These two groups were eligible to be considered using structured and standardized questionnaires, a physical examination, and laboratory analysis after a 12-h overnight fast.

### 2.3. Inclusion and exclusion criteria

Out of those eligible participants, black Bantu adults (≥20 years of age) were included in this study and were examined by trained physicians and specialists after the participants had given their informed consent.

Eligible participants and controls who were excluded were those with a history of smoking, excessive alcohol intake, dysfunctional thyroid, nephrotic syndrome, pregnancy, polycystic ovarian syndrome in women, and diabetes mellitus treatment.

### 2.4. Data collection

Demographic data (sex and age), behavior (smoking and alcohol intake), weight, height, waist circumference, inflammation and oxidative stress markers, lipid profile, fasting blood glucose, uremia, blood pressure, insulin sensitivity, and beta-cell secretion were recorded. Body weight, height, blood pressure, and waist circumference were measured by standard methods for participants wearing light clothes and without shoes as described elsewhere (34).

Glucose levels were measured in fasting plasma samples using the glucose-oxidase method and spectrophotometer (Hospitex Diagnostics, Florence, Italy). Total cholesterol, HDL-cholesterol, uric acid, and triglycerides were measured using enzymatic colorimetric methods (BioMérieux, Marcy l'Etoile, France) at the central Laboratory of LOMO Medical Center, Kinshasa, DRC. Antibodies against oxidized LDL-cholesterol were measured using a solid-phase two-site enzyme immunoassay based on the direct sandwich technique, in which there are two genetic determinants on the oxidized apolipoproteins B molecule (Mercodia AB, Uppsala, Sweden).

*Helicobacter pylori* infection was assayed by the determination of IgG antibodies as described elsewhere (38). Serum was tested for specific IgG class antibodies against *C. pneumoniae* through the use of quantitative in vitro enzyme-linked immunosorbent assays (ELISAs) based on broad-reactive chlamydial inclusions (IgG) (Novagnost Test Kit 96x1, Dade Bahring Marburg GmbH, Marburg, Germany). Serum C-reactive protein (CRP) (Beckman, Fullerton, CA, USA) was determined by a routine laboratory test with intra- and interassay coefficients of variation of <3%. HIV RNA viral load (Nuclisens Easy Q HIV-1, BioMérieux, Boxtel, the Netherlands) were recorded for HIV infection. Malaria and influenza were determined using standard routine techniques. Hepatitis C virus seropositivity was assayed using a Hexagon HCV immunochromatographic rapid test for IgG antibodies against hepatitis virus C (Human, Wiesbaden, Germany).

For each fasting participant, the plasma insulin level was assayed in the same laboratory by an ELISA method using Mercodia kits (Mercodia AB, Uppsala, Sweden). Glycosylated hemoglobin (HbA1c) was measured in fresh blood samples with both migration (HYDRASYS System, Sebia, Lisses, France) and densitometry scanning of unstained gels (HYDRAGEL 7Ms Hb1C on a HYRYS densitometer). Plasma C-peptide levels were analyzed using a solid-phase two-site enzyme immunoassay quantitative method (ELISA) (Mercodia AB, Uppsala,

Sweden). The blood determinations performed in the LOMO Medical Center laboratory were documented to be valid and reliable following internal and external quality control.

### 2.5. Definitions

Type 2 diabetes mellitus was defined according to an expert committee on the diagnosis and classification of diabetes mellitus (14). The homeostatic assessment model for insulin resistance (HOMA-IR) was calculated as follows: fasting plasma glucose (mmol/L) × fasting plasma insulin (μU/mL)/22.5, as described by Matthews et al. (39). Using this method, high HOMA scores of ≥2.5 denoted low insulin sensitivity (insulin resistance: IR-HOMA). Insulin sensitivity (S% = 1/[HOMA-IR]), beta-cell function for insulin secretion (beta% = [20 × insulin]/[(fasting glucose: 18) – 3.5]), quantitative insulin sensitivity check index (QUICKI = 1/[log fasting glucose + log insulin), and reciprocal index of HOMA (RECIHOMA = 405/[fasting glucose × fasting insulin]) were calculated (40). Oxidative stress was defined by antibodies against oxidized LDL-cholesterol levels of ≥60 U/L.

