Injectable Therapy in Diabetes Management

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آشنایی با داروهای کنترل کننده دیابت

دکتر ناصر آقامحمدزاده
استاد دانشگاه علوم پزشکی تبریز
فوق تخصص بیماری های غدد درون ریز

Diabetes prevalence has been estimated less than reality…

Number of people with diabetes has been reported 463 million in 2019, half of which do not know about their disease…

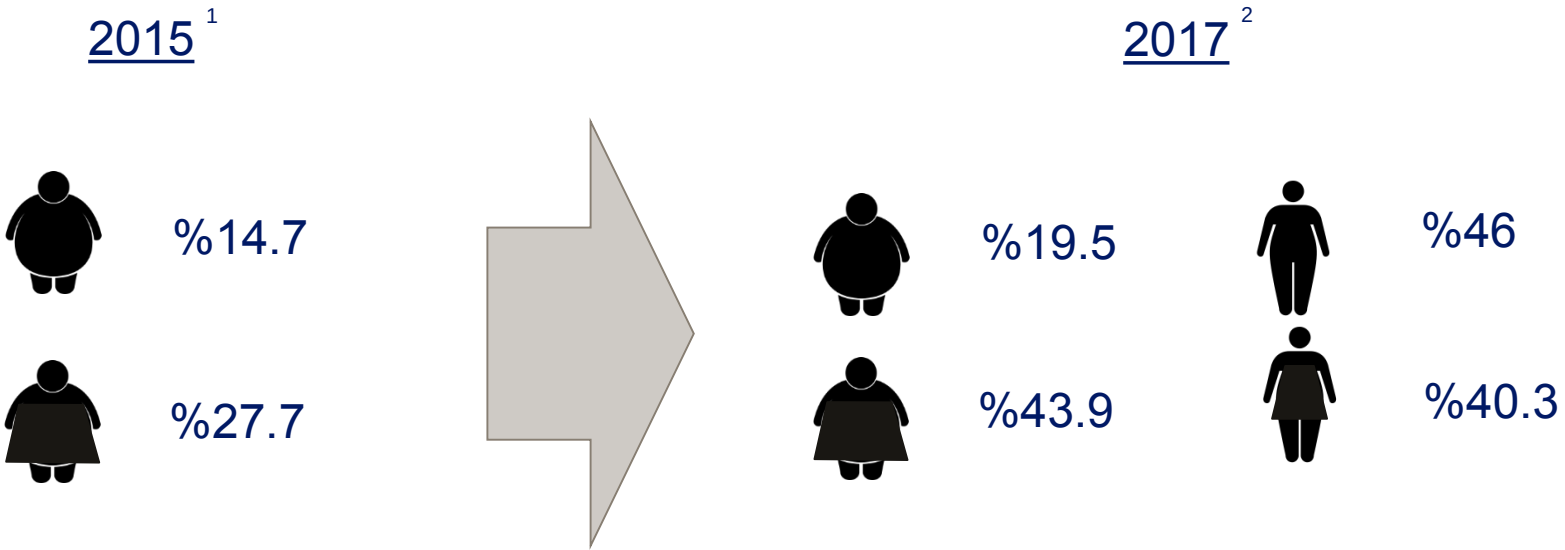
IDF Diabetes Atlas, 9th Edition, 2019

Prevalence of T2DM in Iran in an epidemiological study during 2005-2011

- Prevalence of diabetes has raised by 35.1% from 2005 to 2011
- Undiagnosed diabetes has reduced from 45.7% to 24.7% during 2005-2011

*Alireza Esteghamati , Koorosh Etemad, Jalil Koohpayehzadeh, Mehrshad Abbasi , et al, Diabetes research and clinical practice 103 (2014) 319– 327

Obesity in Iran



1.Bakhshi et al, 2015; Iran Red Crescent Med J. 2015 June; 17(6): e22479.
2.Khabazkhoob et al 2017; *Iran J Public Health, Vol. 46, No.6, Jun 2017, pp.827-834*

Rate of obesity among Iranian people

Not educated

%28.5

Educating

%18.7

Well educated

%13.4

%23.9

%18.4

Bakhshi et al, 2015; Iran Red Crescent Med J. 2015 June; 17(6): e22479.

Treatment goals

- **Fasting plasma glucose: 80-130mg/dl**
- **Post prandial plasma glucose: ≤180mg/dl**
- **HbA_1c: ≤7%**
- **Blood pressure: ≤140/90mmHg**
- **LDL cholesterol: ≤100mg/dl**

ADA Guidelines 2021. Diabetes Care , December 2020

Oral anti-diabetic medications

- Biguanides: Metformin
- Sulphonylureas: Glibenclamide
- Meglitinides: Repaglinide
- Thiazolidinediones: Pioglitazone
- Alfa glucosidase inhibitors: Acarbose
- Dipeptidil peptidase 4 inhibitors: sitagliptine
- Sodium-glucose linked transporter 2 inhibitors: Dapagliflosine

