Exploring the many faces of diabetes

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Exploring the many faces of diabetes mellitus

It is nearly impossible to open a newspaper or magazine without seeing some reference about diabetes. The diabetes epidemic has reached a level of public awareness that is unprecedented. Further, an increasing number of journal articles have explored the relationship of diabetes with other illnesses such as obesity, sleep apnea and Vitamin D deficiency. The great majority of recent press has been focused on adults with type 2 diabetes mellitus (T2DM). However, diabetes is a collection of glucose disorders and proper evaluation and treatment necessitates this recognition. In this issue of the AOA Health Watch series “DOs against diabetes” we explore some unique subgroups of people with diabetes.

First, David J. Valent, DO, and Andrew W. Wapner, DO, discuss how the emerging problem of T2DM in children is currently identified and treated. This is an emerging problem that has huge public health implications. It was once assumed that children with diabetes had type 1 diabetes mellitus (T1DM) but this assumption is no longer true and this article explores the available evidence to screen for and treat T2DM in children and adolescents.

In the second article, Tracy L. Marx, DO, and Rachel M. Holt, OMS IV, discuss the unique circumstances of the older adult with diabetes. Further, they provide suggestions when the older adult with diabetes should be treated aggressively but also share when different treatment guidelines may be appropriate.

Also in this issue, Allison Petznick, DO, reviews the importance of early and aggressive strategies to prevent microvascular complications. She discusses how to address the patient who does not understand the need to take preventive medications when they do not feel bad. Finally, she gives the reader “Take Home” messages about how to help prevent diabetes complications, recognizing that glucose control is not always the most effective strategy.

Finally, in my article I explore a different kind of diabetes: Latent autoimmune diabetes of the adult or LADA. This is an increasingly recognized form of diabetes and may be present in 10% of people who think they have T2DM. The disease progression and treatment is substantially different and, therefore, increased recognition of this condition is important.

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Classically, type 2 diabetes mellitus (T2DM) has been known as a disease of adulthood. As most physicians know all too well, by the time a patient has received a diagnosis of T2DM, he or she has already suffered significant beta cell destruction, resulting in insulin resistance and often leading to early complications. Aided by western society’s high-calorie, high-sugar dietary habit and sedentary lifestyle, the prevalence of obesity has risen significantly among our youth over the past 20 years. This increase coincides with a rise in the diagnosis of T2DM in this population.
Trends suggest that the incidence of T2DM in the pediatric population will soon surpass that of type 1 diabetes mellitus (T1DM). As diabetes is a chronic, incurable disease for which length of disease adversely affects complications, it is paramount that physicians detect and treat these patients early to prevent or alter many of the potential complications. This article will address the unique characteristics of T2DM in youth and the challenges that should be addressed when treating these patients.

**Frequency of T2DM in youth**

Approximately 16% of children aged 6 through 19 in the United States are overweight. In fact, one study, examining sixth-graders in 42 schools in seven cities, found that 49.3% of students had a body mass index (BMI) ≥85th percentile. The direct link between T2DM and obesity in children was confirmed in a study by Lui et al showing that among those children with T2DM, 89.8% were overweight or obese.

Previous studies reported that as many as 45% of newly diagnosed pediatric patients with diabetes suffer from T2DM. More recent data has shown that this is closer to 20%. The overall incidence of T2DM in the pediatric population is 8.1 per 100,000 among 10- to 14-year-olds and 11.8 per 100,000 among 15- to 19-year-olds.

The incidence of T2DM in minority populations appears to be even higher. The reported incidence ranges from 3.7 per 100,000 in the non-Hispanic white population to 38.42 per 100,000 among Navajo Indian women. This difference seems to coincide with the higher incidence of obesity in pediatric minority populations.

The incidence of T2DM in children by ethnic groups is shown in Table 1. Patients in these minority populations have worse glycemic control than non-Hispanic white patients. This may be related to poorer adherence among some minority populations.

The rates among children also seem to differ between genders, where the incidence of T2DM in females is 60% higher than for their male counterparts.

**Screening guidelines**

The American Diabetes Association (ADA) has created screening recommendations for those pediatric patients at highest risk for developing T2DM. These recommendations suggest testing for those patients who are overweight—defined as a BMI ≥85th percentile for age and sex, weight for height ≥85th percentile, or weight >120% of ideal for height—plus any of the two following risk factors:

- family history of T2DM (first- or second-degree relative)
- race/ethnicity that includes American Indian/Native American, African American, Hispanic or Asian/Pacific Islander
- signs of insulin resistance or conditions associated with insulin resistance, including acanthosis nigricans, hypertension, dyslipidemia or polycystic ovarian syndrome.

According to the recommendations, testing should begin at age 10 or at the onset of puberty, whichever comes first. The screening test of choice is a fasting blood glucose, which should be repeated every two years. This suggestion is supported by data showing that approximately one in four obese pediatric patients with impaired glucose tolerance as defined as a measured glucose of 140-200 mg/dl on a two-hour glucose tolerance test developed T2DM within the next two years. Many of these patients will not present with the classic signs of T1DM, such as polyuria or polydipsia. Most often, kids will be diagnosed on screening labs. Therefore, clinical judgment should also be used if these screening criteria are not met.

**Treatment**

Once the diagnosis of diabetes has been made, monitoring the diabetes and its complications is important for quality care in these patients. Because complications increase over time in people with T2DM, we expect that children with diabetes may start suffering complications in their 30s, perhaps their 20s, or even earlier. This could have dramatic public health implications.

Because limited studies exist regarding the treatment of T2DM in this age group, treatment regimens are based on interventions in adults. Table 2 shows ADA treatment guidelines and goals for those patients diagnosed with T2DM in youth. These treatment guidelines have been established to decrease morbidity and mortality in this population.
Lifestyle modifications

The ultimate goal for the treatment of diabetes is to prolong beta cell function and improve insulin sensitivity. This can be accomplished through lifestyle modifications or medications, or a combination of the two.

Several studies, for example, have examined the importance of physical activity in patients with T2DM. Physical activity causes the body to become more insulin sensitive. One hypothesis is that exercise causes an increase in insulin-regulated glucose transporters on the surface of the muscle fibers. These biological changes from exercise lead to improved blood sugar control. This effect is evident even without weight loss. Because many of these children are obese and have a low exercise tolerance, exercise that can be accomplished and performed multiple times per week should be encouraged.

Dietary changes have also demonstrated value as an important component of diabetes treatment. Goals of dietary treatment should be realistic and need to focus on moderate weight reduction. One study examined pediatric patients with T2DM who were on a ketogenic, very-low-caloric diet compared to matched controls. This type of diet was effective in meeting short-term goals, including reducing body mass index, and in achieving glycemic control.

However, in general, diet in this population is difficult to address because the child is dependent on others for food. Low-income students are often reliant on schools for breakfast and lunch, and all children must rely on their parents’ choices for other meals. Therefore, education of the entire family is important for adherence to a proper diet to be a realistic goal. When the entire family is attempting to shift toward a healthier lifestyle, that dynamic may make it easier and more likely that the pediatric patient will comply with the suggested therapeutic changes. The availability of resources, or lack thereof, also needs to be considered by health educators before dietary changes are recommended, as many of these patients are in lower socioeconomic families and may lack necessary funds or even reasonable access to the appropriate foods where they live and shop.

Medications

Although diet and exercise are central for treating T2DM in children, fewer than 10% of pediatric patients with T2DM can be successfully treated with diet and exercise alone. In considering different treatment options, several factors must be evaluated, including efficacy, side effects, simplicity and convenience of the treatment regimen. Medication formulation also needs to be considered for children who cannot swallow pills.

In adults with T2DM, adherence to oral hypoglycemia agents ranged between 36% and 93% in various studies. Less-frequent dosing represents the best option and would facilitate a parent’s task of reminding the patient to take his or her medications, as well as observe the dose being administered. In this respect, extended-release formulations can have additional benefits.

Patients in the pediatric population possess unique characteristics, however, in terms of adherence to medication regimens. For example, they must deal with psychosocial implications associated with the use of medications. Many children do not want to take medication for personal reasons, ranging from the unwanted side effects of the medications to feeling different than their peers and wanting to fit in. Factors that contribute to adherence include the combined effort of parent and child to participate in the prescribed treatment regimen, physical and behavioral changes that occur during childhood and adolescence, and patient lifestyle. Because of these factors, both parent and child should be educated on the diagnosis of T2DM and the significance of tight glycemic control, the importance and specific role of the medications prescribed, and possible side effects of any medications.

