

The Diabetes Mellitus Clinical Practice Guidelines of Singapore – Looking Back and Ahead

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The Singapore clinical practice guidelines (CPG) on diabetes mellitus were first drawn up in 1999. The main aim of the guidelines was to help physicians make sound clinical decisions on the management of diabetes mellitus by presenting up-to-date information on diagnosis, classification, treatment, outcomes and follow-up. The guidelines contained detailed recommendations on many aspects of diabetes care including the screening and diagnosis of diabetes, classification of diabetes, lifestyle modifications, pharmacotherapy, management of diabetic complications, and treatment of associated metabolic disorders. Diabetes management in special populations including children and adolescents, and pregnant women, were also detailed. The CPG was last revised in 2006. Since then, there has been a phenomenal rate of development of knowledge and an explosion of data challenging many traditional notions of diabetes. Therefore, a new working committee has been set up to update the Singapore diabetes mellitus CPG targeted for publication in 2012. In this manuscript, we aim to discuss briefly selected key issues that are likely to be extensively reviewed in our next CPG.

The Diagnosis of Diabetes Mellitus

The 2006 guidelines endorsed the long-held diagnostic criteria of diabetes: random glucose ≥ 11.1 mmol/L (in the presence of symptoms), fasting plasma glucose (FPG) ≥ 7.0 mmol/L and 2-hour post-load plasma glucose (2HPG) in an oral glucose tolerance test (OGTT) of ≥ 11.1 mmol/L.

Recently, the American Diabetes Association (ADA) included the use of glycated hemoglobin (HbA_{1c}) threshold $\geq 6.5\%$ to diagnose diabetes.¹ Epidemiological studies have demonstrated a relationship between risk of retinopathy and HbA_{1c}, similar to FPG and 2 HPG. The convenience of performing HbA_{1c} testing without the need for fasting, and purported reduced day-to-day fluctuations related to stress and illnesses, lend further

support to utilizing HbA_{1c} as a diagnostic test. There are, however, some legitimate concerns. These include limited availability or standardization of the test, especially in developing countries; higher cost; systematic differences dependent on ethnicity²; and the effect of anemia and hemoglobinopathies on HbA_{1c}. Currently, most of the laboratories in Singapore perform HbA_{1c} certified by the National Glycohemoglobin Standardization Program (NGSP), standardized to the Diabetes Control and Complications Trial (DCCT) reference assay. The test is also widely available in Singapore. It is anticipated that the use of HbA_{1c} as a diagnostic test for diabetes will be carefully considered.

Glycemic Targets and Assessment

The 2006 guidelines described glycemic targets of HbA_{1c} 4.5 to 6.4% as “ideal,” 6.5 to 7.0% as “optimal,” 7.1 to 8.0% as “suboptimal,” and $> 8.0\%$ as “unacceptable.” The recent Action in Diabetes and Vascular Disease: Preterax and Diamicon Modified Release Controlled Evaluation (ADVANCE) study, the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial and the Veterans Affairs Diabetes Trial (VADT) have challenged existing paradigms.³⁻⁵ These trials were designed to study the effects of intensive (aiming to achieve near-euglycemia) versus conventional therapy on cardiovascular outcomes in subjects with longstanding type 2 diabetes. Within the period of follow up—although these three trials demonstrated varying degrees of benefit, albeit modest, on the onset or progression of microvascular outcomes—none showed any benefit of intensive control with regard to macrovascular outcomes. Moreover, results from ACCORD showed a significant increase in total (hazard ratio 1.22) and cardiovascular (hazard ratio 1.35) mortality with intensive therapy. These results were in contrast to the findings of the United Kingdom Prospective Diabetes Study (UKPDS), which demonstrated consistent benefits in both microvascular and macrovascular outcomes in

intensively treated patients on long term follow up.⁶ Some reconciliation of inconsistent findings from these clinical trials may be possible upon consideration of the known pathophysiology of diabetes and its vascular complications. For instance, the patient profile of UKPDS, consisting mainly of newly diagnosed diabetics, was different from the longstanding diabetic population of ADVANCE, ACCORD and VADT. This suggests that glycemic targets should be individualized based on age, duration of diabetes, and the presence of advanced vascular disease, amongst other factors.

