

How to Classify Type 2 Diabetes Mellitus and Approach its Treatment in View of Associated Diabetes and Complications-A Short Communication

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Abstract

With the increase in epidemic of obesity, the incidence of type 2 diabetes mellitus (T2DM) is increasing globally so much that the need has arisen for treating the two diseases together with the term diabetes getting coined. Here, we have tried to sub-classify T2DM stage-wise and how the treatment should be aimed keeping in view the use of weight-neutral anti-diabetic drugs. Preferably, insulin needs to be avoided due to its weight gaining effects and use of liraglutide should be preferred in the heavily obese diabetics due to its weight lowering effects. If the patient is in stage 4 group where insulin is practically non-existent, one can try using anti-obesity drugs along with insulin or see which works better with the influence of bariatric surgery seen on controlling diabetes in morbidly obese subjects.

Keywords: obesity, type 2 diabetes mellitus, diabetes, C-peptide, proliferative diabetic retinopathy, diabetic nephropathy, liraglutide, bariatric surgery

Abbreviations: PDR: proliferative diabetic retinopathy; T2DM: type 2 diabetes mellitus; DM: diabetes mellitus; FSG: fasting serum glucose; OGTT: oral glucose tolerance test; PG: postglucose; DKA: diabetic ketoacidosis; HHS: hyperosmolar hyperglycemic state; BOT: basal-supported oral therapy; OR: odds ratio; BS: blood sugar

Introduction

Recently we reviewed how the incidence of diabetes mellitus (DM) and obesity is increasing alarmingly due to which the term diabetes got coined and how one needs to treat these two together and gave some examples of the treatment [1–3].

Currently, no staging system exists for type 2 diabetes mellitus (T2DM). Wu in 2018 gave a staging system that would help clinicians along with patients in the better management of DM and might favourably affect the ultimate prognosis of diabetic subjects [4].

The Proposed Classification

Stage 1 or prediabetes includes that group of patients who were present with a fasting serum glucose (FSG) level of 105–125 mg/dl (5.6–6.6 mM) (altered fasting glucose), along with the following intake of 75 g glucose on 2 h oral glucose tolerance test (OGTT) present with serum glucose (SG) level of 140–199 mg/dl (7.8–11.0 mM) (impaired glucose tolerance), haemoglobin A1c (HbA1c) level of 5.7–6.4% [5, 6]. This stage is irrespective of comorbidities like hypertension, dyslipidemia, and overweight and requires treatment of any comorbidity, counseling for prevention of DM development by lifestyle modifications that include nutritional advice, weight loss strategies along with control of hypertension, dyslipidemia.

Stage 2 or overt diabetes includes that group where overt DM is not associated with any complications. Here subjects present with FSG ≥ 126 mg/dL (7.0 mm), 2 h postglucose (PG) level on OGTT of ≥ 200 mg/dL (11.1 mM), HbA1c level $\geq 6.5\%$, a typical problem associated with high levels of sugar, or a random PG level of ≥ 200 mg/dl (11.1 mM) [5, 7–9]. There might be a presence of decreased insulin sensitivity in these subjects.

Clinically stage 2 might be associated with mild disorders, like acanthosis nigricans, raised blood pressure (BP), disordered lipid profile besides development of Stein-Leventhal syndrome/PCOS or intrauterine growth retardation \Rightarrow low birth weight infants [5]. Management principles are the same *i.e.*, i) basic lifestyle interventions, ii) nutritional advice along with controlling the hyperglycemia with oral anti-diabetic drugs. Treatment can either be started with metformin or biguanides, or addition of insulin might even be needed. The basic aim is to prevent the development of any DM complications. Thus initially a baseline urine status, fundus examination, renal function test needs to be performed to further monitor for complication development along with treating comorbidities. As far as possible, try to initiate treatment with weight neutral drugs and avoid insulin in T2DM with its weight-promoting actions in view of obesity co-existing with T2DM and the vicious effects of weight-promoting anti-diabetic drugs [1].