Of the oral hypoglycemic medications, few have been studied in the pediatric population. In fact, metformin is the only FDA-approved oral medication for pediatric patients aged 10 and older for the treatment of T2DM.
T2DM. However, metformin does not appear to be sufficient for long-term therapy alone.\(^\text{20}\) In fact, hemoglobin A1c levels tended to rise after just two years of monotherapy.\(^\text{20}\) Off-label use of other oral hypoglycemic agents is sometimes used as an adjunct for this population. However, the efficacy, as well as the short- and long-term safety, have yet to be determined.

Insulin has no age limitations and may be a necessary treatment option, particularly if the oral hypoglycemic medications are unable to fully control a patient’s blood glucose. However, adherence to insulin therapy in this age group (between 10 and 20 years old) is very poor for those with T1DM, research suggests,\(^\text{21}\) and this may be suggestive of poor compliance for young patients with T2DM as well. Another factor that must be considered when beginning insulin is treatment-associated weight gain. This may not only become a factor in reducing compliance with treatment, but may also exacerbate other obesity-associated comorbidities such as hypertension and obstructive sleep apnea.

Along with blood sugar management, treatment goals should also include management of coexisting diseases, such as depression, eating disorders and obstructive sleep apnea. For example, one study examined clinically depressive symptoms in urban youth at risk for T2DM. Researchers found that approximately one in five of these children had clinically significant levels of depressive symptoms.\(^\text{22}\) In adult patients with T2DM, depression is associated with a higher hemoglobin A1c.\(^\text{23}\) Possible explanations for this disparity include failure to maintain diet, routine exercise and medication adherence.\(^\text{24}\)

**Need for specific guidelines**

As stated previously, treatment guidelines in the pediatric population with T2DM are formulated from those of adults (see Table 2). Strict glycemic control along with assessment and treatment of diabetic co-morbidities are the basis of therapy. The need for routine examinations for diabetic complications is paramount and should begin at initial diagnosis; health practitioners should also be aware that complications may arise soon after diagnosis. For example, a study by Karabouta et al examining seven adolescents with T2DM found that four had evidence of peripheral neuropathy.\(^\text{25}\)

Studies demonstrate that there are differences in the development of complications from T2DM if the diabetes is diagnosed as a youth as compared to an adult. Making assumptions that T2DM in the pediatric patient will follow the same course as T2DM in an adult is no longer possible. But while the course may be different, the question remains: Should treatment guidelines be the same for these two populations?

No study has yet examined if current recommendations prevent long-term complications. Further, there are few studies examining if physicians are even meeting the treatment recommendations

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Table 2

<table>
<thead>
<tr>
<th>Lab/Examination</th>
<th>Frequency of Exam</th>
<th>Treatment Goal</th>
</tr>
</thead>
<tbody>
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<td>Hgb A1c</td>
<td>Quarterly</td>
<td>&lt; 7.0%</td>
</tr>
<tr>
<td>Blood Pressure</td>
<td>At each visit</td>
<td>&lt; 95 percentile for age and sex</td>
</tr>
<tr>
<td>Lipids</td>
<td>Annually</td>
<td>&lt; 100 mg/dl</td>
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<tr>
<td>LDL</td>
<td></td>
<td>&lt; 150 mg/dl</td>
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<tr>
<td>Triglycerides</td>
<td></td>
<td>&gt; 40 mg/dl</td>
</tr>
<tr>
<td>HDL</td>
<td></td>
<td>&gt; 50 mg/dl</td>
</tr>
<tr>
<td>Males</td>
<td>Annually</td>
<td>Absence of retinopathy</td>
</tr>
<tr>
<td>Females</td>
<td>Annually</td>
<td>Absence of foot ulcers</td>
</tr>
<tr>
<td>Dilated eye exam</td>
<td>Annually</td>
<td>Absence of microalbuminuria</td>
</tr>
<tr>
<td>Foot exam</td>
<td>Annually</td>
<td></td>
</tr>
<tr>
<td>Urine microalbuminuria</td>
<td>Annually</td>
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</table>
in the pediatric population. One study showed that 55% of pediatric patients with T2DM were meeting hemoglobin A1c goal of less than 7%. However, if an “all or none” approach was used, only 12.5% of patients were meeting hemoglobin A1c, blood pressure and low-density lipoprotein goals simultaneously. This is a point of concern, in light of the Steno-2 trial showing that tight control of these three risk factors can substantially reduce macrovascular and microvascular complications.

Youth with T2DM, and in particular adolescents, possess unique characteristics that must be addressed. Also, because of the racial disparities associated with this disease, future research is needed to determine if there are therapies that are more efficacious in specific ethnic or racial groups. This tailoring of treatment to specific patients may lead to better and more effective care, as well as reduce the risk for future complications.

Another consideration is that hormonal changes in the adolescent population can cause significant changes in insulin sensitivity. One study demonstrated a 32% reduction in insulin sensitivity between Tanner stage I and stage III. This decline was observed independent of age, sex and ethnicity. This decrease in insulin sensitivity in turn leads to a rise in fasting glucose, so recognition of these normal physiologic changes is important and could play a role in the treatment guidelines.

Other recommendations
Although they may not have any direct impact on the course of diabetes or even on adherence to treatment plans, physicians should also give consideration to other conditions and factors beyond the basic guidelines.

For example, because of the higher association of diabetes with depression, a psychosocial assessment of some form should be added to the recommendations. This can either be in the form of an informal screening or an assessment tool.

Also, an investigation of other modifiable risk factors for complications should be included, and alcohol and tobacco use should be addressed, at least informally. Furthermore, with the higher rates of obesity in this population, obstructive sleep apnea should be investigated and treated if the patient is found to be suffering from it.

Final notes
The rate of T2DM in children is rising, and the factors contributing to this rise need to be addressed now. Early diagnosis, treatment and monitoring of these patients are all important to prevent long-term complications.

Lifestyle modification is the first-line approach for children with diabetes, and metformin is currently the only oral hypoglycemic medication approved for T2DM in children. Because youth have unique considerations, comprehensive disease management is important to control and avoid complications. Much research continues toward improving treatment options to reduce long-term complications in this population. Specific guidelines or addition of subjective guidelines should be considered for this population.
References


The number of aged individuals in the United States is increasing rapidly as the so-called baby boomers advance into their senior years. People aged ≥65 years represented approximately 12% of the US population in 2000, and this proportion is expected to grow to almost 20% by the year 2020.¹
Increasing age is a known risk factor for diabetes, with disease burden in the elderly (≥75 years) exceeding 20%. The incidence of diabetes is expected to increase dramatically over the next 50 years, with the largest increases occurring in the oldest age groups. The projected 336% increase in diabetes in the aged population (≥75 years) by 2050 will produce an enormous national economic burden and challenge for clinical practice.

Older individuals with diabetes have twice the mortality and suffer from higher rates of functional disability and geriatric syndromes (such as polypharmacy, depression, cognitive impairment, urinary incontinence and injurious falls) than their age-matched counterparts. Care of this clinically and functionally heterogeneous group is often a complex task because many individuals suffer from multiple coexisting illnesses, such as hypertension, hyperlipidemia, coronary heart disease (CHD) and stroke. This complexity of care is confounded by the fact that little has been published regarding the care of this population and many of the current care recommendations are based on data extrapolated from younger populations or on expert opinion.

The American Diabetes Association (ADA) first devoted a section to the care of the older person with diabetes in 2004. In the same year, the American Geriatrics Society (AGS) published its first and only comprehensive guidelines for the treatment of diabetes in this special population. Both organizations advocate for a balanced approach when caring for older individuals with diabetes.

Care plans should be individualized for each patient, taking into consideration the mortality benefit of intensive therapy and the quality of life each patient will face with a given therapy. When determining treatment goals, the following should be evaluated: the life expectancy, functional status and cognitive ability of the patient; the availability of a social support system; and patient preferences.

The ADA and AGS advocate for aggressive management using the same standards in place for younger populations who maintain good functional status. The ADA and AGS guidelines both support aggressive glycemic control (HbA1c ≤7.0%) for aged individuals who are functional, cognitively intact and have significant life expectancy. Individuals in whom a less aggressive treatment (HbA1c ≤8.0%) might be considered are patients with decreased levels of function (limitations in three or more activities of daily living), decreased cognitive impairment, decreased life expectancy (<five years) and those with severe hypoglycemia unawareness.