ADA Guideline 2016. Diabetes Care , January 2016

Injectable therapies in diabetes management

- Insulin
- Glucagon-like Peptide 1 Receptor Agonist

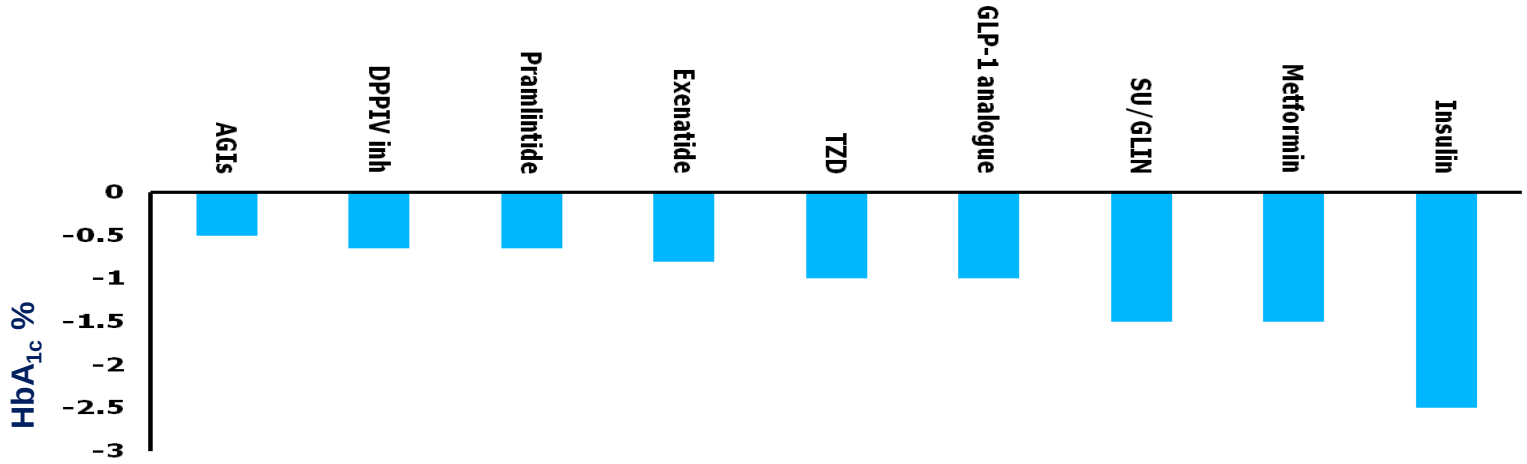
Comparison of different treatments

	SU	TZD	DPP4i	GLP-1 RA	Insulin
↓HbA_{1c}	good	Good	Moderate	Good	Very good
Risk of hypoglycemia	high	Low	Low	Very low	High
Weight effect	↑	↑	↔	↓	↑

DPP-4i, dipeptidyl peptidase-4 inhibitor; GI, gastrointestinal; GLP-1RA, glucagon-like peptide-1 receptor agonist; HbA_{1c}, glycosylated haemoglobin; SU, sulphonylurea; TZD, thiazolidinedione; ↑, weight gain; ↓, weight loss; ↔, weight

ADA Guideline 2016. Diabetes Care , January 2016

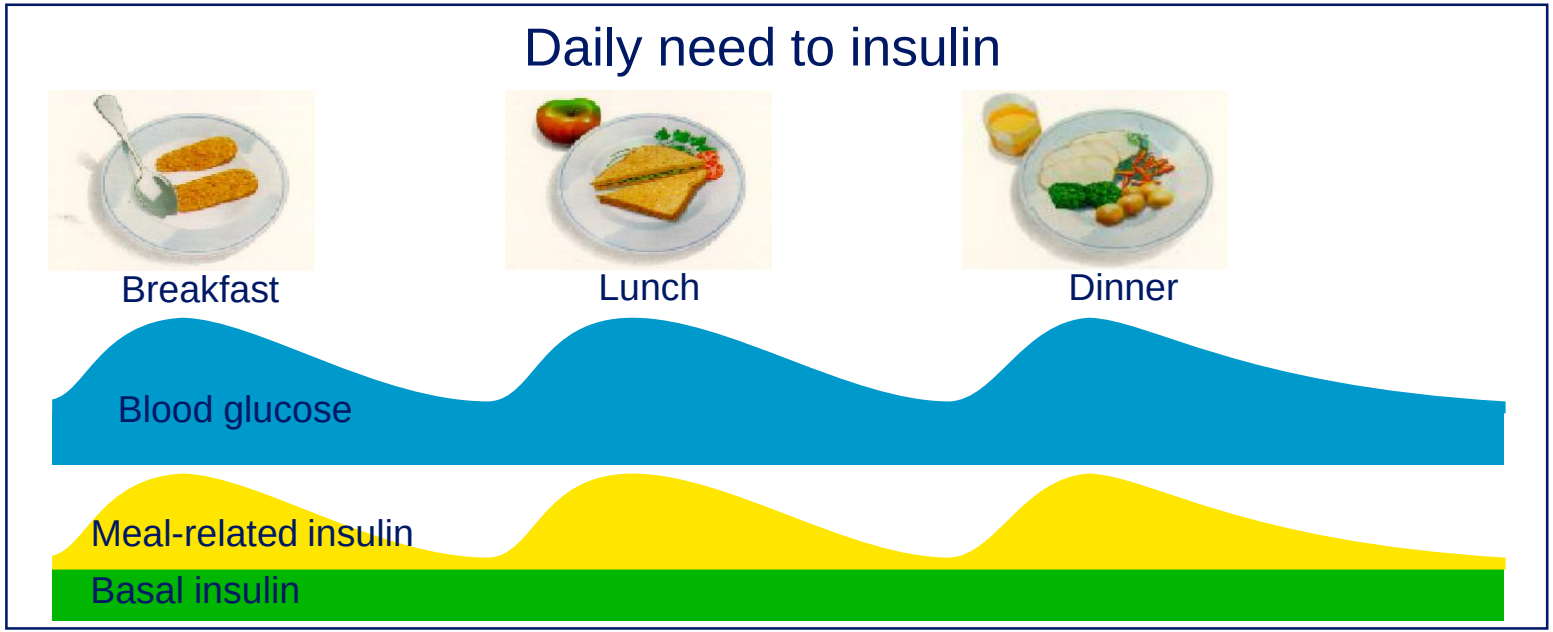
Insulin is the most potent medication in BG control



