CLINICAL IMPLICATIONS OF BASIC RESEARCH

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Engineering an Insulin Complex to Treat Diabetes

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It has been more than 100 years since the discovery of insulin, an advance that changed diabetes from a disease associated with substantial morbidity and mortality to a manageable chronic condition. Today, insulin therapy is closer to the goal of mimicking physiologic endogenous insulin profiles with the availability of rapid and long-acting insulin formulations, continuous glucose monitoring, and hybrid closed-loop systems. Yet, many persons with diabetes who receive insulin therapy continue to have unmet insulin needs and may remain with extended intervals of blood glucose levels above and below the recommended targets. Innovations to improve insulin therapy include the engineering of insulins that primarily act on the liver, as well as "smart" or glucose-responsive insulins (GRIs),[1,2] which are active when the blood glucose level increases and inactive when the level is in the normal range.[1-3] They mimic beta-cell function by releasing insulin when needed on the basis of varying blood glucose levels, increasing time in range for daily glycemic excursions, and reducing hypoglycemia or hyperglycemia in persons with diabetes. Of interest, then, is a new type of subcutaneously injected GRI reported by Zhang et al.[4]

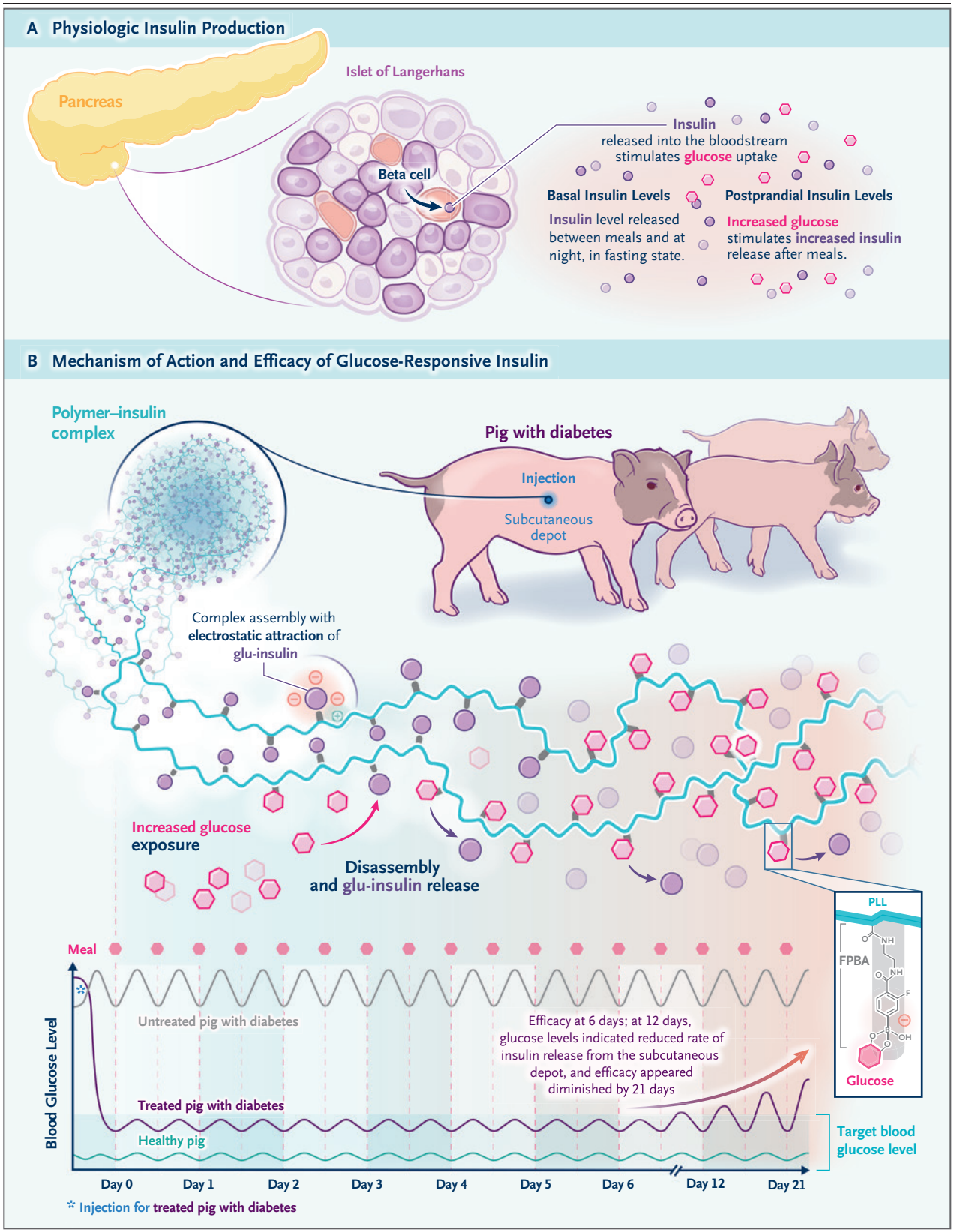
These authors evaluated the GRI conjugate according to its capacity to replace both prandial and basal needs using laboratory-based assessments and preclinical mouse and mini-pig models (Fig. 1). First, they tested the in vitro kinetics of glucose-stimulated insulin release by the GRI complex and found both glucose responsiveness and improved control (mean blood glucose level, <200 mg per deciliter [11.10 mmol per liter]) in mice with streptozotocin-induced diabetes over the course of a week, with diminished insulin release (and efficacy) at 12 and 21 days. Intraperitoneal glucose-tolerance tests showed commensurate glucose responsiveness over this same period.

