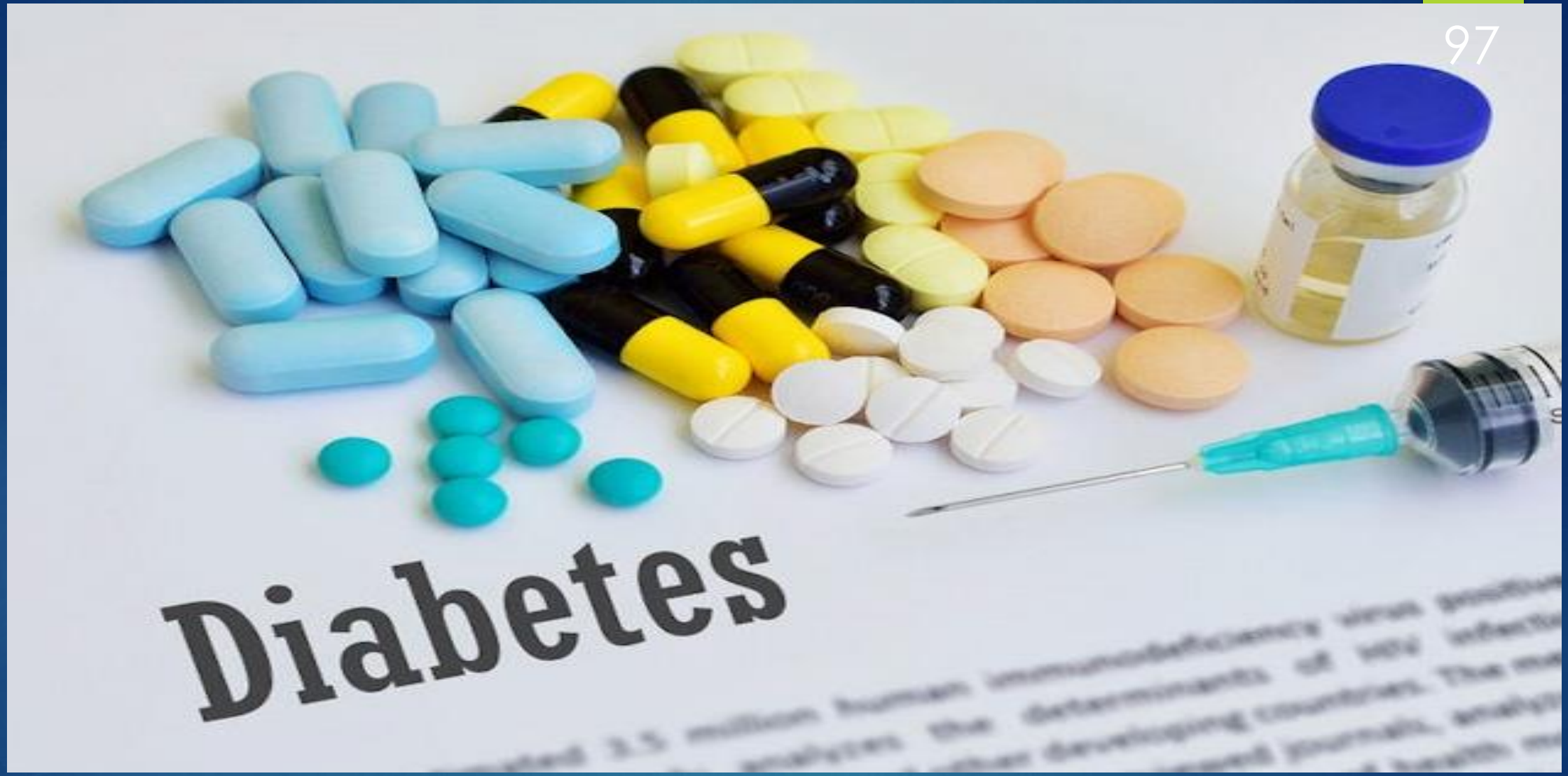
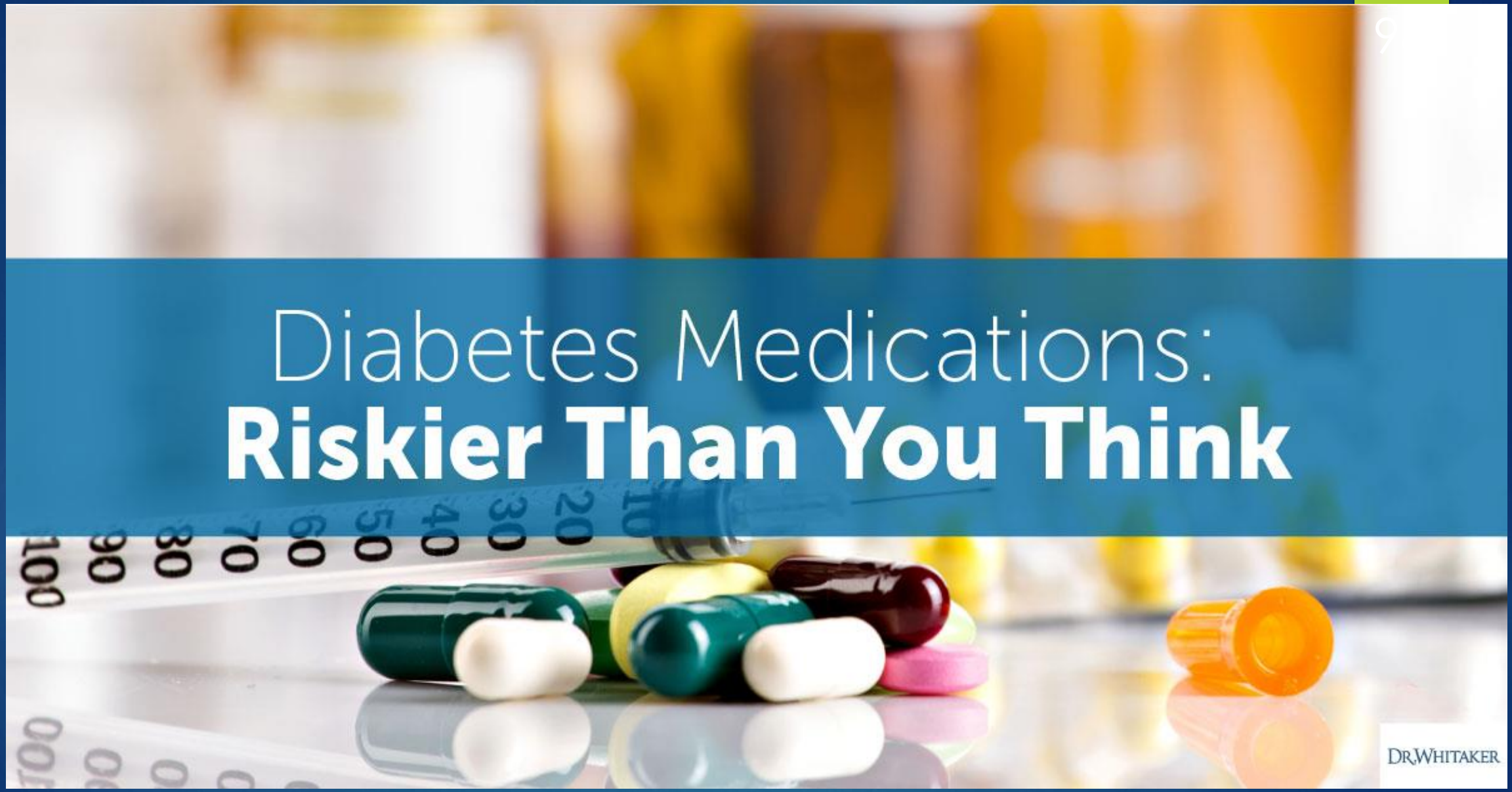


