

Malaria and diabetes

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Abstract

Both malaria and diabetes are more common in the developing world, and are major public health challenges. A direct relationship between these 2 conditions has not been evaluated. This review article assessed the literature guaging the relationship between these two conditions, and suggests a pragmatic approach to management.

References for this review were identified through searches of PubMed, Medline, and Embase for articles published to October 2016 using the terms "diabetes" [MeSH Terms] AND "malaria" [All Fields]. The reference lists of the articles thus identified were also searched. The search was not restricted to English-language literature.

Malaria has been documented to be more common in diabetes, in several studies from Africa. Malarial infection during pregnancy is an important cause of low birth weight and anaemia, and may contribute to the intra-uterine hypothesis explanation for the diabetes epidemic. Prevention and timely/effective management of malaria during pregnancy may therefore be viewed as a primordial preventive strategy against diabetes. Patients with diabetes have atypical malaria presentations. Glucose-6-phosphate dehydrogenase deficiency, which is associated with primaquine failure for radical cure is also associated with dysglycaemia. Type 2 Diabetic mice infected with malaria are more efficient at infecting mosquitoes. A similar synergy in humans warrants evaluation, which would then make "diabetic malaria" a public health problem. Metformin has well known anti-malarial properties.

There is significant literature available highlighting the link between diabetes and malaria, an area warranting active further research. Metformin as a prophylactic agent for malaria prevention warrants evaluation.

Keywords: Malaria, Diabetes, Hypoglycemia, Ketosis, Mortality, Morbidity, Plasmodium, Metformin.

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Introduction

As per the WHO estimates 207 million cases of malaria occurred globally in 2012 and 6,27,000 deaths. African countries contributed 80% of these cases followed by South East Asia Region (SEAR) (13%).¹ India contributes 61% of cases and 41% deaths due to malaria in SEAR.² Globally 422 million adults were living with diabetes in 2014. The global prevalence of type-2 diabetes (T2DM) has nearly doubled since 1980, rising from 4.7% to 8.5%.^{3,4} India is the diabetes capital of the world. Nearly 8-10% of our population (1250 million) has diabetes.^{5,6} There is even a larger population with prediabetes (10-14%).⁷ Indian prediabetics have one of the highest global rates of progression to diabetes. The annual risk of progression is 2.5% in USA, 11.5% in China, which is much lower compared to India (14-18%).⁵⁻⁸

Hence both malaria and diabetes are more common in the developing world, and are major public health challenges. However direct relationship between these two has not been evaluated. Hence this review assessed the relationship between these two conditions, and suggests a pragmatic approach to managing diabetes complicated by malaria or vice versa.

Methods

Search Strategy and Selection Criteria

References for this review were identified through searches of PubMed, Medline, and Embase for articles published to October 2016 using the terms "diabetes" [MeSH Terms] AND "malaria" [All Fields]. The reference lists of the articles thus identified were also searched. The search was not restricted to English-language literature.

Effect of Diabetes on Malarial Risk

T2DM is thought to be an immuno-compromised state, which puts persons at risk for infections.⁹ Malaria is more common in T2DM.¹⁰ A Ghanaian case-control study in 1466 urban adults, found a higher plasmodium infection in T2DM.¹¹ Each mg/dl increase in blood glucose increased risk for falciparum infection by 5%. A glucose concentration of 155 mg/dl was identified as a significant threshold for increased infection (OR 1.63; P = 0.02).¹¹ Impaired defense against liver and blood-stage parasites, decreased T-cell mediated immunity, and increased glucose availability for

falciparum, may be the explanation for it.¹² It is also possible that mosquitoes may prefer to bite persons with hyperglycaemia, based upon olfactory signals.¹³

Effect of Malaria on Risk of Diabetes

The intra-uterine hypothesis has emerged as a plausible explanation for the diabetes epidemic. Intra uterine stress, leading to birth of low birth weight (LBW) babies, is associated with modifications in skeletal muscle and pancreatic morphology and function.¹⁴ This leads to increased skeletal muscle insulin resistance, and reduction in pancreatic insulin secretory capacity. Malaria in pregnancy is an important cause of low birth weight babies (LBW) and anaemia. Placental malaria and anaemia may disrupt nutrient supply and cause hypoxia, thus negatively influencing intra uterine foetal growth. This may be a potential cause of T2DM in later life.¹⁴ Prevention and timely/effective management of malaria during pregnancy may therefore be viewed as a primordial preventive strategy against diabetes.

