DIABETES MELLITUS AND PERIPHERAL ARTERY DISEASE: A TRANSLATIONAL OVERVIEW OF MICROCIRCULATION

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Diabetes mellitus is considered a risk equivalent to atherosclerotic cardiovascular disease, but it is also one of the most powerful predictors of peripheral artery disease (PAD). Current consensus statements advocate routinely screening for PAD in all diabetes patients over age 50 as well as diabetes patients younger than 50 with an additional atherosclerotic risk factor.

ANEMIA AFTER BARIATRIC SURGERY IN PATIENTS WITH TYPE 2 DIABETES MELLITUS

Betty Wedman-St Louis, PhD, RD, LD

The Type 2 diabetes mellitus remission mechanisms following bariatric surgery include metabolic and lifestyle improvement, but nutritional complications also need attention because lifelong deficiencies can have a deleterious effect on health and well-being.

COMMENTARY

Non-medical Switching

Non-medical switching occurs when the formularies change medication in a class, such as basal insulin, and the pharmacy does not recognize it as equal, so the pharmacist sends you a request for a new prescription so that the pharmacy can dispense what is now preferred on the insurance formulary.

JOURNAL WATCH

The papers highlighted in this month’s Journal Watch include a recent analysis of the economic burdens of diabetes projected out to 2030, which is a great resource for public policy but also for planning localized expansion of programs based on these conservative estimates.

EDUCATOR’S CORNER

Missing the Diagnosis: The Overlooked Warning Signs of Type 1 Diabetes

The number of misdiagnosed children and adults who are often eventually diagnosed with diabetic ketoacidosis is alarming. One of the primary symptoms of ketoacidosis is nausea and/or vomiting, which can deflect the health professional into a mind-set of a stomach-flu-like diagnosis. Many certified diabetes educators, physicians and providers connected to the Type 1 diabetes community are aware of horrific cases in which the symptoms were reported and medical attention sought, but Type 1 diabetes was not properly diagnosed.
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ABSTRACT
Diabetes mellitus (DM) is considered a risk equivalent to atherosclerotic cardiovascular disease, including peripheral artery disease (PAD). Prior studies evaluating standard medications that reduce blood glucose failed to show cardiovascular benefits or improved survival. The multicenter Canagliflozin Cardiovascular Assessment Study (CANVAS) showed significant reduction in death from cardiovascular causes, nonfatal myocardial infarction (MI) and nonfatal stroke in patients with Type 2 diabetes at increased risk of cardiovascular disease when treated with canagliflozin. However, canagliflozin was associated with a significant doubling in the risk of amputations, a new finding for which the mechanism is unknown. Therefore, a translational overview of the microcirculation in the context of DM and the development of PAD is needed. Microcirculatory concerns in DM are not new, and there is robust literature regarding microvascular disease. Virchow’s triad describes three broad categories of potential mechanisms for vascular thrombosis.

Introduction: Diabetes and PAD
PAD is currently defined by exertional non-joint-related leg symptoms (e.g., intermittent claudication) and an abnormal resting ankle-brachial index (ABI) of ≤0.90, an abnormal exercise ABI or an abnormal toe-brachial index (TBI) of ≤0.70.1 However, historically PAD has been variably defined in the literature by intermittent claudication or resting ABI ≤0.90. In 2010, PAD affected an estimated 202 million people worldwide—an estimated rate of increase of 23.5% overall, with the most rapid increase in lower-income countries (28.7%).2 Not only does PAD worsen quality of life, but it also increases the 10-year risk of cardiovascular death nearly sixfold.3 While cigarette smoking is associated with more proximal (e.g., aortoiliac) PAD, DM results in more infrapopliteal PAD.4 Infrapopliteal PAD is characterized by more complex, calcific and diffuse atherosclerosis and often involves chronic total occlusions of the runoff arteries. The severe, diffuse nature of infrapopliteal PAD also leads to an increased association with critical limb ischemia (CLI), with up to 50% of CLI patients having concurrent DM. In addition to the increased cardiovascular mortality, 30% of CLI patients will undergo major amputation. Despite advances in surgical and percutaneous vascular interventions, patency rates remain lower than with aortoiliac and iliofemoral PAD interventions.5

DM is considered a risk equivalent to atherosclerotic cardiovascular disease, but it is also one of the most powerful predictors of PAD. Prior studies have demonstrated odds ratios of 1.89 to 4.05.2 In population studies from the Framingham, MESA, Rotterdam and NHANES cohorts, the odds ratios of PAD in DM patients were 1.89–2.71, nearly as high as the odds ratios for cigarette smoking.6-9 Furthermore, in a meta-analysis of community-based studies, the overall odds ratio of PAD in DM was 1.68, second only to current or prior cigarette smoking.2 When comparing diabetic with non-diabetic patients, over 20% of patients with elevated blood glucose have abnormal ankle-brachial index (ABI) versus only 9.5% of patients with impaired glucose tolerance and 7.0% of patients with normal glucose tolerance.10-13 DM severity may also be associated with an increased risk of PAD. The United Kingdom Prospective Diabetes Study reported that for every 1% increase in HbA1c, there was a >25% increase in PAD.12 The prevalence of symptomatic PAD in patients with diabetes approaches 10%, with CLI developing in 1.3%.13 Furthermore, the impact of PAD extends beyond limb amputation and quality of life. PAD patients are at a significantly increased risk of MI, approaching 30% in those with prior limb revascularization, as well as a nearly fourfold increase in those with acute limb ischemia.14

The pathophysiology of PAD involves the imbalance of the circulatory supply of nutrients and oxygen to the metabolic demands of the skeletal muscle. In addition to the abnormalities induced in the skeletal muscle from chronic ischemia (e.g., switch to anaerobic metabolism and decline in exercise tolerance), factors regulating blood flow to the limb are key to the pathobiology. Flow-limiting lesions seen in PAD are appreciable on angiographic imaging, but the microvascular sequelae of accentuated vasoconstriction, impaired vasodilation and abnormal rheology equally contribute to claudication, ischemia and risk of limb loss.15
Pathophysiologic Associations between DM and PAD

The Hagen-Poiseuille equation describes the rate of blood flow to organs (Figure 1). The most clinically important factors affecting blood flow are pressure gradient, radius of the residual lumen and blood viscosity. Virchow’s triad describes three major factors closely related to vascular thrombosis: 1) vascular endothelial injury, 2) changes in the blood composition and 3) blood flow alterations.