Glycemic control

Intensiveness of glycemic control in the aged person with diabetes continues to be an area of debate, in part due to the paucity of data on the topic. In this population, the cardiovascular benefit of tight glycemic control must be balanced with the increased risk of hypoglycemic reactions and adverse side effects from additional medication.

Although no randomized controlled trials like the United Kingdom Prospective Diabetes Study Project exist for the aged population, epidemiologic studies have demonstrated an association between improved glycemic control and reduction in vascular complications, as well as improved neuropsychologic function. A 1% reduction in hemoglobin A1c (HbA1c) is associated with a 37% decline in microvascular complications and a 21% reduction in risk of any endpoint related to diabetes.

Hyperglycemia has also been shown to cause declining mental function in the elderly, which could compromise the individual's ability to participate in diabetes self-care. However, frail older adults are at high risk for serious hypoglycemia, bradycardia, orthostatic hypotension and myalgia—which could all lead to injurious falls or other adverse health effects. In addition, individuals with lower levels of function (limitations in three or more activities of daily living) have not been shown to benefit from tight glycemic control.

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Overt hyperglycemia should be avoided in all individuals regardless of functional status or life expectancy because of the associated morbidity (polyuria, dehydration, urinary incontinence and hyperglycemic hyperosmolar coma), which can significantly impair quality of life. 14, 15 Goals of glycemic control need to be made on an individualized basis, factoring in these issues.

Therapy to maintain euglycemia in the aged population typically requires multiple medications. Caution should be taken before starting metformin in this population because of the increased incidence of impaired renal function. 14, 15 Baseline renal function studies and yearly follow-up levels should be obtained and medication discontinued with serum creatinine of 1.5 mg/dL or greater in men and a level greater than 1.4 mg/dL in women. 14, 15 Sulfonylureas should be used with discretion and long-acting forms (chlorpropamide and glyburide) should be avoided because of the increased incidence of profound and prolonged hypoglycemia in the aged population. 14, 15 For individuals requiring insulin therapy, insulin pens should be considered, particularly for patients with compromised manual dexterity or impaired vision.

Regardless of therapy, self-monitoring of blood glucose (SMBG) should be encouraged. 14, 15 Although studies have yet to demonstrate improved glycemic control with SMBG, its utilization in the elderly is integral to detecting hypoglycemia and, therefore, to improving care and reducing complications. 36 Hypoglycemia incidence in patients with hypoglycemia unawareness, a complication more common in the elderly, may only be detected if SMBG is utilized.

**Cardiovascular risk reduction**

Aged people with diabetes experience twice the mortality as is seen in age-matched controls, with the major killer being macrovascular disease. 27 Approximately 80% of people with diabetes will die from cardiovascular disease. 28 Tight control of blood pressure, lipids and blood glucose have been proved to decrease negative morbidity and mortality outcomes of aging people with diabetes. 21, 29 Data also have shown that people with diabetes receive the greatest mortality benefit from treating hypertension first, lipids second and blood glucose third. 30

Reducing cardiovascular risk in the older adult is of paramount importance because of the increased risk for cardiovascular disease. 15, 18 Despite the known benefit of treatment, studies demonstrate that the treatment and control of cardiovascular risk factors in elderly outpatients with diabetes often does not meet the guidelines. 20

According to the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure, 20% of individuals age 60-79 are not treated for hypertension. 31 Prescribing statins to older patients has been shown to be suboptimal in this population, and adherence to prescribed statins is poor anyway. 32 Lastly, an observational study of institutionalized elderly demonstrated that only 42% of residents with diabetes were receiving aspirin therapy. 33 Following are some key cardiovascular risk-reduction strategies.

**Hypertension**

Hypertension is a common co-existing condition with diabetes in the aged population. Antihypertensive treatment has been shown to reduce coronary artery events by 23%, strokes by 30%, cardiovascular deaths by 18% and total deaths by 13% among the elderly, with the greatest benefit seen in those older than 70 years of age. 34 With only two to four years of treatment needed to realize a mortality benefit, control of this cardiovascular risk factor is appropriate in nearly all people of advanced age. 30

Although most agree that hypertension should be treated in the aged person with diabetes, debate exists on the level of control that should be targeted. The AGS recommends treatment targets of <140/80 mmHg; the ADA does not provide any specific guidelines for aged adults. 15, 17 Although some may advocate for less aggressive hypertension treatment in the elderly because of the increased risk of adverse effects (falls, hypotension and syncope, for example), recent evidence suggests that intensive blood pressure control has added benefit in the elderly population. 35

Regardless of treatment targets, blood pressure should be lowered gradually to avoid complications. 14, 15, 17 Similar to guidelines for younger populations, angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers should be strongly considered on the basis of their renal protective effects. 17 Baseline renal function studies and electrolytes should be performed as well as follow-up labs one to two weeks after starting the medication regimen and after any dosage increase. 14, 15

**Lipids**

The role of statins as a secondary prevention tool for cardiovascular disease in patients with diabetes is well established with their use as a primary prevention strategy increasing in high-risk populations. 17 Currently, the ADA recommends statin use to obtain lipid goals (low-density lipoprotein <100 or <70 for those with one or more CHD risk factors, high-density lipoprotein >40 in men and >50 in women, and triglycerides <150) for all patients with overt CHD and for patients without CHD who are over the age of 40 and have one or more other CHD risk factors. 17 Although the ADA does not provide specific guidelines for treatment of lipids in the aged population, the AGS has suggested that treatment goals for younger patients with diabetes should be applied to the elderly. 15 This is likely due to the fact that only two to four years of lipid control is needed before a mortality benefit is realized.
**Aspirin**

Data have shown that daily low-dose aspirin (100 mg) reduces cardiovascular deaths in at-risk patients by 44%. Current ADA and AGS guidelines recommend aspirin use when not contraindicated. Although some concern may exist in administration of aspirin to the frail aged patient because of the risk of bleeding, research has demonstrated that the risk of a major bleed in elderly nursing home residents on aspirin therapy is very low. Because aspirin should be utilized for primary prevention in virtually all aged individuals with diabetes.

**Screening**

Microalbumin is an early screening tool for cardiovascular disease and also renal failure, for which elderly people with diabetes are at increased risk. Because microalbuminuria is an independent risk factor for cardiovascular disease, yearly microalbumin should be performed in all aged people with diabetes to screen for nephropathy and to help assess cardiac risk.

**Geriatric syndromes**

Such geriatric syndromes as polypharmacy, depression, cognitive impairment, urinary incontinence and injurious falls are more common among aged individuals with diabetes, and account for increased morbidity and decreased quality of life in this population. Because microalbuminuria is an independent risk factor for cardiovascular disease, yearly microalbumin should be performed in all aged people with diabetes.

Polypharmacy is common in all patients with diabetes, but is an even bigger issue among the aged population. Inherent to appropriate treatment guidelines, older adults being treated for diabetes and hypertension will be placed on numerous different classes of medication without even considering any other medical problems, leading to increased potential for drug-drug and drug-disease interactions.

Polypharmacy alone has been shown to contribute to or exacerbate other geriatric syndromes, including falls, depression, urinary incontinence and cognitive impairment. Patients should be encouraged to carry an updated medication list for review by not only their primary care physicians, but all other consultants as well. Reviewing medication lists alone can improve patient care by decreasing inappropriate prescribing.

Older persons with diabetes are significantly more likely to suffer from depression, which may impede diabetes self-management and has been shown to compromise health outcomes if unrecognized. Physicians should screen for depression during the initial evaluation of the patient and after any unexplained decline in clinical status.

Cognitive impairment is more prevalent in the aged person with diabetes than the general elderly population. Because hyperglycemia has been shown to cause declining mental function, glycemic control should be evaluated in any person with diabetes presenting with cognitive decline.

Physicians also must be aware of an individual's cognitive function and available support systems when prescribing treatments, as individuals with impaired cognition may have difficulty participating in diabetes self-care.

Urinary tract dysfunction, including urinary incontinence, is prevalent, particularly among elderly women with diabetes. Risk factors specific to this subpopulation include polyuria due to hyperglycemia, fecal impaction due to autonomic insufficiency, overflow secondary to neurogenic bladder or autonomic insufficiency, urinary tract infection and candida vaginitis.

