



# Diabetes in focus



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## New Drug Update: Insulin Degludec

Contributed by: Shelley Todd Strickland, 4<sup>th</sup> year PharmD Candidate

Insulin glargine (Lantus®) has dominated the market for over a decade with IMS Health reporting \$2 billion dollars in sales for 2011, but Novo Nordisk may have a new product to compete with this mainstay of diabetes therapy.<sup>1</sup> Insulin degludec, an ultra-long acting insulin, has been shown to be non-inferior to insulin glargine and may offer some benefits.<sup>1,2,3</sup>

Insulin degludec's novel mechanism of action has generated much excitement. Upon injection, it forms a depot of soluble multihexamers from which insulin is gradually absorbed. With a half-life of 25 hours and duration of action greater than 40 hours, pharmacokinetic data show insulin degludec provides a steady insulin concentration and reduced variability compared to insulin glargine.<sup>2,3</sup> This novel pharmacokinetic profile spiked interest that the limitations with insulin glargine, namely its inability to cover a full 24 hour period, could be answered with insulin degludec. Further, while rates of hypoglycemia are not high with insulin glargine, hypoglycemia appears to be even less of an issue with insulin degludec.

The Begin 1 and Begin 2 trials, phase III studies evaluating basal insulin therapy in type 1 and type 2 diabetics respectively, compared insulin degludec to insulin glargine. The studies found that insulin degludec had significantly less nocturnal hypoglycemia. Insulin degludec was

also found to be non-inferior to glargine in providing long-term glycemic control, as measured by A1C.<sup>2,3</sup> Because hypoglycemia rates are already so low with long-acting insulin formulations, the clinical value is yet to be determined; however, additional safety that insulin degludec could potentially provide is an intriguing advantage.

Lastly, speculation exists that degludec will be the first basal insulin not to require daily dosing. A phase II trial using two different concentrations of insulin degludec, dosed daily or three times a week, found no difference in glycemic control between treatment groups.<sup>4</sup> Interestingly, Novo Nordisk used the once daily regimen in the phase III trials, but the tri-weekly dosing schedule will probably be explored further after the initial marketing launch.

The FDA will most likely approve insulin degludec this coming spring. Only time will tell how it measures up to insulin glargine, but if its ultra-long duration is any hint, this new insulin has a promising future ahead.

**Much hype surrounds the final FDA approval of insulin degludec, with some speculating that insulin degludec will be the next blockbuster drug.**

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1. IMS National Sales Perspectives. (2012). Top U.S. Pharmaceutical Products by Spending. Retrieved from [http://www.imshealth.com/ims/Global/Content/Corporate/Press%20Room/TopLine%20Market%20Data%20&%20Trends/2011%20Top-line%20Market%20Data/Top\\_Products\\_by\\_Sales.pdf](http://www.imshealth.com/ims/Global/Content/Corporate/Press%20Room/TopLine%20Market%20Data%20&%20Trends/2011%20Top-line%20Market%20Data/Top_Products_by_Sales.pdf)
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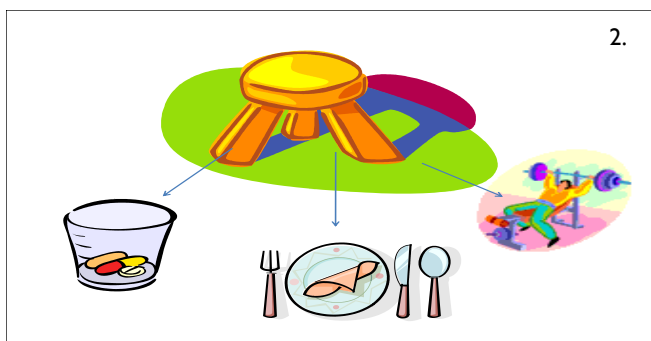
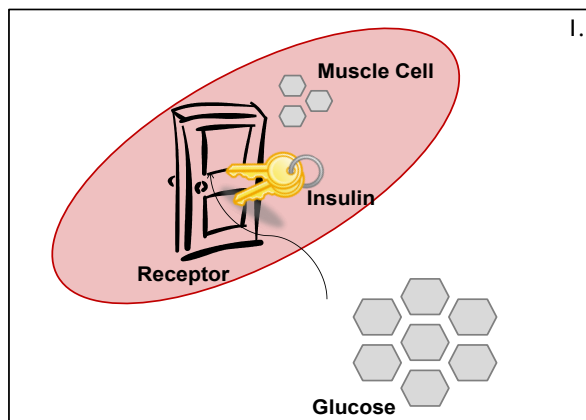
## Patient Counseling Overview

