

Intensive insulin treatment and postprandial control in Type 1 diabetes

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The history of insulin therapy begins in 1922 with the first injection of 15 ml of crude dog pancreatic extract to the young L. Thompson afflicted from a life-threatening disease: diabetes mellitus (1). Though highly impure that insulin preparation saved the life to the young girl who soon gained back all of the lost body weight. It did not take too that long for insulin to generate further expectations and clear therapeutic goals. In 1935, Dr. Elliot Joslin, the founder of the modern diabetology, stated: «*the goals of appropriate therapy for those with diabetes should include a serious effort to achieve levels of blood glucose as close to those in the nondiabetic as feasible*». Since then many efforts have been spent by the patients, their physicians and pharmaceutical companies in order to achieve that goal. Nonetheless, it took another 50 years before experimental evidence was obtained to confirm that intensive insulin treatment ensuring near-normal glycemic control is effective in preventing long-term diabetic complications. In the Diabetes Control and Complication Trials (DCCT) maintenance of HbA_{1c} at an average value of 7% by intensive insulin treatment was associated, as compared to patients on conventional insulin therapy and worse glycemic control (HbA_{1c}~9%), with significant reduction in mean adjusted risk for prevention and progression of diabetic microangiopathy (2). In the primary- and secondary-prevention cohorts, the onset or progression of retinopathy was reduced by 76% and 54%, nephropathy by 50% and 50%, and neuropathy by 60% and 60%, respectively (2). These results have prompted the DCCT investigators to refresh Dr. Joslin's suggestion

by concluding that “*the majority of Type 1 diabetic patients should be treated with intensive therapy with the expectation that their long-term outcome will be measurably improved*”.

Which goal for intensive insulin therapy?

The results of the DCCT has set the goal for insulin treatment in Type 1 diabetes. In particular, the desired value for HbA_{1c} was set at ≤7%. Though HbA_{1c} is the best integrated measure of body tissue exposure to glucose, it was suggested that it may not necessarily reflect all components of glycemic control. Within the DCCT, patients on intensive insulin therapy had lower incidence of microangiopathy as compared with patients on conventional therapy for the same degree of HbA_{1c} (3; DCCT. *Diabetes* 1995; 44: 968). The reason for this difference is not clear, but it was speculated by the investigators that “*other features of diabetic glucose control, which are not reflected by HbA_{1c}, may add to or modify the risk of complications. For example, ...the extent of postprandial glycemic excursion...*” (3). Fig. 1 summarizes this concept indicating how two hypothetical diabetic patients may have similar HbA_{1c} but differ in term of stability and fluctuation of plasma glucose concentrations around the mean level. More recently, Derr. R. showed that HbA_{1c} levels reflect mean daily values of glycemia, but not glycemic instability throughout the day (4). In summary, the risk of developing complications may result from absolute plasma glucose levels as well as