### 2.6. Statistical analysis

Descriptive results of continuous variables were expressed as means ± SD, while those of categorical variables were expressed as proportions (%). Before statistical analysis for continuous variables was conducted, normal distribution and homogeneity of the variances were evaluated using Levene's test.

Differences between groups (type 2 diabetics vs. nondiabetics with inflammation/oxidative stress) were tested with the chi-square test for categorical variables and ANOVA for continuous variables. In this patient-study population (type 2 diabetics + nondiabetics with infection-induced inflammation/oxidative stress status), the relation between variables was tested using simple linear regression. Graphic representations of the hyperbolic relation between beta-cell function and insulin sensitivity were plotted for type 2 diabetics, nondiabetics with inflammation/oxidative stress, and healthy participants with normal glucose tolerance in the same scale of values (<200% beta-cell function and <300% insulin sensitivity), respectively. This was done to demonstrate the intermediate position of inflammation/oxidative stress between normal glucose tolerance and type 2 diabetes.

Because of the drastic loss of insulin sensitivity for certain type 2 diabetics and the lack of normally distributed insulin sensitivity and beta-cell function in the patient-study population, additional graphs of hyperbolic product between QUICKI and RECIHOMA were plotted for type 2 diabetics and nondiabetics with inflammation/oxidative stress, respectively. This was performed to denote their respective departure from the normal curve and the higher rate of insulin resistance due to inflammation. $P < 0.05$ was considered statistically significant. All computations were carried out with SPSS 13 for Windows (Chicago, IL, USA).

## 3. Results

In total, 219 patients (120 men, 99 women; aged 15 to 42 years) and 110 controls (55 men, 55 women; aged 14 to 42 years) were evaluated. The hyperbolic product for infected patients occupied an intermediate position between the hyperbolic product for controls with normal glucose tolerance and that of type 2 diabetics (Figure 1).

Among the 219 patients, the frequency of insulin resistance was estimated at 39.3%. Insulin resistance was

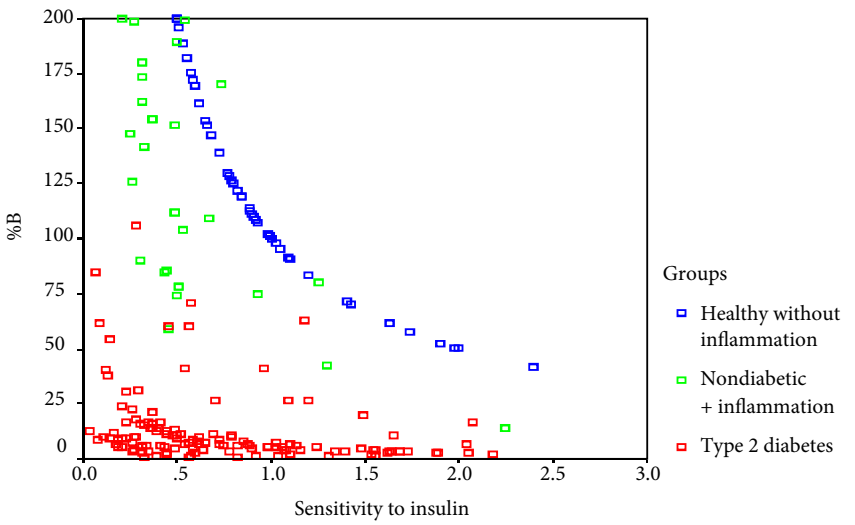


**Figure 1.** Hyperbolic relation between beta-cell function and insulin sensitivity for type 2 diabetics (red color), infected and nondiabetic patients (green color), and controls (blue color).

present more often among infected patients than in type 2 diabetics. However, inflammatory-induced oxidative stress was present in all infected patients (100%), as well as in type 2 diabetic patients (100%).