Many older women assume that urinary incontinence is a natural part of aging and will not offer this as a “problem” without being specifically asked about it. Although commonly undetected by healthcare providers, urinary incontinence should be among the regular screening priorities, as it may be associated with social isolation, depression, falls and fractures.

Injurious falls are more prevalent among the older patients who have diabetes than among their aged-matched nondiabetic counterparts. Like urinary incontinence, falls often go undetected by clinicians. Polypharmacy, peripheral neuropathy, hypoglycemia and declining functional status all contribute to the incidence of falls in this population. Although no trials specific to the aged person with diabetes have investigated this issue, exercise programs aimed at strengthening and balance—as well as elimination of any unnecessary medications, especially psychotropics—have been shown to reduce falls in the general elderly population.

**Final notes**

Aged persons with diabetes present a unique challenge to osteopathic physicians because of their clinical and functional heterogeneity. Care should focus on treatments that will provide realized benefit during the patient's lifespan and minimize any side effects. Physicians should frequently reassess their patient and the treatment goals for them to optimize care. As osteopathic physicians, we have been trained to address the complexity of this population and their disease. Using our holistic, patient-centered approach, we should lead the way in providing excellent evidence-based care for this fast-growing population.
References


Jane is a 32-year-old African-American female who visits her physician’s office and states that emergency department personnel told her that she has high blood sugar and instructed her to see her family physician. She has experienced no obvious symptoms but has a very strong family history of type 2 diabetes mellitus (T2DM). Jane is very concerned about this because her father recently started dialysis following kidney failure.
During her office visit, her blood pressure is 152mmHg/91mmHg and has been above 140mmHg/90mmHg on two other occasions. You recommend that she start lisinopril for her blood pressure and metformin for her elevated blood sugar. She is resistant to this course of action because she feels good now and is worried that the medications are going to cause her to experience cough and diarrhea as side effects.

Jane isn’t alone in either her situation or her concerns. Diabetes mellitus is estimated to affect more than 23 million people in the United States. The majority of these patients have T2DM and are usually asymptomatic at diagnosis. When physicians recommend a plan that includes medications, patients want to know why they need to go on medications that may actually add side effects to their lives when they are currently asymptomatic. What needs to be expressed to them is that the risk of complications from diabetes mellitus is the reason for starting medications now; and the potential health benefits will likely outweigh the inconvenience of potential side effects.

With that in mind, this article reviews the prevention, diagnosis and therapy for common microvascular complications you will see in patients like Jane.

Overview
Diabetes mellitus causes 12,000 to 24,000 new cases of blindness each year in the United States and is the leading cause of kidney failure, accounting for almost 50% of the new cases. In 2004, about 71,000 nontraumatic lower-limb amputations were performed in people with diabetes.

Complications of diabetes result from excessive protein glycation and activation of oxidative stress. It is believed that the initiation of this process is due to overproduction of superoxide by the mitochondrial electron transport chain. Intracellular hyperglycemia increases mitochondrial production of reactive oxygen species (ROS). This leads to activation of the polyol pathway, increased advanced glycation products, activation of protein kinase C, and increased hexosamine pathway.

The combination of these pathways leads to alteration in vascular blood flow, vascular occlusion, pro-inflammatory gene expression and increased ROS. In microvascular disease, this process is believed to be triggered by intracellular hyperglycemia.

Prevention or at least decreased progression of these complications can be accomplished by early and aggressive treatment of associated risk factors, though such actions as glucose control, blood pressure control, cholesterol control and lifestyle modifications (weight loss and smoking cessation). In fact, the combination of glucose, blood pressure and cholesterol control has been associated with a 60% decreased risk of microvascular complications.

Nephropathy
Microalbuminuria affects approximately 33% of patients with type 1 diabetes mellitus (T1DM). Among patients with both T1DM and microalbuminuria, one-third will develop nephropathy over a 10-year period and 75% of those patients will go on to have end-stage renal disease (ESRD) within 20 years. Surprisingly, the prevalence is much lower for patients with T2DM. Some 25% of patients with T2DM will develop microalbuminuria, 10% to 20% of those patients will develop nephropathy and 20% of patients with nephropathy will develop ESRD within 20 years.

The recommended screening method for microalbuminuria is a spot urine test for microalbumin/creatinine ratio. This has been proven to be as effective as the 24-hour urinary protein method and has essentially replaced the 24-hour urine test as a screening tool. A ratio of <30 mg/dl is considered normal, 30 mg/dl to 300 mg/dl is microalbuminuria, and >300 mg/dl is macroalbuminuria or gross proteinuria. For confirming the diagnosis, two out of three tests need to be positive over a three- to six-month period. False positive readings may be due to urinary tract infection, febrile illness, pregnancy, short-term hyperglycemia, marked hypertension, congestive heart failure, hematuria or vigorous exercise.

A plain dipstick urinalysis is not considered a screening tool for microalbuminuria. Some tests are not sensitive enough to pick up protein until there is at least 300 mg, which would be considered gross proteinuria.

Creatinine and glomerular filtration rate (GFR) should be tested as well. GFR is best estimated by the MDRD equation from the Modification of Diet in Renal Disease (MDRD) study. The equation is: GFR = 186 x (Pcr)^-1.154 x (age)^-0.203 x (0.742 if female) x (1.210 if African American).

In the Third National Health and Nutrition Examination Survey (NHANES III), among the patients with T2DM, GFR of < 60 ml/min was found in 30% of patients without evidence of microalbuminuria.

Treatment of microalbuminuria and nephropathy has been shown to decrease the risk for progression to ESRD. Intensive glucose control and especially intensive blood pressure control have shown beneficial outcomes. Angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blocker (ARB) drugs are the preferred agents to use in patients with renal disease. These agents have been shown to not only decrease risk of progression but also increase the chance for regression to normoalbuminuria.

An acute increase in serum creatinine of as much as 30% may be seen when initially starting an ACE inhibitor or an ARB. This usually stabilizes over a two-month period of time and is associated with a long-term preservation of renal function. If the serum creatinine rises above that level, then you should raise your suspicion for renal artery stenosis or more severe renal parenchymal disease. This may be a good time to refer to a nephrologist.

There has been mixed evidence regarding the effectiveness of the combination of an ACE inhibitor and an ARB to improve blood pressure and urinary albumin excretion.
Evidence suggests that the addition of an aldosterone antagonist to an ACE inhibitor is more effective at reducing blood pressure and urinary albumin excretion than either drug alone. One of the most important therapies in delaying progression of microalbuminuria is reduction in protein intake. A low protein diet (< 0.8 g/kg/day) has been shown to decrease the risk of ESRD or death by 76% but has no effect on the decline in GFR.13

Patients with nephropathy need to be evaluated for anemia as well as secondary hyperparathyroidism. Correction of anemia to hemoglobin levels of 11 g/dl to 12 g/dl has been shown to improve quality of life, decrease hospitalization and lower the risk of mortality. However, treatments with erythropoietin agents to hemoglobin levels > 12 g/dl have been associated with increased death, hypertension and thrombosis. Secondary hyperparathyroidism is associated with elevated phosphorous, decreased calcium and elevated intact parathyroid hormone (i-PTH). Most patients will have these conditions monitored and treated by their nephrologist.

Early referral to a nephrologist has been associated with decreased mortality, morbidity and cost. The National Kidney Foundation recommends that every patient with a GFR < 60 ml/min and every patient with microalbuminuria should undergo evaluation and treatment of complications associated with chronic kidney disease. Once the GFR is < 30 ml/min, regular follow-up by a nephrologist is strongly encouraged.

**Take-home points**

1. Microalbumin/creatinine ratio annually for patients with diabetes mellitus.
   a. < 30 mg/dl is normal.
   b. 30 mg/dl to 300 mg/dl is microalbuminuria.
   c. > 300 mg/dl is macroalbuminuria or overt proteinuria.

2. Low-protein diet (< 0.8 g/kg/day) decreases risk of ESRD or death by 76%.

3. Every patient with a GFR < 60 ml/min and every patient with microalbuminuria needs evaluation and treatment of complications associated with chronic kidney disease.

**Retinopathy**

Diabetes is the leading cause of blindness in patients 22 to 65 years of age, with 12,000 to 24,000 new cases of blindness annually.1 More than 90% of patients with T1DM will have evidence of retinopathy by 20 years after diagnosis and about 60% of patients with T2DM will have findings related to retinopathy over their lifetimes.14 Typically, the progression of eye disease is from nonproliferative retinopathy to proliferative retinopathy and finally to macular edema.