Assessment of glycemic control utilizing traditional methods, including glycosylated hemoglobin and self monitoring of blood glucose (SMBG), were included in the 2006 guidelines. Recent advances in newer technology, particularly continuous blood glucose monitoring (CGM), and new data demonstrating its benefits in further improving glycemic control while limiting hypoglycemia, have supported the role of CGM in the management of type 1 diabetics on intensive insulin therapy.⁷ The next revision of the guidelines should perhaps incorporate these evolving technologies, which may serve an ancillary role in the management of diabetes.

Therapeutic Options and Treatment Algorithm for Diabetes

The long term safety of anti-hyperglycemic agents—thiazolidinediones (TZDs) in particular (primarily relating to rosiglitazone)—has been the subject of intense discussion. Rosiglitazone was found to be associated with a significant increase in the risk of myocardial infarction and an increased risk of death from cardiovascular causes as reported by Nissen et al in 2007.⁸ The 2008 ADA and the European Association for the Study of Diabetes (EASD) consensus algorithm recommended against the use of rosiglitazone, owing to safety concerns and the availability of alternative therapies (pioglitazone in particular), which seemed not to share the same concerns. In 2010, the European Medicines Agency suspended sales of rosiglitazone. In the same year, the United States Food and Drug Administration (FDA) restricted its use to patients with type 2 diabetes who cannot achieve adequate glycemic control with other medications. Back in the 2006 guidelines, TZDs had an integral role as an oral therapeutic option for type 2 diabetes. Rosiglitazone was the only TZD available in Singapore at that time. Although rosiglitazone is still available in Singapore, it is unlikely to continue to play a major role as a therapeutic option for type 2 diabetes owing to its safety concerns. The other available TZD, pioglitazone, has its own share of issues including concerns with heart failure, fracture risk and, lately, bladder tumors.⁹ Therefore, the therapeutic placement of TZDs will be reviewed.

The other controversy, which has gathered significant attention in recent years, is with the insulin analog insulin glargine and mitogenicity. In an observational cohort

study published in 2009, Hemkens et al reported that cancer incidence in patients on glargine was higher than expected, than in patients on human insulin.¹⁰ Other epidemiological data largely demonstrated no causal relationship between insulin glargine and cancer risk.^{11,12} Some remain concerned because glargine has a higher affinity for insulin-like growth factor-1 (IGF-1) receptor compared to human insulin, which theoretically could alter mitogenic activity. There is, to date, insufficient evidence to make a recommendation against glargine. Therefore, the epidemiological observation only generates some hypotheses but is unable to establish causation. The CPG committee will carefully consider this issue.

While some therapeutic agents have been under scrutiny for their safety concerns, there have been several new classes of therapeutic agents that may play increasingly important roles in the management of diabetes. These include incretin-based treatment, such as dipeptidyl peptidase-4 (DPP-4) inhibitors and glucagon-like peptide-1 (GLP-1) analogs. These agents have gained increased use in part due to their favorable effect on weight and their postulated beneficial effect on beta-cell function in animal studies.^{13,14} The ADA and EASD consensus algorithm for the initiation and adjustment of therapy in 2008 endorsed the use of incretin-based therapeutic agents as an add-on to metformin, specifically when avoidance of hypoglycemia and weight loss are desirable.¹⁵

Novel technology and techniques have added new options to the treatment armamentarium for diabetes over the years. Insulin pump therapy has evolved to become an established form of intensive insulin therapy in type 1 diabetics. Studies exploring the utility of insulin pump therapy in type 2 diabetic patients have been steadily increasing.^{16,17} The advent of bariatric surgery as a possible option in the treatment of diabetes has presented a provocative challenge to the usual concepts in diabetes treatment.¹⁸ With the emergence of newer therapeutic options and novel concepts on diabetes care, a paradigm shift in the management algorithm of diabetes will be one of the key issues in our next CPG.