1. Endothelial Injury

The endothelial lining of blood vessels is a highly active, single-cellular layer that performs multiple functions. It mediates the interaction between blood cells and the vascular wall, which affects modulation of blood flow, nutrient delivery, coagulation and thrombosis, and leukocyte diapedesis. Most patients with DM (>80%) have a history of hypertension, and the increased shear stress seen in hypertensive states is a major contributor to long-term endothelial injury. The endothelial injury from mechanical forces sets the stage for increased microvascular dysfunction and thrombosis.

One of the more important chemicals released by the endothelium for vascular homeostasis is nitric oxide (NO). NO has antithrombotic activity and indirectly reduces vascular smooth muscle cell movement and proliferation. Elevated glucose decreases the bioavailability of NO and decreases prostacyclin (PGI 2) while increasing synthesis of vasoconstricting prostanoids and endothelin (ET-1) via multiple mechanisms. The loss of NO and PGI 2 leads to impaired vasodilation. The shift in profile of the vasoactive substances results in a net vasoconstrictor effect, which reduces flow in the microvasculature, impairs tissue perfusion and increases risk for thrombosis and limb loss.

Moreover, reduced NO levels cause increased inflammation, which leads to increased plasminogen activator inhibitor-1 (PAI-1) levels, resulting in increased fibrinolytic activity from a reduction in plasmin levels. Hyperglycemia also leads to increased expression of von Willebrand factor and elevated fibrinogen and PAI-1 levels, which further contribute to vascular injury-mediated thrombosis.

Lastly, impeding the anticoagulant activity of antithrombin-III in response to oxidative stress from DM can lead to thrombin hyperactivity. Thrombin has proinflammatory effects that include induction of nuclear factor-kappa B (NF-κB). NF-κB increases transcription of proinflammatory mediators: cytokines (tumor necrosis factor-alpha) and interleukins (IL-1β, IL-6 and IL-8), which further drive the shift toward thrombus formation and subsequent thrombotic events.

2. Changes in Blood Composition

In patients with poor glycemic control, plasma viscosity is increased partly due to structural alterations of the red blood cells (RBCs). In vitro studies have shown changes in RBC deformability, presumably due to membrane protein glycation, that subsequently result in increased whole blood viscosity (WBV). RBCs normally shift into an elliptical shape, align in direction of flow and move with rapid velocity, which allows blood flow to be maintained even with a relatively low hematocrit that approaches 50%. At higher flow rates, RBCs have more fluid properties, but as blood flow is reduced, blood viscosity significantly increases. RBC deformability becomes crucial in the microcirculation where the capillary
Fibrinogen levels

The changes in diabetes affects multiple factors related to the increased prothrombotic state.43-45

Other important high molecular weight particles are fibrinogen, IgM and alpha 2 macroglobulin. The relative effect on aggregation is highest with fibrinogen and less with alpha 2 macroglobulin, haptoglobin and albumin; platelets and white blood cells have little impact on blood viscosity.31 Fibrinogen, factor VIIa and elevated plasminogen activator inhibitor-1 are all significant contributors to the hypercoagulable state of DM, and elevated fibrinogen further increases blood viscosity as well.32

3. Blood Flow Alterations

Blood viscosity has long been associated with vascular thrombosis. In the Edinburgh Artery Study, a five-year study of 4,860 healthy men ages 45-59, 20% of individuals with the highest blood viscosity were matched to the 20% with the lowest blood viscosity. Those in the lowest blood viscosity group had fewer cardiovascular events than those in the highest group, resulting upon a 3.2-fold increased risk.33 DM is accompanied by increases in blood viscosity, with nearly a twofold increase in measured WBV in diabetic versus non-diabetic patients.34,35 Mathematical models have suggested that for every 100 mg/dL increase in blood glucose concentration, there is a linear increase in blood and plasma flow times corresponding to an increase in WBV.29

As blood viscosity increases, blood flow slows and consequently increases the tendency for atherosclerosis (Figure 3).36 The physiologic responses to increased WBV are based upon the Hagen-Poiseuille principle and thus include increases in blood pressure or vascular dilatation. Increased radial forces produce more stretch of smooth muscle cells in the tunica media and, in time, the increased stimulation to the smooth muscle cells will lead to protective hypertrophy. Increased radial forces can also cause endothelial cell activation and damage. Cellular
leakage, inflammation and apoptosis of endothelial cells exposing tissue factor, collagen and other cellular components lead to a prothrombotic state, demonstrating the interplay between endothelial injury and vascular thrombosis (Figure 4).37

**Important Clinical Considerations**

Microcirculatory concerns in DM are not a novel concept, with amputations and retinal changes having been previously studied. Only in recent times has more specialized testing become available to evaluate possible etiologies of microvascular disease.