Decrease in HbA_{1c}: Potency of monotherapy

Nathan et al., Diabetes *Care* 2009;32:193-203.

Normal daily insulin release in the body



Types of insulin

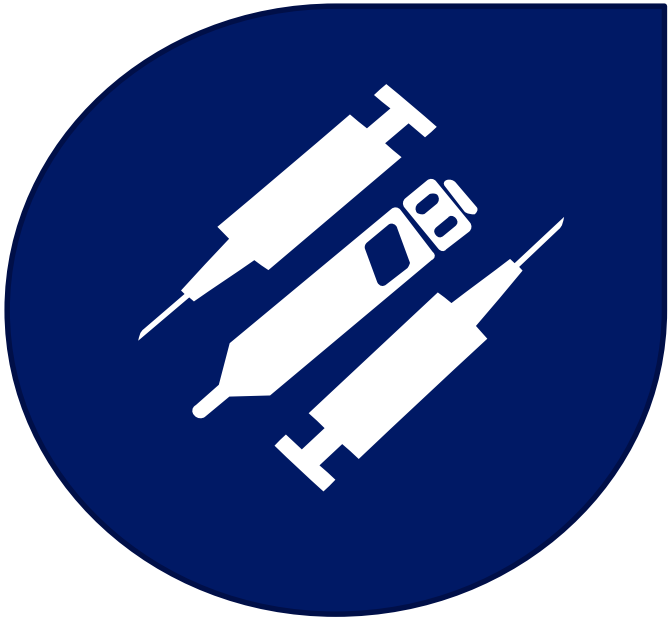
Animal insulin

- Derived from cows and pigs pancreas
- It is obsolete now a days

Human insulin

- Derived from a bacterium
- Regular and NPH insulins
- Premix human insulin

Insulin analogues



Joslin Diabetes Desk Book: A Guide for Primary Care Providers. 2010

Insulin	Onset of Action	Peak (h)	Duration of Action (h)
Rapid-acting			
Aspart(NovoRapid®)			
Glulisine(Apidra®)	10 - 15 min	1 - 2	3 - 6
Lispro(Humalog®)			
Short-acting			
Human Regular	30 - 60 min	2 - 4	6 - 8
Intermediate-acting			
Human NPH	1 - 2 h	4 - 8	12 - 16
Long-acting			
Detemir(Levemir®)	–	–	Up to 24 h
Glargine U100 (Lantus®)	2 - 4 h	-	Up to 24 h
Glargine U300(Toujeo®)	6 h	-	Up to 36 h

* Levemir®; Locally approved labeling in Iran version (STF Q2 2014)

Mudaliar S et al. Endocrinol Metab Clin North Am. 2001 ;30:935-982.; 2. Endotext.com

