Clinical staging of type 2 diabetes: The time has come

In the 2010 October issue of this journal, the Japan Diabetic Society reported the revised version of the diagnostic criteria for diabetes incorporating glycated hemoglobin values[1]. The changes make it easier and simpler to make a proper diagnosis of diabetes as a disease of chronic hyperglycemia reflected by elevated glycated hemoglobin concentrations caused by insufficient insulin action. There appears to arise some misunderstanding, however, that the new criteria might narrow the range of borderline diabetes or reduce its implication. As the revised criteria clearly describes in its statement, it should be re-emphasized that the change does not exclude the category of impaired glucose tolerance (IGT) or impaired fasting glucose (IFG), reserving the importance of the glucose tolerance test (GTT) for confirmation of borderline diabetes. As widely admitted, the diagnosis of diabetes does not itself directly indicate its etiology or the method of treatment, but simply the morbidity. When we are in the muddy stream of a diabetes epidemic, the prevention of diabetes must be a prime target for current health-care projects. The outcome of this effort will be immense, not only for the reduction of the socioeconomic burden, but also for the improvement of quality of life in diabetic patients. One such model might be represented by the results from recent mega-studies that showed a reduction of newly-onset diabetes in a group with suppression of postprandial hyperglycemia treated with α-glucosidase inhibitor or metformin[2].

What should then be done for the patients who already have overt diabetes when the diagnosis is made? The main purpose of treatment in these patients has been the prevention of the onset or halting the development of specific complications of diabetes. Every effort is required for this purpose by maintaining tight blood glucose control with insulin treatment, oral hypoglycemic agents or insulin sensitizers. As a consequence, it is expected that a significant reduction of patients with complications of diabetes, such as blindness, renal failure and limb problems, will be seen. The risk of cardiovascular and brain stroke will also be much decreased. Indeed, the diabetes control and complication trial (DCCT) and epidemiology of diabetes interventions and complications (EDIC) studies confirmed the value of blood glucose control for the prevention of complications, retinopathy, nephropathy and neuropathy. Furthermore, in cases of kidney complications, tight blood glucose control added to angiotensin–renin receptor blockade and a low protein diet might also be expected to cause regression of the kidney complications. In such an effort, validation of the effects might be confirmed by following the guideline of clinical staging of each complication. In each complication, specific indices, such as albuminuria or ophthalmic fundic status, have been used for the evaluation of clinical staging. In neuropathy as well, it has recently been shown that epidermal nerve fiber loss emerges very early in the course of the disease, and gradually the loss will become robust with the duration of diabetes. Intriguingly, lifestyle intervention by regular exercise and lowering bodyweight was shown to successfully not only suppress the progression of nerve fiber loss, but promote regeneration in prediabetic patients[3]. As the presence of subjective symptoms does not indicate the clinical staging of neuropathy, we have to depend on the pathological background or nerve conduction deficits for the clinical staging of neuropathy. Even if severe pain can be alleviated in diabetic neuropathic patients by pregabalin or duloxetine, we should be aware that the treatment is only for symptoms and it does not mean the inhibition of the progression of the disease. By contrast, aldose reductase inhibitor is a real attempt to halt the progression of the disease as a fundamental treatment. Thus, we always have to keep in mind whether the treatment is a symptomatic or fundamental one, although it is desirable that a single treatment has both implications. In this setting, the treatment effects might be evaluated by following specific guidelines of clinical staging.

With the introduction of new criteria for diabetes, what do we consider is the best indicator for the clinical staging of diabetes itself? The question has far-reaching importance for the direction of the treatment of diabetes. Conceptually, type 2 diabetes is classified into borderline diabetes, insulin non-requiring diabetes, insulin-requiring diabetes for glycemic control, and for survival (Figure 1)[1]. However, what determines the insulin requirement in type 2 diabetes – hyperglycemia, glycated hemoglobin, C-peptide, homeostasis model assessment of β-cell function (HOMA-β) or insulinogenic index? Are all patients who require insulin severely diabetic or in the advanced stage? A recent series of studies has shed some light on the pathological background of type 2 diabetes, which is a disease of progressive decline of β-cells in pancreatic islets[4]. The contention is shared by the early reduction of β-cell mass in patients with a prediabetic condition. In fact, even before the diagnosis of diabetes, more than 50% of β-cells have already disappeared in patients with IFG. In the case of overt diabetes, more than 70% of β-cells appear to be diminished[5]. It is therefore likely that β-cell loss starts very early and insidiously proceeds without any signs and symptoms in patients who will develop overt diabetes. During the prediabetic stage, remaining β-cells might be activated to compensate for the lost function caused by cell loss. The overwork of β-cells does not last long, and the patients eventually manifest hyperglycemia sufficient for diagnosis of diabetes. The staging of diabetes might therefore be determined by the amount of β-cell loss, not simply by the insulin requirement or insulin secretory capacity. If the aforementioned story applies to most type 2 diabetic patients, the treatment that protects from cell death and