Effect of Diabetes on Malaria Presentation

Patients with diabetes may have atypical presentations of malaria. Treating physician should maintain a high index of suspicion. In an observational study of 148 patients of severe falciparum malaria from India, absence of fever, multi organ involvement, vomiting, shorter coma onset time, and longer duration of coma was commonly noted in patients with diabetes.¹⁵ Relative bradycardia and ketoacidosis were more frequent in diabetes, while black water fever and hypoglycaemia were encountered more often in non-diabetes controls. Blood urea, serum creatinine and bilirubin were significantly higher in diabetics.^{15,16} Haematocrit was higher in diabetics, while parasite count was significantly lower.^{15,16}

Effect of Malaria on Glycaemic Presentation

Due to non-specific symptoms, diabetes may often be misdiagnosed as malaria. In a study from southeastern Tanzania, diabetes patients reported that they had initially used anti-malarial medicines because they believed their symptoms-like headache, fever, and tiredness-were suggestive of malaria.¹⁷ Undiagnosed diabetes, unmasked by acute infection, stress hyperglycaemia, hyperglycaemia or ketosis due to omission of oral glucose-lowering or insulin dose, and starvation ketosis, due to inadequate oral intake, may be noted in patients with infections including malaria.¹⁵ Hence a low threshold for screening for blood glucose to rule out hyperglycaemia should be kept in patients presenting to hospitals with acute illness, which may appear as an infection.

Also it must be remembered that classically, malaria is

known to cause hypoglycaemia. This may be due to parasitaemia per se, or due to hypoglycaemic effect of quinine.¹⁸ Hypoglycaemia is known to be severe in children with malaria.¹⁹ While adults exhibit hyperinsulinaemia, children with malaria have been shown to have low circulating insulin and high ketonaemia. The glucose turnover rate is markedly increased in adults with malaria, but comes down when quinine is administered.²⁰ This wide spectrum of glycaemic abnormalities requires astute clinical skills and frequent glucose monitoring.

Patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency are not able to use primaquine for radical cure of Plasmodium vivax malaria, which may thus contribute to disease propagation in community. A study from western Brazilian showed G6PD deficient males had more impaired fasting glucose and diabetes, highlighting link between malaria and diabetes.²¹

Outcomes of "Diabetic Malaria"

Even a lower parasitic count can lead to severe manifestations of malaria in people with diabetes. Relative bradycardia may be due to associated autonomic neuropathy, and may be a marker of subclinical macrovascular complications. Similar vascular pathogenetic mechanisms may explain the higher risk of cerebral, renal, hepatic and cardiac dysfunction in coexistent diabetes and malaria.¹⁵ Plasmodium-induced aggregation and sequestration of red blood cells may worsen the already impaired microcirculation in brain, kidney, liver and heart, leading to multi-organ involvement.²² Malaria is also associated with higher mortality in diabetics.

Studies on murine models of T2DM have demonstrated that T2DM mice infected with malaria are more efficient at infecting mosquitoes.²³ These studies showed that a higher percentage of mosquitoes became infected following blood feeding on Plasmodium-infected T2DM mice compared to mosquitoes that fed on infected control animals, despite no significant differences in circulating gametocyte levels.²³ This raises the important question of whether a similar synergy exists in humans, which would then make "diabetic malaria" a public health problem.

Anti-Diabetic Drugs and Malaria

Metformin is perhaps the most widely used oral glucose-lowering drug, known to have anti-malarial properties.²⁴ Paludrine, a drug structurally similar to metformin, was used as a potent anti malarial, and was noted to be effective even in quinine-resistant cases.²⁵

In a large Ghanaian study, persons using metformin for diabetes had significantly lower incidence of malarial infection as compared to those not on metformin.⁹ This adds to the value of metformin, which is already

considered the first line antidiabetic therapy. Metformin may be considered an appropriate primary prevention strategy against malaria, in persons with diabetes or prediabetes, who live in, or travel to, malaria-endemic zones. However, research will be required to confirm this hypothesis as well.

Glycaemic Management of Malaria

Management of malaria should be carried out as per existing guidelines.²⁶ There are no specific recommendations for the management of glycaemia in persons with malaria. The following section shares pragmatic experience-based guidance regarding glycaemic management of diabetes during malaria.

