

## **Type 2 Diabetes**

### **Introduction**

Diabetes is a condition, not a disease. Like any condition it has to be managed, and if managed well diabetes will not significantly reduce life expectancy, increase your risk of heart disease and stroke & will not damage your kidneys, your eyes or your nerves.

Optimal diabetes control requires a partnership between BC Diabetes staff (diabetes specialists, physician assistants, nurses, dietitians, pharmacists & exercise trainers) and you. By partnering with our staff & using our education & empowerment tools and technologies, you can become your own diabetes manager. Eventually you will only need us to provide prescriptions for medication, laboratory requisitions, to make referrals to other health care professionals and to keep you informed of advances in diabetes.

Diabetes is present when the blood glucose (sugar) before breakfast is above 6.9 or when another blood test, the A1c is above 6.4.

Diabetes is caused by a deficiency of insulin. The commonest cause of insulin deficiency is the natural ageing process: as you get older the cells that produce insulin gradually die off. Everybody will develop diabetes if they live long enough; and every person with diabetes will eventually require insulin. Insulin deficiency can also be due to reduced insulin action, also known as “insulin resistance”. Insulin resistance is commonly associated with overweight, deconditioning, a family history of diabetes & certain medication such as prednisone and psychiatric drugs.

### **Diet**

Eating well-balanced meals comprised of smaller portions & healthier high fiber carbohydrates can help to lower blood sugar and to promote weight loss. If you lose weight your insulin will work better. By eating portion-controlled meals with healthy carbohydrates there is a better chance the limited amount of insulin your body makes will suffice.

Carbohydrates or starches like white rice, white bread, white flour, baked goods, instant cereals, potatoes and tropical fruits increase blood sugars quickly. Whole-grain carbohydrates, parboiled or basmati rice, pasta, noodles, waxy or nugget potatoes, sweet potatoes/yams, split peas, lentils and beans cause a lesser rise in blood sugar. Dairy, vegetables, non-tropical fruit and proteins are also healthy choices in making balanced meals that result in improved blood sugar control.

**Exercise**

Exercise is effective because the more physically fit you are, the better your own insulin works; the better your insulin works, the lower your sugar. Exercise also promotes weight loss and healthier eating, and makes many people feel better. Find an exercise program that suits your fitness level, your interests and your stage in life. Walking, cycling and swimming are suitable low-impact options for most people. Whatever exercise you choose, gradually increase the duration and the intensity. Consider joining a gym. Get a pedometer.

**Monitoring your diabetes**

You can tell how well you are doing with your diabetes treatment by testing your sugar. Blood glucose meters are inexpensive and can be bought at any drugstore; pharmacy staff will teach you how to use it. The single best time to test is before breakfast. A good blood sugar before breakfast is 5.0 - 7.0. A perfect reading is 5.0 - 5.7.

Blood sugar testing after a meal will tell you how well your body coped with that meal - a good reading two hours after a meal is 6.0 - 10.0. A perfect reading is 5.5 - 7.0.

If after one to two weeks your sugar before breakfast is still  $> 7.0$  despite diet and exercise (and other lifestyle therapies) medication is required. And even if your blood sugar has been good for months & years it is normal for it to eventually rise – this is because your body gradually runs out of insulin with natural ageing.

If you find pricking your finger particularly unpleasant consider getting a Freestyle Libre continuous glucose meter (CGM, see <https://goo.gl/KA1bhk>). They cost \$6.50 per day and provide sugar values every minutes 24/7 without finger pricking.

**High blood sugar**

In the short term high blood sugar ( $>12$ ) causes thirst, increased urination and weight loss. If blood sugar is high for years it may damage small blood vessels in the eye, kidneys and nerves.

**Low blood sugar**

Low blood sugar is also known as hypoglycemia or “having a hypo” or a “reaction”. Hypoglycemia is present whenever the blood sugar is  $<3.8$  on a blood glucose meter; it should be suspected whenever otherwise unexplained sweating, tremor or rapid heart beat are present or if there is a diminished level of consciousness. Hypoglycemia can be dangerous because sugar is the primary fuel of the body, in particular the fuel of the brain. When a car runs out of fuel it slows down and stops. When the brain runs out of fuel it first causes confusion (like drunkenness), then unconsciousness and finally death if prolonged and untreated.

