The time has come for lab staff to become more proactive in the management of diabetes by helping generalists diagnose several important related risk factors. Doing so will not only dramatically improve overall care of patients and their quality of life but also reinforce the lab’s reputation as an integral member of the healthcare team.

Diabetes is a significant medical problem in this country. Medical costs associated with managing this disease are estimated at $100 billion annually. Moreover, about 30% more US patients die from diabetes than their European counterparts. American diabetic patients also have four times more serious kidney disease than diabetics in the European Union (EU).1,2 In adult patients, diabetes is the leading cause of blindness, amputation, and end-stage renal disease requiring dialysis and renal transplantation.3

About 60% of diabetic patients die of coronary disease, 10% die of stroke, and another 10% suffer from fatal complications related to peripheral vascular disease.4 Diabetic patients who experience a first myocardial infarction have a 25% chance of death within 1 month and a 50% chance within 1 year.5,6

WHY THE DIRE STATISTICS?
A primary reason for these unpleasant statistics is treatment of patients by generalists, many of whom lack proper training in this area. National medical policies established three decades ago set the standard of medical care for diabetic patients at the level of the generalist rather than the specialist. (The reverse is true in the EU.) Primary care physicians (PCPs), internists, and pediatricians, among other generalists, care for more than 70% of US diabetic patients, while diabetologists treat less than 8%.7 Unfortunately, comprehensive diabetes training in US medical schools and residency programs is virtually nonexistent.8

The most efficient approach to diabetes care is simultaneous elimination of all independent macrovascular risk factors, including smoking, hypertension, hyperglycemia, dyslipidemias, and microalbuminuria (see Table 1, page 18).9,10 Each risk factor contributes relatively equal risk toward cardiovascular death, and in each case, preventing macrovascular disease automatically prevents microvascular disease. Still, generalists tend to focus primarily on...
hyperglycemia and to exclude other risk factors, leading to large increases in cardiovascular death (see Figure 1, at right).

Studies evaluating why US medical schools fail to train new doctors and residents in essential skills for diabetic patient care remain obscure.\textsuperscript{10,11} A national phenomenon appears to be that medical school administrators, students, and residents are disinterested in this area of medicine. Medical schools and HMOs are beginning to open one eye, but only long enough to log in the number of hemoglobin A1c or urine analyses tests ordered per year to satisfy current NCQA recommendations. Attempts to realign diabetes care and teaching curricula in this country, even at the local medical school level, have been unsuccessful, as have national patient advocate organizations’ efforts to provide public health solutions. Certainly insurers and managed care organizations have done little to enhance diabetes care.

Given these inherent and seemingly immovable obstacles, it is imperative that physicians receive increased support in this area from other healthcare professionals, including pharmacists, diabetes nurses, dietician educators, and clinical laboratorians, in particular, who are well acquainted with hyperglycemia, dyslipidemias, and microalbuminuria. The following article will focus on these three independent risk factors, explaining their laboratory caveats, appropriate clinical guidelines, and how laboratorians can use this knowledge to help clinicians improve patient care.

HYPERGLYCEMIA

True or false? It appears straightforward to follow the 1997 guidelines of the American Diabetes Association (ADA) for diagnosing diabetes and impaired fasting glucose (IFG)? The answer is false. At least 20 reports from around the globe, including those from third-world countries, indicate these guidelines are inadequate. Experts believe they may falsely indicate that patients do not have diabetes or impaired glucose tolerance testing (IGT), when, in fact, fasting plasma glucose levels indicate the need for oral glucose tolerance testing.\textsuperscript{12-20} Some of these reports describe the under-diagnosis of IGT and diabetes to be as much as 75% using ADA criteria.

It is imperative that clinical laboratorians help generalists to make these diagnoses appropriately based on the best guidelines available. For starters, lab staff can standardize methodology by indicating on lab reports, adjacent to glucose values, that the fasting plasma glucose level is the correct test. (Alternatively, lab staff can transmit this information via telephone, email, laboratory newsletter, and/or laboratory website.) Physicians should be discouraged from ordering whole blood glucose levels and other assays that yield results dissimilar to plasma glucose, as these tests can result in 5%–10% reductions from apparent plasma glucose levels, upon which ADA and World Health Organization (WHO) base their guidelines.\textsuperscript{21,22}

