



Brief Note

Staging of type 2 diabetes mellitus

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ABSTRACT. There is currently no reported staging system for type 2 diabetes mellitus. Here, I attempted to stage type 2 diabetes mellitus in order to help clinicians, patients, and other interested individuals to effectively evaluate patient conditions.

Key words: Type 2 diabetes mellitus; Stage of disease

There is currently no reported staging system for type 2 diabetes mellitus. Here, I attempted to stage type 2 diabetes mellitus to help clinicians, patients, and other interested individuals to effectively evaluate patient conditions. Staging may be helpful in the management of diabetes and could favorably affect health outcomes of patients with diabetes. However, the staging of type 2 diabetes requires revision, and long-term outcome studies are necessary to validate the criteria.

Type 2 diabetes can be classified into five clinical stages:

Stage 1: Pre-diabetes. This group includes patients in the following conditions: a fasting plasma glucose (FPG) level of 100-125 mg/dL (5.6-6.9 mM) (impaired fasting glucose), 2-h plasma glucose (PG) level on oral glucose tolerance test (OGTT) 140-199 mg/dL (7.8-11.0 mM) (impaired glucose tolerance), a hemoglobin A1c (HbA1c) level of 5.7-6.4% (Genuth et al., 2003; Sacks et al., 2011). In the stage, we are irrespective of comorbidities such as hypertension, dyslipidemia, or overweight.

Stage 2: Diabetes with no complications. This group includes patients with a FPG level of ≥ 126 mg/dL (7.0 mM), 2-h PG level on OGTT of ≥ 200 mg/dL (11.1 mM), HbA1C level of $\geq 6.5\%$, classic symptoms of hyperglycemia, or a random PG level of ≥ 200 mg/dL (11.1 mM) (Reaven, 1988; Expert Committee on the Diagnosis and Classification of Diabetes Mellitus, 1997; Genuth et al., 2003; American Diabetes Association, 2010). These patients may or may not have insulin resistance or classic symptoms of hyperglycemia.

Signs of insulin resistance or conditions associated with insulin resistance include acanthosis nigricans, hypertension, dyslipidemia, polycystic ovary syndrome, or small for gestational age birth weight (Genuth et al., 2003).

Stage 3: Diabetes with mild complications. This group includes patients with mild complications, including microalbuminuria and mild diabetic retinopathy (such as microaneurysms, mild hemorrhages) (Ciulla et al., 2003; Levey et al., 2003). Patients may or may not have hyperglycemia or higher or normal levels of fasting and 2-h plasma insulin or proinsulin or C-peptide on OGTT (Chiasson et al., 2002; Nathan et al., 2007).

Stage 4: Diabetes with absolute insulin deficiency. This group includes patients with hyperglycemia, and absolute insulin deficiency which is based on clinical and/or laboratory evidence. Patients may have mild to moderate complications [such as diabetic nephropathy without kidney failure or diabetic retinopathy without proliferative diabetic retinopathy (PDR)] (Ciulla et al., 2003; Fong et al., 2004; KDOQI, 2007).

Laboratory evidence includes levels of fasting plasma insulin or proinsulin or C-peptide lower than the normal lower limit on laboratory's measurement method, or levels of 2-h plasma insulin or proinsulin or C-peptide during OGTT < 5 times of patient's levels of fasting plasma insulin or proinsulin or C-peptide. In addition, the ratio of fasting glucose to insulin or proinsulin or C-peptide, or of 2-h PG to insulin or proinsulin or C-peptide on OGTT (Sacks et al., 2011) may be considered.

Clinical evidence: In order to achieve desired glycemic goals, the optimal treatment is insulin therapy.

Stage 5: Diabetes with serious complications. This group includes patients with serious complications including hyperglycemic crises, as well as microvascular and macrovascular complications. Patients may have hyperglycemia, as well as higher or lower or normal levels of fasting plasma insulin or proinsulin or C-peptide.

Diabetic ketoacidosis (DKA) and hyperosmolar hyperglycemic state (HHS) are the two most serious acute metabolic complications in diabetes. The diagnostic criteria for DKA include plasma glucose level of > 250 mg/dL, arterial pH of < 7.30 , serum bicarbonate level of < 18 mEq/L, and positivity for urine ketone and serum ketone. The diagnostic criteria for HHS include plasma glucose level of > 600 mg/dL, arterial pH of > 7.30 , serum bicarbonate level of > 18 mEq/L, effective serum osmolality of > 320 mOsm/kg, and stupor/coma (Kim, 2007; Kitabchi et al., 2009).