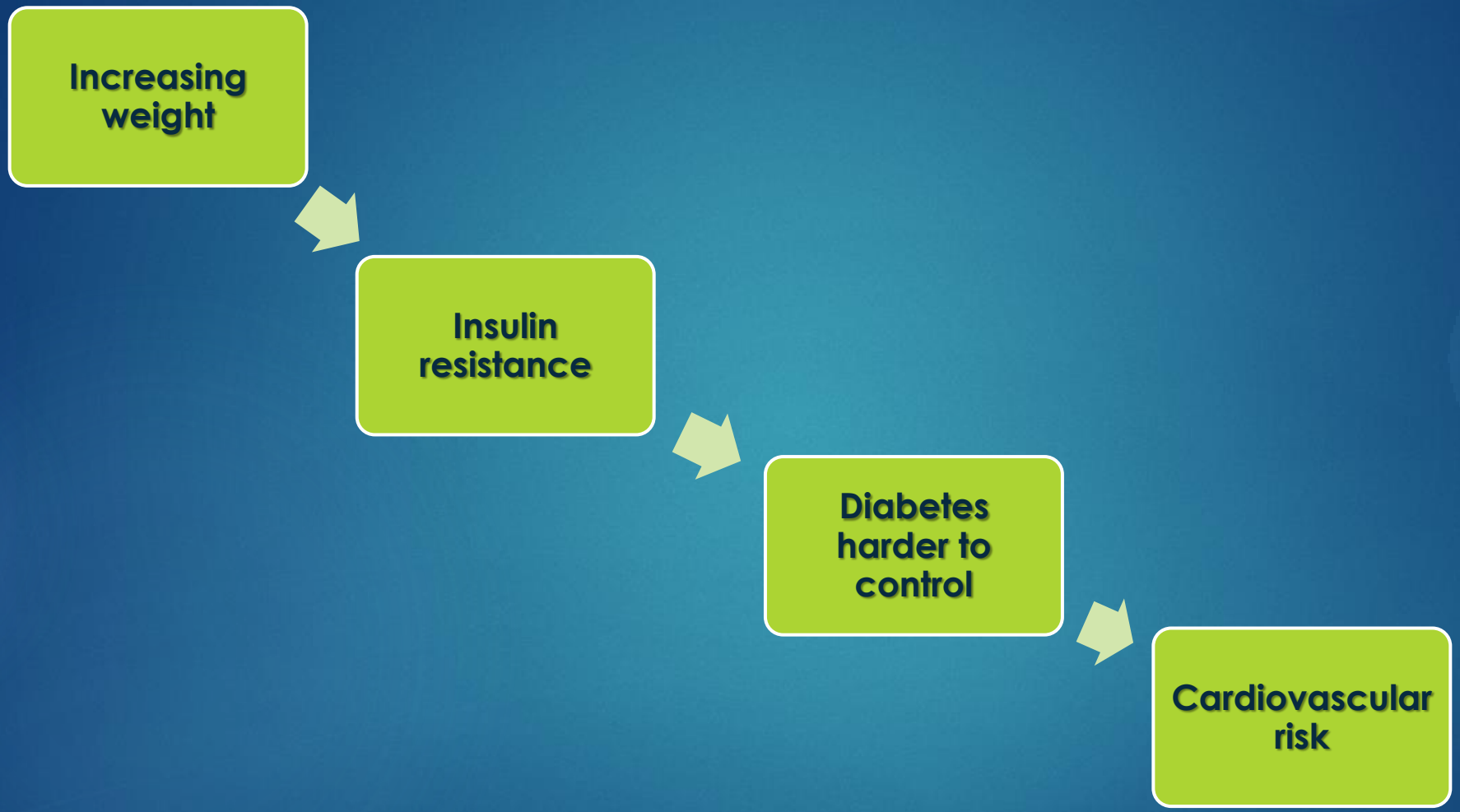
Diabetes medications


Diabetes Medications:
Riskier Than You Think
DR.WHITAKER

Medications for type 2 diabetes have serious side effects, including:

- ✓ **Weight gain**
- ✓ Elevated **triglycerides** and **cholesterol** levels
- ✓ Increased risk of heart disease

- Obesity, particularly **intra-abdominal obesity**, induces **insulin resistance** in muscle and liver that leads to **glucose intolerance** .
- Weight gain can worsen blood glucose control.
- According to the **N**ational **I**nstitutes of **H**ealth, **85 percent** of people with **type 2** are overweight or obese.
- A majority of people with **type 1 diabetes** are overweight or obese.
- A modest amount of **weight loss (5 to 10 percent of body weight**) can improve blood glucose control and prevent **complications** in people with type 2.


Increasing weight
Insulin resistance
Diabetes harder to control
Cardiovascular risk


Insulin

There is considerable variability in the amount of weight gain associated with the use of insulin:

- Genetics
- Dose and speed of release (rapid vs slow)
- Intermediate-acting insulin (+1.9 kg over a 6 month)
- Once-daily insulin injection (+0.4 kg over a 6-month)

Insulin makes people overweight by acting on the brain to **cause hunger,** making the liver manufacture fat and fill fat cells in the stomach.