Management of Diabetic Complications

The management of diabetic microvascular complications, including diabetic nephropathy and eye complications, was well highlighted in the 2006 guidelines. The recommended use of angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs) in the treatment of microalbuminuria or overt nephropathy is established practice applicable even to this day. Over the years, several trials have demonstrated additional albuminuria-lowering benefits with dual blockade of the renin-angiotensin system (RAS) using both ACE inhibitors and ARBs.^{19,20} With dual blockade, studies showing better long-term renal and cardiovascular outcomes are still lacking, and an increased risk of hyperkalemia has also been described. Nevertheless, dual

blockade remains a viable option should patients have persistently significant proteinuria despite optimization of a single RAS-blocking agent. Furthermore, the direct renin inhibitor aliskiren has been approved by FDA for the treatment of hypertension since 2007. Although its role in the prevention of progression of diabetic nephropathy is unknown, data demonstrating its albuminuria-lowering properties has been promising.²¹ Studies also demonstrating additive proteinuria-lowering benefits with the use of spironolactone, an aldosterone antagonist, have been mounting.^{22,23} These additional agents offer a wider range of options in the management of diabetic nephropathy and should be addressed in the next revision to the Singapore guidelines.

Screening for diabetic retinopathy, and management of systemic risk factors for prevention of progression of diabetic retinopathy (including glycemic control, blood pressure control and treatment of hyperlipidemia), were well-detailed in the 2006 guidelines. Intensive diabetes management achieving near normoglycemia has been shown to prevent or delay the onset and progression of retinopathy.²⁴ Lowering of blood pressure is also well established in reducing the progression of retinopathy.²⁵ However, the role of treatment of hyperlipidemia has not clearly been linked to retardation of progression of retinopathy. In recent years, a reduced need for laser treatment for diabetic retinopathy was demonstrated in patients treated with fenofibrate.²⁶ Retardation of progression of diabetic retinopathy with fenofibrate was also observed in the ACCORD Eye Study.²⁷ Further data confirming the benefits of fibrates in primary prevention and progression of retinopathy are highly anticipated and will undoubtedly have an impact on the management of dyslipidemia in the near future.

Diabetes in Special Populations – Diabetes in Pregnancy

The 2006 guidelines included recommendations on the management of women with pre-gestational and gestational diabetes mellitus (GDM). Guidelines on screening for, and detection of, gestational diabetes; glycemic control; and intrapartum and postnatal management; were highlighted. Traditionally, the term “gestational diabetes” was used to define women with onset or first recognition of abnormal glucose tolerance during pregnancy. With the continuing rise in incidence of diabetic patients presenting at an earlier age, it is inevitable to see an increasing trend of patients with diabetes during pregnancy. Diabetes may even antedate pregnancy. With the advent of data from the Hyperglycemia and Adverse Pregnancy Outcomes (HAPO) study, the International Association of Diabetes and Pregnancy Study Groups (IADPSG) and the ADA have recently revised guidelines on the diagnosis and classification of diabetes in pregnancy. The classification of “overt diabetes” has been proposed for diabetes detected on initial antenatal visit using the standard diagnostic test.

Revised 75-gram OGTT criteria for diagnosis of GDM using any one positive criterion (fasting glucose \geq 5.1 mmol/L, 1-hour post-load glucose \geq 10.0 mmol/L or 2-hour post-load glucose \geq 8.5 mmol/L) has been endorsed.²⁸ Besides changes to the diagnostic criteria, data demonstrating the safety of oral hypoglycemic agents in pregnancy, particularly metformin and glibenclamide, have been increasing in recent years.^{29,30} The use of the rapid-acting insulin analogs, lispro and aspart, has also been shown to have acceptable safety profiles and minimal transfer across the placenta, without evidence of teratogenesis.^{31,32} Guidelines on glycemic targets including premeal capillary glucose, peak post-prandial glucose and HbA1C targets for pre-existing type 1 or 2 diabetic women who become pregnant have been updated recently.³³ The relevance and adoptability of these changes will be considered by the new CPG committee.

Conclusion

In the few years since the last revision to the Singapore diabetes CPG in 2006, there has been an astounding avalanche of data challenging traditional notions and bringing new perspectives to diabetes. It is timely that the guidelines be updated to reflect the latest developments and consensus in diabetes care. The challenge lies in adapting this considerable body of data and recommendations to the local setting, making them relevant to local practitioners. Diabetes is a rapidly developing field where exciting new information continues to challenge old practices. We look forward to the next revision to the Singapore Diabetes Mellitus CPG and hope that it will continue to enormously assist our local practitioners in enhancing their care for the diabetic population of Singapore.

The full article of the 2006 Guidelines is no longer available at the Singapore Ministry of Health website as it is currently under review.

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