Table 1 summarizes the general characteristics between the type 2 diabetes mellitus and infection groups. Compared to the infected patients, type 2 diabetics had a higher waist circumference, lower insulinemia, higher fasting glucose, lower C-peptide, higher HbA1c, higher insulin sensitivity, and lower beta-cell function; however, they had similar HOMA-IR scores (Table 1), as well as a similar manner of departing from normal glucose tolerance by the same hyperbolic relation between RECIHOMA and QUICKI (Figure 2).

In all patients, the frequency of metabolic syndrome as defined by the International Diabetes Federation criteria was estimated at 49.8%. The frequency of insulin resistance in patients with metabolic syndrome was similar (P = 0.438) to that of patients without metabolic syndrome. However, there was a significant association between metabolic syndrome and type 2 diabetes. Thus, 66.4% of type 2 diabetics had metabolic syndrome as opposed to 23.5% of infected patients.

In each group of patients, the influence of sex (Figure 3) and that of abdominal obesity (Figure 4) on the hyperbolic relation between RECIHOMA and QUICKI was neutral, respectively.

Table 2 shows the correlation between insulin metabolism with age, waist circumference, fasting blood glucose, HbA1c, and C-peptide in each group of patients. In type 2 diabetics, there was no significant association between age, waist circumference, HbA1c, and insulin metabolism versus a significant negative association between insulin sensitivity, beta-cell function, and fasting blood glucose. In infected patients, the only significant negative association was observed between insulin sensitivity, beta-cell function, and fasting blood glucose. The loss of beta-cell function with increasing blood glucose levels was paradoxically higher in infected patients ($r = -0.757$, $P < 0.0001$) than in type 2 diabetics ($r = -0.592$, $P < 0.0001$). However, the decrease of insulin sensitivity was enhanced more by an increase in blood glucose in type 2 diabetics ($r = -0.418$, $P < 0.0001$) than in infected patients ($r = -0.309$, $P < 0.0001$).

## 4. Discussion

The present findings confirmed the hyperbolic relationship (5–7,9) between insulin sensitivity and beta-cell function in each group mentioned in the study. Furthermore, type 2 diabetics and infected patients with temporary inflammation/oxidative stress depart from the normal hyperbolic product in healthy individuals with normal glucose tolerance (2–4,7). In the same scale, excluding individuals with insulin resistance, nondiabetic patients with infection-induced inflammation/oxidative stress occupied an intermediate position between the hyperbolic product for normal glucose tolerance and that for type 2 diabetes. Strangely enough, the same intermediate position between normal glucose tolerance and type 2 diabetes is occupied by patients with impaired glucose tolerance (5). The reverse applies in healthy participants who had normal blood pressure, waist circumference, inflammation/oxidative stress markers, and lipid profiles. A healthy lifestyle (lack of both smoking and alcohol intake, as well as physical activity), high aerobic capacity, and elevated absolute skeletal muscle mass render those healthy participants insulin-sensitive.

This study was also a report on the frequency of insulin resistance using the HOMA model and metabolic syndrome in Central African patients with type 2 diabetes

**Table 1.** Descriptive characteristics in patients study population.

| **Variables** | Pooled, n = 219 | Type 2DM, n = 134 | Infection, n = 85 | P-value |
|---|---|---|---|---|
| Waist circumference (cm) | 85 ± 16 | 92 ± 11 | 74 ± 17 | <0.0001 |
| Fasting glucose (mg/dL) | 182.5 ± 126.4 | 247 ± 123 | 81 ± 16 | <0.0001 |
| Insulin (μU/mL) | 7.9 ± 6.6 | 4.4 ± 4.5 | 13.3 ± 5.7 | <0.0001 |
| HbA1c (%) | 7 ± 3.2 | 8.5 ± 3.1 | 4.8 ± 1.6 | <0.0001 |
| C-peptide (pmol/mL) | 0.8 ± 0.5 | 0.7 ± 0.4 | 1.1 ± 0.6 | <0.0001 |
| HOMA-IR (score) | 2.7 ± 3.5 | 2.7 ± 1.3 | 2.7 ± 1.3 | 0.975 |
| Insulin sensitivity (%) | | 82.1 ± 78.9 | 59.6 ± 77.8 | 0.040 |
| Beta-cell function (%) | 125.4 ± 234.5 | 12.9 ± 17.2 | 338.6 ± 351.6 | <0.0001 |
| RECIHOMA (index) | | 0.8 ± 0.8 | 0.5 ± 0.4 | 0.004 |
| QUICKI (index) | 6.7 ± 0.8 | 6.6 ± 0.9 | 6.8 ± 0.6 | 0.017 |