Microvascular complications include retinopathy (neovascularization and vitreous or preretinal hemorrhage), nephropathy, neuropathy (sensory, including history of foot lesions, and autonomic, including sexual dysfunction and gastroparesis), and cardiomyopathy, and macrovascular complications include coronary heart disease, cerebrovascular disease, proliferative diabetic retinopathy, peripheral arterial disease, amputation, and foot ulceration (Genuth et al., 2003; Sacks et al., 2011).

A summary of the staging for type 2 diabetes is shown in Table 1.

Table 1. Staging of type 2 diabetes mellitus.

Stages/Description	Blood glucose and insulin analysis	Clinical manifestation	Goals/interventions
Stage 1 Pre-diabetes	FPG 100-125 mg/dL (5.6-6.9 mM) [IFG], OR 2-h PG on OGTT 140-199 mg/dL (7.8-11.0 mM) [IGT], OR HbA1c 5.7-6.4%	With or without other diseases such as hypertension, dyslipidemia, and overweight	Decreasing the rate of onset of diabetes Basic interventions (diabetes education, medical nutrition therapy, exercise, and monitoring of the level of glycemic control), treatment of comorbidities. Glycemic control and prevention of diabetic complications
Stage 2 Diabetes with no complications	HbA1c $\geq 6.5\%$, OR FPG ≥ 126 mg/dL (7.0 mM), OR 2-h PG on OGTT ≥ 200 mg/dL (11.1 mM), OR a random plasma glucose ≥ 200 mg/dL (11.1 ≥ 200 mg/dL (11.1 mM) in a patient with classic symptoms of hyperglycemia or hyperglycemic crisis	With or without classic symptoms of hyperglycemia or signs of insulin resistance	Basic interventions, treatment of other diseases, glucose -lowering drug treatment (oral glucose-lowering agents, maybe insulin).
Stage 3 Diabetes with mild complications	Hyperglycemia and/or higher or normal levels of fasting plasma insulin or proinsulin or C-peptide	Microalbuminuria, mild diabetic retinopathy (microaneurysms, mild hemorrhages)	Glycemic control and delay of diabetic complications Basic interventions, treatment of other diseases, monitoring of complications, glucose-lowering drug treatment (oral glucose-lowering agents, maybe insulin), ACE inhibitors and ARBs
Stage 4 Diabetes with absolute insulin deficiency	Hyperglycemia and absolute insulin deficiency based on clinical and/or laboratory evidence Levels of fasting plasma insulin or proinsulin or C-peptide lower than the normal lower limit on laboratory's measurement method, OR levels of 2-h plasma insulin or proinsulin or C-peptide during OGTT < 5 times of patient's levels of fasting plasma insulin or proinsulin or C-peptide	Mild to moderate complications (such as diabetic nephropathy without kidney failure, diabetic retinopathy without PDR)	Prevent and/or delay the onset and progression of diabetic nephropathy. Glycemic control and delay/treatment of diabetic complications Basic interventions, treatment of other diseases, monitoring of complications, glucose-lowering drug treatment (including insulin oral glucose-lowering agents and insulin)
Stage 5 Diabetes with serious complications	Hyperglycemia and/or higher, lower, or normal levels of fasting plasma insulin or proinsulin or C-peptide	Hyperglycemic crises: diabetic ketoacidosis, the hyperosmolar hyperglycemic state Microvascular: nephropathy, retinopathy (neovascularization, vitreous or preretinal hemorrhage), neuropathy (sensory, including history of foot lesions and autonomic, including sexual dysfunction and gastroparesis), cardiomyopathy macrovascular: CHD, cerebrovascular disease, peripheral arterial disease, amputation and foot ulceration	Glycemic control and delay/treatment of diabetic complications Basic interventions, treatment of other diseases, monitoring and treating complications, glucose-lowering drug treatment (oral glucose-lowering agents, maybe insulin)

FPG = fasting plasma glucose; IFG = impaired fasting glucose; IGT = impaired glucose tolerance; OGTT = oral glucose tolerance test; PG = plasma glucose;
PDR = proliferative diabetic retinopathy; CDH = coronary heart disease.

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