Prevention

Persons at high risk of malaria, i.e., those living in, or travelling to, malaria-endemic zones, should consider metformin for the management of diabetes or prediabetes, if it is already not being taken, provided that it is not contraindicated or not tolerated.

Adequate Oral Intake

Persons with malaria who are able to take orally should continue their preexisting anti-diabetic medication (Table). Frequency of glucose monitoring should be increased, and necessity to take regular meals emphasized. Persons on traditional sulfonylureas with a high propensity of hypoglycaemia (e.g., glibenclamide) may consider a reduction in dose or a change of drug. Persons on human insulin may consider a reduction in dose or a change to insulin analogues, which have a lower risk of hypoglycaemia. Patients of malaria should be encouraged to take frequent meals in moderate quantities.

Inadequate Oral Intake

Persons with malaria who are unable to, or unsure of, taking regular meals, but are unable to, or choose not to, get admitted in a hospital, need special attention. While those on oral anti-diabetic medication may continue pre-existing therapy, the dose of sulfonylureas and metformin may have to be reduced. In a situation where hypoglycaemia is anticipated, expected suspected or experienced, patients may themselves reduce their dosage of sulfonylureas by half.²⁷ The use of scored tablets helps facilitate this decision and action. In case where upper gastrointestinal symptoms (e.g., loss of appetite, nausea, vomiting) are expected or experienced, patients may choose to reduce metformin dose as well.

Diabetics admitted to hospital for malaria should preferably be managed with insulin. Persons who accept oral meals may be treated with subcutaneous insulin. The choice of regime will depend upon the gluco-phenotype. Insulin analogues should be preferred, if available, as they carry a lower risk of hypoglycaemia.

Nil Oral Intakes

Patients who are unable to take oral meals, because of altered sensorium or gastrointestinal function, must be managed with intravenous insulin.²⁸ Frequent glucose and ketone monitoring is essential. Both hypoglycaemia and ketosis should be pre-empted. One should reduce insulin doses during and after quinine administration.²⁹ Intravenous insulin infusion, with the dose modified according to ambient glucose levels, is superior to sliding scale insulin in achieving optimal therapeutic outcomes.

Table: Glycemic management in diabetes complicated by malaria.

Drug class	Oral intake status		
	Full	Erratic	Nil orally
Sulfonylureas: Traditional*	Reduce dose to half	Discontinue, and Shift to modern sulfonylureas	Discontinue, and Shift to insulin if glucose values rise
Sulfonylureas Modern**	Continue same dose	Reduce dose to half	Discontinue, and Shift to insulin if glucose values rise
Metformin	Continue same dose	Reduce dose to half/ consider stopping if GI upset	Discontinue
Pioglitazone	Continue same dose	Continue same dose	Discontinue
DPP4i	Continue same dose	Continue same dose	Discontinue
GLP1RA	Continue same dose	Continue same dose/ consider stopping if GI symptoms	Discontinue
Basal insulin	Continue same dose	Continue same dose of insulin analogues with low risk of hypoglycemia	Reduce dose as required
Basal plus insulin, basal bolus insulin	Continue same dose	Reduce dose of prandial insulin, Prefer analogues, Inject insulin after meal	Shift to intravenous insulin
Premixed insulin	Continue same dose	Reduce dose to half or two thirds	Shift to intravenous insulin

*glibenclamide, gliclazide, glipizide

**gliclazide MR, glimepiride.

Summary

Malaria is associated with both hyperglycaemia and hypoglycaemia. Clinical symptoms of cerebral malaria mimic diabetic ketoacidosis and severe neuroglycopenia. Absence of fever, and relative bradycardia, may confuse the emergency physician. A peripheral blood smear, using Giemsa stain, for detection and diagnosis of malaria, should be carried out in all persons with T2DM with altered sensorium. It must be noted that both diabetic ketoacidosis and severe hypoglycaemia are differential diagnosis.

Management of malaria is similar in persons with diabetes and without diabetes. However, one should watch for hypoglycaemia and cardiac arrhythmias, and pre-empt them by appropriate measures. The aim is to maintain euglycaemia, while avoiding both hyperglycaemia and hypoglycaemia. Regular glucose and ketone monitoring are essential. Lower insulin requirements may be observed in patients on quinine therapy, but a glucose-insulin infusion may be required to maintain euglycaemia and prevent starvation ketosis.

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