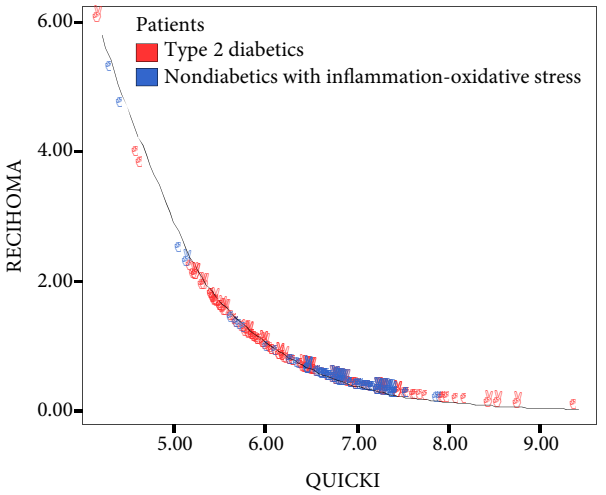


**Figure 2.** Hyperbolic relation between RECIHOMA and QUICKI in type 2 diabetics and nondiabetics with inflammation/oxidative stress.

and infection. The proportions of metabolic syndrome and insulin resistance in these patients were at epidemic levels and higher than those reported for general Central African populations (0%–11%) (36,41); meanwhile, a rate of 26% was reported for developed or emerging countries (42,43). Insulin resistance was more frequent in the group with infection than in the group with type 2 diabetes. A low level of physical activity and a low number and increase in cytokines for nondiabetics with infections may explain the higher rate of insulin resistance among nondiabetics with infections. There was no significant association between insulin resistance and metabolic syndrome in the pooled data of all patients. However, almost 37% of patients with metabolic syndrome had insulin resistance and 42% of patients without metabolic syndrome had insulin resistance. Physical inactivity and heterogeneity in these patients may explain the lack of association between insulin resistance and metabolic syndrome in all patients. In addition, metabolic syndrome was present in 66.4% of type 2 diabetics but in 23.5% of nondiabetics with infection. Therefore, the presence of metabolic syndrome in these black Central African patients multiplied the risk of type 2 diabetes six times. These findings confirmed that metabolic syndrome is highly associated with diabetes, as reported in the Framingham study (44). The findings also highlight the role of inflammation in insulin resistance.

### 4.1. Abdominal obesity, metabolic syndrome, age, and insulin resistance: pathogenesis

In these Central African patients, there was no significant association between sex, age, abdominal obesity, metabolic syndrome, and the presence of insulin resistance. This may be explained by the similar fat mass and girth for men and women in sub-Saharan populations (45).

### 4.2. Hyperbolic relation between insulin sensitivity and beta-cell function

The assessment of insulin sensitivity has become a frequent need for clinical researchers as insulin resistance is identified as one of the significant risk factors of type 2 diabetes (44) and atherosclerosis (21).

The HOMA hyperbolic product (insulin sensitivity × beta-cell function) reflected the true underlying beta-cell function adjusted for individual insulin sensitivity (5). In