One of the early vascular papers by Bailey et al. identified a patient’s preoperative hemoglobin as a predictor of outcome of diabetic amputations. Fifty-nine consecutive diabetes patients required local amputations in the foot and survived for at least one month. Forty patients had digital amputations, and 19 had a metatarsal or transmetatarsal as their primary surgery. In patients who healed after surgery (18 amputations), lower initial hemoglobin levels (<12 g/dl) were beneficial. Thus, they concluded that the effects of increased viscosity from higher hemoglobin concentrations could be the major reason. A 2.7-g/dl increase in hemoglobin would increase blood viscosity about 25% at high shear rates and even more at lower shear rates.37

Recently, the CANVAS trial investigated the benefit of the sodium-glucose cotransporter 2 (SGLT2) inhibitor canagliflozin on cardiovascular outcomes. Prior studies evaluating standard medications that reduce blood glucose failed to show cardiovascular benefits or improved survival. SGLT2 inhibitors have been shown to reduce hyperglycemia, blood pressure and body weight. CANVAS was a randomized, double-blind, placebo-controlled multicenter study involving 10,142 patients with Type 2 diabetes and a history of (or at high risk for) cardiovascular disease that was designed to assess cardiovascular safety and efficacy of canagliflozin. At a mean follow-up of 188 weeks, there was a significant reduction in the risk of cardiovascular death, nonfatal myocardial infarction and nonfatal stroke.38 However, canagliflozin was associated with a significant doubling in the risk of amputations (6.3 versus 3.4 participants with amputation per 1,000 patient-years; HR 1.97), with 71% of affected participants having their highest amputation at the level of the toe or metatarsal. Recent evidence has also found increased risk for reduced peripheral flow to toes with loop diuretics and canagliflozin (Figure 5). The increased rate of amputation is a new finding for which the mechanism is not known. However, understanding the pathophysiology of PAD and the impact of underlying DM with its effects upon fluid dynamics (Hagen-Poiseuille principle) and vascular thrombosis (Virchow’s triad) may help us understand the potential mechanisms for this observed finding.
Vascular dysfunction in diabetes starts with insulin resistance. Subsequently, many pathobiological processes develop that lead to endothelial cell dysfunction and a prothrombotic state. This increases the risk of increased microcirculatory dysfunction in the periphery of diabetes patients. Tesfamariam et al reported in aortic ring tissue that acute increases in glucose reduces endothelial function by increasing reactive oxygen species.\(^{53,54}\)

Univariate analysis of amputation risk factors in the CANVAS trial. Excluding prior amputation, which had the highest hazard ratio (HR 21.42, CI 15.49-29.61), concurrent use of loop diuretics had the sixth highest HR for amputation (HR 2.12, CI 1.50-3.00). This observation may be supported by the underlying pathophysiology of PAD and DM, through the increase in blood viscosity and thus worsened fluid dynamics and increased risk for stasis and thrombosis.\(^{55}\)

**CONCLUSION**

Three important factors relating to enhanced peripheral atherothrombotic risk in diabetes mellitus are vessel wall injury, hypercoagulable state and stasis/impaired blood flow. Indeed, diabetes patients are at very high risk for developing PAD. Current consensus statements advocate routine screening for PAD in all diabetes patients over age 50 as well as diabetes patients younger than 50 with an additional atherosclerotic risk factor. Patients demonstrating reduced peripheral vascular circulation would potentially be at higher risk for atherothrombotic events. Given the potential for increased risk for lower extremity amputation, careful discussion about the risk and benefits of SGLT2 inhibitor treatment is reasonable prior to starting therapy. Future studies would include identifying a definite relationship between canagliflozin use and lower extremity amputations and other potential therapies that might lower amputation risk through improved viscosity, organ flow and endothelial function.\(^{39,40}\)
Bariatric surgery has promoted weight loss and improved glycemic management in obese patients through Roux-en-Y gastric bypass (RYGB) and vertical sleeve gastrectomy (VSG). Obesity plays a pivotal role in the pathogenesis of Type 2 diabetes mellitus, with an estimated 592 million people expected to be diagnosed by 2030. Obese patients have adipose tissue dysfunction characterized by inflammation from over-nutrition and lipid accumulation, which leads to insulin resistance and contributes to liver injury.

The recently published *Bariatric Surgery Patients—A Nutritional Guide* reviews the impact of different bariatric surgery techniques on weight loss with resolution of blood glucose issues. But weight loss is not the only factor for improving Type 2 diabetes mellitus. Gut hormones, rapid transit time reducing ingested nutrient absorption, increased bile acids and alterations in the intestinal microbiome all play a role in obesity and blood glucose management following bariatric surgery.

The Type 2 diabetes mellitus remission mechanisms following bariatric surgery include metabolic and lifestyle improvement, but nutritional complications also need attention because lifelong deficiencies can have a deleterious effect on health and well-being. Nutritional deficiencies prior to surgery may be aggravated by the surgical procedure, causing postoperative complications. More than 250,000 bariatric surgical procedures are performed in the U.S. annually, with iron deficiency anemia being one of the most common complications requiring lifelong monitoring.

**Clinic Survey**

A random survey of 100 female Type 2 diabetes patients ages 22-64 seen for nutrition assessment prior to bariatric surgery during 2014-2017 revealed more than 50 percent had anemia (hemoglobin <12 grams per deciliter) on a complete blood count prior to surgery. Symptoms of anemia—including fatigue, cold hands and feet, headaches, weakness, pale skin and dizziness—that were observed during the assessment had all been written off as “incorrect eating habits” or “result of excess weight gain” by their primary care physicians and/or diabetologists and not considered important enough to need treatment. But numerous studies have found that anemia as well as deficiencies in folate, vitamin B12 and vitamin D may be involved in poor patient prognosis post-surgery.

Pre-surgery supplementation can reduce mortality rates. The most frequently reported nutrient deficiencies were hemoglobin, ferritin, vitamin B12, vitamin D and thiamine.

**Anemia and Iron**

Postoperatively, mild to moderate anemia is usually treated with dietary supplementation of iron despite the unknown cause of the anemia. Ferrous iron is preferred due to its improved absorption over ferric forms. Taking iron with a meal is preferable to improve bioavailability and tolerance. However, calcium blocks the absorption of iron, as do coffee and tea, so counseling can encourage iron supplementation at times when these foods and supplements are not being consumed. Due to increased bone turnover in postsurgical Type 2 diabetes patients, the surgeons referring patients for nutrition assessments stress the importance of calcium supplements but fail to advise using calcium at bedtime to reduce interference with iron absorption. Nutrition counseling is not required post-surgery but should be strongly encouraged.