The performance of this GRI was also evaluated in three diabetic mini-pigs, which more closely model the physiological characteristics of humans. The complex appeared to have sustained efficacy on blood glucose levels for a week and had enhanced efficacy as compared with daily insulin glargine injections. Collectively, these observations suggest that this GRI formulation may have clinical potential as a basal insulin. In both the studies in mice and mini-pigs, minimal hypoglycemia was observed, and the insulin complex had minimal toxicity and caused no apparent formation of fibrous capsules.

This insulin complex formulation has potential for clinical translation, but several challenges must be addressed. First, the GRI must be shown to be responsive to a narrow glucose range, as may be required to adequately maintain blood glucose levels in humans. From the in vivo studies, it is not clear that it meets this requirement, because responsiveness was not proportional to the increment in blood glucose level and was much lower than the amount of insulin release by beta cells in response to glucose changes.[5] Second, the design of the injected formulation is such that there is a reduction in the amount of insulin released after multiple cycles, making it difficult to control the dose — which would be

Figure 1 (facing page). Testing a Subcutaneously Injected Glucose-Responsive Insulin.

Panel A shows physiologic insulin production, and Panel B shows the in vivo effects of the subcutaneously injected glucose-responsive insulin studied by Zhang et al.[4] FPBA denotes 4-carboxy-3-fluorophenylboronic acid, glu-insulin gluconic acid–conjugated insulin analogue, and PLL poly-L-lysine.



particularly problematic for persons with type 1 diabetes. The timing and extent of hyperglycemic episodes would affect the durability of the depot — that is, marked hyperglycemia in the first few days could deplete the depot and thereby impair later glycemic control. Third, demonstration of high selectivity for glucose binding (and thus invulnerability to insulin release induced by other stimuli)[5] would be reassuring.

Another challenge is whether the GRI can really mimic endogenous insulin release by responding to rapid changes in glucose levels and thus be considered for bolus or prandial therapy in studies involving humans. Given the subcutaneous position of the depot, there would be a time lag in glucose diffusion from blood to interstitial fluid at the subcutaneous location of the depot. A GRI that can respond to all kinds of meals and snacks is a steep requirement. However, the data reported by Zhang et al. are consistent with their GRI conjugate serving basal needs. It would also be of interest to compare their GRI formulation with the new weekly formulations in development with respect to patients' burden of care and glucose control. Finally, the short-term data reported by Zhang et al. are encouraging with respect to toxicity, but the potential for long-term toxic effects needs to be addressed.

The study by Zhang et al. adds to the growing body of work on GRIs and provides proof of concept on a biodegradable insulin complex formulation that releases insulin in a glucose-responsive manner, showed long-term efficacy in vivo, and appeared to have minimal toxicity. However, before this agent can become a viable option in humans, additional studies are required.

Disclosure forms provided by the authors are available at NEJM.org.

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