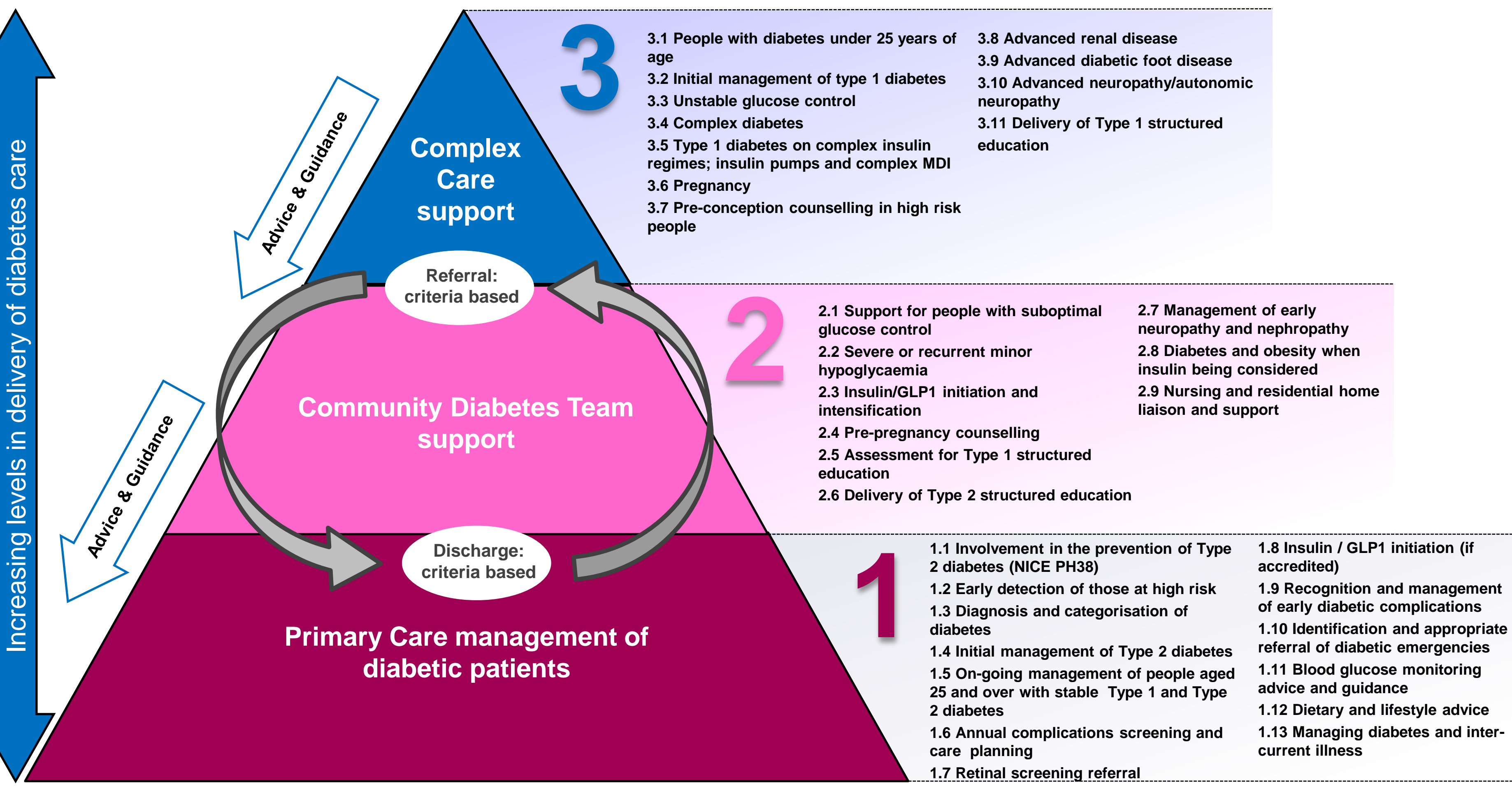
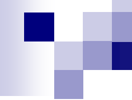
Initiating Injectables in Type 2 Diabetes