Patients with mild anemia may be asymptomatic, but when the anemia worsens, symptoms of fatigue and pallor, along with lab test results, indicate more aggressive treatment is required. Erythropoietin (EPO) has been used in several Type 2 diabetes bariatric surgery cases to stimulate production of red blood cells. Two cases in the survey mentioned above—women three and four years post-surgery—were so happy with their blood glucose management and weight loss that they failed to notice anemia symptoms until routine CBCs continued to show reduced hemoglobin and low ferritin levels. Alexandrou et al. reported a similar rate of anemia in both RYGB and VSG cases.

Iron absorption occurs predominately in the duodenum, but since bariatric surgery reduces gastric acid secretion and pepsin, the solubility of ferric iron supplements is significantly reduced. Erythropoiesis profoundly influences iron absorption and enhances iron uptake from the gastrointestinal tract to meet nutritional needs. Iron is an essential trace element that is incorporated into every red blood cell’s hemoglobin molecule. The average adult produces 2 x 10^11 red blood cells daily, with each cell containing more than a billion atoms of iron (each 1 ml of red blood cells contains 1 mg iron). Iron uptake from the diet pre-surgery...
is estimated at a mere 10 percent.24

When bariatric surgery patients were surveyed about their iron supplementation regimen, most replied that the side effects of the 325-mg tablet of ferrous sulphate (50-60 mg elemental iron) prescribed included constipation and hard stools before surgery, so they frequently stopped taking them within one week and never resumed after surgery. None of them recalled being told they would need to monitor their iron levels for the rest of their lives.

Anemia and Folate
Folate deficiency is also a potential contributor to anemia in bariatric surgery patients due to restrictive and malabsorption issues.25,26 Symptoms include macrocytic anemia, thrombocytopenia, leukopenia and glossitis. It is believed that folate is absorbed throughout the small intestine, so deficiency is induced by reduced consumption of folate-rich vegetables and fresh fruits instead of malabsorption.

Folate supplements (not folic acid) can provide necessary nutrients to convert inactive methyltetrahydrofolic acid into the active tetrahydrofolate acid needed for anemia management.

Anemia and Vitamin B12
Lack of vitamin B12 is a major cause of anemia in bariatric surgery patients following biliopancreatic diversion or Roux-en-Y gastric bypass (not VSG).27,28 Vitamin B12 deficiency results from the inadequate secretion of intrinsic factor, limited gastric acidity and the bypassing of the duodenum where absorption occurs. Once the body’s stores are depleted, anemia due to lack of vitamin B12 leads to neurological and psychiatric symptoms, including memory disturbance, reduced muscle coordination and even dementia.29 Oral and intramuscular methylcobalamin is recommended due to malabsorptive procedures resulting from bariatric surgery.30

Vitamin B12 deficiency can also result from small intestinal bacteria overgrowth due to production of cobamides, biologically inactive vitamin B12 analogues.31 Pre-operative vitamin B12 deficiency needs to be considered in Type 2 diabetes when metformin and proton pump inhibitors (PPIs) are prescribed.32,33

Screening for vitamin B12 deficiency is recommended for all bariatric patients according to joint guidelines published by the American Association of Clinical Endocrinologists, The Obesity Society and American Society for Metabolic and Bariatric Surgery.34

Patient Education
Numerous case studies from the survey of Type 2 diabetes mellitus bariatric surgery patients are included in Bariatric Surgery Patients—A Nutritional Guide.3 One that highlights the importance of setting realistic expectations is a 32-year-old female on a basal-bolus insulin regimen whose surgeon told her the Type 2 diabetes would be resolved post-surgery. Two months postsurgical lab reviews confirmed that she still had Type 2 diabetes, so she would need to continue her insulin regimen and “accept her BMI of 41” in addition to monitoring her nutritional needs.

Non-adherence to recommended dietary supplementation is a major factor in nutritional deficiencies for Type 2 diabetes patients pre- and post-bariatric surgery. This was demonstrated in the survey and reported by Modi et al., Brolin et al. and Andreu et al.37-39 Nutritional surveillance is an essential component in the management of Type 2 diabetes and bariatric surgery. If patients are to maintain a good quality of life after surgery, nutritional deficiencies—including anemia management—must be assessed on a regular basis with patient education built into postoperative protocols. PD

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<th>Causes of anemia post-bariatric surgery</th>
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<td>Iron deficiency</td>
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<td>Pre-existing deficiency</td>
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<td>Lack of iron supplements post-surgery</td>
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<td>Poor absorption of iron post-surgery</td>
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<td>Calcium interference with absorption</td>
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<td>B12 deficiency</td>
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<td>Folate deficiency</td>
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<td>Reduced consumption of folate-rich vegetables</td>
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Many patients exhibit clinical symptoms of deficiency even though vitamin B12 status is within the reference range.31 In a case of vitamin B12 deficiency, intramuscular or subcutaneous administration is the preferred route until stable levels are achieved with 1000 µg i.m./s.c. daily for five to seven days, followed by four to five weekly injections of 1000 µg.36 Intranasal and sublingual applications of vitamin B12 bypass the need for intrinsic factor, but further study in this area is needed.
You may not have heard this term, but you have most likely experienced it every January. It makes you anxious to look at your inbox on the electronic health record or your fax machine because there are so many requests to change brands of certain medications. Please note that this is not the usual request to change to a generic, but a request to change between brands. Of course, it does not arrive with a note informing you of the formulary change, but you figure out pretty quickly the reason for all these identical requests.

Non-medical switching occurs when the formularies change medication in a class, such as basal insulin, and the pharmacy does not recognize it as equal, so the pharmacist sends you a request (demand?) for a new prescription so that the pharmacy can dispense what is now preferred on the insurance formulary.

