Managing diabetes

Recommendations and caveats

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In Canada, most patients with type 2 diabetes are followed exclusively by their family physicians.[1] These patients visit their doctors frequently.[2] This issue of *Canadian Family Physician* features two articles on diabetes-related topics: use of thiazolidinediones (TZDs) and gestational diabetes mellitus (GDM). The authors have addressed these subjects in the context of family practice, highlighting controversies, discussing application of current diabetes management guidelines,[3] and commenting on common pitfalls. These articles suggest practical strategies for family physicians, but also highlight areas of management that appear relatively resistant to change.

Although the authors have graded the evidence they present, readers must be cautious in interpreting the levels of evidence cited because numerous methods and grading systems are used to assess evidence. For example, the grading system in the Canadian Diabetes Association (CDA) 2003 Clinical Practice Guidelines[3] differs from the system used by the Task Force on the Periodic Health Examination.[4] The CDA guidelines assign a D grade to consensus recommendations, while the Task Force assigns a D grade to harmful practices.

While physicians need to base their clinical decisions on the best available evidence, they also need to act in the absence of such evidence. In many situations, good clinical evidence is impossible, unethical, impractical, or too expensive to generate. In the CDA guidelines, many grade D consensus recommendations were deemed extremely important to diabetes management, based on clinical experience, case series, physiologic evidence, and current ideas about disease pathophysiology. The lack of clinical evidence in the areas of treatment, prevention, diagnosis, and prognosis precluded assignment of a higher grade.[3]

Thiazolidinediones

Noble and colleagues highlight some literature on the newest class of antihyperglycemic agents, thiazolidinediones (TZDs) **(page 683)**. While the authors acknowledge many of the benefits of these drugs, they conclude that TZDs should remain adjuncts to treatment with metformin or sulfonylureas. They correctly state that no long-term trials have looked at reduction of complications, and no head-to-head data are available to definitively guide physicians' choice between pioglitazone and rosiglitazone. These data are clearly needed. To state that TZDs should be viewed as third-option drugs (after metformin and sulfonylureas), however, is to ignore TZDs' many benefits. While this prescribing pattern might well reflect current practice, it does not reflect current guidelines, expert consensus, or emerging evidence.

The CDA 2003 Clinical Practice Guidelines are the first guidelines to include a treatment algorithm integrating evidence and expert opinion for management of hyperglycemia in type 2 diabetes. Consistent with the overwhelming evidence that A_{1c} levels below 7.0% are associated with fewer complications, the guidelines recommend aggressive therapy to reach this target quickly (within 6 to 12 months). Metformin is recommended as the first-line drug, and TZDs are ranked as second-line agents, a rating that stems from the important role of insulin resistance in the pathophysiology of diabetes.

Accumulating evidence indicates the benefits of peroxisomal proliferator-activated receptor-gamma, or PPAR-gamma activation, including changes in lipids and inflammation mediators and improvements in endothelial function. Thiazolidinediones not only target a root cause of type 2 diabetes (insulin resistance), effectively reduce hyperglycemia,

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and confer no risk of hypoglycemia, but are also associated with some favourable effects that might reduce cardiovascular morbidity and mortality.[5,6] Unfortunately, Noble et al do not mention that TZDs confer no risk of hypoglycemia, a key advantage to this class of drugs, because hypoglycemia is the main limitation for many patients trying to achieve stringent glycemic targets using insulin or insulin secretagogues. The guidelines also recommend *initial* combination therapy, especially for patients with A_{1c} levels above 9.0%.

Many physicians still worry about risk of edema and congestive heart failure (CHF) with TZDs. Although not cited by Noble et al, the consensus statement of the American Heart Association and the American Diabetes Association[7] concludes that only certain predisposed patients with fluid retention or edema are at risk of developing symptomatic heart failure and that, when these drugs are prescribed according to the product monograph, the risk of CHF is very low. Thiazolidinediones should not be prescribed to patients with signs or symptoms of New York Heart Association class III or IV CHF.[7]

In reviewing the pioglitazone and rosiglitazone studies, the authors point out that some improvements were noted in lipid profiles. It is important to understand, however, that these studies should not be compared with each other or be used to choose one agent over another. The pioglitazone studies were generally smaller and of shorter duration, and patients' baseline characteristics (weight, A_{1c} levels, etc) were not comparable to those of patients taking rosiglitazone. While TZDs might confer some lipid-lowering benefits, dyslipidemia should be treated with lipid-lowering drugs, not antihyperglycemic agents. Statin or fibrate therapy is indicated for many patients with diabetes as part of an overall approach to vascular protection.[3]

Finally, Noble et al raise the important point that TZDs are expensive drugs not currently fully covered by provincial formularies (except in Alberta). It is important to remember that the 2003 CDA guideline recommendations are based on evidence, and as such do not consider economic analyses, formulary issues, or the prevailing political approach to chronic disease management or funding. I hope, however, that policy-makers will bring drug and treatment coverage in line with the evidence. In the meantime, physicians have to balance what would be best for their patients in an ideal world with the constraints of the real world.

Gestational diabetes mellitus

Kelly and colleagues provide readers with a concise overview of the literature on the pathophysiology and outcomes of GDM **(page 688)**. Gestational diabetes mellitus continues to be a controversial topic widely debated in the medical community, a fact highlighted by the difference in screening recommendations in two different sets of national guidelines. The CDA guidelines recommend universal screening,[3] while the Society for Obstetricians and Gynaecologists of Canada's guidelines recommend selective screening.[11] Kelly et al express the hope of many family physicians when they state that the ongoing Hyperglycemia and Adverse Pregnancy Outcome trial will shed light on this area. In the meantime, the CDA recommends universal screening for three important reasons: studies have shown that selective screening still results in missed diagnoses[12]; hyperglycemia is associatied with perinatal morbidity[13]; and GDM is a well established risk factor for subsequent type 2 diabetes in mothers.[14]

While research into the safety of oral agents as therapy for GDM is ongoing, readers are cautioned that current guidelines recommend insulin therapy if lifestyle alone has not achieved glycemic targets. The guidelines also caution against routine use of glyburide until it has been shown to be as safe as insulin during pregnancy.[15] Due to a lack of evidence at the time of guideline development, metformin was not presented as a treatment option. While Kelly et al point to the success of metformin in helping women with polycystic ovary syndrome conceive, it is important to remember that an evidence-based approach does not allow these studies to be used as direct support for treatment of women with GDM. Again, we must await evidence from larger trials involving women with GDM.

With GDM, there is evidence of both impaired insulin secretion and action, defects that persist after the birth and increase the risk of impaired fasting glucose, impaired glucose tolerance, and type 2 diabetes.[14] Insulin resistance is also often associated with cardiovascular risk and is a common finding in women with previous GDM.[16] Diagnosis of GDM could be interpreted as a wake-up call and an opportunity to make changes for the health of mother, baby, and indeed the whole family.

Conclusion

Several randomized controlled trials on diabetes prevention and treatment are under way and could provide evidence supporting revision of the wording or grading of recommendations in the next set of CDA guidelines. In the meantime, the 2003 guidelines provide family doctors with a comprehensive evidence-based framework within which to manage their patients with, or at risk of, diabetes.

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