Insulins can be divided into two categories based on **function**:

- **Basal (long-acting insulin)** insulin is designed to be injected once or twice daily to provide a constant level of insulin action throughout the day. Basal insulin helps keep blood sugars at a consistent level when you are not eating, but it is not enough to cover glucose spikes after mealtime.
  - Basal Analog:(**glargine, detemir, degludec**)
  - Basal Human:(**NPH**)

- **Prandial (rapid-acting or "mealtime")** insulins, on the other hand, are taken at mealtime and act rapidly on the body, serving to bring down the high sugar levels following meals.
  - Prandial Analog:(**lispro, aspart, glulisine**)
  - Prandial Human:(**Regular**)
  - Prandial insulin had a greater weight gain of 6.4 ± 0.5 kg compared with patients on basal insulin of 3.6 ± 0.5 kg.

Insulins can be divided into two categories based on **structure**:

- **Human insulins:** were developed first and are essentially identical in structure to the insulin produced in the body.

- **Analog insulins:** are similar in structure but have minor biological modifications to give them desirable properties. While analog insulins cost more, they generally lead to less hypoglycemia and weight gain. Prandial (mealtime) insulin analogs tend to act faster than human insulin.

Mechanisms for weight gain with Insulin

Direct **anabolic effect** on muscles and adipose tissues

Allows glucose to move from out of the bloodstream into the cells of the body (**fat storage hormone**)

Long-acting insulin creates a pattern of **24-h hyperinsulinemia**, which stimulates **lipogenesis** and inhibits lipolysis

It can causes blood glucose levels to go too low (**hypoglycemia**), then can induce a strong feeling of **hunger**

50% of insulin-induced weight gain is seen during **the first 3 months of its use**

RAPID	Humalog or Lispro	< 15 min	60-90 min	3-5 hrs	• Inject 10-15 min before mealtime • Typically used in conjunction with longer-acting insulin.
	Novolog or Aspart	< 15 min	60-120 min	3-5 hrs	
	Apidra or Glulisine	< 15 min	60-90 min	1-2.5 hrs	
SHORT	Regular (R) Humulin, Actrapid or Novolin	30-60 min	2-5 hrs	6-8 hrs	• Inject at least 20-30 minutes before mealtime
	Velosulin	30-60 min	2-3 hrs	2-3 hrs	
INTERMEDIATE	NPH (N)	1-2 hrs	4-12 hrs	18-24 hrs	• Commonly used twice daily • Often combined with rapid- or short-acting insulin
	Lente (L)	1-2.5 hrs	3-10 hrs	18-24 hrs	
LONG	Ultralente (U)	30 min- 3 hrs	10-20 hrs	20-36 hrs	• Covers insulin needs for 24 hrs • If needed, often combined with rapid- or short-acting insulin
	Lantus or Glargine	1-1.5 hrs	No Peak	20-24 hrs	
	Levemir or Detemir	1-2 hrs	6-8 hrs	Up to 24 hrs	
PRE-MIXED	Humulin 70/30	30 min	2-4 hrs	14-24 hrs	• Combination of intermediate- and short-acting insulin • Commonly used twice daily before mealtime
	Novolin 70/30	30 min	2-12 hrs	Up to 24 hrs	
	Novolog 70/30	10-20 min	1-4 hrs	Up to 24 hrs	
	Humulin 50/50	30 min	2-5 hrs	18-24 hrs	
	Humalog 75/25	15 min	30 min-2.5 hrs	16-20 hrs	

Insulin lispro

- Short-acting insulin
- With shorter duration than regular insulin
- It induces similar **weight gain** to regular insulin in both type 1 and type 2 diabetics.
- Less weight gain when compared to glibenclamide
- Insulin lispro induced a weight gain of 2.3 kg in comparison to 1.6 kg weight gain with glargine insulin(long acting)

Insulin aspart

- **Short-acting** insulin
- When used as monotherapy, it caused an average of 0.4 kg of weight gain after 10 weeks of treatment
- When it was used as monotherapy, induced less weight gain than when it was combined with TZDs or SUs

Thiazolidinediones(pioglitazone)

Insulin glulisine

- **Short-acting** insulin
- It induced **weight gain** when was injected **pre-meal**
- In patients with type 1 diabetes, post-meal injection of insulin glulisine was shown to induce less weight gain than pre-meal regular insulin

Glargine insulin

- It is one of the most widely prescribed longacting insulins
- In comparison to NPH insulin, glargine insulin induced significantly less weight gain in patients with type 1 diabetes after 16 weeks of intervention.
- Many of the previous studies showed that glargine insulin did not induce weight gain during the first 4 weeks of its use and that most of the weight gain was seen with longer duration of use.

Detemir insulin

- It is a long-acting insulin that induces less weight gain than other insulin preparations.
- In a large trial of > 10,000 participants with type 1 and type 2 diabetes, body weight did not change significantly from baseline after 14.5 weeks of its use.
- In a 52-week randomized, open-label, multinational trial, detemir induced less weight gain in comparison to glargine insulin .
- Interestingly, small amount of **weight loss** was seen in patients with type 2 diabetes with BMI > 35 kg/m2. The average weight loss was 0.5 kg.
- Other trials in type 1 diabetes showed that detemir insulin was weight-neutral in comparison to NPH insulin after 6 and 12 months of intervention.

- The reason(s) for the detemir weight neutrality is not clear.
- In comparison to NPH, detemir caused less hypo-glycemic episodes.
- Its lipophilic characteristics and ability to cross the blood brain barrier differentiate it from other insulins.
- It is not clear if this central access has any relation to its effect on body weight.