The objective of rational diabetes therapy is to safely and affordably reduce blood sugar while maintaining a high quality of life

**Routine blood glucose lowering medication:**

Diabetes medications work by either improving the action of your own insulin, by helping your body to produce more insulin or by complex mechanisms. Blood glucose lowering medication is added in stepwise fashion as necessary to control blood sugar usually starting with pills and ultimately with insulin.

Reimbursement for medication: Only 17% of British Columbians qualify for Pharmacare subsidies. Pharmacare subsidies do not kick until an individual (or family) has spent >2% of pre-tax income on medication. If for example the pre-tax family income is \$50,000, the threshold is \$1,000. The threshold is reset every January 1. The subsidy covers only 70% of the cost of the drug (and 100% once the 3% threshold has been met). Most drugs that cost > \$5 per day are not covered by Pharmacare, even if a Special Authority form is completed by BC Diabetes. In this article drugs not currently covered by Pharmacare have an \* beside their generic name. Drugs marked with \*\* may be covered by Pharmacare after completion of a Special Authority form.

Metformin: this will be first medication used for most individuals with Type 2 diabetes. Metformin works by improving the action of your own insulin on the liver, in addition metformin reduces the risk of heart attack and stroke, helps prevent weight gain & may reduce the risk of many cancers. The only common side-effect of metformin is stomach upset (nausea, diarrhoea): this can be minimized by taking metformin with meals and by starting with a small dose. Metformin should be used with caution and in lower than usual doses with individuals with kidney, liver or heart disease. Metformin usually comes in 500 mg tablets (\$0.14) – the usual starting dose is 1/2 pill with breakfast and 1/2 pill with dinner; after 1-2 days the dose should be increased to one pill with breakfast & one pill with dinner; if sugar is still too high it is usually increased again to two pills with breakfast & two pills with dinner. The final dose of metformin will depend on kidney function. A “slow-release” once-daily form of metformin “Glumetza” is an excellent alternative. It comes in 500 mg (\$0.61) & 1000 mg (\$1.20) tablets.

If the blood sugar is still above target after full doses of metformin have been used for 2-3 days more medication is required. Metformin should not be stopped – more medication should be added. There are many possibilities for the next line of therapy.

The order in which subsequent oral medication is described in this article reflects the usual order in which BC Diabetes would consider prescribing. Drugs described in italics are seldom used at BC Diabetes.

SGLT2 inhibitors. This class of drug lowers blood sugar by preventing sugar being reabsorbed in the kidney. This leads to wasting of sugar from the urine: this phenomenon is called “glycosuria” or “glucosuria”. Sugar in the urine represents a loss of calories and is associated not only with lower blood sugar but with weight loss. These drugs increase the volume of urine (diuresis). They triple the risk of genital yeast infections (yeast infections respond well to standard treatments such as fluconazole (pill) or 2% ketoconazole (cream)). There are three SGLT2 inhibitors available in Canada: canagliflozin\* (usual dose 100 mg once daily), dapagliflozin\* (usual dose 5 mg once daily), and empagliflozin\* (usual dose 10 mg once daily). These drugs should be used with caution in the presence of reduced kidney or cardiac function.

Because of the potential to occasionally worsen kidney function, a blood test to check kidney function is recommended two weeks after starting such medication.

DPP-4 inhibitors. This class of drugs includes sitagliptin\*, linagliptin\*\*, & saxagliptin\*\*. These medications lower blood sugar by a complex mechanism that includes improving the action of insulin & increasing the amount of insulin. They have no common side effects. They do not cause weight gain. They cost \$2.42-\$2.92 per day.

Sulfonylureas. The class of drugs includes glyburide, gliclazide, glimepiride\*, glipizide\* and others. These medications increase insulin levels by “squeezing” the cells to release all their stored insulin. The only common side effect is low blood sugar (hypoglycemia). This can be potentially serious and requires the consumption of sugar or starchy food. These medications tend to cause weight gain. The preferred sulfonylurea at BC Diabetes is gliclazide SR\* (slow release): it comes in 30 mg (\$0.15) & 60 mg (\$0.28) tablets: it is taken once daily at breakfast in a starting dose of 30 mg per day: the maximum dose is 120 mg/day.

Meglitinides. *This class of medication is very closely related to the Sulfonylureas discussed above. Repaglinide\* is a medication in this class - it is short-acting & designed to be taken immediately before meals. It comes in 0.5 mg (\$0.16), 1 mg (\$0.16) and 2 mg (\$0.38). Maximum dose is 12 mg/day.*

Acarbose\* works by delaying the absorption of starch from the bowel. It is relatively ineffective and causes flatulence (gas). It comes in 50 mg (\$0.28) & 100 mg (\$0.39) tablets. The usual dose is 50-100 mg with the first bite of every meal.