The major frustration for our clinic is the sheer volume of these requests every January. We have tried to think of strategies to manage this sudden workload. If one agrees conceptually to the switch, then the clinic could set up a protocol whereby a nurse reviews each request and approves it. If one does not agree, each request must be reviewed. Either strategy still involves a lot of work for the clinic staff.

From the medical perspective, the important issue is that the insurance company is now deciding that certain medications are “equal,” regardless of the prescriber’s opinion. This means that if the insurance company decides there is no difference between two insulins, they simply refuse to pay for one. The options are limited: go along with the switch or, with a great deal of paperwork (the infamous “prior authorization” or “PA”) and possibly a phone call, you can demand the medication that you had originally chosen. Even if you do get it approved, the cost may be prohibitive since it is no longer “preferred,” thereby requiring a higher copay or no copay.

Although your choice may have been based on specific evaluation of the individual patient, or what is called “personalized medicine,” the insurance company has made a medical practice decision that the two medications are sufficiently similar, rendering your individual assessment irrelevant. In truth, if not for the pharmacy having a different National Drug Code for the newly preferred medication, we would not know about the switch until the next clinic visits, which could be three to 12 months later.

This then raises the question of whether there is a problem with such switches. There are examples in the literature of alteration in clinical status and increased utilization of health-care resources after such switches. Examples include a 2018 study evaluating the impact of a formulary switch of an SGLT-2 and prior studies with SSRIs or an anti-tumor-necrosis-factor (anti-TNF) biological agent.

The argument in support of such switches contends that on a population level, a 10% to 15% difference probably would not have much impact on the cost for the insurance carrier. One approach is to argue that if a study comparing the two agents (i.e., insulins) showed non-inferiority, the two could be interchangeable. However, it is rare to have head-to-head studies of medications in the same class. Therefore, the insurance company’s formulary would have had to compare reportedly “similar” studies to conclude that the agents are interchangeable. While this is actually something we do in practice when we review the medical literature to decide the benefits and risks of medications, we do not read the literature to look for interchangeability but for differences that would suggest which patient characteristics identify those more likely to respond to one medication over the other.

Despite our opinions of the literature, the insurance formularies make a decision that exerts a wide impact on patients’ medical care. The result of the switch could include a worsening of his or her medical condition and increased utilization of health resources, as shown in the studies cited. Additionally, nonmedical factors need to be considered, such as patients’ satisfaction with their care, the burden to the clinic and possible abandonment of therapy by the patient. Furthermore, this is one more step in removing the physician’s autonomy. At the most extreme, one could perceive it as an indication that insurance formulary believes they can make medical decisions regarding therapy, so physician input may no longer be needed for implementing the medical care plan.

While there is no obvious solution to this problem, awareness of it may allow you to plan your clinic time in January a little differently and perhaps create some handouts to explain to patients how to transition between the insulins, what to expect in transition and when to call in (rather than going to the emergency department) so that we can help with the dose adjustments. PD
JOURNAL WATCH

The papers highlighted in this Journal Watch include an analysis of the economic burdens of diabetes projected out to 2030, which is a great resource for public policy and planning localized expansion of programs based on these conservative estimates. The ODYSSEY DM-DYSLIPIDEMIA trial is an important demonstration of not just safety but also efficacy in lipid lowering in those tough patients with Type 2 diabetes mellitus and mixed dyslipidemia who are not at goal on maximally tolerated statins. The FREEDOM-1 trial is included because it demonstrates that a three- to six-month implant can effectively improve glucose control in Type 2 diabetes. Lastly, cystic fibrosis-related diabetes (CFRD) is addressed with a study showing that oral repaglinide has no benefit over the current standard of care, which is insulin, in a two-year study.

**Title:** Global Economic Burden of Diabetes in Adults: Projections From 2015 to 2030

**References (related):**

**Sponsor:** none

**Study Design:**
The authors modeled the absolute and gross domestic product (GDP)-relative economic burden of diabetes in individuals aged 20-79 years using epidemiological and demographic data, as well as recent GDP forecasts for 180 countries. They assumed three scenarios: 1) prevalence and mortality increased only with urbanization and population aging (baseline scenario), 2) increased in line with previous trends (past trends scenario) and 3) achieved global targets (target scenario).

**Results:**
The absolute global economic burden is estimated for 2015 at $1.3 trillion (95% CI 1.3-1.4) in 2015. Depending on the model, it will increase to $2.2-2.5 trillion by 2030. This translates to an increase in costs as a share of global GDP from 1.8% (1.7-1.9) in 2015 to a maximum of 2.2% (2.1-2.2).

**Summary:**
This paper estimates the absolute global economic burden of diabetes in U.S. dollars in 2015 and then develops projections through the year 2030. This information is valuable to clinicians and health policy-makers. The figures provide an excellent visual representation of the current and projected burden of diabetes. The current burden is staggering and likely to increase faster than the near-doubling over 15 years that is projected here. Although progress has been made toward early diagnosis, prevention strategies must start prior to the onset of “prediabetes” to truly impact the growth in this epidemic.

**Title:** A Randomized, Open-Label, Parallel Group Study to Evaluate the Efficacy and Safety of Alirocumab Versus Usual Care in Patients with Type 2 Diabetes and Mixed Dyslipidemia at High Cardiovascular Risk with Non-HDL-C Not Adequately Controlled with Maximally Tolerated Statin Therapy

**ClinicalTrials.gov Identifier:** NCT02642159

**References (related):**
Design papers:


**Results paper:**

Sponsor: Sanofi

Study Design: Randomized, open-label, parallel group

Intervention: Alirocumab 75 mg subcutaneous (SC) injection every two weeks (Q2W) added to insulin or other antihyperglycemic drugs, stable maximally tolerated dose of statin therapy without other lipid-modifying therapy (LMT) for 24 weeks. Alirocumab dose uptitrated to 150 mg Q2W from week 12 when non-high-density lipoprotein cholesterol (non-HDL-C) levels ≥100 mg/dL (2.59 mmol/L) at week 8.