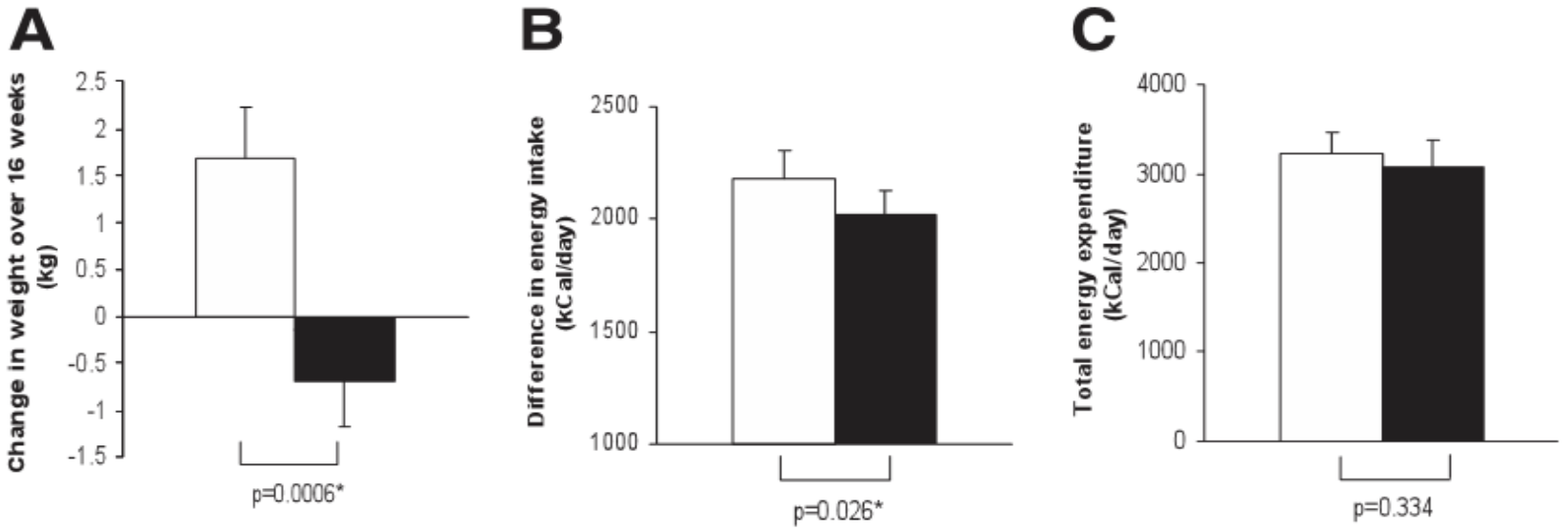
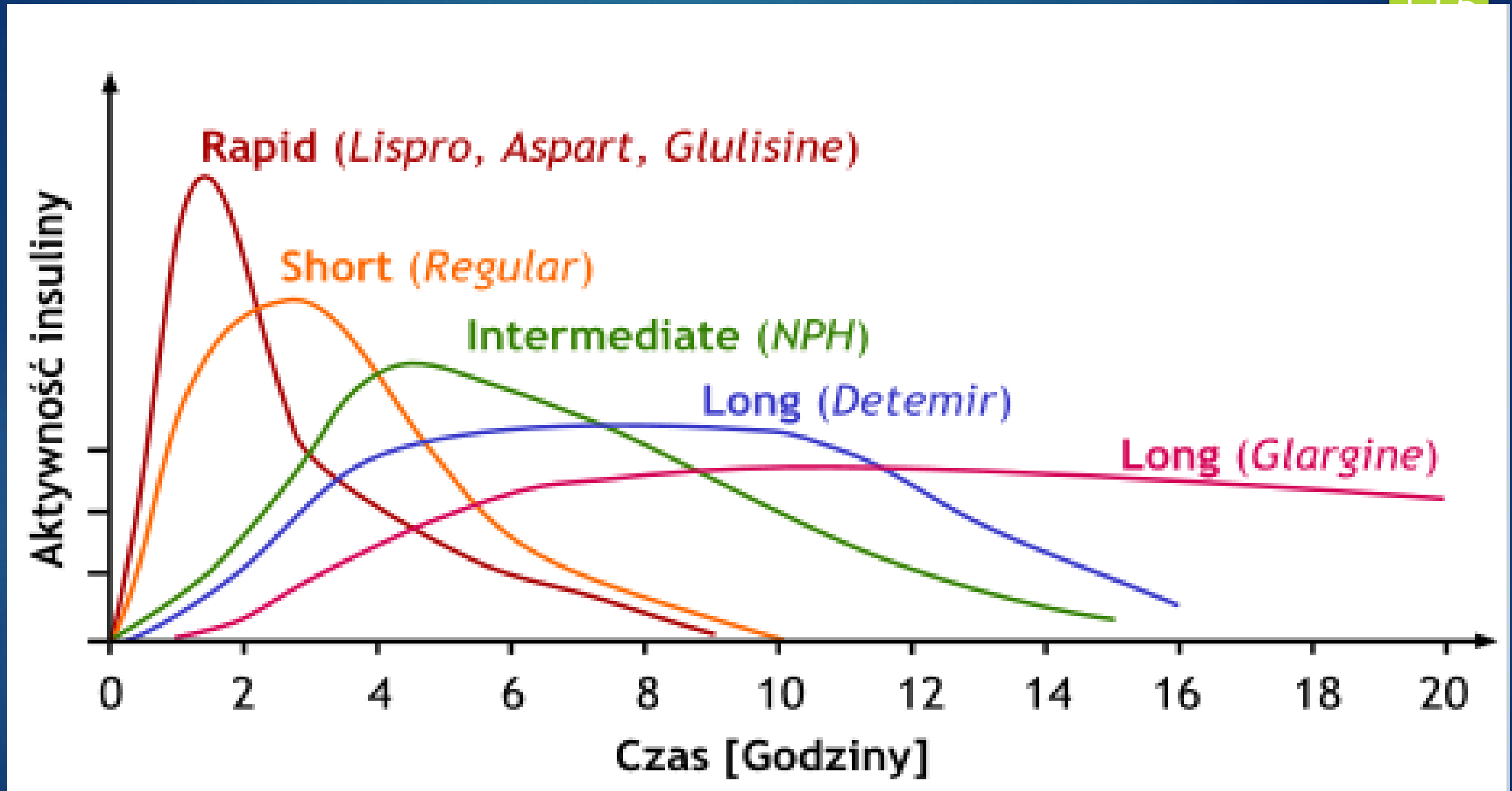


Figure 1—A: *Changes in body weight after 16 weeks of treatment.* B: *Change in energy intake after 16 weeks.* C: *Change in total energy expenditure after 16 weeks.* □, *NPH insulin;* ■, *insulin detemir.*

- **Detemir insulin** is preferred as it causes **less weight gain** than NPH and glargine insulin.
- Short-acting insulin may be injected immediately **after meals** or **within 20 min from the start of the meal**.
- By administering the short-acting insulin after meals, patients had the opportunity to calculate the short-acting insulin dose based on the food that they actually consumed and not on the amount of food that they presumed to eat.