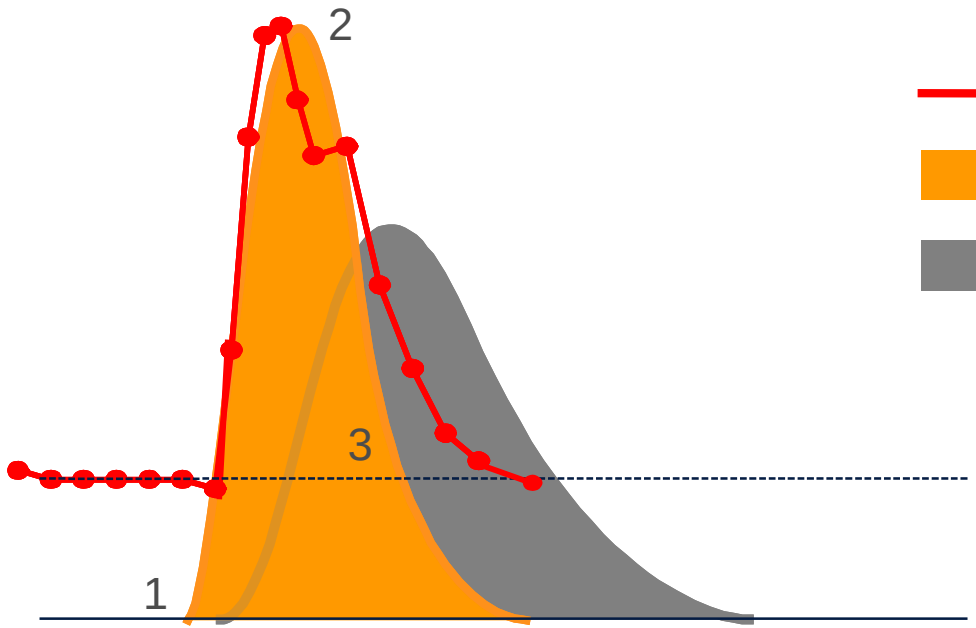
NovoRapid®

Insulin aspart

Insulin aspart

Novo Nordisk Iran. NovoRapid®; locally approved labeling in Iran Version (STF March 2017)

NovoRapid® mechanism of action



Physiological pattern of insulin release

NovoRapid®

Regular insulin

*Novo Nordisk Iran. NovoRapid®; locally approved labeling in Iran Version (STF March 2017)

Clinical advantages of NovoRapid®

- Indicated in pediatric population ≥1 y o
- In elderly
- During pregnancy
- During lactation

Novo Nordisk Iran. NovoRapid® locally approved labeling in Iran Version (STF March 2017)

Storage conditions

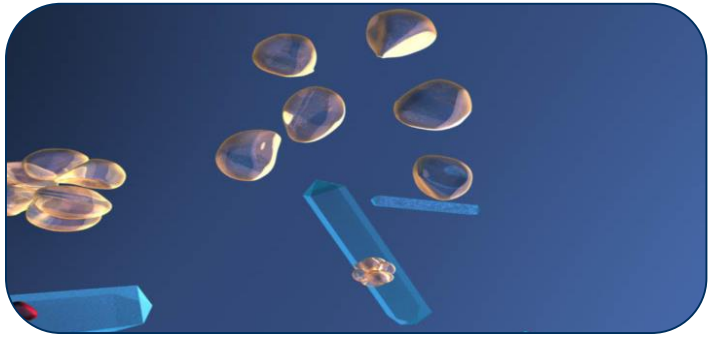
- Before opening store in a refrigerator(2-8^{0}C)
- Do not freeze
- Keep the pen cap on the pen in order to protect from light
- After opening 4 weeks can be stored
- During usage or when carried as a spare must be stored for a max 4 weeks below 30^{0}C

Novo Nordisk Iran. NovoRapid®; locally approved labeling in Iran Version (STF March 2018)