Contributed by: Andrea Sikora, 4<sup>th</sup> year PharmD Candidate

Patient counseling is one of the most important services a pharmacist can offer a patient, but in the rush and bustle of daily pharmacy, counseling on a topic as complex as diabetes can seem overwhelming. The following is an outline of how to convey some key points about diabetes in a relatively quick counseling session:

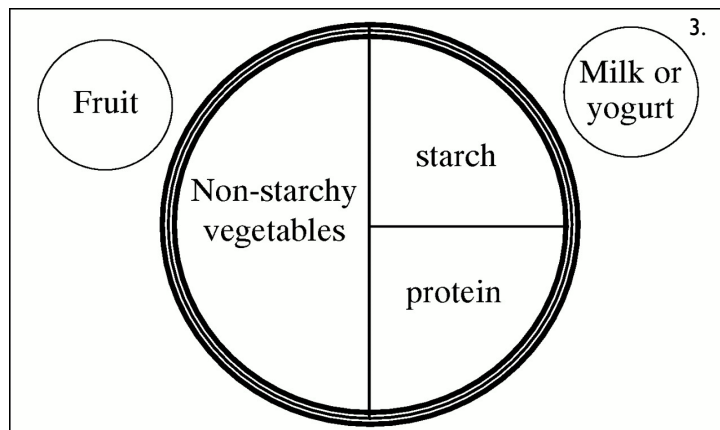
### What is diabetes?

Diabetes is when you have high amounts of sugar in your blood. The problem is you don't really need sugar in your blood, you need it in your muscle cells for energy. Imagine a lock and key system. Glucose cannot get past the locked door of your cell, so it needs a key. The key is insulin. In diabetes, you have either lost the key or the key is so rusty it only works some of the time. (see figure 1). Imagine spilling a Coke and letting it dry on the counter and how it feels sticky. Further, dirt gets stuck on the dried Coke, so now the counter is sticky and dirty. This is very similar to what is happening in your body, and this stickiness can be very damaging over time leading to lots of complications.



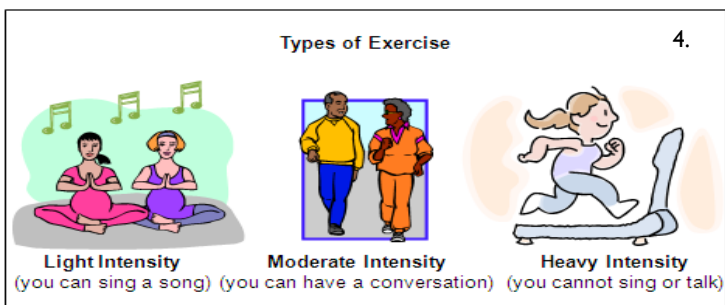
### How do I know what to eat?

Diet really comes down to a few key concepts. First, don't deny yourself. If you love Little Debbie Cakes, make sure you find a way to keep some Little Debbies in your diet. The second is portion control and the third is the right dietary choices. An easy way to help with portion sizes and choices is the use of the plate method. 50% of your plate should be vegetables, ideally green, leafy veggies. 25% of your plate should be protein, ideally in the form of a lean meat like boneless, skinless chicken, fish, meats that end in 'loin'. The fewer legs an animal has, the less fat it has. Thus, a pig with 4 legs has more fat than a chicken with 2 legs which has more fat than a fish with "0" legs. 25% of your plate should be a starch or carbohydrate like rice or a sweet potato. On either side can be a serving of low-fat dairy and a serving of fruit. Portion sizes are controlled because this is a 9" or salad plate (see figure 3).