IFG/IGT diagnoses

Current ADA guidelines effectively eliminate oral glucose tolerance testing despite an increased need for this test, which begs the question, “At which glucose window is such testing recommended?” While there is no simple rule, evidence based on cardiovascular death and fasting plasma glucose levels provides some reasonable solutions. The top 25\textsuperscript{th} percentile of individuals within the normal fasting plasma glucose range (86–109 mg/dL) have 40% increased cardiovascular death rates compared to individuals in the lower percentiles.\textsuperscript{23} Once a subject has IFG or IGT, cardiovascular death risk increases by 60%.\textsuperscript{24} The only way to know whether a patient has IGT is to perform an oral glucose tolerance test, which, therefore, should be run on subjects with repeated fasting plasma glucose levels exceeding 90 mg/dL (see Table 2, on page 18). Recent investigation reveals that 71% of high-risk subjects exhibiting a fasting plasma glucose of 100–109 mg/dL also had two-hour oral glucose tolerance tests confirming either IGT (42%) or diabetes (29%).\textsuperscript{20}

According to ADA criteria, a patient whose fasting plasma glucose repeatedly exceeds 126 mg/dL has diabetes and thus does not require additional glucose tolerance testing. Considering the high cardiovascular risk, however, the window for this test should be made wider, not narrower. Both ADA and WHO criteria are based on the reduction of microvascular complications.

Continues on page 18
Only recently has a relationship between macrovascular death and glucose become available. If there are errors to be made, laboratorians must err in the direction of running too many glucose tolerance tests and diagnosing too many patients with IGT. Overdiagnosis is basically a nonissue, however. Only 2 million glucose tolerance tests are performed annually in this country for these purposes, despite common belief that as many as 50 million Americans may actually require this test.

Recent epidemiological studies involving subjects age 20 and older report 10.2 million known diabetic patients in the US and another 5.4 million individuals with unknown diabetes. Even more alarming, another 13.4 million Americans between the ages of 40 and 74 have been diagnosed with IFG. Given the WHO criteria described above, this estimate may be closer to 20 million or 30 million. If the number of diabetic and IGT patients are extrapolated to the total US population, a minimum of 30 million, or as many as 50 million, individuals are involved (see Table 3, page 20).

Clearly, these numbers indicate the need for clinicians to become more proactive in this area, which requires increased awareness of IFG/IGT diagnoses and the risk factors associated with these disorders, which virtually are the same as those for diabetes. To enhance awareness of the IGT diagnosis, lab staff should indicate on reports that if a fasting plasma glucose level exceeds a certain level (eg, 90 mg/dL or 110 mg/dL, the current ADA guideline), oral glucose tolerance testing is warranted.

Current investigation indicates future guidelines for diagnosing diabetes will be more complicated than current protocol. All the more reason for generalists and laboratorians to focus more attention not only on the oral glucose tolerance test but also the hemoglobin A1c assay, which may be useful in diagnosing dysglycemic syndromes of IGT and diabetes. Unfortunately, the hyperglycemic risk factor is complicated by the diagnostic problems described above and by glycemic monitoring methods.

The hemoglobin A1c is the only test currently valid for long-term glycemic monitoring of diabetic patients. This test has been used in large-scale, randomized, prospective, and controlled clinical intervention trials comparing A1c levels to chronic micro- and macrovascular complications. Results from the United Kingdom Prospective Diabetes Study (UKPDS) and the Diabetes Control and Complications Trial (DCCT) clearly indicate that hemoglobin A1c levels are strongly linked to cardiovascular death in type 2 diabetes as well as to microvascular complications (eg, retinopathy and nephropathy in both type 1 and type 2 diabetes). The A1c threshold for glucose-induced macrovascular disease is lower than that for microvascular disease.

Of the 80 glycated hemoglobin tests available, the hemoglobin A1c was the only test used in the above clinical trials. As a result, various companies have several different formats of A1c assays, all measuring the same analyte, but with incongruous results. When comparing A1c results using several dissimilar HPLC methods, for instance, A1c results are discordant by 1.7 A1c percentage points. Thus in one A1c assay, a patient’s result could be 7.0% and in another, 8.7%. This discrepancy is significant due to the steep slope of complication rates versus A1c in this A1c range (see Figure 2, page 17).

According to the author, other glycated hemoglobin assays (eg, total glycated and other A1c tests) can vary by as much as three glycated hemoglobin percentage points. Consequently, an individual who has a 7% glycated hemoglobin in one assay may actually have a 10% value, placing that patient at high risk for micro- and macrovascular disease. If this hypothetical standard were not linked or traceable to the UKPDS or DCCT results, then it, too, could be misleading for generalists and patients. Fortunately, a normalization process is available for glycated hemoglobin assays to mathematically “adjust” or “normalize” all assay format results to the hemoglobin A1c assay specifically used in the UKPDS and DCCT, termed “traceable” to the DCCT.

Continues on page 20
How to increase awareness among physicians of the variance among glycated hemoglobin assays remains a major dilemma. Experts at the University of Missouri are trying to resolve this problem by developing normalization and calibration procedures. These analyses, presented in a simple format on the Internet, clearly indicate which assays are normalized or traceable to the DCCT for proper diabetic chronic complication assessment and which are calibrated for assay quality control.32 (Refer to www.missouri.edu/~diabetes/ngsp/ to ensure your lab’s A1c assays are certified by the University of Missouri’s National Glycohemoglobin Standardization Program.)