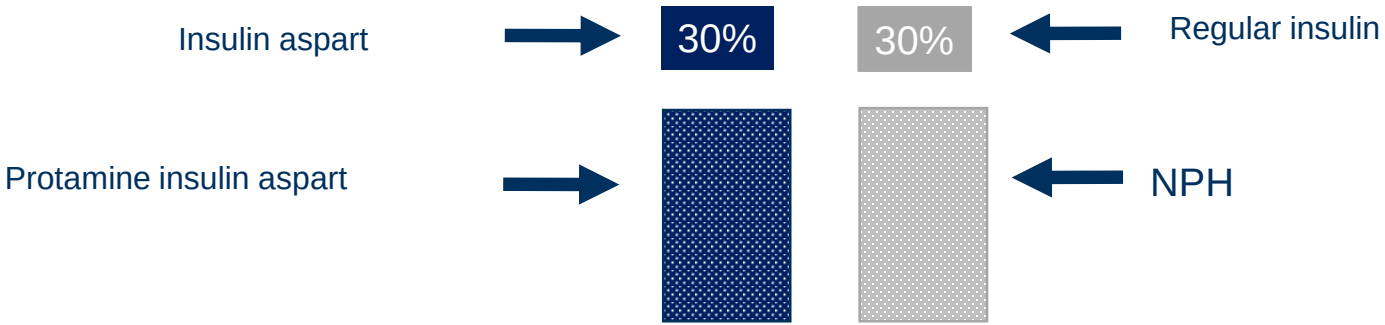
NovoMix® 30

Premix insulin aspart

NovoMix® 30 insulin formulation

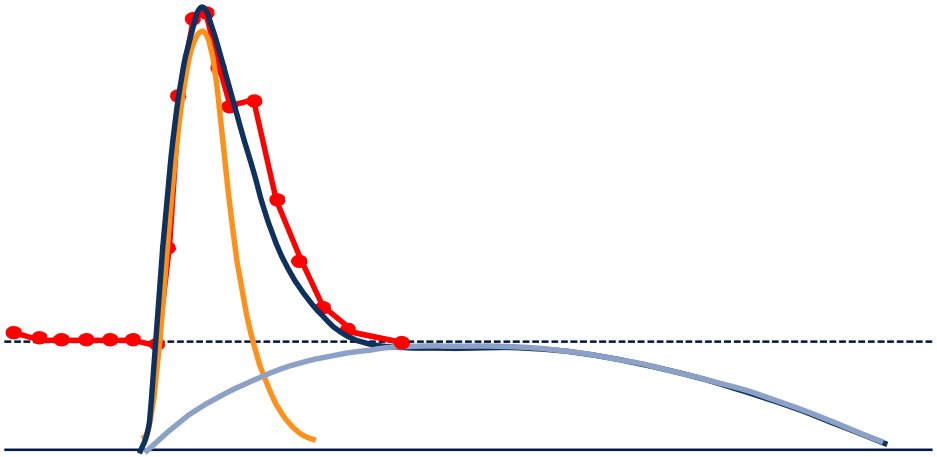


Premix insulins contain:



Novo Nordisk Iran. NovoMix® 30 locally approved labeling in Iran Version STF Q3 2014

Insulins’ mechanism of action:



Physiological insulin release

Insulin aspart

Protamine insulin aspart

NovoMix® 30 insulin

Novo Nordisk Iran. NovoMix® 30 locally approved labeling in Iran Version STF Q3 2014

NovoMix® 30 flexpen® features:

- Treatment indications:
- In people with T2DM with or without OADs
- It can be used in combination with liraglutide
- In elderly(evidence in use among those ≥75 y o is limited)
- Kidney and liver impairment: probable requirement for insulin dose reduction
- Pediatrics: in those older than 10 y o, when premix insulin is preferred(in younger population data is limited)
- Pregnancy: data is limited
- During lactation can be used

Storage conditions

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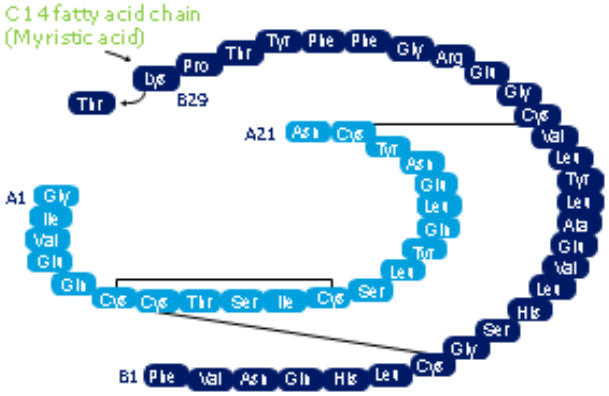
Levemir®

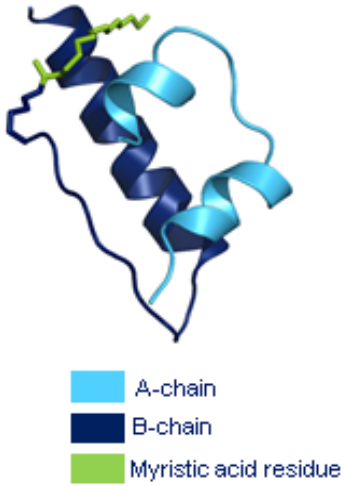
Detemir insulin

Insulin Levemir®

Insulin detemir molecule: monomer

Des threonine (B30) + myristic (mir) acid (B29)