Tara Kadis
Team Leader
Diabetes Nurse Specialist
York Teaching Hospital



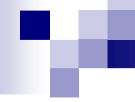
Increasing levels in delivery of diabetes care
Advice & Guidance
Advice & Guidance
3
Complex Care support
3.1 People with diabetes under 25 years of age
3.2 Initial management of type 1 diabetes
3.3 Unstable glucose control
3.4 Complex diabetes
3.5 Type 1 diabetes on complex insulin regimes; insulin pumps and complex MDI
3.6 Pregnancy
3.7 Pre-conception counselling in high risk people
3.8 Advanced renal disease
3.9 Advanced diabetic foot disease
3.10 Advanced neuropathy/autonomic neuropathy
3.11 Delivery of Type 1 structured education
Referral: criteria based
2
Community Diabetes Team support
2.1 Support for people with suboptimal glucose control
2.2 Severe or recurrent minor hypoglycaemia
2.3 Insulin/GLP1 initiation and intensification
2.4 Pre-pregnancy counselling
2.5 Assessment for Type 1 structured education
2.6 Delivery of Type 2 structured education
2.7 Management of early neuropathy and nephropathy
2.8 Diabetes and obesity when insulin being considered
2.9 Nursing and residential home liaison and support
Discharge: criteria based
1
Primary Care management of diabetic patients
1.1 Involvement in the prevention of Type 2 diabetes (NICE PH38)
1.2 Early detection of those at high risk
1.3 Diagnosis and categorisation of diabetes
1.4 Initial management of Type 2 diabetes
1.5 On-going management of people aged 25 and over with stable Type 1 and Type 2 diabetes
1.6 Annual complications screening and care planning
1.7 Retinal screening referral
1.8 Insulin / GLP1 initiation (if accredited)
1.9 Recognition and management of early diabetic complications
1.10 Identification and appropriate referral of diabetic emergencies
1.11 Blood glucose monitoring advice and guidance
1.12 Dietary and lifestyle advice
1.13 Managing diabetes and inter-current illness



Key Challenges of Type 2 Diabetes

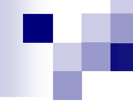
Diabetes is a progressive multi-system disease characterised by:

- Declining beta-cell function
- Insulin resistance – increasing body weight
- Increased risk of cardiovascular disease



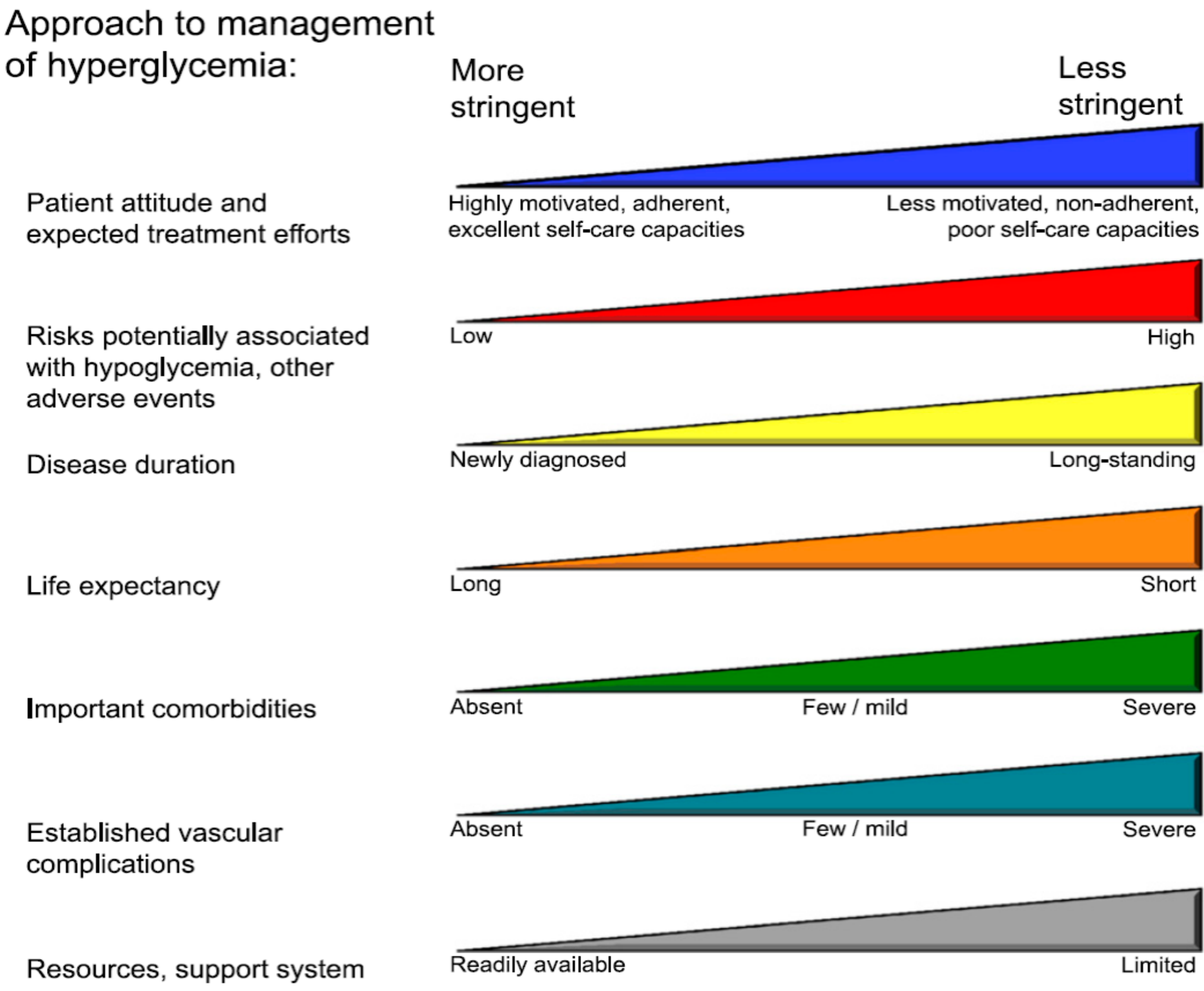
The trade off !

