Diabetes mellitus is a unmet medical need of significant social and economical impact. Diabetic foot is a chronic and avoidable complication, and still the source of non-traumatic amputations, with metabolic imbalance, macro- and micro-angiopathy, and ulceration or trauma contributing to its development. The introduction of Heberprot-P to treat diabetic foot ulcers has been a tremendous advance to reduce the amputation index and disability among patients. However, it is essential to guarantee an optimal and personalized glycemic control for achieving even more favorable results. This can be attained by implementing an intensive therapeutic strategy with multiple doses of insulin since the very first diagnose of the lesion. Due to the relevance of this topic for medical practice, here is reviewed how to establish such a therapy, and the goals for glycemic control to achieve a better quality of life when attending diabetic foot ulcer patients.

**Keywords:** Diabetes mellitus, diabetic foot, glycemic control, metabolic control, Heberprot-P

**Introduction**

Diabetes mellitus is an unmet medical need of important social and economic impact. It is estimated that about 200 million diabetic patients, suffer from diabetes mellitus type 2 (MD2) and by the year 2025 the figure is expected to be about 64 millions in Africa. The higher the population of diabetics, the higher the amount of them with chronic complications; diabetic foot among them [1-10].

Despite being one of those preventable complications, the diabetic foot is the cause of most of non-traumatic amputations. Metabolic disorders, macroangiopathy, microangiopathy, and ulceration or trauma, contribute to its development. Epidemiological studies show that 15% of diabetic patients will develop foot ulcers, which will affect their quality of life [1-10].

Always preventing ulceration, amputation and disability of people affected with DM at all cost, will be the target task of the Cuban health system, by achieving an adequate and metabolic control with the implementation of health educative strategies. However, once a wound has arisen, the opportune treatment requires fast and efficient care by a multidisciplinary team to improve diagnosis and prevent patient’s disability [7].

**Why are efficient glycemic and metabolic control important for the prevention and treatment of the diabetic foot?**

Although a relation between complications of diabetes and hyperglycemia was postulated early last century, evidences of such hypotheses have been obtained just since the last decades. The results of the study on diabetes control and those of its complications (Diabetes Control and Complications Trial, DCCT) showed that the reduction of blood glucose levels retarded the start and progression of microvascular complications in DM1 [11]. For its part, secondary analysis to this study evidenced a close correlation between the risks of developing these complications and the time of exposure to glycermia: as the levels of glyceremia came closer to the results of the study.
normal values, complications decreased [12, 13]. Other clinical studies also support the correlation between glycemic control and diabetic complications in patients with DM2. A controlled study in 110 Japanese patients with DM2 showed that a better glycemic control was achieved by administering insulin multiple injections, evidenced by lower levels of glycated hemoglobin (HbA1c = 7.1%), than with conventional treatment (HbA1c = 9.4%), and diabetic microvascular complications were reduced significantly [14, 15]. The extension of risk reduction in this Japanese study was identical to that observed in DCCT, which confirms the hypothesis that glycemic control is important in both types DM. United Kingdom Prospective Diabetes Study (UKPDS) has been the most numerous study on patients with DM2. This study included 5102 patients with recently diagnosed DM2 from 23 care centers between 1977 and 1991. Its follow-up lasted for about 10 years and it was determined that the application of intensive treatment to reduce the levels of blood glucose linical benefits, for instance, the reduction of microvascular and macrovascular complications. This study showed that each 1% reduction of HbA1c was associated with a risk lower than 21% of deaths caused by DM and less than 37% for microvascular complications, although increases the risk of hypoglycemia when HbA1c levels were lower than 7% [16].

Therefore, the intensive control of hyperglycemia in diabetic patients is very important to prevent as well as to treat associated complications as it is the case of foot ulcers. The adequate metabolic control is achieved when glycemy follow-up is accompanied by the control of other parameters, such as body weight index (BMI), arterial tension, sanguinous lipids and urine excretion, and albumin urinary excretion.

**How can an optimum metabolic control be guaranteed?**

Various studies back up intensive treatment with insulin to achieve glycemic control and the prevention or delay of complications in patients with DM, or simply, to guarantee a satisfactory evolution in acute and complex situations, as in the case of the diabetic foot. The publication of DCCT study [11] and that on interventions and diabetes epidemiological complications (EDICO) [12, 13], among others, confirm this. Besides its hypoglycemic effect, immunomodulator actions are attributed to insulin, and also as growth factor [1].

The intensive multiple dose treatment with insulin should be applied as soon as the diabetic foot arises (Wagner grade I), either with regular insulin or with fast action analogous, before breakfast, lunch and dinner and intermediate insulin (NPH) or analogous of prolonged lengthy action before going to bed. The initial dose of insulin should fluctuate between 0.25 and 0.5 U/kg body weight/ day. It is recommended to start at the lower limit to avoid poor adhesion to the treatment by the patient due to periods of hypoglycemia as well as not to administer more than 60 U of insulin per day because glycemic control improves very little while hypoglycemia frequency and weight increase. The abdominal region is the best to administer insulin, because it is absorbed with less variations: 2 cm in the outer part of the umbilical scar, and with a clockwise application sequence to prevent fat degeneration in the long term. The front and lateral part of the thigh, the back part of the arm and the gluteal region.