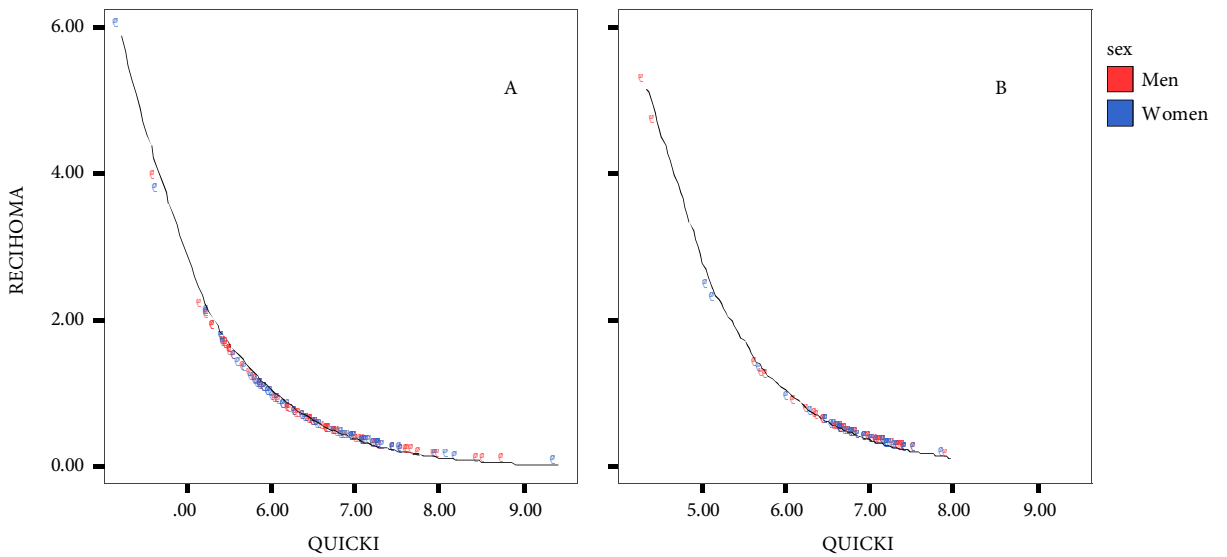


**Figure 3.** Hyperbolic relation between RECIHOMA index and QUICKI by sex in type 2 diabetics (a) and nondiabetics with inflammation/oxidative stress (b).

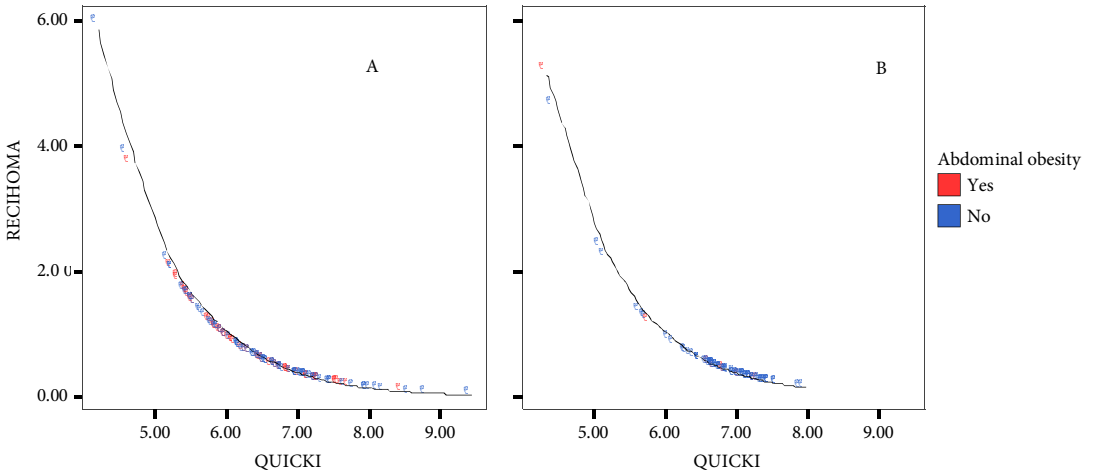


**Figure 4.** Hyperbolic relation between RECIHOMA index and QUICKI by abdominal obesity presence in type 2 diabetics (a) and nondiabetics with inflammation/oxidative stress (b).