Generalists who send their tests to numerous clinical labs must be reminded that these facilities most likely use different glycated hemoglobin assays and, therefore, must be careful when choosing a glycated hemoglobin assay. The test need not be an A1c test, since the normalization process will bring the value of a total glycated hemoglobin assay in line with the DCCT A1c value. Lab personnel must remember to report the A1c format, however, not the total glycated value or another value. Furthermore, lab reports should indicate the assay is traceable to the DCCT and UKPDS. Note: Glycemic monitoring tests that aren’t used in large, randomized, prospective, controlled clinical intervention trials comparing glycemia and chronic complications, or tests that have not been calibrated and normalized to the DCCT/UKPDS, should not be used for long-term monitoring of glycemic control in diabetic patients.

**DYSLIPIDEMIAS**

Diagnosis and treatment of dyslipidemias are extremely important. While current ADA guidelines have become stringent regarding the lowering of LDL and raising of HDL cholesterol, this protocol has had a limited positive effect on overall improvement of diabetic care.5 Recent data describing the use of HMGCoA reductase inhibitors (eg, statins such as pravastatin and simvastatin) indicate marked reductions in cardiovascular death rates of up to 55% in diabetic patients.14,33 Significant numbers of patients taking statins are still dying, however. Furthermore, these results appear to be somewhat unrelated to LDL cholesterol.16,37 Statin studies suggest that other dyslipidemias may be important as well.

**LDL, HDL, Lp(a) abnormalities**

Recently, experts at the author’s facility found a high prevalence of newer dyslipidemias when they were considered as a composite amongst diabetic patients.38 These newer dyslipidemias, which are easily treatable, include abnormalities of LDL particle size (small, dense LDL), HDL particle size (HDL2), and Lp(a). The atherogenic lipid profile (ALP) is composed of hypertriglyceridemia and abnormalities of LDL particle size, total HDL cholesterol, and HDL particle size. Each lipid is involved in a tightly linked metabolic pathway,39 beginning with the hepatic production and secretion of VLDL1, an abnormally large VLDL molecule (see Figure 3, below).

VLDL1 leads to the generation of LDL molecules that ultimately are smaller or thicker than the typical, more buoyant LDL, which binds with the LDL receptor. Small, dense LDL 1) binds poorly to the LDL receptor while binding well to the vascular intima (eg, in coronary vessels); 2) is more susceptible to oxidative stress than buoyant LDL; and 3) has a longer residence time in vascular intima and the systemic circulation.39,40

LDL particle size abnormalities are extremely prevalent in diabetes. Some 57% of 130 subjects in the author’s study had LDL peak particle diameters $>263D$. (Other laboratories describe similar prevalence.) Data from the author’s research also showed that 60% of patients had abnormalities of HDL fraction 2 (ie, HDL2 <40% of the total HDL cholesterol mass) and 35% of subjects displayed abnormalities of Lp(a) (ie, values $>25$ mg/dL). These prevalence rates are high relative to total LDL cholesterol abnormalities, which in the author’s research had a prevalence rate of only 35% among the same diabetic group.

Equally relevant, these newer dyslipidemias are

**Table 3**

<table>
<thead>
<tr>
<th>Estimates of glucose tolerance abnormalities</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
</tr>
<tr>
<td>Actual (*)20 years old</td>
</tr>
<tr>
<td>Known diabetes</td>
</tr>
<tr>
<td>Unknown diabetes</td>
</tr>
<tr>
<td>Impaired fasting glucose (IFG)</td>
</tr>
<tr>
<td>Impaired glucose tolerance (IGT)</td>
</tr>
<tr>
<td>Total individuals involved</td>
</tr>
</tbody>
</table>

(*m = million)
more toxic. They are associated with a three- to seven-fold increase in cardiovascular event rates for LDL particle size abnormalities and a three-fold increased rate for Lp(a).41,42 The bad news: These dyslipidemias are not only more prevalent than LDL cholesterol but also more toxic by as much as two-fold. The good news: Niacin, extended release niacin, and niacin combinations with atorvastatin completely correct these abnormalities in 60%–70% of diabetic patients who can tolerate niacin products.43-46 (Table 4, above, highlights recommended dyslipidemia guidelines for diabetic patients.)

A limited number of clinical laboratories in the US currently measure LDL and HDL particle size abnormalities as these tests typically involve gel electrophoresis (see Table 5, page 23). Considering the importance of these dyslipidemias, the author’s facility established a lab for performing these assays both for research and clinical purposes.