### How much should I exercise?

The American Diabetes Association recommends 150 minutes of moderate-intensity aerobic exercise per week. This comes to about 30 minutes 5 days per week and can even be split up into 15 minute sessions. Everyone has different classifications of intensity for different activities. There are three categories of exercise: light, moderate, and heavy. (see image 4). The intensity of exercise can be classified using whether or not you are able to have a conversation or sing a song while exercising. Moderate intensity exercise means that you can have a conversation but would feel out of breath if you tried to sing a song. Remember to start out with shorter workouts and build up your stamina over time!



## A<sub>1c</sub>: What Does it Represent?

Contributed by: Robert Newsome, 4<sup>th</sup> year PharmD candidate

A<sub>1c</sub> is a simple blood test that is used to test how well a diabetic patient's blood glucose is controlled. Formerly, a lab test that had to be ordered by a prescriber, A<sub>1c</sub> test kits that are quite similar to glucometers are now available over-the-counter. With the advent of OTC A<sub>1c</sub> test kits, it is important for pharmacists to understand what information the test provides and how the test can be used in a community setting.

A<sub>1c</sub> is able to offer this more global picture because it takes advantage of the 120 day life-span of erythrocytes (red blood cells).<sup>2</sup> A<sub>1c</sub> can also be translated into

A1C (%)	Average Plasma Glucose (mg/dL)
5	80
6	120
7	150
8	180
9	210
10	240
11	270
12	300
13	333
14	360

<sup>1</sup>Table adapted from the Mayo Clinic

an average plasma glucose level. A rule of thumb is that each 1% in A<sub>1c</sub> correlates to 30 mg/dL change in blood glucose.

People without diabetes have an A<sub>1c</sub> between 4.5% and 6%, and an A<sub>1c</sub> greater than 6.5% on two separate occasions is diagnostic for diabetes. Once diagnosed, the American Diabetes Association (ADA) recommends an A<sub>1c</sub> of less than 7%, whereas the American Academy of Clinical Endocrinologist (AACE) has a stricter target of less than 6.5%. While a physician must be involved to make a formal diagnosis of diabetes, community A<sub>1c</sub> testing offers pharmacists a valuable tool in patient education, counseling, and pharmacotherapy recommendations.

Because patients now have the option to test their A<sub>1c</sub>, more questions will probably arise about frequency. Checking A<sub>1c</sub> more than every 3 months is unnecessary because it only significantly changes with red blood cell turnover. Further, since A<sub>1c</sub> is a test that uses erythrocytes, any variable that affects red blood cells can cause variation in A<sub>1c</sub>. Blood transfusions, genetic variations in hemoglobin, diseases that cause decreased erythrocyte lifetime, and anemia can all cause changes in A<sub>1c</sub>; therefore, an A<sub>1c</sub> of a person that has received a recent blood transfusion is not clinically relevant without waiting 3 months.<sup>3</sup>

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## Obesity & Microvascular Degeneration

Contributed by: Islam N. Mohamed, B. Pharm, MS, PhD Graduate Student

Obesity is one of the highest risk factors for vascular diseases. Our research focuses on a specific mechanism by which obesity can result in retinal microvascular degeneration. Our recent studies in rats fed with a high fat diet showed that obesity can result in increasing the expression of thioredoxin interacting protein (TXNIP) in the eye. TXNIP is known to decrease the anti-oxidant defense mechanisms of the cells. In addition, it also activates a protein complex called the inflammasome, which is responsible for the activation of inflammatory molecules in retinal microvessels. Therefore, we are testing whether decreasing TXNIP expression can protect against retinal microvascular degeneration, which is the basis for developing diabetic retinopathy.

In order to test our idea, we are asking two specific questions: first; whether TXNIP expression, induced by obesity, is responsible for activating the inflammasome protein complex in retinal endothelial cells, the building unit for retinal microvasculature? Second: Whether treatments targeting TXNIP protein can protect against increased inflammation and hence increased retinal microvascular degeneration. We will be answering these questions by inhibiting TXNIP protein expression in isolated human retinal endothelial cells and by using mice that either lack a functioning TXNIP protein or are treated with drugs that decrease TXNIP expression.