Rapid (Lispro, Aspart, Glulisine)
Short (Regular)
Intermediate (NPH)
Long (Detemir)
Long (Glargine)
Aktywność insuliny
0
2
4
6
8
10
12
14
16
18
20
Czas [Godziny]

Drug Class	Medication Name	Mode of Action	Side Effects
Sulfonylureas	Gliclazide **Glybenclamide** Glimepiride	Stimulate the beta cells in the pancreas to release more insulin	Increased risk of cardiovascular events and death, hypoglycemia, **weight gain**, heartburn, nausea, diarrhea, and loss of appetite
Biguanides	Metformin	Lower the amount of glucose produced by the liver and make muscle tissue more sensitive to insulin so glucose can be absorbed	Lactic acidosis, diarrhea, nausea, vomiting, abdominal bloating, and **loss of appetite**
Thiazolidinediones	Pioglitazone	Reduce production of glucose in the liver and help insulin work better in muscle and fat tissue	Increased risk of cardiovascular events and death, **weight gain, Edema,** upper respiratory infections, headache, muscle ache, sore throat, and sinus irritation

Drug Class	Medication Name	Mode of Action	Side Effects
Alpha-glucosidase inhibitors	Acarbose	Block the breakdown of starches and slow the breakdown of some sugars in the intestines	Bloating, diarrhea, gas, stomach pain, and **weight gain**
Meglitinides	Repaglinide	Stimulate the beta cells in the pancreas to release more insulin	Hypoglycemia, **weight gain**, headache, joint pain, nervousness, and sweating
DPP-4 Inhibitors (Dipeptidyl peptidase-4 inhibitor)	Sitagliptin, Linagliptin	Block an enzyme that keeps insulin circulating in the blood(reduce glucagon and blood glucose levels)	Upper respiratory infections, sore throat, and headache

Drug Class	Medication Name	Mode of Action	Side Effects
Glucagon-like peptide (GLP-1) agonists **(New)**	Liraglutide Semaglutide	Bind to a membrane GLP receptor, insulin release from the pancreatic beta cells is increased	**weight loss,** gastrointestinal side-effects,
SGLT-2 inhibitors (Sodium-glucose co-transporter 2) **(New)**	**Dapagliflozin** **Canagliflozin** Empagliflozin	Block the re-uptake of glucose in the renal tubules, promoting loss of glucose in the urine	**mild weight loss,** hypoglycemia, urinary tract infections
Combination Pills	Pioglitazone & metformin Glyburide & metformin Glipizide & metformin Sitagliptin & metformin Repaglinide & metformin	Combine the actions of each pill used in the combination formula	Side effects are the same as those of each pill used in the combination

Sulphonylureas

- They are for type 2 diabetes.
- Work by **stimulating the pancreas** to produce more insulin.
- Glimepiride, Gilbenclamide and Gilclazide
- SUs are known to induce **weight gain**; however, the amount of weight gain is variable according to the compound used and the duration of its exposure.
- The 3-year follow-up report showed that **glibenclamide** caused more weight gain in comparison to diet intervention (**5 kg/6 years**)
- Most of this weight gain occurs during the first year of treatment
- The **GAME regimen** (Glimepiride at night, pre-meal insulin Aspart and Metformin) did not show weight gain during the first 3 months of therapy, but weight gradually increased after 1 year of treatment.

Weight gain:

- Insulin> Sus=Pioglitazone > Repaglinide

- Mechanisms of weight gain in association with SUs may be related to **increased food intake** to compensate for hypoglycemia and/or 'defensive snacking' for fear of hypoglycemia.

- In the UKPDS study, **27.8% of patients** treated with **glibenclamide monotherapy** had **hypoglycemic** episodes in comparison to 1.2% in those treated with diet only.

Biguanides (Metformin)

- Over 80% of patients who have type 2 diabetes also having obesity.
- Metformin is a first-line treatment option for type 2 diabetes and is associated with favorable weight outcomes.
- Weight loss is reported as a known side effect of this medication, with average decreases of 1.0–2.9 kg.
- According to research, metformin can help some people lose weight.
- Mechanism:
- Reducing appetite
- Decreases hepatic glucose production,
- Decreases intestinal absorption of glucose,
- Improves insulin sensitivity
- Metformin does not produce hypoglycemia in either patients with type 2 diabetes or normal subjects and does not cause hyperinsulinemia.

Thiazolidinediones (Glitazones)

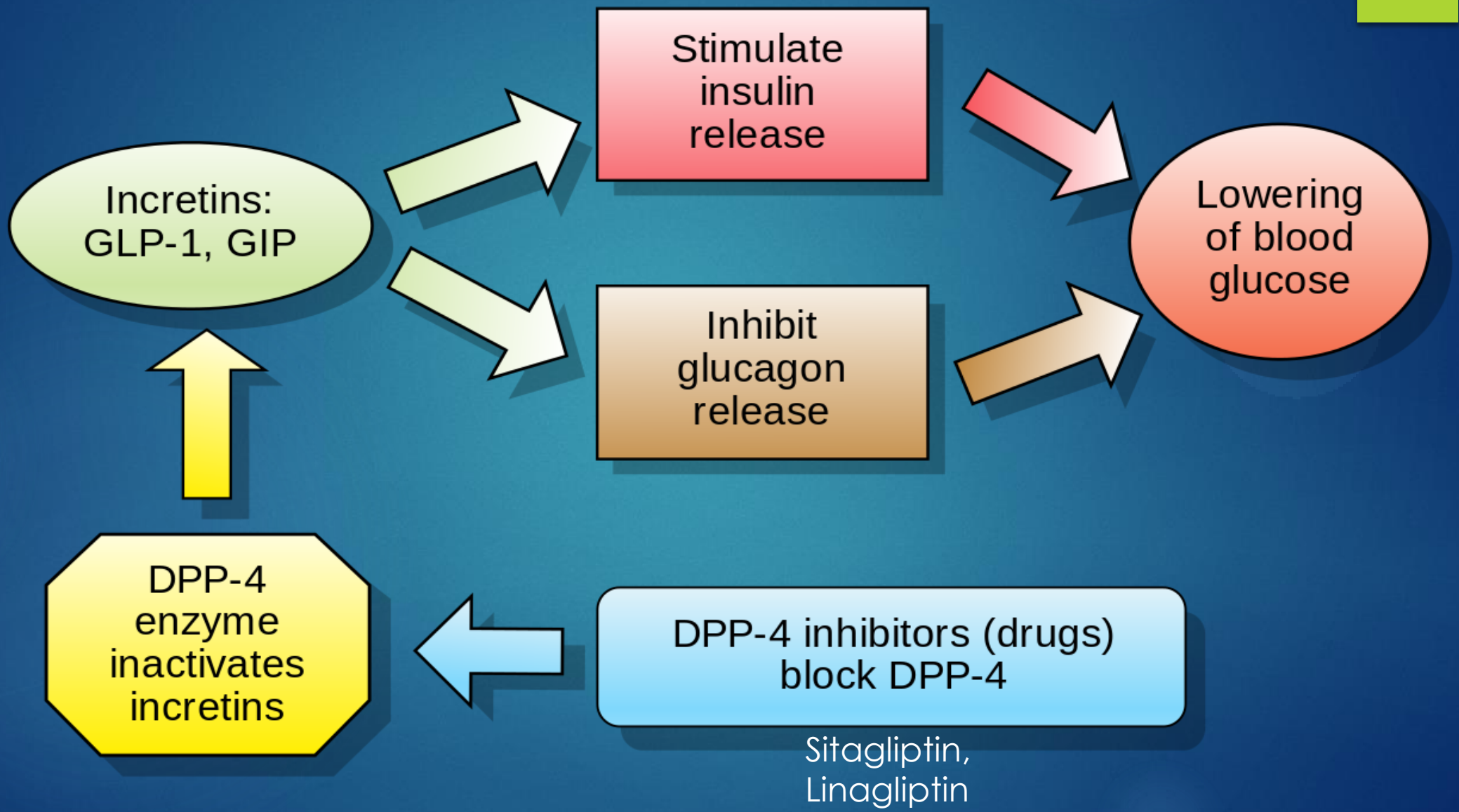
- **Help to improve insulin sensitivity**
- **Weight gain** was more prominent in patients on **higher doses of TZDs** and in patients with **higher body mass index (BMI)** at baseline.

