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Beta Cell Deficit in Diabetes: Implication for Treatment of Type 2 Diabetes

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There is global consensus that type 1 diabetes is characterized by a loss of beta cells, mainly through autoimmune-mediated beta cell destruction [1]. On the other hand, obesity, hyperinsulinemia and insulin resistance have often been emphasized as characteristics of type 2 diabetes in contrast to type 1 diabetes. However, studies have shown that if hyperinsulinemia is corrected by insulin sensitivity, insufficient insulin secretion in patients with type 2 diabetes and even those with Impaired Glucose Tolerance (IGT) becomes apparent [2-4].

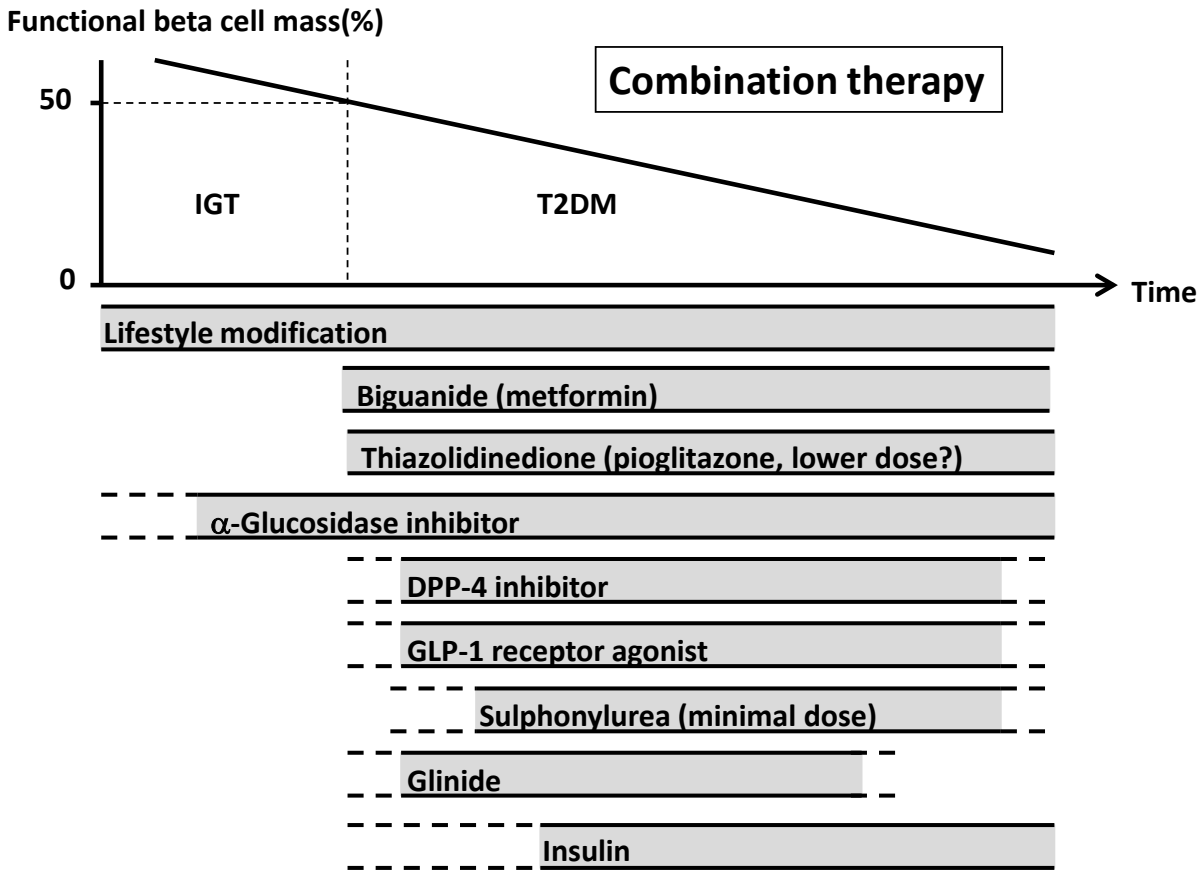
Moreover, recent autopsy studies consistently demonstrated that beta cell mass is reduced by approximately 30 to 65% in patients with type 2 diabetes compared with non-diabetic subjects [5-7]. Although the extent of the reduction in beta cell mass differs between patients with type 2 diabetes and those with type 1 diabetes in whom beta cell mass is reduced by approximately 90 to 98% [8,9], these results strongly suggest that beta cell deficit is a core pathogenetic feature of not only type 1 but also type 2 diabetes. The deficit in beta cell mass in type 2 diabetes remains to be established because of the inevitable limitations of histological studies of the human pancreas; however, collectively, “functional beta cell mass” must be reduced in patients with type 2 diabetes.

In patients with type 2 diabetes, there is a deficit in functional beta cell mass, and more importantly, it progressively deteriorates with time [10-12]. This decline in functional beta cell mass in patients with type 2 diabetes is associated with deterioration of glycemic control [13] and probably glycemic variability [14]. Thus, preservation or recovery of functional beta cell mass is an important therapeutic strategy for the treatment of type 2 diabetes as well as type 1diabetes.

A proposed concept of a treatment strategy for type 2 diabetes in relation to functional beta cell mass is shown in Figure 1. Currently, the most effective way to preserve or restore beta cell function is to reduce beta cell workload [11,15]. Since metformin

reduces insulin demand and beta cell workload through lowering hepatic glucose production, the use of metformin in addition to lifestyle modification should be considered in as an early stage of diabetes as possible, if not contraindicated. Since incretin therapy is expected to improve beta cell function in addition to its glucose-lowering effect [16], it also can be considered in a broad range of disease stage. In contrast, the use of insulin secretagogues, sulphonylureas, may not be considered as initial therapy but rather for use at a lower dose aiming to support the insulinotropic effect of incretin therapy. Since to date neither drug can cure diabetes, combination therapy should be considered in most cases.

Figure 1. Proposed concept of treatment strategy for type 2 diabetes in relation to functional beta cell mass. Medications not approved in Japan (as of September 2013) are not included in the figure. IGT; Impaired Glucose Tolerance, T2DM; type 2 diabetes.



Beta cell functional capacity may also be involved in the different phenotypes of type 2 diabetes among ethnics. There is a striking difference in mean BMI between Asian patients with type 2 diabetes (approximately 23) compared with Caucasian patients with type 2 diabetes (approximately 30) [17,18]. Recent studies suggested that functional beta cell capacity is different among ethnicities, and less in Asians compared to Caucasians [19,20]. Thus, a treatment strategy to preserve or restore functional beta cell mass may be more important in Asians than in Caucasians. Further research is needed to clarify this issue.

In conclusion, a deficit in functional beta cell mass is a core pathogenetic feature of not only type 1 but also type 2 diabetes. Establishment of a treatment strategy aiming at preservation or restoration of functional beta cell mass is an urgent issue for the treatment of type 2 diabetes.

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