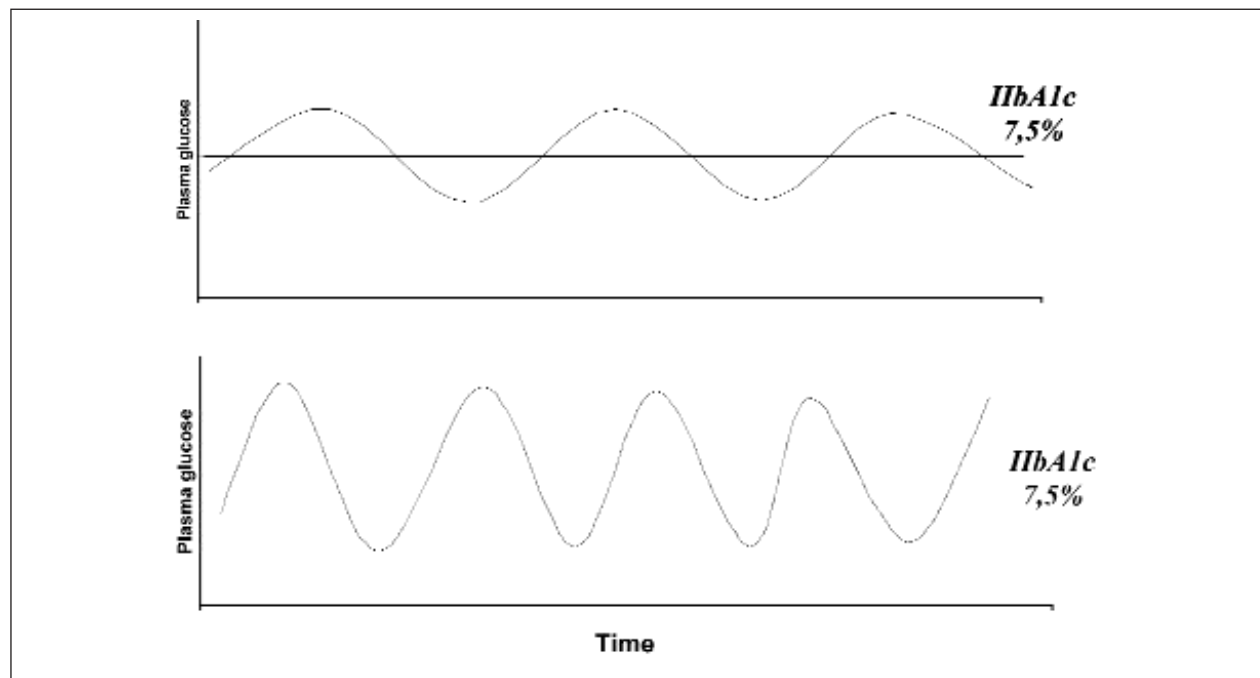


Figure 1. Two hypothetical diabetic patients may have similar HbA_{1c} but differ in term of stability and fluctuation of plasma glucose concentrations around the mean level

their rapid changes (fluctuations). It is not so infrequent to observe in insulin-treated Type 1 diabetic patients wide swings in glucose levels going from hypo- to hyperglycemia.

Evidence for a negative role of glucose fluctuations

Several in vitro studies provide evidence that rapid changes in glucose concentration can trigger mechanisms involved in the pathogenesis of diabetic complications. Rapid drops in glucose concentration have been shown to induce apoptosis in retinal capillary pericytes cultured in the presence of high glucose (5). Acute hyperglycemia is associated with many negative effects (revised in Del Prato et al., 6). It causes an increase in retinal blood flow and is associated with a concomitant increase in the glomerular filtration rate in patients with diabetes. Moreover, intermittent rather than constant hyperglycemia induces an increase in collagen production by cultured mesangial cells.

Rapid changes in plasma glucose concentration reduce motor and sensory nerve conduction velocity. Mealtime glucose excursions exert marked effects on the coagulation process by shortening the half-life of fibrinogen and increasing the circulating levels of fibrinopeptide A, thrombin, prothrombin fragments, and factor VII. Hence, the acute changes in plasma glucose concentrations may result in a thrombophilic condition as platelet adhesion is also enhanced by hyperglycemia. A significant activation of PKC- α , β 1 and β 2, beta1 has been observed in platelets from healthy subjects undergoing a 2-hr hyperglycaemic clamp. The atherogenic process may be facilitated by the increase in adhesion proteins triggered by hyperglycemic peaks. Finally, acute hyperglycemia causes endothelial dysfunction, possibly through a reduction of nitric oxide availability. The negative effects of acute hyperglycemia are likely the result of labile non-enzymatic glycation and production of free radicals with ensuing oxidative stress (7). Taken altogether this information supports the need for a stricter control of

glucose fluctuations. Since fluctuations are mainly associated with meal ingestion, control of post-prandial hyperglycemia may be critical in ensuring overall glycemic control as well as avoiding excessive glucose fluctuation.

Management of post-prandial hyperglycemia

The need for more comprehensive glycemic control has been acknowledged in the guidelines of all major scientific and professional associations (Tab. 1), though some differences in the post-prandial glucose levels still exists. Thus, while for the American Diabetes Association the recommended value is <180 mg/dl, a lower post-prandial glucose concentration (<140 mg/dl) is indicated by the American Association of Clinical Endocrinologists and the American College of Endocrinology.

Control of post-meal plasma glucose levels requires a careful reconstruction of physiologic plasma insulin profile. This goal is nowadays facilitated by the availability of fast-acting insulin analogs (lispro, aspart, and in the near future glulisine insulin) which ensure a more rapid increase of insulin levels with meal ingestion, lower post-prandial glucose, and reduced risk for late hypoglycaemia (8). Replacement of regular insulin with human insulin lispro (9) or aspart (10) was associated with moderate though significant reduction of HbA_{1c} in Type 1 diabetic patients. Moreover, the fast kinetics of these insulin analogs provides greater therapeutic flexibility. Although pre-meal administration of insulin aspart is always the preferred time of administration of fast-acting insulin analogs, post-prandial administration of insulin aspart in children and adolescent with Type 1 diabetes was found to be an effective and safe alternative in the limited case

this approach may be needed (11). Other components of diabetes management should be necessarily taken into account in order to ensure accurate post-meal glucose control. With this respect medical nutrition therapy (12) and diabetes self-management education (13) play an essential role. Several studies have showed a strong relationship between premeal insulin dosage, carbohydrate content of the meal, and post-prandial glucose levels (14-17). In type 1 diabetic patients the total amount of carbohydrates in the meal does not influence glycemic control as far as premeal insulin dosage is accordingly adjusted (14). This can be obtained only by adequate education and training of diabetic patients.