**Table 2.** Correlation coefficients between insulin metabolism with cardiovascular risk factors in each group of patients.

| | Age (years) | WC (cm) | Glucose (mg/dL) | HbA1c (%) | C-peptide (pmol/mL) |
|---|---|---|---|---|---|
| In type 2 diabetics | | | | | |
| Insulin (μU/mL) | –0.094 | –0.163 | –0.013 | 0.164 | 0.163 |
| Insulin sensitivity (%) | 0.077 | 0.061 | –0.418*** | –0.156 | –0.208* |
| Beta cell function (%) | –0.054 | –0.135 | –0.592*** | 0.124 | 0.159 |
| In nondiabetics with inflammation/oxidative stress | | | | | |
| Insulin (μU/mL) | –0.064 | 0.074 | 0.013 | –0.112 | –0.208 |
| Insulin sensitivity (%) | 0.206 | 0.094 | –0.309** | 0.070 | 0.133 |
| Beta cell function (%) | 0.039 | 0.023 | –0.757*** | –0.172 | –0.050 |

WC: Waist circumference; *: P < 0.05; **: P < 0.01; ***: P < 0.001.

type 2 diabetics, the HOMA hyperbolic product underlies the need for successive exogenous insulin treatment (21). In these Central African patients, the hyperbolic product was significantly higher in infected nondiabetics than in type 2 diabetics, with or without metabolic syndrome. The true residual beta-cell function in these Central African type 2 diabetics showed accelerated deterioration compared with Caucasians (21). This more rapid deterioration hypothesis may be easily explained by the higher levels of fasting blood glucose and HbA1c observed in this study.

### 4.3. Clinical implications

Regardless of the diagnostic criteria used, there is complete agreement that a therapeutic lifestyle change, with an emphasis on weight loss and physical activity, constitutes the first-line therapy for metabolic syndrome and insulin resistance. Moreover, antibiotic treatment to directly destroy *Helicobacter pylori* has significantly prevented metabolic syndrome/insulin resistance in Central African patients (38). Metformin, TZDs, statins, and fibrates may be used to reduce the insulin resistance and metabolic syndrome effects. The pleiotropic effect of statins may control the inflammatory/oxidative stress status.

### 4.4. Limitations

This was a cross-sectional study that established association but not causality. Certain biases could tend to underestimate the observed prevalence of insulin resistance and metabolic syndrome, respectively. For example, the fact that insulin resistance might cause increased susceptibility to infection cannot be excluded. Further investigations to determine whether antibody scores represent reinfection, reactivation, persistence, or nonspecific immune stimulation are required.

It was not possible to determine whether malnutrition, physical activity, or environmental factors deleterious for

beta-cell function and smoking (exclusion criteria) may hint at insulin resistance in nondiabetics with inflammation and type 2 diabetes. It is known that these factors are responsible for immunodepression and earlier onset of hyperglycemia in younger and leaner patients. The present cross-sectional design was also unable to incriminate any genetic (younger age or genes) or environmental (malaria, HIV, *Helicobacter pylori*, steatosis, diet, or glucolipotoxicity) factors that are responsible for the steeper slope of beta-cell function in these type 2 diabetics and lower insulin sensitivity in older, nondiabetic Central Africans than in northern Caucasian type 2 diabetics (37). Genetics might be more related to this accelerated deterioration of true residual beta-cell function (hyperbolic product beta secretion × insulin sensitivity) in these native Central Africans, as was reported in Central African type 2 diabetics living in Belgium, who had an earlier onset of diabetes mellitus, concurrent insulin resistance, and earlier loss of insulin than Belgian Caucasian type 2 diabetics (32).

### 4.5. Conclusions

In the subjects of this study, the proportions of insulin resistance and metabolic syndrome are unexpectedly higher in Central African type 2 diabetics and infected nondiabetics with inflammation than in the general population. Clearly, metabolic syndrome was associated with type 2 diabetes, whereas abdominal obesity, sex, age, metabolic syndrome, C-peptide, and HbA1c were not associated with insulin resistance in type 2 diabetics, as well as in infected nondiabetics with inflammation.

Insulin resistance was more prevalent in nondiabetics with infection-induced inflammation/oxidative stress than type 2 diabetics, while the hyperbolic product (insulin secretion × sensitivity) showed a similar and faster deterioration than in Caucasian type 2 diabetics. Infected nondiabetics with inflammation/oxidative stress occupied an intermediate position between controls with normal glucose tolerance without inflammation/oxidative stress and those with type 2 diabetes mellitus and inflammation/oxidative stress.

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