Type 2 Diabetes Mellitus and Increased Risk for Malaria Infection

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A case–control study of 1,466 urban adults in Ghana found that patients with type 2 diabetes mellitus had a 46% increased risk for infection with Plasmodium falciparum. Increase in diabetes mellitus prevalence may put more persons at risk for malaria infection.

In sub-Saharan Africa, infectious diseases remain the predominant cause of illness and death. Plasmodium falciparum malaria alone causes an estimated 1 million deaths annually. At the same time, sub-Saharan Africa faces the world’s highest increase in type 2 diabetes mellitus; adaptation to Western lifestyles and genetic predispositions may accelerate this trend. A decade ago, type 2 diabetes prevalence in urban Ghana was 6.3% (1). By 2030, ≈20 million affected persons may live in sub-Saharan Africa. Type 2 diabetes mellitus increases susceptibility to common infections. In sub-Saharan Africa, the emerging co-occurrence of type 2 diabetes mellitus and tropical infectious diseases thus may have substantial implications. We describe prevalence of malaria infection in adults with and without type 2 diabetes mellitus residing in Kumasi, Ghana. Malaria transmission in Kumasi is low but patchy; mosquito breeding sites also occur in urban agricultural areas.

The Study

A case–control study of risk factors for type 2 diabetes and hypertension was conducted from August 2007 through June 2008 at Komfo Anokye Teaching Hospital, Kumasi, Ghana. The patients’ clinical and biochemical signs and symptoms were secondary objectives (I. Danquah et al., unpub. data). The study protocol was approved by the Ethics Committee, University of Science and Technology, Kumasi, and participants gave informed written consent.

Patients attending the diabetes (n = 495) or hypertension center (n = 451) were recruited. These patients promoted participation as preliminary (i.e., to be confirmed) controls to community members, neighbors, and friends (n = 222). Further preliminary controls were recruited from the outpatient department (n = 150) and among hospital staff (n = 148).

Participants were told to fast, abstain from alcohol and nicotine use, and avoid stressful and physical activities beginning at 10:00 pm the day before examination. On the day of examination, participants were asked about medical history and socioeconomic background, underwent physical examination, and provided venous blood and urine samples for laboratory testing.

Fasting plasma glucose (hereafter referred to as glucose concentration; fluoride plasma at 4°C) and hemoglobin (Hb) concentrations were measured (Glucose-201+, B-Hemoglobin; HemoCue, Angelholm, Sweden). Irrespective of symptoms, malaria parasites were counted per 500 leukocytes on Giemsa-stained thick blood films. Plasmodium infection and species were ascertained by PCR that included positive and negative controls.

Patients with type 2 diabetes mellitus were defined as those receiving documented treatment with antidiabetes medication or having a glucose concentration ≥7 mmol/L (8); patients with hypertension were defined as those receiving documented antihypertension treatment or having mean blood pressure ≥140/90 mm Hg for 3 measurements (9). Controls had neither condition.

Between-group comparisons were performed by the Mann-Whitney U, χ², and Fisher exact tests. Logistic regression produced adjusted odds ratios (aORs), and 95% confidence intervals (CIs).

Of the 1,466 study participants, 675 (46%) had type 2 diabetes (Table 1). Among these, 655 (97.0%) received antidiabetes treatment, but 317 (47.0%) had increased glucose concentration (>7 mmol/L; p = 0.004). Patients with type 2 diabetes mellitus were defined as those receiving documented treatment with antidiabetes medication or having a glucose concentration ≥7 mmol/L (8); patients with hypertension were defined as those receiving documented antihypertension treatment or having mean blood pressure ≥140/90 mm Hg for 3 measurements (9). Controls had neither condition.

According to microscopic examination, 13 (0.9%) of all participants had malaria parasites at low density (median 880/μL, range 80–4,960/μL). Reexamination by PCR showed that 206 (14.1%) were infected with Plasmodium spp., largely P. falciparum (189, 12.9%). Infected persons were afebrile, but mean hemoglobin was reduced (~0.4 g/dL; p = 0.004).