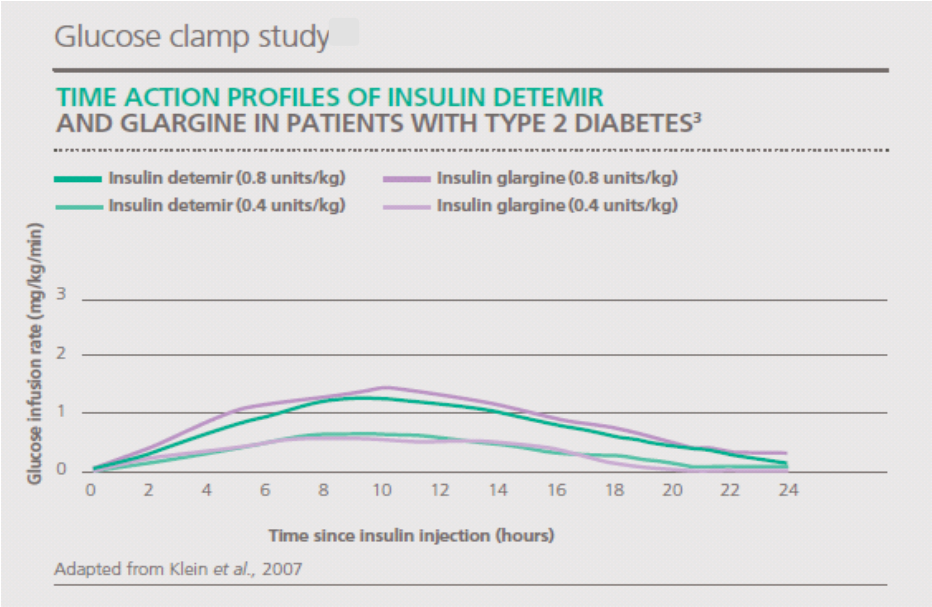




Novo Nordisk. Insulin detemir prescribing information, 2015

Insulin Levemir®

- **Levemir® is a basal analogue insulin**
- **With a long-acting profile, capable to cover blood glucose for 24 h.**



Insulin Levemir® features

- Vast majority of patients can reach HbA_1c control
  - 64% of patients reached $HbA_1c \leq 7\%$
- Low risk of hypoglycemic events
  - 65% less nocturnal hypoglycemia compare to NPH users
- Less weight gain compared to glargine and NPH
  - 40 % less weight gain than glargine
- Approved in pregnancy and in population older than 1 y o
- It can be used in combination with OADs, prandial insulins, liraglutide

1. Novo Nordisk Iran .Levemir®locally approved labeling in Iran Version(STF May 2017)
2-Blonde, L., et al. Patient-directed titration for achieving glycaemic goals using a once-daily basal insulin analogue: an assessment of two different fasting plasma glucose targets – the TITRATE™ study. Diabetes Obes Metab, 2009. 11(6): p. 623-31.**3.** Philis-Tsimikas, A., et al. Comparison of once-daily insulin detemir with NPH insulin added to a regimen of oral antidiabetic drugs in poorly controlled type 2 diabetes. Clin Ther, 2006. 28(10): p. 1569-81 **4.** Swinnen, S.G., et al. Insulin detemir versus insulin glargine for type 2 diabetes mellitus. Cochrane Database Syst Rev, 2011(7): p. CD006383. **5.** Horvath, K., et al. Long-acting insulin analogues versus NPH insulin (human isophane insulin) for type 2 diabetes mellitus. Cochrane Database Syst Rev, 2007(2): p. CD005613. **6.** Rosenstock J et al. A randomised, 52-week, treat-to-target trial comparing insulin detemir with insulin glargine when administered as add-on to glucose lowering drugs in insulin-naive people with type 2 diabetes. Diabetologia 2008;51:408–16.

Storage conditions

- Before opening store in a refrigerator(2-8^{0}C)
- Do not freeze
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- After opening 6 weeks can be stored
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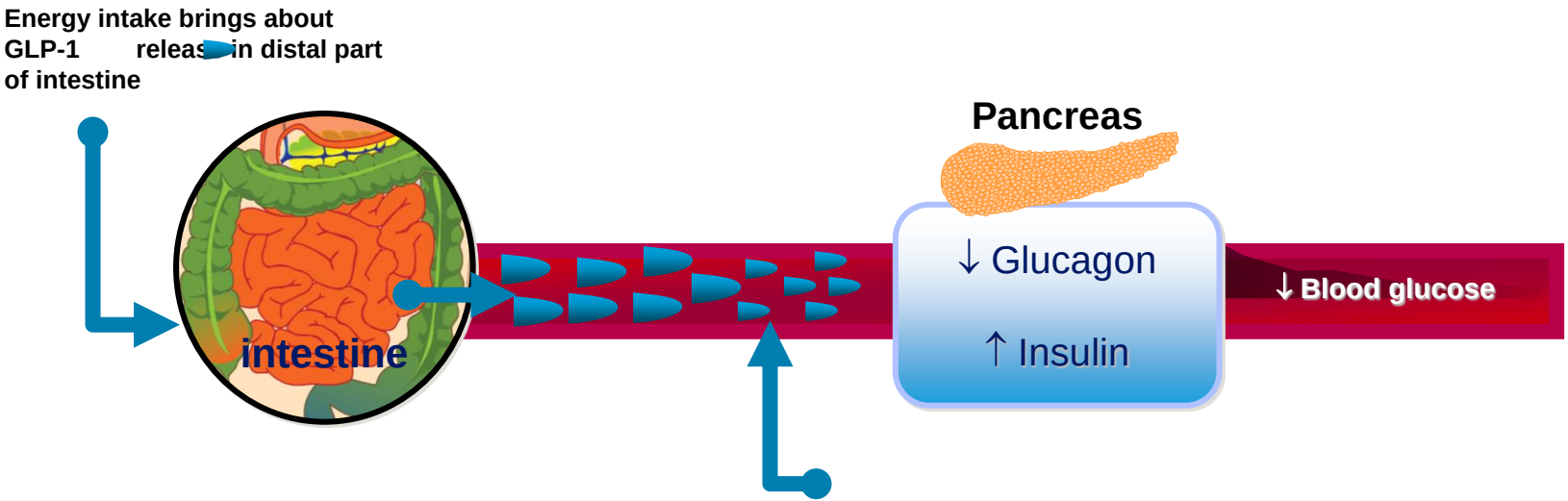
1. Novo Nordisk Iran .Levemir®locally approved labeling in Iran Version(STF May 2017)

New modalities in diabetes management

Incretin release mechanism

- Incretins are the polypeptide hormones that will be released in response to energy intake
- GLP-1 is an incretin, that after release from distal part of intestine, circulates in the blood and affects pancreas and other organs.