Meglitinides (Repaglinide)

- Short-acting secretagogues that enhance insulin synthesis and release.
- Meglitinides induce **weight gain** whether used alone or in combination with others.

Glucagon-Like Peptide-1 (GLP-1) Analogs

- **Liraglutide** is more recently approved by FDA (January 2010) to be used as a once-daily subcutaneous injection for type 2 diabetes.
- Similar to native GLP-1, Saxenda® works in the brain to **decrease appetite** and thereby reduce food intake.
- One of their advantages over older insulin secretagogues, such as sulfonylureas or meglitinides, is that they have a lower risk of causing hypoglycemia.


Incretins:
GLP-1, GIP
Stimulate
insulin
release
Inhibit
glucagon
release
Lowering
of blood
glucose
DPP-4
enzyme
inactivates
incretins
DPP-4 inhibitors (drugs)
block DPP-4
Sitagliptin,
Linagliptin

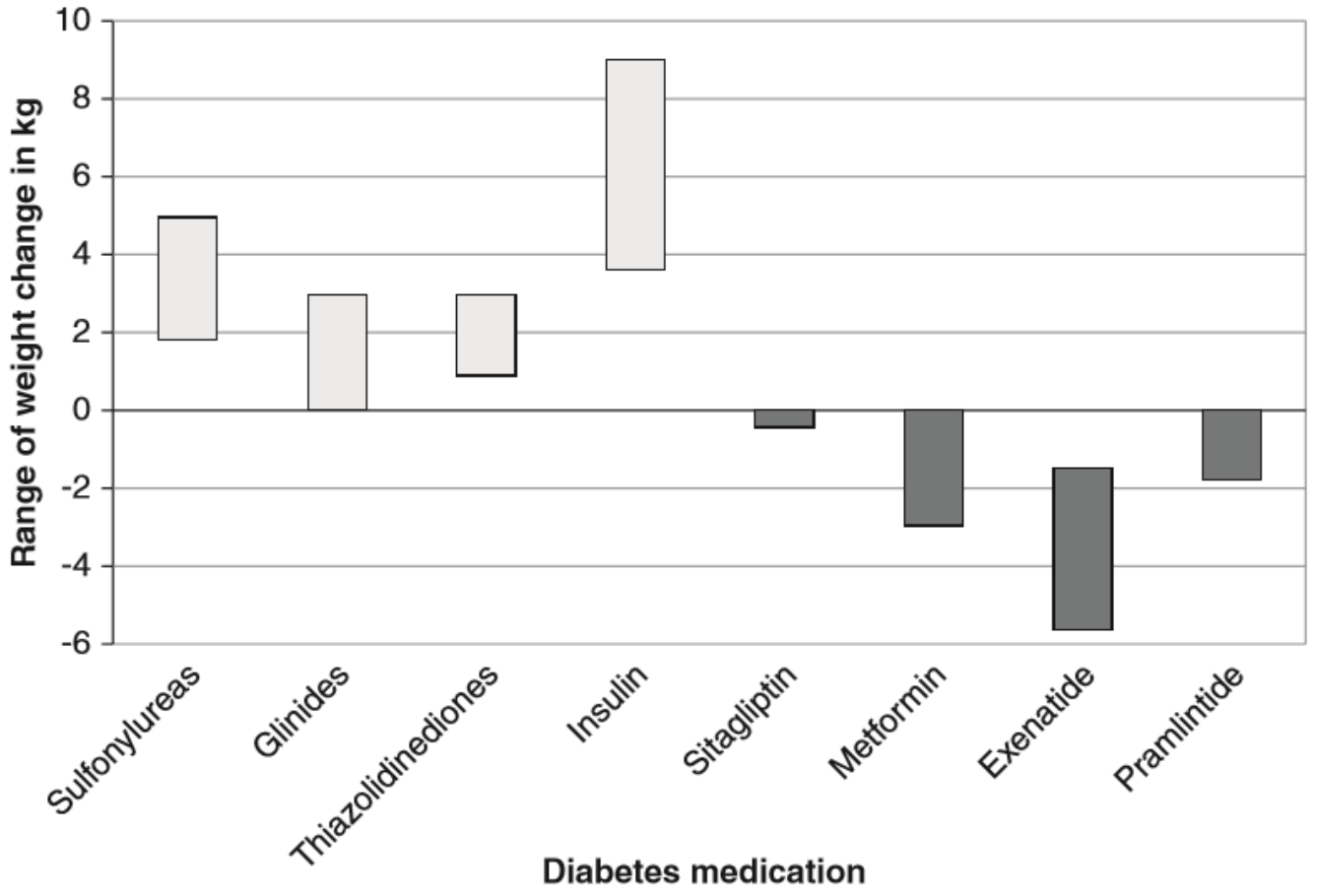
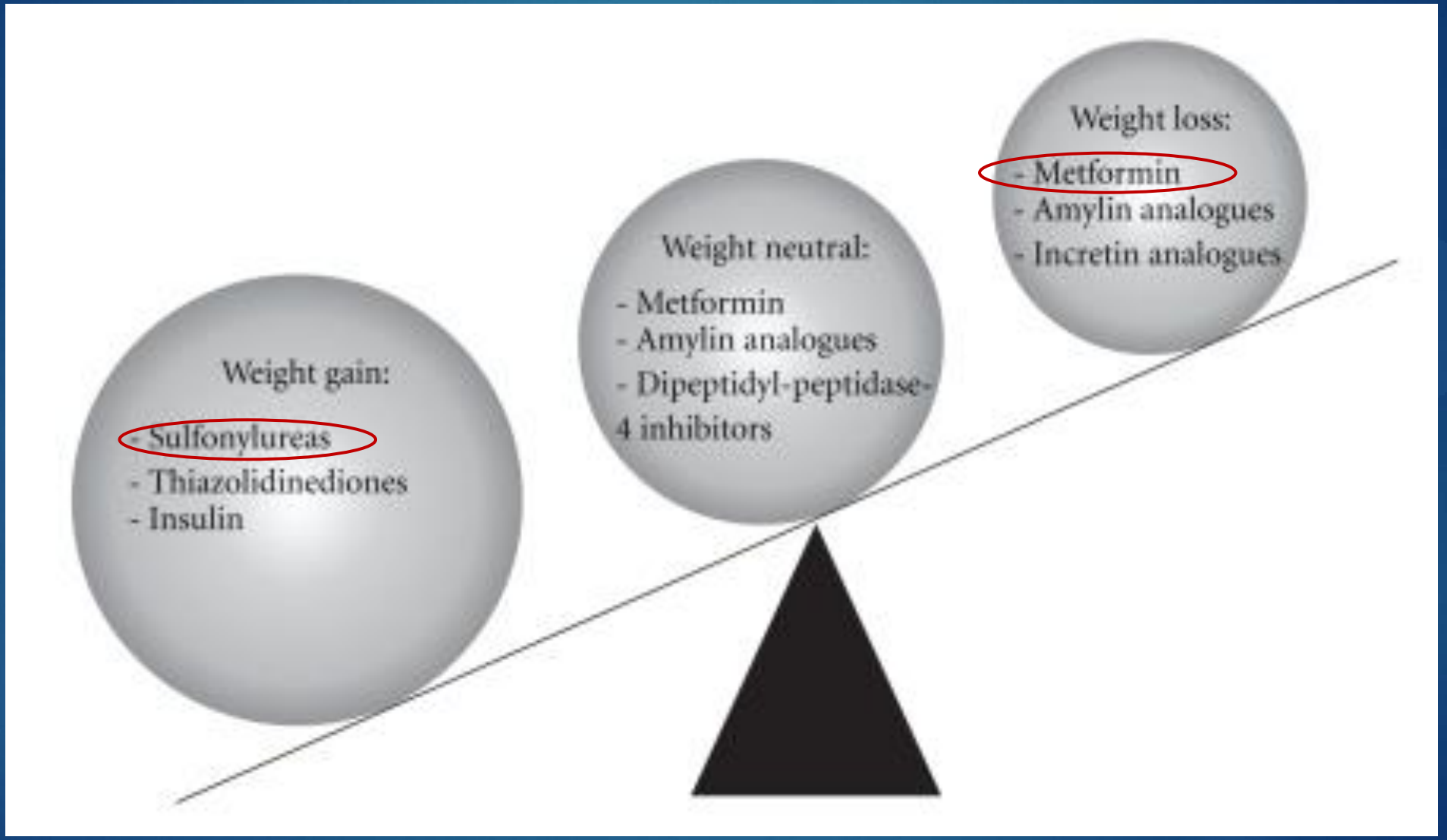


