

Managing Hyperglycaemia in Diabetic Foot.

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Abstract: Type 2 diabetes has gained epidemic proportions and its complications pose a major health burden to all segments of the society. Diabetic foot ulcers are common in diabetic patients, having a cumulative lifetime incidence rate as high as 25% and are the harbingers of lower extremity amputations. The triad of neuropathy, ischaemia and infection is involved in the pathophysiology of diabetic foot ulcers. It is imperative that chronic hyperglycaemia which predisposes to this triad is addressed to prevent and manage diabetic foot ulcers effectively. Insulin therapy is the cornerstone in managing hyperglycaemia in diabetic foot patients in view of their long duration of diabetes and co-existent microvascular complications and other co-morbidities. Insulin-sensitising drugs (metformin and pioglitazone) and other oral antihyperglycaemic agents can be used as an adjunct. Achieving euglycaemia is one of the cornerstones of effective management of diabetic foot ulcer.

India faces a mammoth burden of type 2 diabetes and its complications with prevalence of diabetes being around 10% reported from several parts of the country. Unfortunately, the epidemiology of type 2 diabetes in Indians has shown a demographic transition as well, with rising prevalence observed in the young and also the adolescents and children¹.

Apart from the microvascular complications, the loss of a limb or foot is the most feared complications of diabetes and still, the foot problems are neglected and remain one of the commonest reasons for diabetic patients to be hospitalised². Diabetic foot ulcers are common in diabetic patients, having a cumulative lifetime incidence rate as high as 25% and frequently become infected³. This is apart from the corns and calluses which are routinely seen in our day-to-day practice and in diabetics these minor routine lesions can be the harbinger of infections and diabetic foot ulcers and eventually lead to complications. Diabetic foot ulcers precede almost 85% of amputations.

The foot complications occur in both types of diabetes and is more related to the duration of diabetes rather than the age of onset of diabetes. Protracted hyperglycemia has a number of deleterious effects on the body, the major complications include accelerated peripheral atherosclerosis, complicated coronary artery disease, obesity, renal insufficiency, visual deterioration and peripheral neurologic degeneration inevitably compromising on the quality of life of diabetics and shortening the life span⁴.

The two main pathologies contributing to a diabetic foot are diabetic neuropathy (microvascular complication of diabetes) and peripheral vascular disease (macrovascular complication of diabetes). Diabetic neuropathy especially sympathetic autonomic neuropathy results in reduced sweating and dry skin which results in cracks and fissures, especially in the lower limbs. Sensory neuropathy results in decreased pain and position sense and motor neuropathy results in intrinsic muscle wasting and foot deformity. Hence, **diabetic neuropathy** is the single most important determinant for development of diabetic foot ulcers. **Peripheral vascular disease** is another component which predisposes to diabetic foot. Hypertension and smoking are known risk factors for development of peripheral vascular disease. **High plantar pressures**, especially in the presence of diabetic neuropathy, is known contributor to development of diabetic foot ulcers. **Limited joint mobility** is another factor which contributes to abnormal mechanics in the diabetic foot and predisposes to diabetic foot ulcers. Glycosylation of collagen in tendons and ligaments results

in limited motion of foot joints. **Abnormal footwear** obviously also contributes. **Chronic infection**, which in the setting of uncontrolled hyperglycaemia continues unabated and causes a chronic diabetic foot ulcer may go on to amputation.

The **triad of neuropathy, ischaemia and infection**; resulting from chronic hyperglycaemia and contributing to the pathophysiology of diabetic foot has consistently been emphasised⁵. Incidentally, a Jamaican study also reported high prevalence of peripheral vascular disease (66.6%), peripheral neuropathy (50%), hyperglycaemia (75.6%) and increased duration of diabetes (17.5 years) among the diabetic foot patients studied⁶.

The management of diabetic foot disease is focussed primarily on prevention of development of diabetic foot ulcers and on avoiding amputation of lower extremities. The main strategies include-identification of "at-risk" foot, treatment of acutely diseased foot and prevention of further problems.

The various pathophysiologic determinants of diabetic foot ulcer are all related to hyperglycemia as is shown in Figure 1.