Comprehensive glycemic control: the indissolubility of fasting and post-prandial glycemia

If introduction of fast-acting insulin analogs has provided a valuable tool for more effective control of post-prandial hyperglycemia, they have also stressed the need for accurate replacement of basal insulin. In a group of well controlled Type 1 diabetic patients (HbA_{1c}: 6.67±0.10%), administration of human insulin analog lispro at mealtime together with low dose NPH-insulin lowered post-prandial as well as pre-prandial plasma glucose concentration leading to a small though highly significant reduction of HbA_{1c} (-0.33) (18). The use of multiple dose of NPH, however, may be seen cumbersome by patients if not by physicians themselves. Moreover, NPH insulin does not provide the desirable kinetics capable to ensure a flat, constant basal insulinization. The ideal solution could be the use of continuous sub-cutaneous insulin infusion of fast-acting insulin analogs. This result in constant basal insulin levels which can be modified on the basis of the circadian needs while ensuring rapid increase in plasma insulin at the time of the meal bolus (19, 20). Similar insulin profiles as obtained by CSII have been reported with the use of glargine, a long-acting insulin analog (21). The change in the isoelectric point of this analog causes precipitation at the neutral pH of subcutaneous tissue that is followed by constant release into the blood stream. This confers to insulin glargine a peak-less plasma insulin profile

Table 1. American Diabetes Association (ADA)- and American Association of Clinical Endocrinologists (AACE)/American College of Endocrinology (ACE)-recommended goals for glycaemic control.

Biochemical Control	Recommended Goals	
	ADA	AACE/ACE
HbA _{1c} (%)	<7.0	≤6.5
Fasting Plasma Glucose (mg/dl)	90-130	<110
Post-Prandial Glucose (mg/dl)	<180	<140

lasting for no less than 24hrs, making it ideal for once a day administration. Substitution of NPH-insulin with glargine was not found to determine significant reduction in HbA_{1c}, though fasting plasma glucose can be reduced (22) with significant reduction in the number and severity of nocturnal hypoglycaemias (23). Insulin glargine is the first of a new generation of long-lasting insulin. As opposed to glargine, insulin detemir is an acylated insulin preparation that upon injection is bound to albumin from which is detached at regular rate (24). The clinical investigations so far available indicate that detemir insulin may provide advantages with respect to NPH-insulin. Thus, detemir insulin, administered twice a day, was associated with more predictable glycemic control and lower risk of hypoglycaemia than NPH-insulin in patients with Type 1 diabetes on a basal-bolus regimen with pre-meal insulin aspart (25).

Conclusions

After almost 70 years the suggestion of Dr. Joslin has not lost actuality. If any it has been gathering more and more support with the accumulation of clinical data. The goal of treatment in Type 1 diabetes must be a life as long as possible free of complications. Achieving near normal glycemia while reducing the risk for threatening hypoglycaemia is the way. Any period of such a strict glycemic control is going to be rewarding. The Epidemiology of Diabetes Interventions and Complication (EDIC) trial Research Group has been responsible for the post-DCCT surveillance. Four years after closing the DCCT with its intensive patients' reinforcement, the HbA_{1c} difference between intensive and conventionally treated patients has become thinner and thinner. In spite of similar HbA_{1c}, the cumulative incidence of diabetic microangiopathy remains significantly lower in patients belonging to the original intensive treatment group (26). This has potent clinical implications as it implies that a sort of conditioning effect exists from antecedent glycemic control. The implication is also evident for children with Type 1 diabetes: the effort should be to find the way to guarantee strict metabolic control, a tough line but a rewarding one for the young patient.

In the attempt to reach such an ambitious goal the diabetologist must appreciate all components of glycemic control. HbA_{1c} is a solid marker for tissue body glucose exposure, but it must be recognized that both fasting, pre-prandial and post-prandial plasma glucose levels contribute to its value indicating the need for a comprehensive approach. This is what we have defined as the quantitative effect of hyperglycemia leading to diabetic complications through the mechanisms elegantly described in the recent review by Brownlee (27). However, the diabetologist must be aware of a "qualitative effect" of hyperglycemia according to which poor stability in glycemic control contributes to the risk of diabetic complication on top and above the quantitative effect (28). More therapeutic tools are available nowadays to fulfil Dr. Joslin's precious suggestion.

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