Figure 1. Range of weight change (in kilograms) in response to diabetes medications.

Table 2. Use of diabetes medications during weight management.

Medications to be reduced (weight fury)	Medications to be added or increased (weight friendly)
Insulins	*Metformin*
NPH	*DPP-4 inhibitor*
Glargine	Sitagliptin
Aspart, Aspart 70/30	*Alpha-glucosidase inhibitors*
Lispro, Lispro 75/25	Acarbose
Glulisine (pre-meal)	Miglitol
	Amylin analogue
Sulfonylureas	Pramlintide
Glyburide	*GLP-1 receptor agonist*
Glipizide	Exenatide
Glimepiride	*Insulin*
Glinides	Detemir
Nateglinide	Glulisine (post-meal)
Repaglinide	
Thiazolidinediones	
Pioglitazone	
Rosiglitazone	


Weight loss:
- Metformin
- Amylin analogues
- Incretin analogues
Weight neutral:
- Metformin
- Amylin analogues
- Dipeptidyl-peptidase-4 inhibitors
Weight gain:
- Sulfonylureas
- Thiazolidinediones
- Insulin

Effect on body weight

tend to cause weight gain:

- insulin
- sulfonylureas
- meglitinides
- thiazolidinediones (TZDs)

tend to cause weight loss:

- metformin
- GLP-1 agonists
- pramlintide
- SGLT2 inhibitors

Route of administration

oral drug:

- metformin
- sulfonylureas
- meglitinides
- thiazolidinediones (TZDs)
- DPP-4 inhibitors
- SGLT2 inhibitors

must be injected:

- insulin
- GLP-1 agonists
- pramlintide

Place in therapy

treatment for type 1 diabetes mellitus:

- insulin
- pramlintide

treatment for type 2 diabetes mellitus:

- insulin
- metformin
- sulfonylureas
- meglitinides
- thiazolidinediones (TZDs)
- GLP-1 agonists
- DPP-4 inhibitors
- pramlintide
- SGLT2 inhibitors

Drug name	Weight effect
α-glucosidase inhibitors	
Acarbose[5,77,87,105]	–[a]
Glucagon-like peptide I receptor	
Exenatide[5,100,108,109]	– –
Liraglutide[5,91,102]	– –
Inhibitors of dipeptidyl peptidate-4	
Alogliptin[97–100]	Neutral
Linagliptin[90,100,106,107]	–[a]
Saxagliptin[100,103–105]	–[a]
Sitagliptin[100–103]	–[a]
Insulin[85,86,88,118]	+ +[a]
Insulin secretagogues	
Meglitinides	
Nateglinide[5,95,96]	Neutral
Repaglinide[79,89,109,a]	+[a]
Sulfonylurea drugs	
Chlorpropamide[84–86]	+ +
Gliclazide[75,80,94]	+ +[a]
Glimepiride[5,90–93]	+ & –[a]
Glyburide[78,88,89]	+ +[a]
Tolbutamide[5,76,87]	++
Insulin sensitizers	
Biguanides	
Metformin[5,75–78]	–
Thiazolidinedione	
Pioglitazone[5,79–81]	+ +
Rosiglitazone[78,82,83]	+ +
SGLT2 inhibitors (or gliflozin)	
Canagliflozin[93,110,111]	– –
Dapagliflozin[112–114]	– –[a]
Empagliflozin[115–117]	–

- Treatment-emergent weight changes associated with antihyperglycemics

- **Notes:** +=>1 kg. Neutral=±1 kg. –=<–1 kg. Additional + or – refers to ≥3 kg weight change. [a]Articles cited included ≥1 weight neutral estimate(s).