TZDs This drug class includes pioglitazone\*\* and rosiglitazone\*\*. These drugs tend to cause weight gain and water retention: for these reasons BC Diabetes does not routinely recommend either of these medications. Cost is around \$3/day.

## **Injectable therapies**

When blood sugar is above target despite lifestyle therapy, and oral medication (if desired) the next therapy is an injection. The usual injection is with insulin

### **1) Insulin**

Insulin has one direct effect - it lowers sugar. If too much insulin is given low blood sugar (hypoglycemia) may result, this can be dangerous (see discussion above).

Insulin has one common indirect effect: weight gain. Insulin does not intrinsically cause weight gain (other than as a rare side effect of salt and water retention). Weight gain is caused by a net caloric surplus. It occurs when there are more calories going in (diet) than calories going out (exercise or being wasted in the urine). When insulin is started sugars typically go from high to lower. This is associated with a loss of calorie wasting in the urine. If fewer calories are going out but calories in (food) are unchanged then there will be a net caloric surplus = weight gain. Ironically therefore, when insulin is started and blood sugar high (say above 10), to avoid weight

gain calories in must be reduced (less food) or calories out must be increased (exercise or with SGLT2 inhibitor medication).

### Basal Insulin

Basal insulin is the single most effective medication for diabetes. It is usually added to oral medication (pills) when the fasting blood sugar is no longer controlled. Basal insulin can be given as first line therapy (before oral medication such as metformin and other medication discussed above). At BCDiabetes the preferred basal insulin is the insulin glargine given once daily. Cost is approximately \$0.05 per unit; an excellent alternative is insulin detemir. A third inexpensive quasi-basal insulin (\$0.02 per unit) is NPH that has the disadvantage of usually being given twice daily. Other insulins such as short-acting insulin (see below) = "regular insulin" (also known as "Toronto") is available in pre-mixed combination with NPH (as 30/70 or 50/50 insulin): BCDiabetes does not routinely recommend such pre-mixed insulins.

Insulin glargine is given by a single daily injection, usually before breakfast (it can however be given at anytime of day). The starting dose is usually 6-10 units per day. The dose is normally increased every day by 1-2 units until the sugar before breakfast is < 7.0. If the sugar is < 5.0 the dose should be reduced by 4 or more units. Detailed instructions for taking insulin glargine "Lantus" are available separately. Typical doses of insulin glargine range from 10 – 100 units per day.

Once blood sugar has stabilised with basal insulin, oral agents such as DPP-4 inhibitors and sulfonylurea agents are usually not renewed. SGLT2 inhibitors, because of their tendency to cause weight loss are generally continued indefinitely.

### Rapid insulin

Rapid insulin may be prescribed in addition to basal insulin - rapid insulin is given immediately before meals in doses sufficient to produce a sugar of 6.0-10.0 two hours after the meal. The dose can be adjusted based on how much carbohydrate or starch is expected (see article on "carb-counting"). For reasons of price, BC Diabetes's preferred rapid insulin, because of price, is insulin glulisine; other excellent rapid insulins include insulin lispro & insulin aspart. Detailed instructions for taking rapid insulin are available at BC Diabetes under "Handouts/Physicians/Diabetes/Rapid insulin". Typical doses of rapid insulin are from 4-10 units before meals. Rapid insulin doses may be modestly increased if the blood sugar before a meal (ideal is 5.0-7.0) is above target. This kind of increase is called a "correction".

### Short-acting insulin

*Short-acting insulin ("regular insulin" sometimes known as "Toronto") is seldom recommended by BC Diabetes. This is because rapid insulin (see above) is safer & faster than short-acting insulin & is only marginally more expensive.*

## **2) GLP-1 agonists**

GLP-1 agonists are also given by injection. They have the benefit over insulin of not only lowering sugar but of lowering weight. Sugar lowering is caused by a modest increase in natural

insulin secretion and by blockade of the action of glucagon, a natural hormone that raises blood sugar. Weight loss is caused by a central suppression of appetite and by delaying the emptying of the stomach (causing a sense of fullness). Twenty percent of individuals treated with GLP-1 agonists experience substantial weight loss (of >5%). Most weight loss is seen in the first 3 months of treatment. Weight maintenance occurs only as long as the medication is continued. Nausea is a relatively common side effect - approximately 15% individuals stop GLP-1 agonists because of nausea.