4.

Nearly 75 millions of U.S. adults are obese and are at higher risk for developing diabetes and cardiovascular complications. Successful completion of our studies will provide new direction to prevent or treat vascular complications in obese subjects. Our research will identify one of the mechanisms by which obesity induced by high fat diet can result in the degeneration of small blood vessels and hence increased vascular complications. Our work will highlight new protein targets such as TXNIP for developing novel therapeutic agents and as such it will have strong impact on cardiovascular disease.

## Exercise Improves Vascular Reactivity of Pre-Diabetic Patients

Contributed by: Meghan Caylor, 4<sup>th</sup> year Pharm.D. student

While the benefits of exercise in the prevention and progression of diabetes are common knowledge by now—including improving insulin sensitivity, lipid profiles, and weight loss—there is new evidence that implies endothelial cell dysfunction that begins to occur even in the pre-diabetic state can be improved through regular exercise.

In May, researchers presented results of a study at the AACE 21<sup>st</sup> Annual Meeting that highlighted a more specific link between exercise and vascular reactivity. This study included 20 pre-diabetic adult patients who were divided into two groups in a crossover design: one group completed 150 minutes of aerobic exercise a week for 6 weeks, while the other group did not exercise; after a 4 week washout period the two groups were switched. The main measure of endothelial cell function was vascular reactivity, measured via flow mediated dilatation (FMD) studies before and after each of the phases. The mean FMD was 5.7% in the non-active group, compared to 11.2% in the exercise group. This points to a significant improvement in the vascular reactivity, and thus endothelial cell function, even with no significant weight loss occurring during the study period. They also noted reductions in several inflammatory biomarkers, decreases in fasting triglyceride and LDL levels, and improved insulin sensitivity. Fasting blood glucose, HDL, and HbA<sub>1C</sub> remained unchanged, though a 6-week study period is not a long enough trial to measure A<sub>1C</sub> because of the 3-month lifespan of erythrocytes.<sup>1,2</sup>

FMD provides a numerical measurement of the vasculature's pliability. Vascular reactivity is diminished in diabetic patients and serves as an early marker of arteriosclerosis—stiffening of the arteries—which is a common pathogenesis of many co-morbid complications of diabetes, in-

cluding hypertension and cardiovascular disease<sup>3</sup>. Because the endothelium is largely in control of the vasculature's ability to dilate (by way of synthesizing nitric oxide), measuring the % change in diameter within an individual is an indirect way of characterizing endothelial cell function<sup>3,4</sup>. Using high-resolution vascular ultrasound to measure the brachial artery's diameter, FMD is expressed as a % change. Higher percentages indicate a greater ability of the artery (and systemic vasculature in general) to dilate<sup>4</sup>; thus, a significant improvement of FMD after just 6 weeks of exercise is a very promising finding.

Much remains to be elucidated about the various pathological pathways that are present in diabetic and pre-diabetic patients, though ongoing research in this arena is immense. The results of this small study shed more light on processes that occur early on in the disease state, as well as give hope to being able to prevent the disease as well as its progression. We now have more evidence to reinforce the importance and numerous benefits of exercise in this disease state, and we as pharmacists can play a pivotal role in promoting and encouraging regular exercise in our encounters with our diabetic and pre-diabetic patients.

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### SDC Member Highlights

- Brian Griffin presented "Diabetes: When To Do More" to the Central Savannah River Area Senior Citizen Council Meeting as means of educating senior citizens about diabetes.
- Lindsay Schaak was named SDC Treasurer.
- Paul Hansen presented his research from Dr. Segar's laboratory on metformin inhibiting smooth muscle contraction.
- Bobby Newsome and Andrea Sikora developed an insulin dosing tool for GHSU's upcoming Insulin Protocol.



*Featured Above:* Gourmet Lunch Fundraiser raised awareness and donations for the American Diabetes Association. A big thanks to the Mays for their generous support!