Hyperglycemia, hyperlipidemia and hypertension all contribute to the pathogenesis of retinopathy. Endothelial damage, loss of pericytes, thickening of the capillary basement membrane and retinal leukostasis lead to abnormal vascular flow, disruption in permeability and occlusion of capillaries. Initially this leads to nonproliferative retinopathy, which appears clinically as dot hemorrhages, microaneurysms, cotton wool spots and hard exudates. The retinal hypoxia and ischemia then stimulate neovascularization that is mediated by vascular endothelial growth factor (VEGF), resulting in proliferative retinopathy.15,16 Vascular proliferation and hemorrhage of these new vessels may lead to fibrous tissue proliferation, tractional retinal detachment and vitreous hemorrhage. In macular edema, patients will experience a breakdown of the blood-retinal barrier leading to leakage of plasma into the macula, swelling of the central retina and severe central visual loss.16

Intensive control of hyperglycemia, hyperlipidemia and hypertension has been shown to prevent retinopathy and delay the progression of diabetes. Proper visualization of the eyes with an annual dilated eye exam by an ophthalmologist is essential to catch the early stages of retinopathy.

Once a patient has retinopathy, multiple therapies are available that may prevent severe visual impairment. Scatter (panretinal) laser photocoagulation decreases the risk of severe vision loss and decreases progression in high-risk patients to less than 2% over five years.14 Focal laser photocoagulation is beneficial for patients with macular edema when it threatens the center of the macula. Vision loss is decreased by approximately 50% with this therapy.14 Vitrectomy is beneficial for vitreous hemorrhage or retinal detachment, and it may restore useful vision or prevent loss of vision. Patients with proliferative retinopathy should avoid activities involving valsalva response, as this may worsen their disease.
Recent studies have indicated that physicians may find potential benefit for the use of candesartan, fenofibrate and anti-VEGF agents in treating patients with diabetic retinopathy and diabetic macular edema. Candesartan reduces incidence of retinopathy in patients with T1DM and favors regression in T2DM. Fenofibrate reduces the progression of existing diabetic retinopathy. Anti-VEGF agents—such as pegaptanib, ranibizumab and bevacizumab—are currently used in patients with wet age-related macular disease, and studies appear to be showing promising results for their use in diabetic retinopathy and macular edema.17

### Table 1: Common medications in the treatment of peripheral neuropathy

<table>
<thead>
<tr>
<th>Medication</th>
<th>Dose range</th>
<th>NNT*</th>
<th>Time to effect</th>
<th>Adverse events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amitriptyline</td>
<td>100-150 mg</td>
<td>2.1</td>
<td>6-8 weeks</td>
<td>Anticholinergic, weight gain, arrhythmias</td>
</tr>
<tr>
<td>Desipramine</td>
<td>200-250 mg</td>
<td>2.5</td>
<td>6 weeks</td>
<td>Anticholinergic, weight gain, arrhythmias</td>
</tr>
<tr>
<td>Duloxetine</td>
<td>60-120 mg</td>
<td>4</td>
<td>4 weeks</td>
<td>Nausea, sedation, dizzy, increased HR and BP</td>
</tr>
<tr>
<td>Venlafaxine</td>
<td>150-225 mg</td>
<td>5.5</td>
<td>4-6 weeks</td>
<td>Nausea, sedation, dizzy, increased HR and BP</td>
</tr>
<tr>
<td>Topiramate</td>
<td>300-400 mg</td>
<td>7.4</td>
<td>12 weeks</td>
<td>Dizzy, cognitive slowing, kidney stones, glaucoma, weight loss, ataxia, speech difficulties</td>
</tr>
<tr>
<td>Gabapentin</td>
<td>2400-3600 mg</td>
<td>3.9</td>
<td>4 weeks</td>
<td>Sedation, dizzy, ataxia, weight gain</td>
</tr>
<tr>
<td>Pregabalin</td>
<td>300-600 mg</td>
<td>4.2</td>
<td>4-6 weeks</td>
<td>Edema, dizzy, sedation, weight gain, rhabdomyolysis</td>
</tr>
<tr>
<td>Capsaicin</td>
<td>0.075% cream</td>
<td>6.7</td>
<td>8 weeks</td>
<td>Localized burning and itching</td>
</tr>
<tr>
<td>Tramadol</td>
<td>200-400 mg</td>
<td>3.5</td>
<td>6 weeks</td>
<td>Nausea, sedation, tremor, seizures</td>
</tr>
<tr>
<td>Lidocaine</td>
<td>5% patch</td>
<td></td>
<td>Immediate</td>
<td>Local site irritation</td>
</tr>
</tbody>
</table>

*NNT: number needed to treat to achieve 50% reduction in pain

**Take-home points**

1. More than 90% of patients with T1DM will have evidence of retinopathy by 20 years after diagnosis, and 60% of patients with T2DM will have findings over their lifetime.

2. Intensive control of blood glucose, hypertension and hyperlipidemia prevents retinopathy and delays the progression of diabetes. Laser photocoagulation decreases vision loss in 50% of patients who have macular edema that threatens the center of the macula.

**Peripheral neuropathy**

Distal symmetric sensorimotor polyneuropathy is the most common cause of peripheral neuropathy in patients with diabetes mellitus. This usually consists of burning, paresthesias and aching pain in a stocking-and-glove distribution. The feet are involved initially but then symptoms move up the legs to the knees and, at that point, the fingertips may be involved. Neuropathy affects lightly myelinated, small unmyelinated and large myelinated fibers.

Small fiber neuropathy will often present with loss in pain sensation and temperature perception.
Large fiber neuropathy leads to nerve conduction slowing, decreased sensation to touch, pressure, two-point discrimination and vibratory sense. In severe cases, this may lead to sensory ataxia and gait disturbances.

The electromyelography (EMG) will only be positive if the large myelinated fibers are damaged, which may lead to a false-negative result. There are multiple other causes of peripheral neuropathy that can occur in patients with diabetes. Other treatable causes need to be ruled out, including thyroid disease, B12 deficiency and alcohol abuse.

This is one of the most difficult complications to treat in patients with diabetes. The only therapy that has been shown to reduce the incidence and slow the progression of neuropathy is tight glycemic control. Pharmacologic therapies are only used for symptomatic management (See Table 1). It is very important that patients’ expectations are set at an attainable level. Studies for these medications are considered to be effective if there is a 50% reduction in symptoms.

Duloxetine and pregabalin are the only medications that are FDA-approved for the treatment of peripheral neuropathy. However, there are many other agents utilized—and some other agents may be more effective. Tricyclic antidepressants work centrally by decreasing reuptake of serotonin and norepinephrine, but also block alpha-adrenergic, histamine, cholinergic and NMDA receptors. Amitriptyline is the most studied of these agents and probably the most effective, with an average response rate of 30%. Desipramine and nortriptyline may not be as efficacious but are usually tolerated better by patients. Caution needs to be used in patients with a history of cardiovascular disease and patients over 65 years of age. Duloxetine and venlafaxine also work centrally by blocking reuptake of serotonin and norepinephrine, but they tend to have fewer side effects due to their selectivity. In one study, duloxetine’s response rate was 47% to 48%.

Anticonvulsants have shown some efficacy in symptomatic treatment as well. Carbamazepine, lamotrigine, valproate and topiramate all act peripherally as sodium channel blockers. There has been mixed evidence to support the efficacy of these medications and they are associated with significant side effects. Gabapentin and pregabalin work peripherally on the GABA system and their efficacy is believed to be associated with the voltage-gated calcium channels. Sixty percent of patients on high-dose gabapentin, compared to 40% to 50% of patients on pregabalin, had at least a 50% reduction in pain. Pregabalin binds to the receptor with a better affinity, is associated with less sedation, and dose titration is easier than with gabapentin.

Capsaicin is an alkaloid derived from chile peppers that works by depleting the neurotransmitter substance P from sensory nerves. It may be associated with a burning pain during application, but that usually decreases after the first week of use. Patients must wash their hands immediately after application, and they must apply the capsaicin four times a day to the entire painful area.

Metanx is a B-complex vitamin that has shown some efficacy in the treatment of diabetic neuropathy. It is believed that elevated homocysteine exhibits toxic effects on the vascular endothelial cells. It is unknown if hyperhomocysteinemia is related to neuropathy, and therefore unclear if the use of this B-complex vitamin to decrease homocysteine levels is effective. Other possible treatments include tramadol, long acting opioids, lidocaine patches and transcutaneous electrical nerve stimulation.