The usual care (UC) group continued on insulin or other antihyperglycemic drugs, stable maximally tolerated dose of statin therapy without additional LMT or with either ezetimibe, fenofibrate, omega-3 fatty acids or nicotinic acid as per Investigator’s judgment for 24 weeks.

Primary Outcome Measure:
Percent Change From Baseline in Non-HDL-C at Week 24: Overall Intent to Treat (ITT) Analysis
Percent Change From Baseline in Non-HDL-C at Week 24: ITT- Intent to Prescribe Fenofibrate Stratum

Results:
In all, 413 individuals were randomized, with 276 in the alirocumab group and 137 in the usual care (UC) group. At baseline, 77% were treated with a biguanide, and 37-40% were treated with insulin. HDL-C levels were not low at 40-41 mg/dL. Triglycerides (TGs) were mildly increased at 212-215 mg/dL.

In all, 63.6% were maintained on 75 mg every two weeks of alirocumab, while 36.4% required uptitration to the 150 mg Q2W therapy.

At week 24, the mean non-HDL-C reductions were superior with alirocumab (-32.5% difference versus UC, 97.5% confidence interval -38.1 to -27.0; P < .0001).

Alirocumab significantly reduced LDL-C (-43.0%), apolipoprotein B (-32.3%), total cholesterol (-24.6%) and LDL particle number (-37.8%) at week 24 versus UC (all P < .0001).

Alirocumab was not superior to UC in reducing TGs.

The authors do point out that because of the hierarchical nature of testing, the significant increase in HDL-C levels (+6.2%) and significant reductions in LDL particle number (−37.8%) and LDL particle size (−1.8%) relative to UC should be considered nominal.

Alirocumab was superior to fenofibrate in reducing non-HDL-C (33.3% versus fenofibrate), ApoB (35.2%), Lp(a) (22.8%), total cholesterol (25.3%) and measured LDL-C (55.7%). At week 24, the percentage change from baseline in the fenofibrate group was equivalent to the alirocumab group in lowering TG and raising HDL-C, when added to maximally tolerated statin therapy.

The incidences of treatment-emergent adverse events were 68.4% (alirocumab) and 66.4% (UC). No clinically meaningful effect on A1C or change in number of glucose-lowering agents was seen.

Summary:
This study shows that in patients with Type 2 diabetes mellitus and mixed dyslipidemia, the addition of alirocumab to maximally tolerated statin therapy decreases LDL-C, non-HDL-C and TC, thereby getting more patients to their lipid targets.

Because this study was not designed to assess cardiovascular (CV) outcomes, it is not possible to compare CV events or mortality between the two groups. However, with the significant residual CV risk for patients with Type 2 diabetes mellitus, these data provide an option to further decrease lipids with a goal of decreasing the devastating CV events that are the leading cause of mortality in people with diabetes.
Study Title: FREEDOM-1 Trial

ClinicalTrials.gov Identifier: NCT01455857 & NCT01785771

References (related):


Sponsor: Intarcia Therapeutics

Study Design: Randomized, parallel assignment, quadruple masked (participant, care provider, investigator, outcomes assessor)

Intervention:
NCT01455857: ITCA 650 (exenatide in DUROS) at 20 mcg/day for 13 weeks, then 40 or 60 mcg/day for 26 weeks versus ITCA placebo (placebo in DUROS)

NCT01785771: ITCA 650 (exenatide in DUROS) at 20 mcg/day for 13 weeks, then 60 mcg/day for 26 weeks

Primary Outcome Measure: Change in A1C over 39 weeks

Results: ITCA 650 is a subdermal osmotic minipump that continuously delivers exenatide subcutaneously for three to six months.

The first paper from the FREEDOM-1 Trial describes the phase 3, double-blind, placebo-controlled trial that randomized 460 patients for 39 weeks of treatment at 40 or 60 mcg/day. The change in A1C was -1.1% for ITCA 650 40 mcg/day versus -1.2% for ITCA 650 60 mcg/day and -0.1% for placebo. Both doses of ITCA 650 were statistically significant compared with placebo. Greater A1C reductions occurred in patients not receiving sulfonylureas (SUs) versus those receiving SUs (-1.7% versus -1.2%). Each group was assessed to see if A1C attained target of <7% with 37% in the ITCA 650 at 40 mcg/day and then 44% of ITCA 650 at 60 mcg/day and 9% in the placebo group.

Change in body weight was greater with the study drug and significantly different from placebo: -2.3 kg ITCA 650 at 40 mcg/day, -3.0 kg for ITCA 650 at 60 mcg/day and -1.0 kg in the placebo group.

Nausea was the most common adverse event and subsided over time, with 7.2% in the ITCA group versus 1.3% in the placebo discontinuing because of gastrointestinal side effects.

The second paper describes the poorly controlled patients with Type 2 diabetes who were ineligible for participation in FREEDOM-1 because of severe hyperglycemia with A1C >10%.

This was a 39-week, open-label, phase 3 trial that enrolled patients ages 18-80 years with A1C >10% but ≤12% and BMI 25-45. There was no placebo group due to the severe hyperglycemia. Participants received ITCA 650 20 mcg/day for 13 weeks, then 60 mcg/day for 26 weeks. The primary endpoint was change in HbA1c at week 39.

Baseline A1C was 10.8% with a mean reduction of -2.8% at week 39.

Weight loss was -1.2 kg (P = 0.105).

In all, 25% of patients achieved A1C <7%, with 90% decreasing their A1C by at least 1%.

Only four patients (6.7%) discontinued for gastrointestinal side effects.

