Lipid Management in Patients With Diabetes

Translating guidelines into action

“...with fat diabetes begins. From fat diabetics die, formerly of coma and recently of...arteriosclerosis.”

Three-quarters of a century ago, Dr. Elliot Joslin succinctly summarized two of the lethal consequences of diabetes before (ketoacidosis) and after (cardiovascular disease [CVD]) the discovery of insulin (1). As we progressively refine our ability to normalize blood glucose with increasingly complex regimens of new oral and injectable agents, the excess cardiovascular mortality from diabetes remains unabated (2). With diabetes increasing worldwide due to decreased physical activity and an aging and more obese population, and with type 2 diabetes being diagnosed at earlier ages (3,4), without effective preventive strategies the associated atherosclerotic complications are likely to soon reach unmanageable proportions. This prediction lies in sharp contrast to a decrease in cardiovascular mortality in the general population that has been recently reported (5).

The precise link between CVD and diabetes is not completely understood, but it is clearly multifactorial, involving the deleterious effects of hyperglycemia itself, resulting in endothelial dysfunction, hypercoagulability, increased oxidative stress, and protein glycosylation. In the setting of type 2 diabetes, there are the additional contributions of obesity, hypertension, dyslipidemia, insulin resistance, and further abnormalities in fibrinolysis and endothelial function (6). With the onset of diabetic nephropathy the risk of macrovascular disease is compounded. The exact role of each of these derangements is complicated by their complex interrelationships. In the midst of such a large number and variety of risk factors, however, dyslipidemia remains a key determinant of CVD. While the U.K. Prospective Diabetes Study (UKPDS), the largest prospective trial of type 2 diabetes, showed that glucose control decreased the microvascular complications of diabetes, the trial demonstrated that elevated LDL cholesterol (LDL-C) and decreased HDL cholesterol (HDL-C) levels were among the strongest predictors of fatal and nonfatal myocardial infarction (7)—stronger even than other well-known modifiable risk factors, such as systolic blood pressure, smoking, and HbA1c.

The association among LDL-C, diabetes, and cardiovascular morbidity is interesting, insofar as patients with diabetes, as a group, are not known to have particularly elevated LDL-C concentrations when compared with the population at large (8). Indeed, generally speaking, both mean total and LDL-C concentrations are “normal” in patients under good glycemic control (8) when their increased risk for CVD is not taken into consideration. In insulin-resistant patients with type 2 diabetes, the most common lipid abnormalities are increased triglycerides (and VLDL cholesterol) and decreased HDL-C (9). There are, however, well-recognized qualitative LDL abnormalities in diabetes, such as an increased percentage of small, dense LDL subparticles (subclass B), as well as further modification of LDL by oxidation and glycation, each of which increases the lipoprotein’s atherogenic potential (10).

There are few data available from trials specifically designed to assess the effects of improving lipid levels in diabetic patients. Most of our knowledge in this regard comes from subgroup analyses of large coronary artery disease (CAD) prevention trials. These include both primary [Helsinki Heart Study (11), Heart Protection Study (12)] and secondary prevention trials [4S (13), CARE (14), VA-HIT (15)]. In each of these investigations, three of which involved statin therapy (12–14) and two of which utilized fibrates (11,15), the diabetic subgroup enjoyed the same or even greater relative risk reduction with active treatment as compared with the nondiabetic group. Therefore, due to their overall increased mortality from CVD, the absolute benefit of aggressive lipid management in patients with diabetes is significantly greater. This realization has prompted various professional organizations to designate diabetes as a CHD risk equivalent even in the absence of known CHD and to set forth increasingly stringent guidelines for lipid screening and treatment in diabetes. The most widely publicized of these, those of the National Cholesterol Education Program (NCEP) (16) and the American Diabetes Association (ADA) (17), recommend that first priority be given to lowering LDL-C to achieve the goal of <100 mg/dl. Therapeutic lifestyle change including diet, exercise, and weight loss are recommended, with pharmacological therapy indicated when the LDL-C is ≥130 mg/dl or, in those with vascular disease, ≥100 mg/dl. Secondary targets include the control of HDL-C and triglycerides. (The NCEP recently recommended that “non-HDL cholesterol [total cholesterol – HDL-C] <130 mg/dl be a secondary target of therapy.)

Current LDL-C goals may indeed not be low enough, when one considers recent results from the Heart Protection Study, which demonstrated a benefit on CVD outcomes from statin therapy in diabetic patients at all levels of baseline LDL-C, even in those <100 mg/dl (12). These important data suggest that LDL-C reduction is beneficial at any baseline for high-risk patients or, perhaps, that statins have other effects that may lower risk. Future research will need to differentiate these important issues. In the meantime, a focus on the current guidelines will save lives.