More Plasmodium spp. infections were observed in persons with type 2 diabetes mellitus than in those without the disease (Table 1); most infections were caused by P. falciparum (16% vs. 10%; p = 0.001). This difference was
not attributable to recent antimalarial medication (7 persons with type 2 diabetes mellitus vs. 13 persons without type 2 diabetes mellitus; p = 0.32), and, notably, 74/524 (14.1%) of the patients with type 2 diabetes mellitus who took metformin-based drugs were infected compared with 34/131 (26.0%) of those who did not (p = 0.01). Among controls and patients with hypertension, the \textit{P. falciparum} prevalence was similar (35/377, 9.3% for controls; 46/411, 11.2% for patients with hypertension; p = 0.38), and in each case, it was comparatively higher among patients with type 2 diabetes mellitus (p = 0.003 for controls; p = 0.03 for patients with hypertension).

Several factors that differed between persons with and those without diabetes mellitus (Table 1) were associated with \textit{P. falciparum} infection (Table 2). However, age-adjusted multivariate analysis confirmed that the odds of \textit{P. falciparum} infection in patients with type 2 diabetes mellitus were increased (aOR 1.46; Table 2). This risk increase was still discernible in the same model comparing patients with type 2 diabetes mellitus with controls (aOR 1.68, 95% CI 1.06–2.65; p = 0.027) or patients with hypertension (aOR 1.38, 95% CI 0.94–2.02; p = 0.096), or when separating into metropolitan area (aOR 1.67, 95% CI 1.12–2.48; p = 0.01) and other residence (aOR 1.32, 95% CI 0.76–2.29; p = 0.33).

According to the multivariate model, exchanging type 2 diabetes mellitus with glucose concentration showed that each mmol/L increase in blood glucose increased the risk for \textit{P. falciparum} infection by 5% (aOR 1.05, 95% CI 1.02–1.09; p = 0.002). Among patients with type 2 diabetes mellitus, a stepwise approach identified 8.6 mmol/L glucose concentration as the significant threshold of risk increase (aOR 1.63, 95% CI 1.07–2.48; p = 0.02).

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### Table 1. Demographic and clinical characteristics of 1,466 urban residents of Kumasi, Ghana, 2007–2008*

| Characteristics | Persons with type 2 diabetes mellitus, n = 675 | Persons without diabetes, n = 791 | p value |
|-----------------|-----------------------------------------------|-----------------------------------|---------|
| Age, y, mean (range) | 54.7 (18–92) | 47.1 (18–100) | <0.0001 |
| Male gender | 471 (25.3) | 182 (23.0) | 0.299 |
| Wealth score <25th percentile† | 265 (39.6) | 271 (34.3) | 0.044 |
| Illiteracy | 308 (45.8) | 206 (26.1) | <0.0001 |
| Formal education, none | 240 (35.7) | 130 (16.5) | <0.0001 |
| Crowded living condition‡ | 177 (26.7) | 120 (15.3) | <0.0001 |
| Smoking, current or quit | 49 (7.3) | 35 (4.4) | 0.024 |
| Akan ethnicity | 592 (87.8) | 685 (86.6) | 0.480 |
| Residence | | | |
| Kumasi metropolitan area | 476 (70.8) | 603 (76.2) | |
| Kumasi suburbs | 174 (25.9) | 162 (20.5) | |
| Elsewhere§ | 22 (3.3) | 26 (3.3) | 0.048 |
| Occupation | | | |
| Public servant | 44 (6.5) | 194 (24.6) | |
| Trader | 198 (29.5) | 190 (24.1) | |
| Farmer | 65 (9.7) | 48 (6.1) | |
| Unemployed | 248 (36.9) | 138 (17.5) | |
| Other¶ | 117 (17.4) | 218 (27.7) | <0.0001 |
| FPG, mmol/L, mean (range) | 8.3 (1.3–37.1) | 4.5 (2.9–7.0) | <0.0001 |
| Hemoglobin, g/dL, mean (range) | 12.9 (5.8–19.1) | 13.6 (4.9–19.1) | <0.0001 |
| Fever, ≥37.5°C | 2 (0.3) | 4 (0.5) | 0.693 |
| History of fever, preceding week | 95 (14.1) | 93 (11.8) | 0.182 |
| Respiratory tract infection | 5 (0.7) | 11 (1.4) | 0.232 |
| Urinary tract infection# | 14 (2.1) | 7 (0.9) | 0.076 |
| \textit{Plasmodium} spp. infection, by microscopy | 5 (0.7) | 8 (1.0) | 0.582 |
| Parasite density, per μL, median (range) | 1,160 (160–2,480) | 860 (80–4,960) | 0.770 |