Campbell JE et al. Cell Metab. (2013)

DPP4 production by the body, causing degradation of GLP and GIP

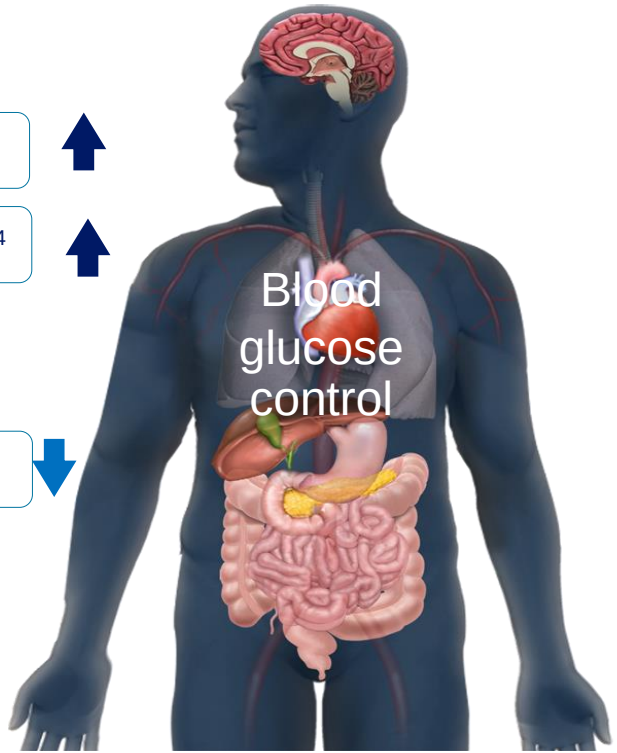
GLP-1 has a various physiological effects on the organism

Pancreas

- Increases insulin secretion[2,3]
- Insulin production[4]

Glucose dependent

- Reduces glucagon secretion[3]



Brain

- Weight reduction
- Satiety[5-7]

Cardiovascular system

- Reduces CV death[9]
- Reduces SBP[8]

Liver

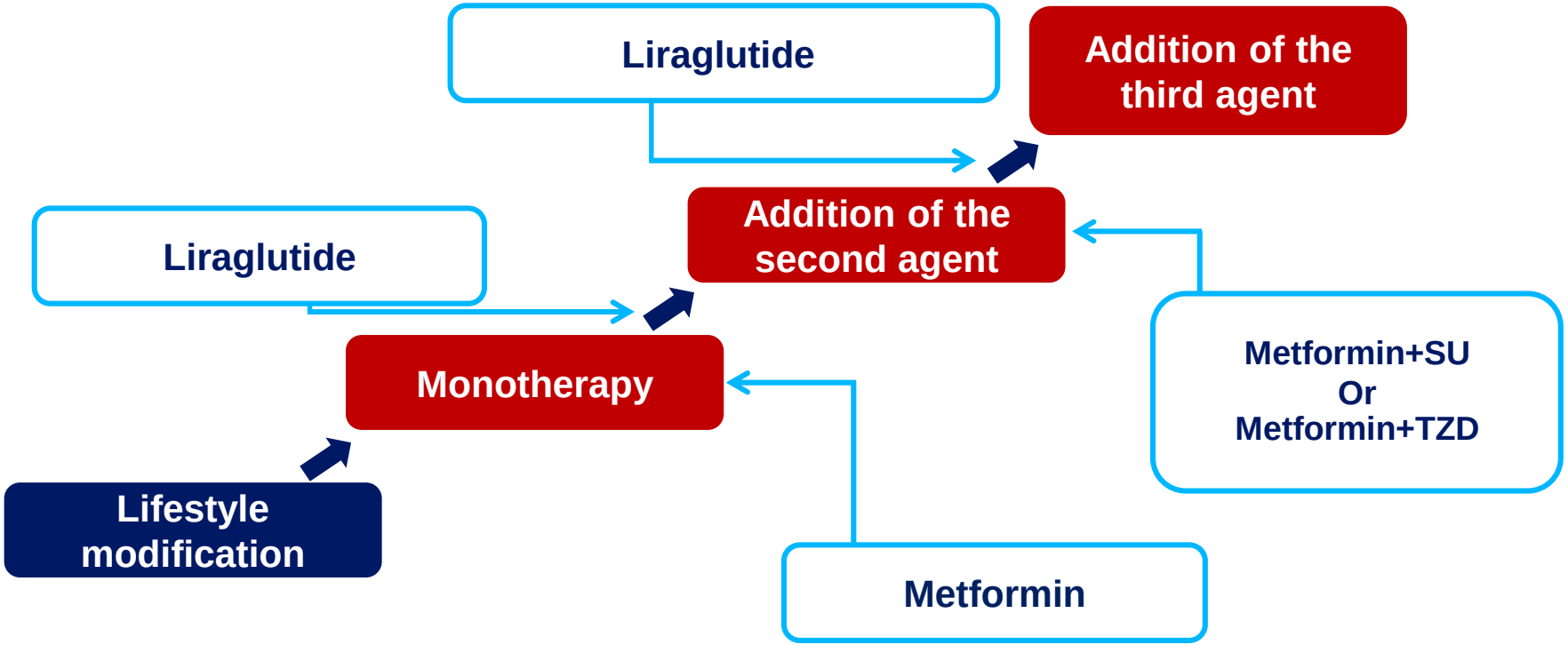
- Reduces hepatic glucose output[4]