There are three GLP-1 agonists on the Canadian market, liraglutide, exenatide and dulaglutide. Liraglutide is given once daily: at full dose it is \$10/day while exenatide & dulaglutide are given once weekly and cost \$5-7/day. Overall liraglutide is the most effective drug with dulaglutide and exenatide close seconds.

## **Other routine medication used in diabetes**

### Cholesterol-lowering medication

Most patients with Type 2 diabetes will be treated with a cholesterol-lowering medication known as a “statin”. Other than quitting smoking taking a statin is the single best way for a person with diabetes to reduce the risk of heart attack, stroke and death – they reduce this risk by 35% or more. These include rosuvastatin, atorvastatin, simvastatin & pravastatin. Rosuvastatin 40 mg one tablet daily, usually taken before breakfast (\$0.64) is the most commonly prescribed statin. These medications are usually prescribed in doses sufficient to lower either the apoB to < 0.8 or the LDL (bad cholesterol) to <2.0. Note if apo B is being measured fasting is not required. Side effects from statins, the commonest being persistent muscle aches and pain are reported in 1 in 15 individuals on average, inflammation of the liver (hepatitis) is a rare side-effect.

Another class of cholesterol-lowering medication is the PCSK9 inhibitor class: these include alirocumab & evolocumab. Both are given by injection every 2 to 4 weeks. They are expensive at \$20 per day. They lower LDL cholesterol by an additional 50-70% on top of the effect of statins.

### Blood pressure-lowering medication

Most patients with Type 2 diabetes will be treated with blood-pressure lowering medication either to lower their blood pressure to < 140/80, to reduce the level of protein in the urine, to delay progression of kidney damage & to prevent (or treat) heart disease. There are many classes of anti-hypertensive drugs. Commonly used classes include ACE inhibitors (ramipril, enalapril, perindopril), ARBs (losartan, valsartan, candesartan), diuretics (HCTZ, chlorthalidone), aldosterone antagonists (spironolactone), beta blockers (atenolol, bisoprolol, nadolol), & calcium channel blockers (amlodipine, nifedipine, verapamil). Most anti-hypertensive medications cost \$0.25-\$0.42 per day. Most patients require two or more anti-hypertensive medications (one from a number of different classes). Reducing alcohol, reducing salt intake & losing weight also help to lower blood pressure.

### Aspirin (ASA)

ASA 81 mg per day “baby aspirin” is prescribed to all individuals with Type 2 diabetes who have heart disease or a history of stroke or mini-stroke. ASA is no longer routinely prescribed to all

individuals with diabetes. ASA works by reducing the risk of blood clots. It increases the risk of bleeding slightly.

## **Research**

Research forms the basis for advancement in medicine. As such research and clinical trials are a fundamental part of the BC Diabetes operation. Our staff may approach you to become involved in one or more research projects (see below). You are under no obligation to participate. Non-participation will not affect the quality or amount of care that BC Diabetes staff offer you.

Quality-of-Life (Depression and Diabetes) questionnaire : All patients newly referred to BC Diabetes are invited to complete a survey to study whether there is any relationship between diabetes and symptoms of distress &/or depression. Follow up questionnaires every 6 to 12 months may also be requested to see whether working with BC Diabetes staff is associated with any changes.

### Investigational diabetes strategies

BC Diabetes is investigating whether a number of non-medication-related interventions improve diabetes outcomes and quality of life: these include a smartphone app, yoga, meditation, peer and group support and the role of vulnerable connection to enhance personal relationships.

### Investigational medications for diabetes, blood pressure & cholesterol

BC Diabetes is currently studying 5 different classes of medication for Type 2 diabetes (and two classes for Type 1 diabetes) in a total of 12 clinical trials. Most clinical trials include a randomization to active therapy or placebo. Active therapy is the research medication being tested. Placebo is a tablet (or injection) that has no active ingredient but which is required to prove whether or not the active therapy is truly effective.

The chances of getting placebo are 20-50%. Most clinical trials involve “blinding” of active agent vs placebo. This means that neither BC Diabetes staff nor the study volunteer knows whether active agent or placebo has been dispensed. At the completion of the study “unblinding” occurs - at this time all become aware of whether active drug or placebo was prescribed. Regardless of whether volunteers receive active drug or placebo, all Individuals who are involved in clinical trials derive some benefit. This is because the interaction between the study participant & Dr. Elliott and his staff improves motivation & adherence to existing therapy.