Neuropathy may also be associated with acute hyperglycemia, as well as a reduction in glucose from treatment. The theory behind this is that improved glycemic control may initiate regenerating axonal sprouts that generate ectopic nerve impulses. This gradually improves with treatment—within days to weeks—and it is important to reassure your patients with this information.

Metformin has also been associated with neuropathy due to the depletion in folic acid. Supplementation with folic acid may be needed in these patients.

There are multiple other forms of neuropathy that must be considered in patients with diabetes; however, these are beyond the scope of this article.

Take-home points
1. Small fiber neuropathy presents with loss in pain sensation and temperature perception, while large fiber neuropathy manifests as decreased sensation to touch, pressure, two-point discrimination and vibratory sense.
2. Tight glycemic control is the only therapy shown to reduce the incidence and slow the progression of neuropathy.
3. Acute hyperglycemia as well as reduction in hyperglycemia from treatment may lead to transient neuropathy.
4. Metformin has been associated with neuropathy due to depletion of folic acid.

Amitriptyline is the most studied of these agents and probably the most effective, with an average response rate of 30%. Desipramine and nortriptyline may not be as efficacious but are usually tolerated better by patients. Caution needs to be used in patients with a history of cardiovascular disease and patients over 65 years of age. Duloxetine and venlafaxine also work centrally by blocking reuptake of serotonin and norepinephrine, but they tend to have fewer side effects due to their selectivity. In one study, duloxetine’s response rate was 47% to 48%.

Anticonvulsants have shown some efficacy in symptomatic treatment as well. Carbamazepine, lamotrigine, valproate and topiramate all act peripherally as sodium channel blockers. There has been mixed evidence to support the efficacy of these medications and they are associated with significant side effects. Gabapentin and pregabalin work peripherally on the GABA system and their efficacy is believed to be associated with the voltage-gated calcium channels. Sixty percent of patients on high-dose gabapentin, compared to 40% to 50% of patients on pregabalin, had at least a 50% reduction in pain. Pregabalin binds to the receptor with a better affinity, is associated with less sedation, and dose titration is easier than with gabapentin.

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Diabetic foot

One of the complications from peripheral neuropathy, as well as peripheral vascular disease, is the formation of ulcerations, osteomyelitis and Charcot arthropathy. More than 85% of amputations among patients with diabetes are preceded by ulceration. Neuropathy predisposes patients to the formation of an ulcer by atrophy of intrinsic muscles, which leads to collapse of the arch and depression of the metatarsal heads. This increases pressure points on the feet and leads to callus formation and ulceration. Patients are also at increased risk due to peripheral vascular disease, which often accompanies diabetes. With decreased blood flow to the area, sores and ulcerations heal slowly and sometimes are unable to heal at all.

An important consideration for physicians is to palpate pulses to evaluate for peripheral vascular disease. However, most patients with diabetes have microvascular disease and may still have normal pulses upon palpation, and some patients have calcification of their arteries—both of which can offer a sense of false security. An ankle brachial index should be performed on patients in whom peripheral vascular disease is suspected, even if normal pulses are palpated.

Most ulcerations are not infected, but there is an increased risk for osteomyelitis if the ulcer is more than 2 cm wide or 3 mm deep. If the ulceration is infected, then antibiotics are recommended. The choice of antibiotic depends on the severity of the infection.

Mild infections typically grow Staphylococcus or Streptococcus, moderate infections are usually polymicrobial, and severe infections are also polymicrobial with anaerobes and aerobes. Osteomyelitis is the most dreaded complication of diabetic ulcerations.

Methods to evaluate ulcerations for osteomyelitis include X-rays, ability to probe bone, magnetic resonance imaging, erythrocyte sedimentation rate, and the gold standard of bone biopsy. X-rays may lag behind by about two weeks and usually are normal until 50% of the bone is destroyed. The ability to probe the bone has a sensitivity of about 90% for osteomyelitis. Treatments for ulcerations include debridement, diminishing edema, decreased weight bearing and topical agents used to promote healing.

The most important treatment, however, is prevention. Patients need to be encouraged to examine their feet daily, wear proper footwear and moisture-wicking socks and use moisturizer creams. Physicians can decrease the rate of amputations dramatically just by having patients take off their shoes and inspecting their feet at each visit. It is also important to look for neuropathy by checking a monofilament test and vibration sense testing using a 128 Hz tuning fork. Patients may get prescription diabetic shoes yearly with inserts every four months if they have neuropathy and other risk factors for ulceration, such as a history of ulcers, peripheral vascular disease, Charcot arthropathy, contractures, calluses and corns.

Charcot arthropathy is a painless, progressive, degenerative arthropathy of at least one joint due to neurologic deficits. Patients usually present with erythema, warmth, anhidrosis, bounding pulses, absent or minimal pain, and neuropathy. Physical exam will usually reveal a rocker bottom foot with medial tarsal subluxation and hypermobile joints.

Charcot arthropathy has three different stages, consisting of an acute (development) phase, a coalescence phase and then a reconstruction phase. X-rays will show a destructive degenerative arthritis with subchondral sclerosis and resorption of the metatarsal heads and shafts, giving a penciling appearance to the phalanges. The most important therapy for this condition is immediate and complete cessation of weight bearing. Patients will typically need to be non-weight bearing for eight to 12 weeks. Once the condition has stabilized, most of these patients will need molded or accommodative footwear and may even need surgery for removal of bony prominences.
Autonomic neuropathy

Autonomic neuropathy can be severely debilitating to patients, and it affects a variety of organ systems. The onset of autonomic neuropathy increases mortality, and 25% to 50% of patients will die within five to 10 years of diagnosis.

Cardiovascular neuropathy is associated with elevated resting heart rate, diminished heart rate variability and recovery with exercise, blunted angina symptoms and orthostatic hypotension. Genitourinary neuropathy is associated with urinary retention, overflow incontinence and erectile dysfunction. Gastrointestinal neuropathy consists of constipation, diarrhea and gastroparesis. Sudomotor neuropathy manifests as anhidrosis of extremities and hyperhidrosis of the trunk. Patients may also experience hypoglycemia unawareness due to impaired catecholamine response.

Final notes

Microvascular complications are prevalent in patients with diabetes mellitus and are feared by both patients and physicians. As osteopathic physicians, we play a vital role in the prevention and treatment of complications from diabetes.

Most patients with diabetes—and therefore their diabetes-related complications—are asymptomatic, which is why screening with laboratory tests, as well as taking thorough histories and conducting physical exams, are essential.

In previous years, the tools were not available and diabetic complications were almost inevitable. Now we have the tools and knowledge to prevent and delay progression of nephropathy, retinopathy, neuropathy and ulceration. Treatment of risk factors—including hyperglycemia, hypertension, hyperlipidemia, obesity and tobacco abuse—are very important not only in the prevention of diabetes, but also in the delay of progression of the disease.

References


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The nomenclature for diabetes mellitus has changed during the past 40 years. In the 1970s, age was the main characteristic by which diabetes was classified. This classification was based on the concept that type 1 diabetes mellitus (T1DM) affected children with insulin insufficiency but no insulin resistance, whereas type 2 diabetes mellitus (T2DM) affected adults with insulin resistance but no initial insulin insufficiency.

Latent autoimmune diabetes of adulthood: classifying type 1.5 diabetes mellitus
Table 1
Baseline Characteristics of Patient

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Patient’s Value</th>
<th>Reference Range/Goal</th>
</tr>
</thead>
<tbody>
<tr>
<td>HgA1c, %</td>
<td>5.8</td>
<td>4.0-5.9</td>
</tr>
<tr>
<td>TSH/Free T4</td>
<td>1.28/1.54</td>
<td>0.50-4.55/0.58-1.64</td>
</tr>
</tbody>
</table>

Lipid Profile, mg/dL

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Patient’s Value</th>
<th>Reference Range/Goal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total cholesterol</td>
<td>226</td>
<td>125-200</td>
</tr>
<tr>
<td>LDL-C</td>
<td>114</td>
<td>&lt;100</td>
</tr>
<tr>
<td>HDL-C</td>
<td>101</td>
<td>&gt;40</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>53</td>
<td>40-154</td>
</tr>
</tbody>
</table>

Abbreviations: HgA1c, glycosolated hemoglobin; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TSH, thyroid stimulating hormone; T4, thyroxine.