Measuring postprandial glycemia at 2 hours is the best parameter to adjust doses that are performed in 2 UI steps when hyperglycemia or hypoglycemia is detected one right after the other at the same time of the day (increase or reduce 2 UI with respect to the dose of insulin applied before measuring glycemia [1, 5, 7].

This multiple dose treatment plan is valid for any type of DM (Table 1).

If conventional intensive treatment is applied, fast insulin should be administered 30 minutes before eating any food. It is not the same with fast insulin analogous since starting its action takes less time (30-50 minutes in fast conventional insulin compared with 5-15 minutes in those analogous) [1, 5, 7]. An analysis of glycemia should be performed before eating anything, 2 hours after eating foot and before going to bed to evaluate metabolic control. Having a glucometer would facilitate monitoring glycemia. If not available, glycemic profiles will be performed by the clinic laboratory, while the patient is hospitalized. Glucosuria will be used as a guide for the management of insulin if there are not previous complications such as the neurogenic bladder and chronic renal failure. The possibility of determining HbA1c or fructosamin and glycemia before eating anything and postprandial (it gives immediate information) would be ideal for the management of the metabolic control diabetic patients [1, 5, 7, 17, 18]. Particularly, HbA1c will back up the 12-week control period while fructosamin shows 2 to 3 glycemia a week on average and it is recommended for patients that can not undergo HbA1c (eg., with hemoglobinopathies).

**Glycemia-regulator oral drugs are not recommended during the treatment of this condition, because they do not ensure a better glycemic control in those patients [1]. Moreover, the use of metformin could cause more serious complications. A conventional treatment with two doses of intermediate-acting insulin could be attempted in case of patients who undergo HbA1c (eg., with hemoglobinopathies).**

Health professionals should transmit therapeutic education to those people with diabetic foot, together with sustained medical care, because the success of the treatment will depend on both aspects to a great extent. Education and care should always go together.

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**Table 1. Example of treatment chart with multiple insulin doses**

<table>
<thead>
<tr>
<th></th>
<th>Intensive conventional treatment</th>
<th>Breakfast</th>
<th>Lunch</th>
<th>Dinner</th>
<th>10:00 p.m.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>fast 20% of the total dose</td>
<td>fast 30%</td>
<td>fast 30% of the total dose</td>
<td>NPH 20% of the total dose</td>
<td></td>
</tr>
</tbody>
</table>

*Modified from: Manual for the prevention, diagnosis and treatment of the diabetic foot [reference [1]].

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What are the goals for glycemic control in people with diabetic foot ulcers and that are under treatment with Heberprot-P?

1. **Goals for glycemic control should be established in patients with diabetic foot ulcer treated with Heberprot-P to assure drug effectiveness and diminish the occurrence of adverse events.** In case of risk of hypoglycemia (elderly, renal or hepatic failure, cardiovascular disease, among others), the doses of insulin are adjusted to achieve acceptable goals of glycemic control.

2. **Once ulserous wounds are healed, patients may go back to initial treatment for diabetes control, with drug dose readjustment, and always under the strict follow-up of preprandial and postprandial glycemia.**

**Conclusions**

- **Given the disability caused by ulcerous wounds in the feet of patients with diabetes mellitus, the medical activity focused on the prevention and early detection of this condition becomes extremely important.** Once diagnosed, the intervention of a multidisciplinary medical team is imperative not only to give guidance on healing the wounds and the imposition of the best specific treatments, but also towards the optimum control of diabetes and other comorbidities. In this sense, the importance of achieving good glycemic control as a target, by using multiple dose of insulin in an individualized way during the treatment with Heberprot-P. Likewise, therapeutic education aimed at achieving the adequate metabolic control as well as preventing the occurrence or relapse of future ulcerous wounds, becomes the cornerstone in patients’ follow-up.

| Table 2. Targets for glycemic control parameters in patients with DM2 |
|------------------|----------------|----------------|----------------|
| Nivel | Good control | Acceptable control | Bad control |
| HbA1c (%) | < 7 | 7 - 7.9 | ≥ 8 |
| Fasting glucose | 4.0 - 5.6 | 5.6 - 6.9 | ≥ 10.0 |
| mmol/L | mg/dL | mg/dL | mg/dL |
| Glycemia 2 hours postprandial | 5.6 - 7.8 | 7.8 - 9.9 | ≥ 10.0 |
| mmol/L | mg/dL | mg/dL | mg/dL |

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27. WHO Consultation: Definition, diagnosis and classification of diabetes mellitus and its complications. WHO/NCD/NCS/99.2