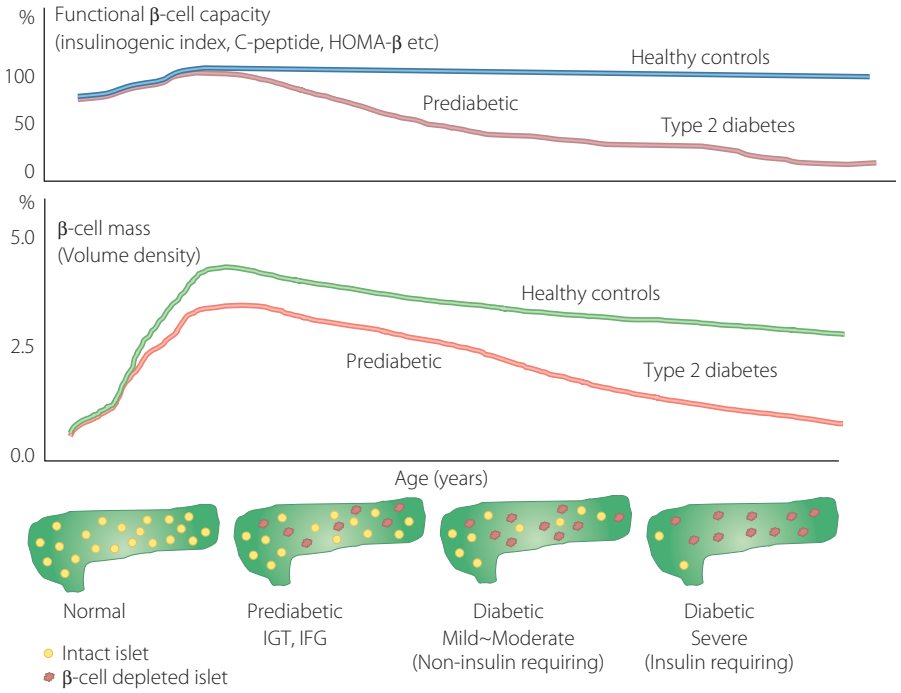

Figure 1 | Natural history and clinical staging of diabetes. Over the development of type 2 diabetes, islet β-cell function might gradually be deteriorated. It might be reflected by the elevation of fasting blood glucose, reduced insulin secretion or lowered insulinogenic index. In contrast, progressive depletion of islet β-cell mass is a pathological hallmark of type 2 diabetes. The clinical staging of diabetes might be determined by the extent of the deficit of β-cell mass. HOMA-β, homeostasis model assessment of β-cell function; IFG, impaired fasting glucose; IGT, impaired glucose tolerance.

promotes replication of β-cells should be essential. Whether such benefits are obtained from the new treatment with incretin or other compounds currently under the clinical trial should carefully be evaluated in future investigations on humans. Perhaps the effects might be different when comparing the results between the early stage and advanced stage of type 2 diabetes.

It is just the beginning of a new era where clinical staging of diabetes based on pathological background is considered to be crucial for the direction of treatment. However, how can we estimate the severity of β-cell loss in living diabetic patients? To solve this problem, much effort for body imaging of β-cells using appropriate markers and sophisticated machines is now in progress to quantify the exact mass of β-cells in living bodies. Data on β-cell dynamics in aging or the effects of obesity are now accumulating from the studies on humans. We have to also explore the relationship between islet β-cell mass obtained from autopsy or surgical cases and functional measures of β-cells when the tissues are taken. Of course, we have to take dysfunction of β-cells into account for the severity of disease, but the ultimate feature of this disease might be a marked reduction of β-cells, requiring insulin replacement. It might be too simplistic to consider in this way, but the introduction of β-cell loss into the severity of disease is meaningful and translatable to determine the method of treatment and to what extent it will be effective. Unfortunately, the data on β-cell mass are not always consistent or comparable among the laboratories. To this end, establishing systems for easy use of human samples and standardization of measurement of the islet β-cell mass is urgently required so that the worldwide comparisons become feasible.

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