In light of these recent developments, the results of the article by Massing et al. (18) in this issue of Diabetes Care are disturbing. The investigators utilized a large database involving over 47,000 patients with CAD who were treated at nearly 300 practices between 1996 and 1998. Using
chart review, they quantified lipid testing and treatment rates and the actual serum lipid concentrations. The data were then analyzed over time to assess for trends. Encouragingly, testing and treatment increased, and mean LDL-C and non-HDL-C levels decreased significantly over time, suggesting an evolving, more aggressive approach to managing hyperlipidemia in these high-risk patients. In contradistinction, patients with diabetes remained 30% less likely to have a lipid profile and 20% less likely to receive lipid-lowering therapy than their nondiabetic counterparts. In addition, this therapeutic “gap” did not diminish during the observation period. Lastly, the trend for improved lipid concentrations was less striking in those with diabetes, despite the growing recognition that these patients are at significantly increased risk.

Similar data have been assembled by others in a variety of practice and geographic settings (19–23). Using the NHANES III database (1988–1995), Saadine et al. (19) found that only 42% of diabetic patients in the U.S. had an LDL-C <130 mg/dl. Surveys involving more recent practice (20–23), including that supervised by (21) or conducted at (22,23) academic centers, suggest comparatively modest interval improvement in the management of dyslipidemia, as well as other cardiovascular risk factors such as blood pressure. This failure to substantially meet treatment goals has been ascribed to “clinical inertia” and is believed to result from a variety of factors, including the overestimation of the quality of care provided, the use of “soft” reasons to avoid intensifying therapy, and a lack of education, training, and/or practice organization targeted at achieving the goals (24). In addition, the fact that patients do not “feel” these risk factors, the high cost of medication and intervention programs, as well as the failure of treatment to improve quality of life, complicate intervention and compliance (25).

Clearly, observational studies based on medical record review alone, as in the study by Massing et al., are fraught with interpretive challenges. The actual, complex interchange between physician and patient at each office visit cannot be fully assessed by abstracting an often hurriedly recorded chart note. For example, it is impossible to assess if the reason for less frequent monitoring of lipid levels resulted from the failure of the physician to order the test, the failure of the patient to actually undergo the test ordered, or inadequate communication between multiple care givers as to who is actually responsible for lipid management. The precise reason for suboptimal compliance with guidelines can only be known through more thorough inquiry, which would be impractical with such a large and impressive database as used by Massing et al. Nonetheless, the data generated by such research are certainly important because they clearly point out that patients are not being ideally diagnosed or treated. Their results and its implications must lead to introspection and hopefully action on the part of the health care community, particularly those involved in the primary or subspecialty care of patients with diabetes.

The reason that compliance with treatment guidelines in diabetes has proven so difficult may be the same reason that compliance is so important. Diabetes is a complex and serious disease, associated with a myriad of vascular risk factors and, unfortunately, a myriad of vascular complications. The needed team approach involving physicians, nutritionists, and diabetes educators may not be available in all settings or may be too costly or time consuming. The multiple lifestyle and pharmaceutical interventions for control of diabetes, obesity, hypertension, dyslipidemia, and smoking, even before complications are present, are complex and costly and may be overwhelming to the patient, especially since he or she often does not feel any better or may indeed feel worse with treatment. The busy primary care physician may likewise feel overwhelmed, having to deal with more stringent sets of guidelines to incorporate, the possibility of adverse effects from drugs, drug-drug interactions, and the never-ceasing and frequently divergent demands of patients and insurers. Not surprisingly, the result is frequently inadequate control of CVD risk factors.

It is unlikely that increased publicity of guidelines or recommended interventions to either patients or physicians will fully address these issues. Instead, it is now important for those engaged in clinical outcomes research to focus on process-oriented investigations to improve care. That is, now that we know the data and understand the guidelines, how can we best translate this knowledge and understanding into effective action? Potential strategies include novel practice organizational schemes for providing team-based care to patients with diabetes; enhanced reimbursements for outpatient diabetes care that would allow for more comprehensive office interactions with the physician as well as nutritionists and diabetes educators; and/or computer-based disease management systems to ensure timely tracking and treatment of risk factors. Small studies that have examined some of these approaches have thus far had encouraging results (25,26). Whether they can be applied to all practice settings, particularly in such a diverse and often inequitable arena that defines the U.S. health care system, remains unclear. Moreover, whether enhanced compliance with guidelines outside of clinical trials will necessarily lead to improved clinical outcomes is not entirely guaranteed. Hopefully, however, such efforts will assist us in finally realizing the benefit of delaying or preventing CVD in our patients with diabetes.

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References


