Editorial

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# Lessons from Diabetes Research: Should We Change Our Way of Thinking on Diabetes to Prevent or Better Treat This Pandemic?

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Diabetes is a pandemic disease. According to the International Diabetes Federation, the number of people with diabetes over the world is projected to reach 415 million in 2015 and to rise to 642 million in 2040 [1]. Every 6 seconds, a person dies from diabetes (5.0 million deaths in 2015). The cost of diabetes treatment is estimated to be 12% of global health expenditure (673 billion dollars in 2015). Diabetes is not only a medical problem but also one of the biggest socioeconomic problems in the world.

Most patients with diabetes are classified as having type 2 diabetes (T2DM). T2DM is characterized by insulin resistance and beta cell dysfunction [2]. Since people with T2DM are typically characterized by obesity, insulin resistance and hyperinsulinemia, T2DM is often assumed to contrast to type 1 diabetes (T1DM) in which beta cells are destroyed by autoimmune attack, and the significance of beta cell dysfunction in T2DM is often underestimated or even ignored.

However, recent studies have shown that beta cell mass is decreased in both T1DM and T2DM suggesting the presence of beta cell deficit in T2DM. The deficit of beta cells in patients with T2DM is observed across ethnic groups suggesting that a deficit of beta cells is a universal pathological feature of T2DM [3-9]. Thus, the concept of diabetes is now changing to a new one in which deficit of beta cells is a common pathological feature of both T1DM and T2DM [10]. The distinctions between the two are the cause (autoimmune vs. insulin resistance) and the extent of deficit (almost complete vs. partial) (Figure 1).


**Figure 1:** Changing concepts of pathogenesis of type 1 and type 2 diabetes in the past and present.

Recent studies have also shown that diabetes is a progressive disease. Progressive loss of beta cell function has been reported, while insulin resistance remains unchanged with the disease duration suggesting that the progressive nature of T2DM is mainly due to progressive loss of beta cell function [10,11]. The UK Prospective Diabetes Study (UKPDS) showed that beta cell function assessed by homeostasis model assessment (HOMA) was decreased by ~50% at the time of diagnosis of T2DM, and progressively decreased by ~5% per year [12]. This also suggests that loss of beta cell function begins ~10 years before the onset of T2DM. These findings highlight that beta cell loss has already started far before the onset of hyperglycemia (Figure 2).

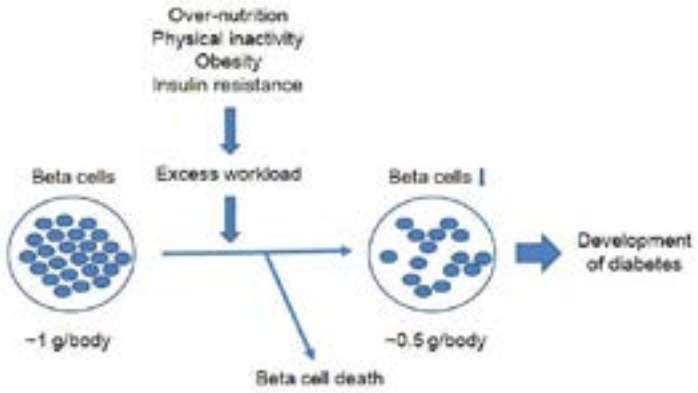


**Figure 2:** Change in functional beta cell mass during the development of T2DM. Recent studies have suggested that functional beta cell mass is already reduced at the onset of T2DM. Excess workload on beta cells induced by insulin resistance continues, stress-induced beta cell death may eventually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

This new concept indicates that T2DM does not develop in the absence of beta cell dysfunction. That is, beta cell deficit is necessary for the development of T2DM (Figure 3). It has been

shown that, unlike in rodents, compensatory beta cell expansion in response to insulin resistance is very limited in humans [8,9,13,14]. Based on these findings, we here propose the beta cell workload hypothesis [10]. In the face of insulin resistance, beta cells work harder to secrete more insulin to maintain normoglycemia. If excess workload on beta cells continues, stress-induced beta cell death may eventually occur and beta cell mass is reduced. Once beta cell mass is reduced, each residual beta cell will be exposed to an even greater workload, which results in a vicious cycle fostering further beta cell loss, reflecting the progressive nature of this disease. Since unfortunately the current therapy for T2DM does not reverse or cure the disease, this concept emphasizes the importance of beta cell preservation for the prevention of T2DM.