Summary:
These data show that ITCA 650 is well tolerated and significantly reduces A1C and weight compared with placebo. It is concerning that the subset not on SUs responded better than those on SUs because many patients still receive SUs as their first- or second-line therapy. The companion paper showing treatment of those with A1C of 10-12% demonstrated an A1C drop that would bring that population to an A1C of approximately 8%, which would be very helpful in many of our uncontrolled Type 2 diabetes patients. These two studies demonstrate the safety and efficacy of this new delivery system for exenatide that could be inserted during routine clinic visits every three or six months once it is approved by the U.S. Food and Drug Administration.
Title: Open Randomised Prospective Comparative Multi-centre Intervention Study of Patients with Cystic Fibrosis and Early Diagnosed Diabetes Mellitus

Study Title Acronym: None

ClinicalTrials.gov Identifier: NCT00662714

References (related):


Sponsor: Mukoviszidose eV, Vaincre la Mucoviscidose, ABCF Association, and Novo Nordisk.

Study Design: Randomized, parallel assignment, open label comparing pre-meal dosing of oral repaglinide with SQ human regular insulin

Primary Outcome Measure: Change in A1C after two years

Secondary Outcomes: Mean change in A1C from baseline to 12 months of treatment, mean changes in BMI Z score, FEV1 and FVC from baseline to 12 months and 24 months, and changes in blood glucose profiles during the intervention.

Results: There was no difference between groups in absolute A1C values at baseline, 12 or 24 months. There was also no change in mean A1C from baseline to 12 or 24 months.

The mean final daily dose of repaglinide was 2.6 mg/day (range 0.5-12.0), and that of human regular insulin was 18.6 IU/day (range 4.5-72.0).

A significant change in BMI Z score was seen after 12 months, but not after 24 months. Changes in glucose profiles and in percentages of predicted FEV1 and FVC did not differ between groups after 12 or 24 months. The most frequent adverse event was pulmonary symptoms.

Symptomatic hypoglycemia was reported in 44 (64%) of the 69 patients and was equal in both groups (22 per group). The only severe hypoglycemia was one person in each group having an episode requiring assistance.

Summary: The two-year duration of this study is valuable as prior data were up to only 12 months. However, as clearly reviewed by the accompanying editorial, it is not sufficiently compelling to change standard of care from insulin to repaglinide. PD
EDUCATOR’S CORNER

MISSING THE DIAGNOSIS: THE OVERLOOKED WARNING SIGNS OF TYPE 1 DIABETES

When a patient presents with the classic symptoms of diabetes and is undiagnosed or misdiagnosed, heartbreaking consequences can result. This occurs all too often due to lack of symptom awareness and must be addressed by health-care professionals as well as the community at large. One of the primary symptoms of ketoacidosis is nausea and/or vomiting, which can deflect the health professional into a mind-set of a stomach-flu-like diagnosis. Many certified diabetes educators, physicians and providers connected to the Type 1 diabetes community are aware of horrific cases in which the symptoms were reported and medical attention sought, but Type 1 diabetes was not properly diagnosed.

Diabetes and DKA by the Numbers
The number of people with diagnosed Type 1 diabetes globally is staggering. The number of misdiagnosed children and adults who are often eventually diagnosed with diabetic ketoacidosis (DKA) is alarming, devastating and often deadly.

Many cases have been reported in which a child or an adult was brought to a health-care provider several times in the days, weeks and sometimes months before being admitted to the ICU in DKA. These scenarios, which were once only shared at scientific meetings, are now the subject of discussions on social media and throughout peer support communities.

Alarming Statistics

- 30.3 million people in the U.S. have diabetes; one in four doesn’t know it.1
- Half a million children worldwide have been diagnosed with Type 1 diabetes.2
- The incidences for Type 1 diabetes are rising sharply. Between 2001 and 2009, the prevalence in people under the age of 20 rose 21%.3
- Researchers in Colorado have documented a more than 50% increase in the incidence of diabetic ketoacidosis (DKA) at diagnosis of Type 1 diabetes in children between 1998 and 2012.4

Why is Type 1 diabetes misdiagnosed?
While endocrinologists and certified diabetes educators recognize the symptoms of Type 1 diabetes, parents, pediatricians, health-care providers, educa-
tors and caregivers may not be aware of the typical symptoms or at least may not recognize them as they become prevalent. In truth, the probability is that they are indeed caused by a stomach flu and nothing more. That said, the danger is no less when the missed diagnosis occurs. In fact, in some cases, the missed diagnosis has a catastrophic result. Therefore, increasing Type 1 diabetes symptom awareness and the basics of DKA is imperative within the community at large. We believe that a basic understanding of Type 1 diabetes, the warning signs of onset and explanation of the dangers of DKA will save lives.

DKA is a serious and dangerous complication of uncontrolled Type 1 diabetes and occurs when the body produces a high level of blood acids or ketones. DKA develops when the body can’t produce enough insulin, causing the body to use muscle and fat as fuel, producing a dangerous buildup of ketones in the bloodstream. Onset of DKA is typically accompanied by nausea, vomiting and severe abdominal pain—all red-flag symptoms of Type 1 diabetes. DKA requires immediate medical treatment to prevent the life-threatening events metabolic acidosis, coma and even death.6

Missing the diabetes diagnosis is not a problem due to lack of technology. Presented with the symptoms, we possess the tools to properly diagnosis and treat Type 1 diabetes in a timely manner. We have urine dip sticks and blood glucose monitors. We have manufactured insulin, continuous glucose monitor sensors, insulin infusion pumps and other technological advancements to help manage Type 1 diabetes once it’s diagnosed. However, the condition cannot be addressed or managed if it remains undiagnosed.

**Registries and Statistical Data**

While significant data indicate an increase in the incidence of misdiagnosed Type 1 diabetes, the reason for this is multifaceted and complex. Emerging data are beginning to address the issues surrounding misdiagnosis.