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*Values are no. (%) unless otherwise indicated. p values were calculated by Mann-Whitney U test or Fisher exact test, as applicable. FPG, fasting plasma glucose concentration.
†<25th percentile of a calculated index of 11 markers of wealth: electricity, pipe-borne water, radio, fan, cupboard, television, bicycle, motorbike, refrigerator, car/truck/tractor, cattle.
‡>75th percentile of the number of persons living in the household.
§Hinterland and environs.
¶Includes casual laborer, artisan, and others.
#By nitrite-positive urine dipstick test (Combur 10, Roche Diagnostics, Mannheim, Germany).
Conclusions

This study provides evidence for increased risk for *P. falciparum* infection in patients with type 2 diabetes mellitus (Table 2). Most infections were detected by PCR exclusively, and all were asymptomatic.

Submicroscopic and asymptomatic *P. falciparum* infections are common in areas where malaria is endemic. In adults, PCR may identify up to 50% of infections, although only a few infections are diagnosed by microscopy (10). These submicroscopic infections tend to increase in areas of low endemicity and with patient age (10).

An increased risk for *P. falciparum* infection in persons with diabetes mellitus might become clinically relevant (and microscopically detectable) under several conditions. The impact of semi-immunity on controlling parasitemia may weaken with advancing type 2 diabetes mellitus and immune dysfunction (5), as suggested by the observed risk increase with increasing glucose concentration. Conversely, children who lack semi-immunity but have more severe type 1 diabetes mellitus may be particularly prone to malaria. Such vulnerability is also conceivable for women with gestational diabetes whose immune

| Parameter                          | Total no. patients | *P. falciparum* infection, no. (%) | Univariate analysis | Multivariate analysis |
|-----------------------------------|--------------------|-----------------------------------|---------------------|----------------------|
|                                   |                    | OR (95% CI) p value aOR (95% CI) p value |
| Diabetes mellitus type 2          |                    | Univariate analysis | Multivariate analysis |
| No                                | 791                | 81 (10.3) 1 | 1.67 (1.22–2.27) 0.001 | 1.46 (1.06–2.03) 0.021 |
| Yes                               | 675                | 108 (16.0) | 1 | |
| Gender                            |                    | 124 (11.2) | 1 | |
| F                                 | 1,113              | 103 (10.9) | 1.63 (1.20–2.23) <0.0001 | 2.13 (1.50–3.03) <0.0001 |
| M                                 | 353                | 65 (18.5) 1 | 1 | |
| Wealth score                      |                    | 94 (10.2) | 1 | |
| >25th percentile                  | 923                | 94 (10.2) | 1.88 (1.38–2.56) <0.0001 | 1.76 (1.27–2.42) 0.001 |
| <25th percentile †                | 536                | 94 (17.6) | 1 | |
| Literacy                          |                    | 103 (10.9) | 1 | |
| Able to read                      | 947                | 103 (10.9) | 1 | |
| Unable to read                    | 514                | 85 (16.8) | 1.54 (1.11–2.15) 0.010 | |
| Formal education                  |                    | 126 (11.6) | 1 | |
| Any                               | 1,091              | 126 (11.6) | 1 | |
| None                              | 370                | 62 (16.8) | 1 | |
| Living condition                  |                    | 133 (11.6) | 1 | |
| Uncrowded                         | 1,147              | 133 (11.6) | 1 | |
| Crowded‡                          | 297                | 52 (17.5) | 1.61 (1.14–2.29) 0.007 | |
| Smoking                           |                    | 171 (12.4) | 1 | |
| Never                             | 1,380              | 171 (12.4) | 1 | |
| Current or quit                   | 84                 | 18 (21.4) | 1.92 (1.11–3.32) 0.019 | |
| Ethnicity                         |                    | 156 (12.3) | 1 | |
| Akan                              | 1,277              | 156 (12.3) | 1 | |
| Others                            | 188                | 33 (17.6) | 1.52 (1.01–2.30) 0.045 | |
| Residence                         |                    | 121 (11.2) | 1 | |
| Kumasi metropolitan               | 1,079              | 121 (11.2) | 1 | |
| Kumasi outskirts §                 | 336                | 64 (19.2) | 1.87 (1.34–2.61) <0.0001 | |
| Elsewhere                         | 48                 | 4 (8.3)    | 0.72 (0.25–2.03) 0.533 | |
| Occupation                        |                    | 17 (7.1) | 1 | |
| Public servant                    | 238                | 17 (7.1) | 1 | |
| Trader                            | 388                | 50 (12.9) | 1.92 (1.08–3.42) 0.026 | |
| Farmer                            | 113                | 34 (30.6) | 5.74 (3.04–10.86) <0.0001 | |
| Unemployed ¶                      | 335                | 38 (11.3) | 1.66 (0.92–3.02) 0.095 | |
| Unemployed ¶                      | 386                | 49 (12.8) | 1.90 (1.07–3.39) 0.029 | |