**Does treating the new dyslipidemias help?**

Researchers have yet to prove that treating the new dyslipidemias actually lowers mortality rates. Back in the 1970s, however, niacin was shown to save lives during dyslipidemic treatment.47 More recently, a clinical trial showed LDL particle size to be the most important determinant of reducing coronary plaque.36 Another study suggests that “isolated” abnormalities of total HDL cholesterol can improve cardiovascular mortality and event rates by about 22%.48 Close examination of these data reveals that gemfibrozil-mediated improvement in total HDL cholesterol was only 6%, a rise from a mean of 32 to only 34 mg/dL. More importantly, mean triglyceride levels were reduced 31%, from 160 to 110 mg/dL. Consequently, triglyceride reduction improved the lipid pattern distal to VLDL1 (see Figure 3, page 20), with possible resultant improvements of LDL particle size and other toxic lipoproteins, shown after niacin treatment.

The relationship of circulating triglyceride levels in diabetic and nondiabetic patients is shown in Figure 4, below. Interestingly, small, dense LDL (depicted as type B subjects in Figure 4) is linked to triglyceride levels. Hence one rationale for the target recommendation for triglycerides noted in Table 4. Here again, laboratorians need to communicate the facts noted above to generalists via phone, email, and/or short write-ups adjacent to traditional LDLc, HDLc, or triglyceride values on lab reports.

**MICROALBUMINURIA**

Besides being an independent risk factor related to cardiovascular death, microalbuminuria defines a clear-cut, early onset of diabetic nephropathy.49,50 As a result, laboratorians should advise generalists to perform microalbumin levels on all patients with fasting plasma glucose levels in the diabetic range (ie, fasting plasma glucose >126 mg/dL or a two-hour oral glucose level exceeding 200 mg/dL). Lab staff also should consider educating patients via tutorial flyers regarding the existence of this simple urine test.

Microalbuminuria is defined as the amount of albumin excreted in the urine for a finite period of time, eg, 24 hours. If a 24-hour timed specimen is used, normal individuals excrete less than 20 mg/day.
Diabetes a must

Uncovering microalbuminuria is extremely significant as it helps predict death amongst diabetic patients.52,53 Virtually all type 1 patients with microalbuminuria also develop clinical renal disease within 10 years. Individuals with this condition already have developed histopathological changes at the electron microscopic level within the glomerulus.54,55 These changes are identified as widening of the spaces between the foot processes of the podocytes that envelope and provide structural integrity for the glomerular capillaries. Other dimensions of histopathological abnormalities exist among patients with microalbuminuria as well. These early electron microscopic changes are reversible, however, if appropriate treatment is initiated.

Both type 1 and 2 diabetic patients have microalbuminuria, although it is more prevalent in type 1 patients, with rates ranging from 30%–40%. Prevalence rates among type 2 patients range from 25%–30%. These numbers indicate that roughly a third of diabetic patients in the US remain undiagnosed and unmanaged, which is unfortunate, considering how easily this ailment can be treated.

Microalbuminuria is closely associated with other risk factors, eg, dyslipidemias such as LDLc and Lp(a), further increasing one’s risk of death.56-58 It is crucial generalists consider the potential risk of microalbuminuria early on, when there is time to avoid more serious progression by reducing dietary protein, controlling hypertension and blood glucose, and increasing the use of ACE inhibitors.

Test alternatives

Considering the sensitivity of dipsticks at 200–300 mg/day of albumin, and the upper normal range of <20 mg/day, a window from 20 to 200–300 mg/day remains invisible (see Figure 5, above). This window of urinary albumin excretion (ie, microalbuminuria) can be assessed using radioimmunoassay (RIA) or newer dipsticks/test tablets, the latter of which provide the sensitivity to measure albumin down to normal range.

A patient’s microalbuminuria level can be assessed easily using timed one- to four-hour urine samples. Thus a 24-hour timed collection is no longer mandatory. Results from shorter timed tests can be expressed in micrograms of urinary albumin excreted per minute (µg/min), while results from the 24-hour collection are expressed in milligrams per day (mg/day). Both unit systems yield almost identical results, ie, roughly 20-30 per day or per minute.

Newer dipstick or tablet technology (eg, monoclonal antibodies embedded in solid-phase strips) is extremely useful for screening large numbers of subjects. These tests are only semi-quantitative, however, so they should be reserved for initial screenings. Patients who test positive should undergo measurement of a quantitative albumin excretion using technology such as RIA.

The author’s clinic performs 24-hour screening collections to obtain microalbumin diagnoses in addition to measuring creatinine clearance and urinary urea, both of which are performed on all new patients and for annual follow-up on patients with normal values. Measurement of urinary urea helps the generalist determine daily protein intake—the first line of treatment for microalbuminuria.

References