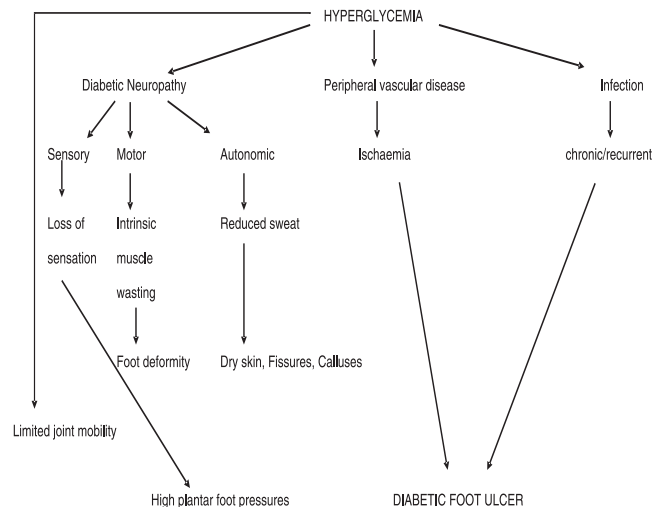


Figure 1- Role of Hyperglycemia in pathogenesis of diabetic foot ulcer.

Hyperglycemia plays a pivotal role in the genesis of diabetic foot ulcers, in its recurrence, chronicity, and worsening of diabetic foot ulcers and eventually contributing to amputations. It has been shown recently that careful glucose control can significantly decrease the complications of diabetes⁴. Much effort has gone into trying to help diabetics maintain near-normal glucose levels and those patients who have been successful in achieving euglycaemia definitely have better outcomes. It has been conclusively proved as well that patients with chronic diabetic foot ulcers with better glycaemic control had much better wound healing than those with poor glycaemic control⁷. Marston et al in 2006⁷, reported for the first time that patients whose HbA1c increased during their study (n=101), 20.7% of all wounds and 21% of dermal substitute-managed wounds (n=105) healed; whereas, in patients whose HbA1c levels remained stable or decreased, 26.3% of all wounds and 47% of dermal substitute-managed wounds healed ($p < 0.05$).

However, in a majority of diabetic patients, for a variety of reasons, good blood glucose control is not easily obtained. Therefore, the management of diabetic complications still remains a major area of focus. Well-controlled diabetes is also reported to decrease the prevalence of diabetes-specific cutaneous disorders associated with chronic hyperglycaemia⁸. In fact, among diabetic patients with an initial complication also, tight glycaemic control has been associated with reduced risk of additional complications in other organs⁹.

Control of hyperglycaemia and achieving euglycaemia in a patient with diabetic foot ulcer is of paramount importance because hyperglycaemia can predispose to new infections, delayed wound healing and spreading of existing infections, septicaemia and its attendant complications. In fact, foot infections are common in patients with diabetes and are associated with high morbidity and risk of lower extremity amputation¹⁰. Apart from aggressive surgical debridement, wound management, effective antibiotic therapy, achieving euglycaemia ranks foremost among the other measures.

Glycaemic control has been enunciated as the foremost principle in effective management of diabetic foot ulcers and preventing amputations¹¹. A target HbA1c of $< 7\%$ is acceptable in diabetic patients and is applicable for diabetic foot ulcer patients as well¹². Despite the advent of newer therapies the average level of glycaemic control remains unsatisfactory. Failure of individual therapies to achieve adequate glycaemia with a single oral agent, has led to a search for various permutations and combinations. Combination therapy offers the physician an opportunity to tailor a pharmaceutical regimen to individual patient needs-improving compliance, facilitating weight loss or reducing cardiovascular risk factors.

Euglycaemia is best achieved by prescribing insulin therapy to these patients. Patients with diabetic foot ulcers usually have had long-standing diabetes and have microvascular complications. Not only is diabetic neuropathy, sort of *since qua non*, but co-existent retinopathy and nephropathy and occult/overt coronary artery disease make insulin therapy the ideal regimen for treating hyperglycaemia in these patients and achieving euglycaemia. Besides, diabetic foot ulcer patients do harbour infections and insulin is the recommended agent to control glycaemia during an intercurrent illness or to control and eliminate infections. Moreover, insulin regimens can be tailor-made to suit the needs of an individual patient. Some possible ones are outlined:

- 1) Single dose regimens:
 - a.) Single daily injection of intermediate acting insulin before breakfast.