Stage 3 is the stage where overt DM is associated with mild complications. Stage 2 comprises of subjects having mild complications, like low levels of albumin in urine and mild diabetic changes in retina (like microaneurysms, few haemorrhages) [10–12]. These subjects might present with increased blood glucose, or normal value of fasting/2 h plasma insulin or pro-insulin or C-peptide when OGTT is performed [13, 14]. Aim of management again remains the control of high sugar levels with the use of oral anti-diabetic drugs/insulin along with delaying the development of DM complications, besides basic lifestyle interventions, use of ACE inhibitors if required. Further, prevent or delay the onset and progression of diabetic nephropathy [15–18].

Stage 4 is a stage in DM where insulin is practically non-existent. Stage 4 comprises of subjects having raised blood sugar (BS), almost complete absence of insulin as is reflected by both clinical and laboratory testing. This condition may be associated with mild to moderate disorders like diabetic nephropathy without renal failure or proliferative diabetic retinopathy (PDR) [10, 19, 20].

On testing for fasting plasma insulin or pro-insulin or C-peptide, they are found to be lower as compared to normal lower limit of the reference laboratory, or ratio of fasting glucose to insulin or pro-insulin or C-peptide on OGTT might be considered [6].

In this group for achieving the required blood glucose control goal, ideally, insulin is proper therapy. While treating with insulin in combination with oral hypoglycaemics, warning of hypoglycemia are at (BS) level < 80 mg increased insulin seen, with BS level < 70 mg% increased glucagon is observed, with BS level < 60 mg% increased autonomic nervous symptoms are the presenting symptoms and with BS level < 50 mg% cognitive dysfunctions present, once glucose falls to < 40 mg% patient becomes drowsy, below 30 mg% goes into coma, left untreated under 20 mg% convulsion results and finally < 10 mg% patient dies. Thus immediate measures required are to give some oral glucose (2–3 tablespoon full of plain glucose in water but not in milk or fruit juice or if possible give immediate intravenous 10% dextrose as per the severity. Further, the aim is treat other diseases, monitor for development of DM complications and delay them as late as possible.

Stage 5 is the stage where DM is present with advanced complications. This group of patients were present with hyperglycemic crisis and micro/macrovacular problems. Here subjects may have very high blood glucose associated

with fasting insulin levels or pro-insulin that are either greater or lesser than the levels considered to be normal and same for C-peptide (Table 1).

Stage	Blood Glucose and Insulin Check	Clinical Problems	Aim of management
I Prediabetes	FSG 100–125 mg/dl (5.6–6.6 mM (IFD) or 2 h PG on OGTT 140–199 mg/dl (7.8–11.0 mm) (impaired glucose tolerance) or HbA1c 5.7–6.4%	With or without other diseases hypertension, dyslipidemia/obesity	Reducing rate of T2DM basic action (diabetes education, nutritional advice, exercise, check glucose) Rx of comorbidities
II Diabetes Mellitus (no complications)	HbA1c \geq 6.5% or FSG \geq 126 mg/dl (7.0 mm) or BS \geq 200 mg/dl (11.1 mm) in patient with classic symptoms of hyperglycemia	With or without classic symptoms of hyperglycemia or sign of IR	Glycaemic control Rx other diseases, oral anti-diabetic drugs, may need insulin
III Diabetes Mellitus (with mild complications)	Hyperglycemia and/or higher/nor levels of fasting plasma insulin /pro-insulin or C-peptide	Microalbuminuria, mild diabetes retinopathy (microaneurysms, mild haemorrhage)	Glycaemic control/delay diabetes complications, basic interventions, Rx other diseases, oral anti-diabetic drugs/insulin, ACE inhibitors
IV Diabetes Mellitus (with absolute insulin deficiency)	Hyperglycemia and absolute insulin deficiency based on clinical and/or fasting plasma insulin/pro-insulin or C-peptide lower than normal limit of lab or level of 2 h plasma insulin or pro-insulin or C-peptide during OGTT $<$ 5 times of pts fasting plasma insulin or pro-insulin or C-peptide	Mild-moderate complications like diabetes nephropathy without kidney failure, diabetes retinopathy without proliferative diabetic retinopathy	Glycaemic control/delay Rx diabetes complications, basic interventions, Rx other disease monitor complications, oral anti-diabetic drugs and insulin
V Diabetes Mellitus (with advanced complications)	Hyperglycemia or higher/lower/normal levels of fasting plasma insulin or C-peptide	Hyperglycemic crises, diabetic ketoacidosis, hyperosmolar hyperglycaemic state, microvascular, neovascularization preretinal vitreous haemorrhage, neuropathy (sensory foot lesions, autonomic nervous system, sexual dysfunction, cardiomyopathy), macrovascular (coronary heart disease, cardiovascular disease, peripheral artery disease)	Glycaemic control and delay Rx diabetes complications, Rx with oral anti-diabetic drugs (insulin)

Table 1: Proposed staging of type 2 diabetes mellitus (T2DM).