*OR, odds ratio; CI, confidence interval; aOR, adjusted odds ratio. Age and gender were a priori included in the multivariate model. Further variables for inclusion in the model were identified by factor analysis excluding multicollinear parameters (1: retained diabetes, excluded occupation; 2: retained literacy, excluded education, smoking; 3: retained wealth, excluded living condition, ethnicity). The same model results from a logistic regression analysis initially including all above listed parameters, and then removing in a stepwise backward fashion all factors not associated with *P. falciparum* infection in multivariate analysis (p > 0.05). Inserting any of the excluded variables back into the model did not change the aOR of patients with type 2 diabetes mellitus by >7% each, suggesting the absence of substantial confounding. Leaving all parameters in the model yielded an aOR for patients with type 2 diabetes mellitus of 1.36 (95% CI, 0.98–1.90; p = 0.07). Alternatively, propensity score adjustment of that analysis, i.e. reducing covariates into a single variable, produced aOR = 1.41 (95% CI, 1.02–1.95; p = 0.04).

†Crowded living condition, >75th percentile of the number of persons living in the household, i.e., n>8.

§Hinterland and environs.

¶Includes casual labourer, artisan, and others.
systems are relatively naive with regard to pregnancy-specific \textit{P. falciparum} (11). Moreover, low-level infections in patients with type 2 diabetes mellitus may constitute an unrecognized infectious reservoir in areas where malaria is endemic (10). The lowered \textit{P. falciparum} prevalence under metformin medication accords with the biguanides’ antimalarial efficacy (12).

Our data stem from a study that was not designed to assess influences on \textit{P. falciparum} infection in a heterogeneous population. Multivariate analysis cannot exclude unmeasured confounders, and association does not mean causality. As a limitation, factors influencing infection were not specifically identified during recruitment and thus were not included in analysis. Also, despite adjusting for proxy indicators, e.g., wealth, exposure to infection might still have differed between the study groups, considering the patchy malaria transmission in Kumasi (6). Nonetheless, increased odds of \textit{P. falciparum} in patients with type 2 diabetes mellitus were found after stratification by subgroups or residence. Ultimate corroboration would need a prospective, longitudinal study controlling for exposure (possibly monitored by serologic markers of transmission).

Although the actual reasons for the increase of \textit{P. falciparum} infection are unclear, the risk increase with rising glucose concentration is a sign of biologic plausibility. Such risk could result from impaired defense against liver and/or blood-stage parasites and from prolonged persistence. In type 2 diabetes mellitus, decreased T cell–mediated immunity but limited impact on humoral responses are discussed (5). Mechanistically, increased glucose availability may feed \textit{P. falciparum} growth as seen in vitro (13). Also, patients with diabetes might receive more infectious mosquito bites: olfactory signals mediate mosquito attraction (14), and these, including expiration, are subtly altered in persons with type 2 diabetes mellitus (15).

The rapid proliferation of type 2 diabetes mellitus in sub-Saharan Africa may put an increasing number of persons at risk for \textit{Plasmodium} infection and malaria. Thus, the magnitude of both diabetes mellitus and malaria in sub-Saharan Africa warrants further investigation into the relevance and causes of our finding.

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