**The Philadelphia Pediatric Diabetes Registry**

Terri Lipman, assistant dean of community engagement at the University of Pennsylvania School of Nursing, developed the Philadelphia Pediatric Diabetes Registry, which accounts for cases of Type 1 diabetes in children residing in Philadelphia and the surrounding area. This is a U.S. registry of diabetes in children that has collected data continuously since 1985. Lipman’s data show a dramatic increase in the incidence of Type 1 diabetes in children over the past 20 years, as well as a marked increase in children under the age of 5 who have been diagnosed with Type 1 diabetes. This rapid increase in Type 1 diabetes in young children requires immediate attention to the signs and symptoms because these children are at the highest risk of death as a result of their delayed diagnosis.6

Lipman points out that the incidence of Type 1 diabetes in children in the Philadelphia area has increased an average of 1.5% each year, and while it was stable over the first 15 years of the study, it has risen markedly since 2000. This upward trend adds to the evidence of an increasing incidence of diabetes in the U.S. and worldwide.7

While these results are geographically limited, Lipman has stated that she believes her information/research is indicative of what’s happening in other parts of the country as well as globally. It is critical to continue to investigate risk factors that may be associated with the increased incidence of Type 1 diabetes, the marked rise in the incidence in young children, as well as cases where it is misdiagnosed altogether.

**Glu/T1D clinical registry**

The T1D Exchange Clinic Registry includes patient-reported electronic health data from people living with Type 1 diabetes. Eighty-three percent of 3,030 participants who completed the survey met the inclusion criteria. Ages range from less than 1 year old to 93, spanning a range of demographic parameters, socioeconomic status and care regimes. According to T1D, these findings will be reported in much greater depth and with additional content in a future publication. Some of the results from the registry reporting misdiagnosis were staggering. Based on documented responses, prior to 1980, only 12.2% of respondents were misdiagnosed versus 30.2% after 1980. Even worse, 52.8% of respondents reported that it took over a month to be correctly diagnosed, and 20% of participants reported being admitted to the ICU, with 24% of pediatric patients unconscious on admission (16% of adults).

The T1D registry respondents conveyed other sobering statistics as well. Thirty-five percent
reported that they were not diagnosed until more than one month after noticing symptoms. Another 415 participants reported being diagnosed in DKA. Incredibly, 24% of participants reported being misdiagnosed with another condition before receiving an accurate diagnosis of Type 1 diabetes.8

These symptoms need to be addressed early on by health-care providers. Nausea and vomiting are the symptoms of diabetes and should not be confused with the stomach flu or acid reflux. It should also be noted that should the symptoms of Type 1 diabetes be missed, the only indications of the disease become the symptoms of DKA. At this point, education needs to be addressed. Just as a throat culture is done for a differential diagnosis, a simple blood or urine test should be done to help determine a diagnosis of Type 1 diabetes.

**Diabetes Symptom Awareness Initiatives: Time to save lives**
The North Carolina legislation known as Reegan’s Rule followed the death of 16-month-old Reegan Oxendine, who died unnecessarily from misdiagnosed Type 1 diabetes. Although her mother sought medical treatment on several occasions, her doctors originally diagnosed her with a virus and acid reflux. After Reegan passed away, family, friends and supporters started a social media campaign to require testing for Type 1 diabetes in all young children. This outcry (and the efforts of many in the diabetes community, including Tom Karlya, co-author of this article) eventually led to an agreement by lawmakers that recommends doctors educate parents and guardians on Type 1 diabetes symptoms from birth to 60 months of age. While the bill was not passed as originally crafted, Reegan’s Rule has distinguished North Carolina as the first state in the U.S. to pass this type of bill for diabetes. This law became a benchmark and community outcry for better awareness. What started out with a grassroots effort that continues to this day (GetDiabetesRight.org and others) has become an undertaking by major organizations like Beyond Type 1 as an all-out education campaign. The American Academy of Pediatrics has adopted the campaign in 18 states and 22,000 pediatric offices thus far (https://beyondtype1.org/our-dka-campaign/) and will continue to expand it.9

As more children and adults were harmed by misdiagnoses, several groups began initiatives to gather scientific proof that this was occurring and, ultimately, to effect policy change. What started out even smaller than a completely grassroots effort has grown into a full-court press to get the word out not only to medical professionals but also to parents.

**Getting the word out at school**
The National Association of School Nurses (NASN) also became interested in the important message and has crafted a letter describing the symptoms of Type 1 diabetes that can be distributed to parents and guardians by any school nurse belonging to the association. This is especially important during flu season, when parental concerns may be overlooked when reporting symptoms to a health-care provider. This letter can be shared and sent to local school districts.

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**Infectious to Increase Diabetes Symptom Awareness**

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<tr>
<th>Initiative</th>
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<tr>
<td>DPAC: Diabetes Patient Action Coalition</td>
<td><a href="http://diabetespac.org/">http://diabetespac.org/</a></td>
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<td>T1D Exchange: Myglu.org</td>
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<td>Beyond Type 1</td>
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<td>Test 1 Drop – T1D Awareness</td>
<td><a href="http://www.test1drop.org/">http://www.test1drop.org/</a></td>
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**REFERENCES**

Read all of this issue’s references online at bit.ly/2DxxSMA

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Dear Parent/Guardian of _____________,

Your child came to the health office today complaining of flu-like symptoms. We send this notice home to make you aware of the symptoms of diabetes. For a small number of children, flu-like symptoms may be the first sign of diabetes, and we want you to be aware of what to look for. Symptoms of diabetes in children include:

- nausea
- vomiting
- feeling very tired
- heavy, labored breathing
- increased thirst and hunger
- frequent urination and new bedwetting
- sudden weight loss
- blurred vision.

If you notice that your child continues to complain of flu-like symptoms and has additional symptoms from the list above that seem to be getting worse, you may want to ask your pediatrician or health-care provider to perform a simple blood and/or urine test to check for diabetes. In most cases your child’s complaints are caused by a virus, but I also want you to be aware of the less common symptoms that could be the first sign of diabetes. For further information or action to take, call your pediatrician or healthcare provider. PD
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