The most damaging complications in T2DM are diabetic ketoacidosis (DKA) and hyperosmolar hyperglycemic state (HHS). Diagnosis for DKA requires a level of PG to be more than 250 mg/dL associated with a low pH in the arteries with a level < 7.30, and serum bicarbonate levels lower than 18 mEq/L and presence of both urinary and serum ketones like acetoacetic acid beta-hydroxybutyric acid. The diagnostic criteria for HHS include PG level higher than 600 mg/L, arterial pH over 7.30, and serum bicarbonate levels more than 18 mEq/L, and the ultimate osmolality in blood over 320 mOsm/kg, resulting in a semi-conscious or comatose state [21, 22].

Complications which involve the smaller vessels are retinopathy (secondary to development of new vessels in the retina resulting in either vitreous or preretinal bleed), renal impairments, nerves involvement [at sensory level with a history of foot lesions being part of this stage along with a variety of autonomic dysfunctions which might cause erectile dysfunctions like impotence and altered motility of stomach and gastrointestinal tract (GIT)] and dilated heart. At macro level, complications are in the coronary arteries that may cause myocardial infarction in the blood supply of the central nervous system (CNS) which might result in a stroke, proliferated blood vessels in retina secondary to DM referred to as PDR which may cause loss of vision [23], peripheral arterial involvement specially of the foot that ultimately may land the subject in gangrene, amputation of foot along with non-healing foot ulceration [5, 6].

Further, we had reviewed the importance of combining SGLT2 inhibitors with metformin as initial treatment for T2DM and advantages of oral fixed drug pill like empagliflozin/metformin in patients with cardiovascular and renal risk for getting better glycaemic control as early as possible [24].

Pfohl et al. [25] aimed to find out predictors of long-term response to the initiation of basal-supported oral therapy (BOT) with insulin glargine (IGlar-100). Patients from the observational titration and optimisation (TOP) registry were grouped into those who had achieved (responders) and who had not achieved (non-responders) their HbA1c target and FBG \leq 110 mg/dL 12 months after IGLar-100 initiation. Independent predictors of treatment response were identified by regression analysis. Data for 2444 patients were analyzed (responders: n = 1610; non-responders: n = 834). Though the IGLar-100 dose increase over 12 months was large for non-responders (+12.83 vs. +9.46 U/d; $p < 0.0001$), the corresponding reduction in HbA1c was smaller (-0.88% vs. -1.57%). Independent predictors of response included a lower BMI (Odds Ratio, 0.97; 95% CI, 0.95–1.00), lower FBG (OR, 0.98; 95% CI, 0.97–0.98) and HbA1c values at bedtime (OR, 0.24; 95% CI, 0.18–0.31), a more lenient HbA1c target (OR, 5.07; 95% CI, 3.37–7.63) and bedtime administration of IGLar-100 (OR, 1.55; 95% CI, 1.12–2.14). Thus concluding, HbA1c was the clinical most significant baseline characteristic predictive of response to BOT. This might implicate an advantage for IGLar-100 initiation prior to excessive hyperglycemia escalation.

Conclusion

With the increasing incidence of obesity and a corresponding increase in T2DM, more awareness is needed to treat diabetes simultaneously. Preferably, one should attempt to treat DM with weight neutral anti-diabetics or liraglutide which has weight losing properties. Initially, insulin should be avoided as far as possible due to its weight increasing properties. Further, once T2DM is diagnosed; one needs to see the severity of the disease. Hence, the need for approaching the patient stage-wise both for the clinician, to understand the significance of how seriously it needs to be taken and for the patient to prevent the development of complications both micro and macrovascular like proliferative retinopathy, nephropathy, renal failure, diabetic gangrene, diabetic foot along with the prevention of the development of life threatening conditions like DKA, severe hypoglycemia and thus avoiding both morbidity and mortality associated with T2DM.

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