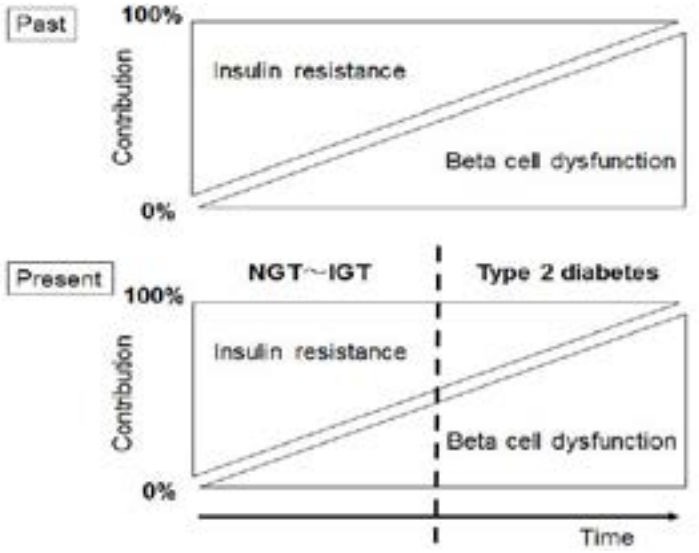


**Figure 3:** New concept of relative contributions of insulin resistance and beta cell dysfunction in type 2 diabetes. Type 2 diabetes never develops without beta cell dysfunction. This new concept indicates the need for beta cell protection before the onset of T2DM. NGT; normal glucose tolerance. IGT; impaired glucose tolerance.

This change in the concept of diabetes is important because current therapy for diabetes cannot reverse or cure the deficit of beta cells. From knowledge obtained from a number of clinical studies in patients with T2DM and prediabetes, we now appreciate that reduction of beta cell workload is a key strategy to preserve residual beta cell function [10,15]. Elimination of insulin resistance by metabolic surgery is expected to be a potential therapy leading to a cure for diabetes [16]. However, even if drastic weight loss can be achieved after surgery, remission of diabetes occurs only in a small proportion of subjects [17]. This suggests that even if insulin resistance can be eliminated, beta cell deficit remains in patients with T2DM.

So, what should we learn from this fact? We really need to focus on the protection of beta cells prior to the development of diabetes, emphasizing education not only of people with diabetes but also those without diabetes. We need to share this new and important concept of diabetes with the general population all over the world and recognize that most of the functional beta cell mass is already lost when hyperglycemia develops. Development of hyperglycemia in the diabetic range may indicate that the person has already crossed the point of no-return in terms of beta cell reserve.

A key to the prevention of T2DM is lifestyle modification, including a healthy diet and increased physical activity [18,19]. Lifestyle modification is indeed the most fundamental and effective therapy for patients with T2DM as well [20,21]. Considering the fact that one in eleven adults throughout the world are assumed to have diabetes lifestyle modification for patients with T2DM should apply to most adults (and children) all over the world [1]. Thus, we should learn from patients with T2DM.

Lifestyle modification requires self-management. It is therefore important for not only patients with T2DM but also the general population to correctly understand diabetes in order to empower them. Our mindset should change from saying that a bad lifestyle is not good for your health to saying that your beta cells should be protected through a healthy lifestyle, to prevent the development of T2DM. There is a limited source of beta cells in the human body, which weigh only ~1 g. Having a healthy lifestyle is a consequence of individual choice. To maintain individuals' motivation to continue making healthy choices in their daily life, imagining protecting their own beta cells from overwork that leads to beta cell death or "karoshi" could empower and motivate them to make good choices.

So, diabetes is now a serious social problem throughout the world. Patients with T2DM provide an important message to our society. Lifestyle modification is the most fundamental treatment for T2DM as well as its prevention. A huge body of work has revealed that protection of beta cells is undoubtedly a key message to achieve this goal. We should learn from patients with T2DM and fight with them to prevent this pandemic disease.

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