Table 2
Results of Patient’s Endocrine and Autoimmune Laboratory Tests

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Patient’s Value</th>
<th>Reference Range/Goal</th>
</tr>
</thead>
<tbody>
<tr>
<td>C-peptide, mg/mL</td>
<td>1.2</td>
<td>0.5-2.0</td>
</tr>
<tr>
<td>Autoantibodies, U/mL</td>
<td></td>
<td></td>
</tr>
<tr>
<td>GAD</td>
<td>85.6</td>
<td>0-1.5</td>
</tr>
<tr>
<td>Insulin</td>
<td>2.8</td>
<td>0-5.0</td>
</tr>
<tr>
<td>Islet cell</td>
<td>Negative</td>
<td>Negative</td>
</tr>
</tbody>
</table>

Abbreviations: GAD, glutamic acid decarboxylase.

It later became clear that the incidence of T1DM in patients older than 30 years was greater than previously thought.\(^1,2\) New findings led to the classification of diabetes mellitus by the need to take insulin. Years ago, T1DM was classified as insulin-dependent diabetes mellitus, and T2DM was classified as noninsulin-dependent diabetes mellitus. However, this classification was not accurate since most people with T2DM eventually have complete ß-cell exhaustion and will then need to take insulin.

Currently, the classification of diabetes is based on pathogenesis. T1DM is characterized by the destruction of insulin-secreting ß cells of the pancreas, resulting in severely deficient insulin production or no insulin production at all. If patients with diabetes have measurable autoantibodies, they have type 1A diabetes mellitus. If they have no measurable autoantibodies, they are classified as having type 1B diabetes mellitus.

T2DM is characterized by insulin resistance, abnormal hepatic glucose production and a relative deficiency in insulin secretion. Approximately 10% of people with newly diagnosed T2DM have autoantibodies directed against pancreatic ß cells, which will eventually result in absolute insulin insufficiency.\(^4,5\)

This reclassification of diabetes led to the designation of latent autoimmune diabetes of adulthood (LADA) as a separate clinical entity.\(^1,5\) The term was introduced by Paul Zimmet, MD, PhD,\(^1\) in 1995 to describe cases of adult-onset T1DM in which patients do not have an immediate need for insulin. This condition has also been coined type 1.5 diabetes mellitus or a slowly progressive T1DM. The case presentation reported in this article provides a typical example of a patient with LADA.

Case presentation
A woman aged 43 years visited her physician to discuss her diabetes mellitus. She had been diagnosed with T2DM three years previously, when she experienced frequent urination and unintentional weight loss. She was found to have a urinary tract infection and was treated for this condition. However, her glucose level at that time was 300 mg per deciliter. As a result, she was told that she had diabetes mellitus as well.

After beginning to take glyburide, the patient initially responded well. However, within a couple of months she found that very high glucose levels developed anytime she ate food containing carbohydrates. Her glucose logs revealed that her morning glucose level was usually normal to slightly high (90-130 mg/dL), but the glucose level shot up to the 200-300 mg/dL range after eating carbohydrate-containing meals. It would then take her the rest of the day to get her glucose levels back within an acceptable range. To help keep her glucose levels under control, she started to eat a diet very low in carbohydrates.

The patient was not overweight, with a body mass index of 22. In addition, she had normal results on her physical examination.

The patient’s medical history consisted of hypothyroidism (resulting from Hashimoto’s thyroiditis), which was diagnosed about 10 years previously. She was currently taking levothyroxine (88 mcg daily) and was euthyroid (ie, had normal thyroid gland function) for the past five years. She had no family history of diabetes mellitus.

She smoked 1.5 packs of cigarettes daily. She did not drink alcohol or use recreational drugs. She did not get regular exercise. She had not lost weight recently. The patient had no health complaints other than the previously mentioned glucose problems.

The patient underwent laboratory tests two weeks prior to her physician’s appointment. Results of these tests are shown in Table 1.

In light of her history and her laboratory test results, the possibility...
**Case discussion**

The case reported in this article is unique in a number of ways. Most people with T2DM have a family history of that condition or of obesity. However, this patient had a family history of neither condition—not was she herself obese, unlike the great majority of people with T2DM. Furthermore, she had a personal history of autoimmune disease (Hashimoto’s thyroiditis). Autoimmune diseases tend to “travel together.” Thus, this patient was at increased risk of other autoimmune diseases, such as T1DM.

Another clue that this individual may not have had T2DM was the fact that she did not have diabetic dyslipidemia. Diabetic dyslipidemia—present in people with insulin resistance, metabolic syndrome and T2DM—is characterized by low levels of high-density lipoprotein cholesterol (HDL-C) and high levels of triglycerides. By contrast, this patient had high levels of HDL-C and normal levels of triglycerides—even though she had hyperglycemia. Behaviors that could have raised her HDL-C level were regular exercise and drinking alcohol. She did neither of these.

**Latent autoimmune diabetes of adulthood**

Latent autoimmune diabetes of adulthood is believed to be a form of T1DM resulting from an autoimmune process. Although LADA does not have a single definition, it is most often characterized as a condition in which an adult has autoimmune diabetes mellitus that is not immediately (ie, within six months after diagnosis) insulin dependent. As previously mentioned, this condition is sometimes referred to as type 1.5 diabetes mellitus or slowly progressive T1DM.

Most people with T1DM have one or more of the following autoantibodies: tyrosine phosphatase-like insulinoma-associated protein 2 (IA-2); tyrosine phosphatase-like IA-2β; glutamic acid decarboxylase (GAD); islet cell cytoplasmic; islet cell complement-fixing; and insulin antibodies. The autoantibody titer most commonly used to identify LADA in patients is the GAD autoantibody. The presence of GAD autoantibodies has been associated with rapid decline of β-cell function, resulting in absolute insulin deficiency.

People with T2DM do not exhibit these GAD antibodies and typically can maintain their β-cell function for more than 12 years after diagnosis. The antibodies seen in patients with type 1A diabetes mellitus and LADA are believed to be only markers of the disease—and not necessarily pathogenic. Fewer than half of patients with LADA have positive results in titers of T1DM autoantibodies—raising the question of whether LADA is a unique disease with a separate pathogenesis from T1DM or merely a variant of T1DM.

A patient with LADA typically has the phenotype of a person with T1DM. However, the patient may appear to be more like a person with T2DM at clinical presentation, because β-cell destruction in LADA is typically slower and more subtle than in T1DM. Unlike most people with T1DM, individuals with LADA do not immediately lose all β-cell function.

T2DM is most often diagnosed based on results of screening laboratory tests. Symptoms of T2DM are usually nonspecific in nature, such as fatigue or increased rate of infections. Many people first discover that they have T2DM when a complication develops. For example, 30% of people who suffer

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**Table 3**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>T1DM</th>
<th>LADA</th>
<th>T2DM</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean Age, y</td>
<td>44.5</td>
<td>59.0</td>
<td>63.0</td>
<td>&lt;.001*</td>
</tr>
<tr>
<td>C-peptide, ng/mL</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fasting</td>
<td>0.46</td>
<td>0.53</td>
<td>1.23</td>
<td>.02†</td>
</tr>
<tr>
<td>1-10 years postdiagnosis</td>
<td>0.03</td>
<td>0.4</td>
<td>0.68</td>
<td>.03*</td>
</tr>
<tr>
<td>BMI</td>
<td>23.1</td>
<td>23.5</td>
<td>29.1</td>
<td>&lt;.001†</td>
</tr>
<tr>
<td>HDL-C, mg/dL</td>
<td>1.2</td>
<td>1.4</td>
<td>1.1</td>
<td>&lt;.001†</td>
</tr>
<tr>
<td>Triglycerides, mg/dL</td>
<td>1.4</td>
<td>1.2</td>
<td>6.0</td>
<td>.001†</td>
</tr>
</tbody>
</table>

* LADA vs T1DM
† LADA vs T2DM

**Abbreviations:** BMI, body mass index; HDL-C, high-density lipoprotein cholesterol; LADA, latent autoimmune diabetes of adulthood; T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus.

Adapted from Hosszufalusi et al. *Diabetes Care.* 2003;26:452-457.13
from an acute myocardial infarction discover that they have diabetes at the time of the heart attack. Only those individuals with decompensated T2DM and extreme hyperglycemia will have weight loss, polydipsia and polyuria at presentation. This collection of symptoms represents absolute insulin deficiency and is the hallmark of T1DM.