1. Holst JJ et al. *Trends Mol Med* 2008;14:161–168; 2. Flint A et al. *Adv Ther* 2011;28:213–226; 3. Degn K et al. *Diabetes* 2004;53:1187–1194; 4. Baggio LL & Drucker DJ. Gastroenterology 2007;132:2131–2157. 5. Horowitz M et al. *Diabetes Res Clin Pract* 2012;97:258–266; 6. Vilsbøll T et al. *BMJ* 2012;344:d7771. 7. Niswender K et al. *Diabetes Obes* Metab 2013;15:42–54; 8. Fonseca V et al. *Diabetes* 2010;59(suppl 1):A79 (296-OR). 9. Marso SP, Daniels GH, Brown-Frandsen K, et al; the LEADER Steering Committee on behalfof the LEADER Trial Investigators. Liraglutide and cardiovascular outcomes in type 2 diabetes. N Engl J Med. 2016;375(4):311-322.

Victoza®

Liraglutide in diabetes

Liraglutide can be considered in various treatment regimens



Victoza® Locally Approved Labeling in Iran Version STF Nov-2016 (Approval package Sep 2017)

Pen properties and administration

- Prefilled pens for SC injection
- 3ml and 18 mg medicinal substance
- Once a day injection should be administered
- Injection can be administered anytime in a day, preferably in a specific time
- There is no relation to energy intake and injection
- No need for SMBG

Victoza® Locally Approved Labeling in Iran Version STF Nov-2016 (Approval package Sep 2017)

Treatment considerations

Indications

- The only GLP1-RA approved by ADA to be considered for people with T2DM with CV risk
- Liraglutide can be used in combination with insulin
- No need for dose adjustment among those older than 65 y o
- No need for dose adjustment among those with different levels of renal impairment(eGFR≥15ml/min/1.73m^2)
- No need for dose adjustment for those with hepatic impairment

Contraindications and warnings

- It should not be administered in pregnancy and lactation periods
- It should not be used in those with T1DM or DKA
- Liraglutide is not an alternative to insulin

Victoza® Locally Approved Labeling in Iran Version STF Nov-2016 (Approval package Sep 2017)

Liraglutide dose

- To overcome transient GI complications, start with 0.6mg dose

Start with 0.6mg and continue for a week

Increase dose to 1.2mg
and
Continue for a week

If patient did not reach the target, increase to max dose 1.8mg

Victoza® Locally Approved Labeling in Iran Version STF Nov-2016 (Approval package Sep 2017)

Storage conditions

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Saxenda®

Liraglutide 3 mg

Saxenda®

- Prefilled injectable soluble
- 1 ml of soluble contains 6 mg liraglutide, a pen contains 3 ml of soluble, which contains 18 mg of the API
- 6 mg/dL is the start dose
- Dose should be increased after a week by 0.6mg/dL to avoid GI intolerance, which is transient
- If the patient could not tolerate the side effect after two consecutive weeks, treatment should be discontinued

novo nordisk®

Indications:

- Saxenda® besides low-calorie diet and increased physical activity in weight management in adults with BMI as below:
- ≥30kg/m^2(obese)
- ≥27kg/m^2, with at least one of weight related morbidity:
- Dysglycemia(prediabetes, diabetes)
- Hypertension
- Dyslipidemia
- OSA

In case the patient did not lose 5% of their baseline weight after 12 weeks treatment with full dose 3mg per day, the treatment should be stopped.

novo nordisk®

Demonstrate the first injection in the office to help patients get started

1. Check the Saxenda® pen

2. Attach a new needle

3. Check the Saxenda® flow

4. Select the dose

5. Inject the dose

6. Remove the needle

- The Saxenda® pen is designed to be used with needles up to a length of 8 mm and as thin as 32G, such as the NovoFine® or NovoTwist® needles.

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novo nordisk®