- b.) Single daily injection of biphasic (regular + intermediate acting insulin) before breakfast. Mixed regular & NPH (or premixed, such as 70/30, 75/25, 50/50) insulin can be used for the purpose.
 - c.) Control of Fasting plasma glucose is critical; bedtime NPH insulin treatment for this purpose is specially useful.
 - d.) For control of the post-prandial glucose excursions, insulin lispro has been shown to be effective.
- 2) Twice daily regimens:
 - a. Twice daily NPH insulin
 - b. Mixed regular & NPH (or premixed) insulin twice daily.
 - c. Biphasic insulin before breakfast and Lente/NPH insulin before dinner/bedtime.
 - 3) Basal-bolus regimens: With advent of basal insulins- glargine and detemir, which can be administered once a day, the prandial glucose excursions can be controlled with short-acting insulin analogues.
 - 4) More intensive regimen of daily multiple subcutaneous insulin injections (MSII), e.g. premeal regular (or lispro) with bedtime NPH.
 - 5) Continuous subcutaneous insulin infusion (CSII) pump therapy.
 - 6) Implantable intraperitoneal pumps.
 - 7) Subjects with erratic food intake like elderly patients, may benefit particularly with insulin lispro since it can be given immediately after the patient has eaten. Alpha glucosidase inhibitors (acarbose, voglibose and miglitol) can also be used as oral agents for the purpose.
 - 8) For patients inadequately managed with large doses of insulin, addition of an oral agent may improve control (specially the insulin sensitisers- metformin and pioglitazone).
 - 9) Those patients who are on oral hypoglycaemic agents can be started on single daily dose of an intermediate acting insulin, the classically know bedtime insulin and day-time sulphonylurea (BIDS) regimen can be used. Even a single morning dose of insulin may be beneficial. Alternatively, a basal insulin injection shot can be given viz. insulin detemir or insulin glargine.
 - 10) Patients who have secondary sulphonylurea failure, should be started on a split-mix regimen as already outlined above. Alternatively, a basal-bolus regimen can also be initiated.

Use of oral antihyperglycemic agents is not contraindicated and a plethora of such agents are available viz. sulphonylureas, glinides, metformin, thiazolidinediones (pioglitazone), alpha-glucosidase inhibitors, DPP-IV inhibitors/GLP-1 analogues. However, the treating physician should be careful in this regard because patients with diabetic foot ulcers, having long-standing diabetes may not respond to oral antihyperglycaemic agents so effectively. Moreover, these patients harbouring infections do have an insulin resistant state wherein even insulin may be required in high dosages. Sulphonylureas have been in use for decades and have the largest experience associated with them. The newer generation sulphonylureas like glimepiride (1-8 mg/day in 1-2 divided doses) or gliclazide (40-320 mg/day in 1-2 divided doses) have lower risk of hypoglycaemia associated with them. Glipizide (5-20 mg/day in 2-3 divided doses) has an additional advantage since it has a short half-life and so can be given immediately before meals minimising chances of hypoglycaemia. Weight gain and hypoglycaemia are the two main side-effects with sulphonylurea drugs. Metformin (500-2500 mg/day in 1-3 divided doses) is the biguanide which has stood the test of time with minimum of side-effects and has the