Clinical criteria for LADA are loosely defined. The key features are: adult onset, lack of initial need for insulin therapy, low C-peptide levels and the presence of antibodies directed against pancreatic islet cells. However, there is no clear age that defines typical age of onset of LADA. Most clinical studies use a mean age of onset of 30 years, but some studies avoid defining a typical age of onset. In addition, the presence of autoantibodies is not specific to T1DM/LADA, because these autoantibodies are also present in other autoimmune disorders.

Nora Hosszufalusi et al reported significant differences between mean characteristics of patients with T1DM, LADA and T2DM. These differences are highlighted in Table 3.

Treatment of patients with LADA

Individuals with LADA should ultimately be treated like those with T1DM—using insulin as the primary therapy. Studies have demonstrated that residual β-cell function in patients with LADA is extended with the use of insulin therapy and shortened with the use of insulin secretagogues. Evidence also suggests that exogenous insulin administration slows the loss of β cells by reducing glucose toxicity—providing an important reason for early diagnosis and treatment.

Who to screen?

Spiros Fourlanos et al suggested a set of clinical criteria for determining which patients should get tested for anti-GAD autoantibody titers as a way of screening for LADA. These criteria include diagnosis before age 50 years, acute symptoms of insulin deficiency (ie, “the polys”), body mass index less than 25, and a personal or family history of autoimmune disease. If a patient meets two or more of these criteria, it is recommended that he or she be tested for anti-GAD autoantibodies.

Take home messages

It is important to distinguish LADA from T1DM and T2DM. Because LADA may be present in as many as 10% of people with presumed T2DM, a clinician is likely to encounter cases of LADA. Most patients with LADA do not receive the correct diagnosis at initial presentation. Typically, a patient with LADA presents with an episode of the “polys” that is responsive to intermediate treatment options, such as administration of fluids and correction of hyperglycemia with insulin or oral agents. Such responsiveness, however, is believed to be temporary and can follow a widely variable course.

People with LADA are more likely than people with T2DM to have complications at the time of diagnosis, and they may also have microvascular complications earlier in the course of the disease. In addition, people with LADA have an autoimmune disease process and are more likely than people with T2DM to have other autoimmune conditions.

If a patient was initially diagnosed with T2DM, he or she may be rediagnosed as having LADA when the condition deteriorates to diabetic ketoacidosis. However, such patients are sometimes considered to have “brittle type 2” diabetes mellitus, in which case they may never be properly diagnosed.
Final notes
In summary, the clinician should consider LADA when a patient with presumed diabetes mellitus has any of the following clinical characteristics:

- age >30 years
- lack of family history of T2DM
- personal or immediate family history of autoimmune disorders
- body mass index <25
- lipid panel results not showing diabetic dyslipidemia
- period during which patient had “the polys” and weight loss

References

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This quiz provides a convenient means for osteopathic physicians to assess their understanding of the scientific content of the December 2009 issue of AOA Health Watch.

To apply for one hour of Category 1-B continuing medical education credit, AOA members may take this quiz online at www.docmeonline.com, where this and other quizzes can be accessed by clicking on the link at the bottom of the home page. Quizzes that are completed online will be graded and credited to members’ CME activity reports.

Alternatively, osteopathic physicians can complete the print version of this quiz and send it to the mailing address or fax number below by June 30, 2011. For those who mail or fax this form, the AOA will record the fact that they submitted this quiz for Category 1-B CME credit.

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So that osteopathic physicians can easily check their answers to the quiz, the correct answers will be published in the next issue of AOA Health Watch. If you mail or fax this form to the Division of CME, the AOA will record the fact that you have submitted this form for Category 1-B CME credit for the current CME cycle.

For each of the questions that follow, circle the letter next to your answer.

1. Diabetes mellitus is:
   a. the leading cause of adult legal blindness
   b. the number one cause of end stage renal disease leading to dialysis
   c. the leading cause on non-traumatic limb amputations
   d. all of the above

2. The recommended screening test for microalbuminuria (nephropathy) is:
   a. a spot urine test for microalbumin/creatinine ratio
   b. the 24-hour urinary protein test
   c. routine urinanalysis dipstick
   d. serum creatinine

3. Patients with nephropathy need to be:
   a. evaluated for anemia
   b. evaluated for secondary hyperparathyroidism
   c. should go on a low carbohydrate/high protein diet
   d. both a and b

4. Complications of diabetes are believed to be due to:
   a. excessive protein glycation
   b. activation of oxidative stress
   c. activation of the polyol pathway
   d. all of the above

5. Gastrointestinal neuropathy consists of:
   a. gastroparesis
   b. intractable diarrhea
   c. rapid transit through colon
   d. colon polyps

6. Data has shown that people with diabetes receive the greatest mortality benefit from:
   a. treating hypertension first, lipids second, and blood glucose third
   b. treating blood glucose first, hypertension second and lipids third.
   c. treating hypertension first, blood glucose second and lipids third.
   d. none of these treatments improve mortality

7. Older persons with diabetes are significantly more likely to suffer from:
   a. depression
   b. cognitive impairment
   c. unrecognized hypoglycemia and unrecognized hyperglycemia
   d. all of the above

8. People with latent autoimmune diabetes of adulthood (LADA) are more likely to:
   a. have complications at the time of diagnosis
   b. have other autoimmune conditions than the person with type 2 diabetes
   c. normal HDL and triglyceride levels
   d. all of the above
Quiz and answers to AOA Health Watch

DOs Against Diabetes Part 8  Volume 4, Number 1  January 2009

The correct answers to the following questions appear in **bold** type.

1. Symptoms of patients with diabetic ketoacidosis (DKA) are attributed most frequently to the effects of:
   a. dehydration
   b. metabolic acidosis
   c. both a and b

2. The treatment of patients with DKA is based on which of the following principles?
   a. replacement of intravascular volume with isotonic fluid.
   b. cessation of ketosis via insulin administration.
   c. both a and b

3. How many diabetes screening tests per year are covered for individuals who have diagnosed prediabetes?
   a. one
   b. two
   c. three

4. Which of the following are referred to as prediabetic states?
   a. patients with fasting (ie, eight hours after a meal) glucose levels between 100 and 125 mg/dL (6.1-7.0 mmol/L)
   b. patients with plasma glucose levels at or above 140 mg/dL (7.8 mmol/L) at two hours after a 75 g oral glucose load.
   c. both a and b

5. Low serum and intracellular magnesium levels are associated with:
   a. insulin resistance
   b. impaired glucose tolerance and decreased insulin secretion
   c. both a and b

6. Omega-3 fatty acids can improve a multitude of parameters in patients with diabetes. A good source of Omega-3 fatty acids can be found in which of the following?
   a. anchovies
   b. strawberries
   c. none of the above

7. Which of the following statements about myopathy are true?
   a. myopathy is a disease of the muscle fiber and would not generally present the same as diabetes
   b. myopathy would not present as weakness
   c. none of the above

8. Which of the following severe complications of a wound infection should be considered medical emergencies in individuals with diabetes mellitus, necessitating immediate hospitalization and multidisciplinary treatment?
   a. rapidly progressive or deep-tissue infection
   b. tissue necrosis or gangrene
   c. both a and b
Check out the following Web sites for additional news, information and guidelines about diabetes:

- American Academy of Family Physicians (AAFP)
  www.aafp.org

- American Association of Clinical Endocrinologists (AACE)
  www.aace.com

- American Association of Diabetes Educators (AADE)
  www.diabeteseducator.org

- American College of Osteopathic Family Physicians (ACOFP)
  www.acofp.org

- American College of Physicians (ACP)
  www.acponline.org

- American Diabetes Association (ADA)
  www.diabetes.org

- American Dietetic Association
  www.eatright.org

- American Geriatrics Society (AGS)
  www.americangeriatrics.org

- American Heart Association
  www.americanheart.org

- American Medical Association (AMA)
  www.ama-assn.org

- American Osteopathic Association (AOA)
  www.osteopathic.org

- Centers for Disease Control and Prevention (CDC) — Diabetes Home Page
  www.cdc.gov/diabetes

- National Diabetes Education Program (NDEP)
  ndep.nih.gov

- National Institute of Diabetes and Digestive and Kidney Diseases
  www2.niddk.nih.gov

- National Library of Medicine — Medline Plus
  medlineplus.nlm.nih.gov

- US Department of Veterans Affairs — VA Diabetes Program
  www1.va.gov/Diabetes