Hypertention medications

Beta blockers

- **Atenolol, Metoprolol, Propranolol**
- Beta blockers ease stress on your heart by slowing its rate and lowering blood pressure.
- Decreases body's reaction to exercise so patient won't burn as many calories (altered metabolism and decreased basal metabolic rate and inhibition of lipolysis).
- Many of the older beta blocker drugs can lead to fatigue or dyspnea , which may be responsible for some of the weight gain. Patients may be tired, have lack of energy, and in general slow down, which may affect the number of calories burned each day.

- **Beta-blockers** are typically associated with weight gain for the first few months of treatment, followed by a plateau.
- However, the amount of weight gain associated with beta-blockers is moderate and may not be clinically significant.
- Of the commonly prescribed beta-blockers, **atenolol** (–0.5 to +3.4 kg), propranolol (–0.5 to +2.3 kg) and metoprolol (1.2–2.0 kg) are associated with the highest weight gain.
- Newer beta blockers, such as carvedilol, don't usually cause weight gain as a side effect.

- For **alpha-blockers (clonidine, prazosin)**, weight gain is not a commonly reported side effect.

- Other blood pressure medications like the **calcium channel blockers (Amlodipine, Diltiazem)** and **ACE inhibitors (Enalapril, Lisinopril)** are less likely to cause weight gain.

Drug name	Weight effect
Alpha-blockers	
Clonidine[155,156]	+[a]
Prazosin[157,158]	Neutral
ACE inhibitors	
Enalapril[131–133]	– –[a]
Lisinopril[124,137,138]	–[a]
Perindopril[134–136]	+ & – –[a]
Ramipril[139–141]	–[a]
ARBs	
Irbesartan[161,165,166]	Neutral
Losartan[131,163,164]	– –[a]
Olmesartan[161,162,165]	Neutral
Telmisartan[159–162]	–[a]
Valsartan[167–169]	+[a]
Beta-blockers	
Acebutolol[153,154]	Neutral
Atenolol[143–145]	+ +[a]
Metoprolol[148,149]	+[a]
Propranolol[146,147]	+[a]
Timolol[150–152]	–[a]
CCBs	
Amlodipine[170–172]	Neutral
Diltiazem[173–175]	+[a]
Direct renin inhibitors	
Aliskiren[176–178]	Neutral
Diuretics	
Chlorthalidone[122,125,126,a]	–[a]
Furosemide[122,123,130a]	– –
Hydrochlorothiazide[121–124,a]	–[a]
Indapamide[127–129,a]	–[a]

Notes: +=>1 kg. Neutral=±1 kg. –=<–1 kg. Additional + or – refers to ≥3 kg weight change. [a]Articles cited included ≥1 weight neutral estimate(s).
Abbreviations: ACE, angiotensin converting enzyme; ARB, angiotensin II receptor blocker; CCB, calcium channel blocker.

- **Diuretics**
- Hydrochlorothiazide, are associated with modest weight losses of 0.4–2.7 and furosemide (–4.1 to +0.3 kg) being similarly associated with weight neutral to weight loss effects.

- **ACE inhibitors**
- Enalapril (−3.0 to +0.4 kg) is associated with the greatest amount of weight loss.
- Lisinopril (−1.5 to 0.0 kg) and may also be associated with weight loss, but appear to be more weight neutral.

- **Angiotensin II receptor blockers:**
- Telmisartan (–2.1 to +0.2 kg) and **losartan** (−4.2 to –0.1 kg) are associated with the greatest amount of **weight loss**.
- Valsartan (0.6–2.4 kg) is primarily weight neutral, but can be associated with modest weight gains.

- **Calcium channel blockers:**
- Amlodipine (–0.7 to +0.8 kg) and diltiazem (–0.1 to +1.2 kg), are relatively weight neutral with <1.5 kg weight changes on average.

- Several antihypertensive medications cause peripheral edema notably the calcium channel antagonists by redistributing body water to the extravascular space, but they do not usually cause actual weight gain.
- Thiazide diuretics and angiotensin-converting enzyme inhibitors typically cause a transient loss of 1-2 kg body weight in the first 6-8 weeks.
- One class of antihypertension medications that does cause true weight gain is the β blockers.
- The United Kingdom Prospective Diabetes Study Group (UKPDS) reported a mean weight gain of 3.4 kg in the **atenolol** group vs. 1.6 kg in the **captopril** group over 9 years of observation.(In the first months)
- This weight gain was sustained after 3 years and independent of age, sex, degree of physical activity, and discrepancies in the use of diuretics.


Anti Histamines

Why Antihistamines Cause Weight Gain

- Antihistamines are oral medications that are commonly used to treat symptoms of allergic rhinitis and allergic conjunctivitis.

- They work by blocking the actions of histamine, a chemical released by body's mast cells. Our bodies need histamine.

- Antihistamines are particularly good at treating allergy symptoms such as sneezing, runny noses, and itchy, watery eyes. While antihistamines are considered a relatively safe medication, they can come with side effects, including the possibility of weight gain.

Evidence That Antihistamines Cause Weight Gain

- Older antihistamines, such as diphenhydramine, have well-known side effects such as drowsiness, dry mouth, and urinary retention(antimuscarinic).
- Fexofenadine, tend to have less of these side effects.
- Of the almost 900 people studied, those taking antihistamines—such as Cetrizine and fexofenadine—were more likely to be overweight or obese than those not taking antihistamines.
- The researchers theorized that antihistamines have a similar chemical structure to certain psychiatric drugs that are known to be associated with **weight gain**.

- Antihistamines may also **increase appetite**, which can cause weight gain.
- Older antihistamines, such as **cyproheptadine**, have actually been used for the purpose of increasing appetite and weight gain in underweight children and cancer patients undergoing chemotherapy.
- Levocetirizine, an antihistamine similar to Cetrizine:
- Very small percentage of patients who used the drug during trials experienced—extra pounds.

How we can manage medicine-related weight gain?

- Nonpharmaceutical:

Lifestyle modification

Dietary counseling

Exercise interventions

- Treatment will depend on the situation. In some cases, healthcare provider will recommend switching to another medicine that's not as likely to cause weight gain. This is especially likely **if patient has gained a lot of weight and health is affected.**
- In other cases, it may not be possible to stop taking the medicine that is causing weight gain. There might not be another medicine available that can effectively treat your symptoms. In that case, you might be able to **switch to a lower dose of the medicine.**
- Getting more exercise can also help treat weight gain. Limiting your portion sizes and eating more slowly at meals can also help.

- In many cases, there might be an alternative medication with less effect on weight; in other cases the medications that cause weight gain may be preferable to alternatives. The risks of stopping or changing medication should be balanced against the risks of obesity and related co-morbidities.

- It is important to note that not all patients respond similarly to these medications.