Prevention of type 2 diabetes: Prevention of beta cell “karoshi”

The number of patients with type 2 diabetes (T2DM) continues to increase despite the recent advances in pharmacological therapies for T2DM. This fact indicates that we still may not sufficiently understand the pathophysiology of this disease.

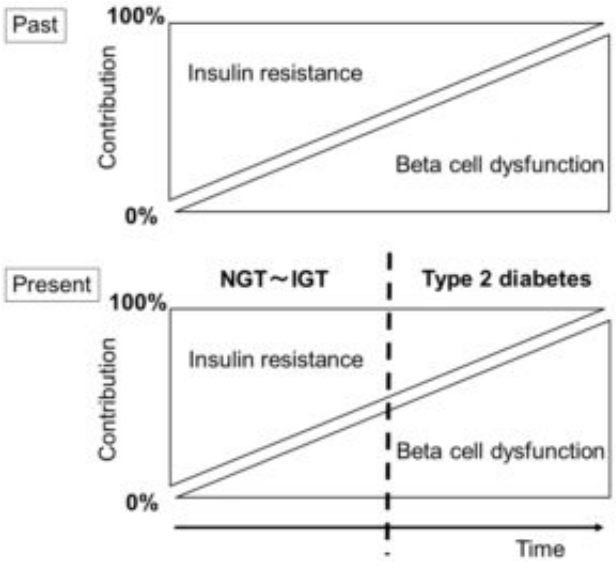

Fig. 1. New concept of relative contributions of insulin resistance and beta cell dysfunction in type 2 diabetes. Type 2 diabetes never develops without beta cell dysfunction. This new concept indicates the need for beta cell protection before the onset of T2DM. NGT; normal glucose tolerance. IGT; impaired glucose tolerance.

By using human pancreas tissue, we and others have shown that the number of beta cell which secrets insulin is reduced by half in patients with T2DM. UK Prospective Diabetes Study (UKPDS) has also shown that beta cell function was reduced by half at the time of diagnosis and further progressively declines by 5% per year in patients with T2DM. Although T2DM is characterized by obesity and insulin resistance, these findings highlight the critical role of deficit of beta cell for development and progression of T2DM and change the current concept of T2DM (Fig. 1).

We have also found that beta cell function assessed by C-peptide measurement progressively declines with disease duration of T2DM in Japanese population. In that study we found that the decline of beta cell function was steeper in patients with obesity compared with those without obesity.

What does this mean? Obesity induces insulin resistance and in this setting beta cell will

compensate by increasing insulin secretion. In humans, since the number of beta cell increases to a lesser extent, insulin secretion per beta cell, i.e., beta cell workload increases. Therefore, these findings imply that excess workload of beta cell likely causes further damage of beta cell. Further damage of beta cell eventually leads to beta cell death. So we propose that we should call this “beta cell karoshi”. Once beta cell died and the number of beta cell reduced, the rest of the beta cell needs to work even harder, causing next “karoshi”. This explains the progressive nature of T2DM (Fig. 2). The key strategy to avoid beta cell “karoshi” is thus to reduce the beta cell workload.

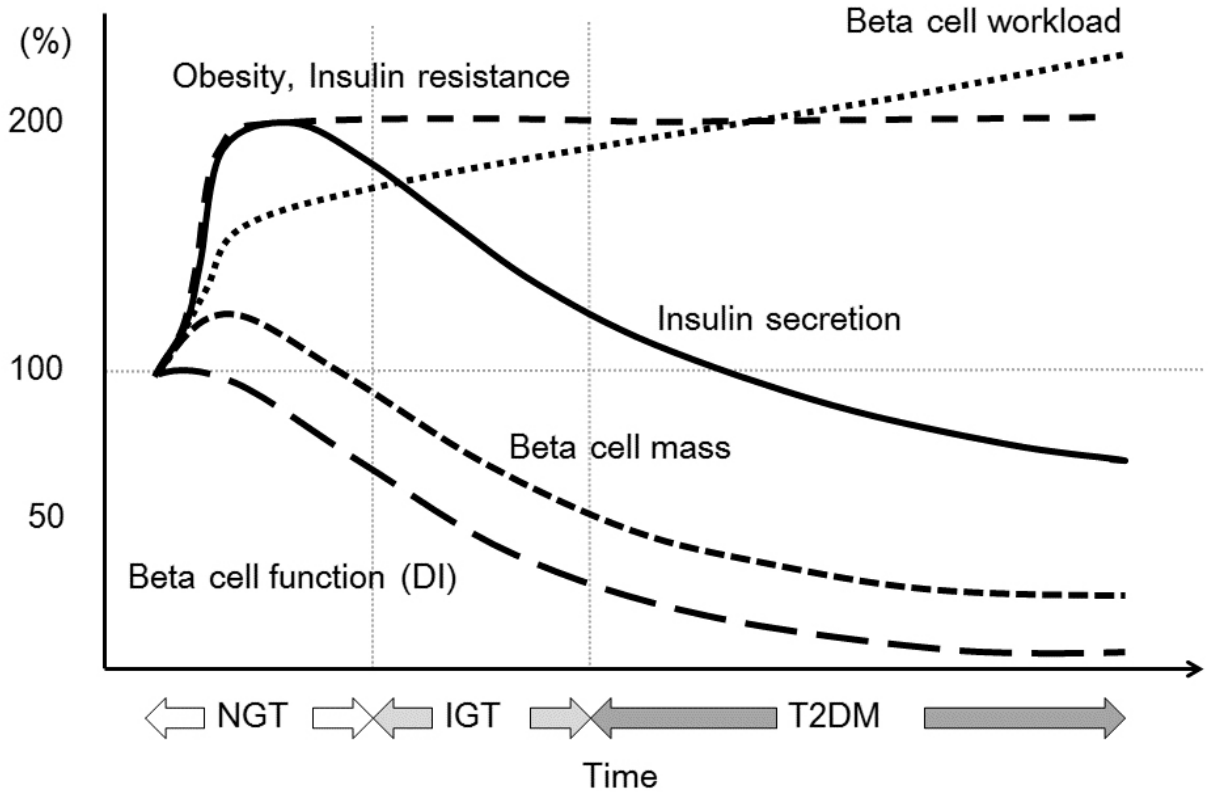

Fig. 2. Change in functional beta cell mass during the development of T2DM. Recent studies have suggested that functional beta cell mass is already reduced at the onset of T2DM. Excess workload on beta cells induced by insulin resistance continues, stress-induced beta cell death, “karoshi”, may eventually occur, and beta cell mass is reduced even before the onset of diabetes.

So, what should we learn from this? It is clear that healthy lifestyle is important for prevention and treatment of T2DM. However, it is not easy to keep healthy lifestyle in daily life. The motivation is one of the most important factor to foster us to keep healthy lifestyle. The motivation stems from the correct understanding of the nature of the disease. It is thus important for us to acknowledge that our beta cell is a precious and limited resource for prevention of T2DM and we need to protect

them from “karoshi”. This concept may change our motivation to adhere healthy lifestyle and protect us from the development of T2DM.

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Publication

Postprandial C-Peptide to Glucose Ratio as a Marker of ? Cell Function: Implication for the Management of Type 2 Diabetes.
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