benefit of reducing appetite and weight gain and is also in vogue because of its insulin-sensitising effect. However, caution needs to be exercised in patients with renal failure and those with septicaemia or heart failure because in such patients tissue hypoxia or acidosis can precipitate or mask development of metformin-induced lactic acidosis. Gastro-intestinal disturbances are commonly witnessed with metformin use. Thiazolidinediones are also insulin-sensitisers, but have been bogged down by controversies one after the other. Troglitazone, the first thiazolidinedione had to be withdrawn because of cases of hepatic failure while rosiglitazone was withdrawn because of cases of heart failure/sudden death. Pioglitazone is presently considered safe and can be used (15-45 mg single daily dose) but the glycaemic effect takes up to 3 weeks to establish because of its mode of action on the cellular transcription process. Also fluid retention of 1.5 kg to 12 kg may be witnessed and could be problematic in some patients. Pioglitazone may be used for achieving euglycaemia in the long run in cases of diabetic foot ulcer, but because of its delayed action and fluid retention, would seem improper to initiate in the patients of diabetic foot ulcer who require an early control of their hyperglycaemia. Thiazolidinediones also cause reduction in bone mineral density and consequently increase fracture risk. Alpha-glucosidase inhibitors like acarbose, miglitol and voglibose do not cause a very great decline of HbA1c; 0.6% as compared to 1-1.7% with sulphonylureas and metformin. Alpha-glucosidase inhibitors inhibit alpha-glucosidase enzyme in the gut and thus, reduce absorption of glucose from the gut in to the blood stream. These agents need to be taken with the first bite of each meal and the anti-hyperglycaemic effect is meal-related, and so theoretically there are virtually no chances of hypoglycaemia with these agents. Glinides (repaglinide and nateglinide) are non-sulphonylurea insulin secretagogues and do carry a risk of hypoglycaemia because of their very nature of causing insulin release. However, their duration of action is short and so need to be administered before a meal and can be used as effective prandial glucose regulators like alpha-glucosidase inhibitors.

These oral agents address various aspects of the pathophysiology of diabetes, but the concomitant hyperglucagonaemia associated with insulin deficiency was never addressed. In the last decade, incretin-based therapies (dipeptidyl peptidase-4, DPP-4 inhibitors and glucagon like peptide-1, GLP-1 analogues) have evolved and are increasingly finding a place in the management of diabetes¹³. However, advocating their role in management of hyperglycaemia in diabetic foot ulcer will be too premature. The experience with them is limited and is gradually building up and primarily their role can be advocated for controlling hyperglycaemia. Incretins exert their effects in a variety of different target tissues- glucose disposal is facilitated in peripheral tissues such as muscle due to improved insulin secretion; directly reduce hepatic glucose production by decreasing glucagon, increasing insulin secretion and eventually suppressing fasting hyperglycaemia; directly inhibit gastric emptying; exert effect on hypothalamus to reduce appetite and eliminate cravings. Additionally, incretin-based therapies are vasodilators and so increase cardiac output slightly by improving endothelial dysfunction in the arterial tree. In fact, GLP-1 receptor agonists cause acute significant drops in systolic pressure with some reflex increase in cardiac output. The incretin-based therapies hold great promise and their exact place in the armamentarium of diabetes apart from management of hyperglycaemia, especially in

situations wherein complications of diabetes have set in will unfold in the coming years.

It is important to realise that achieving euglycaemia at the earliest possible is of foremost importance in diabetic foot ulcer patients and insulin does fit the bill in its prowess of achieving euglycaemia in a couple of days under expert hands; and fares much better over oral agents which take days to weeks to achieve euglycaemia. Also titration of drug can be done easily in case of insulin and can be done rapidly, wherein with oral agents, that is not the case. There are a number of side-effects and contraindications and care which needs to be exercised with oral agents, while with insulin it is only hypoglycaemia which in a case of overt hyperglycaemia indicates achievement of target rather than a side-effect. Additionally, it is important to realise that patients with diabetic foot will have other micro- and macrovascular complications and in most cases would be heading for secondary oral hypoglycaemic agents failure; and herein also achieving control with insulin would be more feasible and prudent. The role of oral agents specially insulin sensitisers can not be totally ruled out since they may act in concert to address insulin resistance and thus reduce insulin requirement. Prandial regulators (alpha-glucosidase inhibitors and glinides) can be used to achieve control of post-prandial hyperglycaemia as an adjunct to insulin therapy, once fasting hyperglycaemia has been brought under control. Incretin-based therapies are the new drugs in their infancy, and their place is also likely to settle down soon.

It is important to understand that chronic hyperglycaemia is at the centre-point of diabetic complications and predisposes to the triad of neuropathy, ischaemia (peripheral vascular disease) and infections, which variably combine together to produce a diabetic foot ulcer, which in turn is the harbinger of lower extremity amputations. It is pertinent to address hyperglycaemia and achieve euglycaemia to prevent diabetic foot ulcer, manage diabetic foot ulcer effectively, and prevent complications of diabetic foot ulcer including gangrene, septicaemia and lower extremity amputations.

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