- As diabetes treatments are added to improve glucose control, clinicians & patients face trade-offs such as:
  - Hypoglycaemia
  - Weight gain
  - Complex treatment regimens



- Weight gain and hypoglycaemia associated with traditional therapies
- Delay in progressing with medication
- Patients see themselves as failures due to progression of therapies

An Aid to Decision Making in Type 2 Diabetes

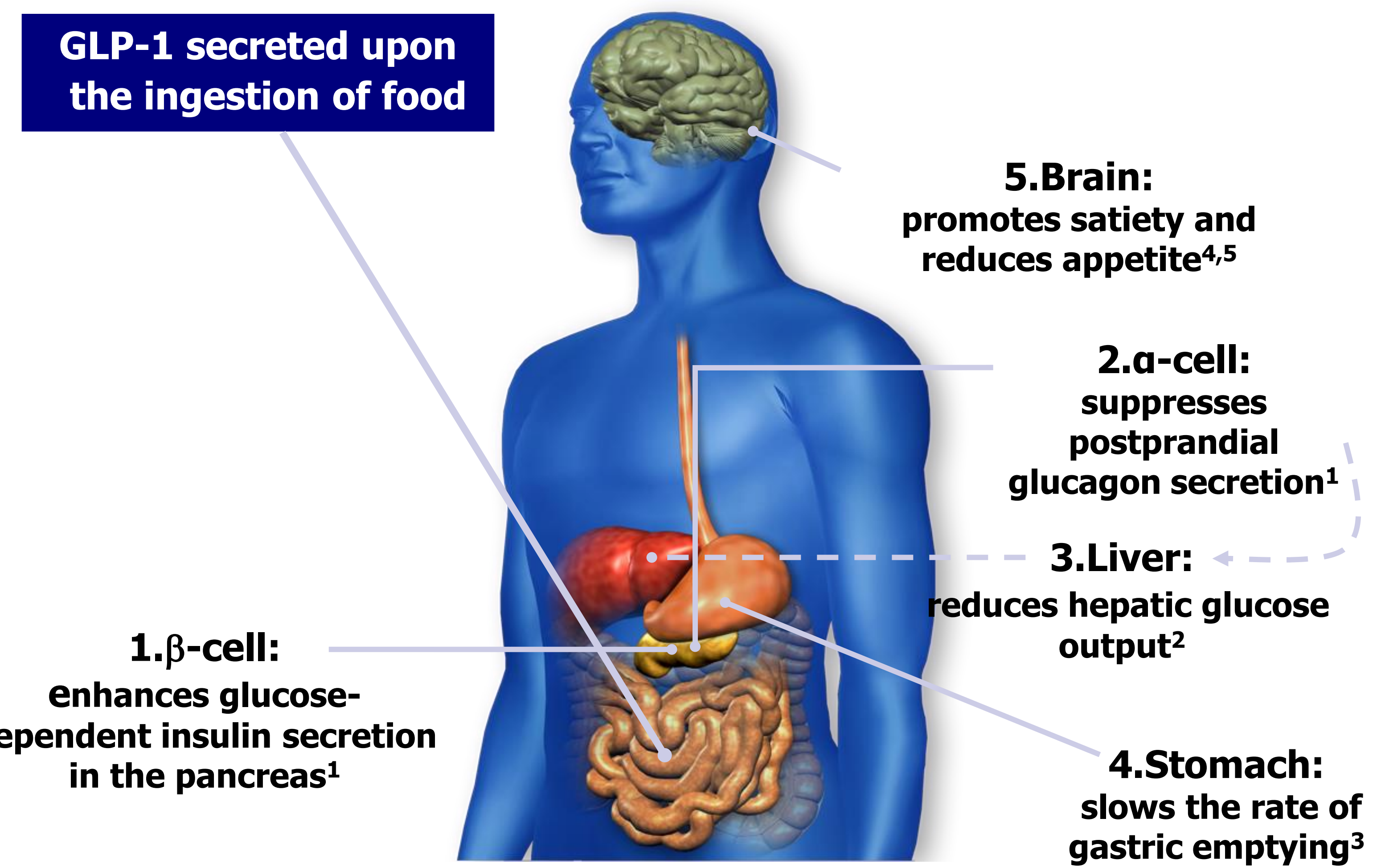


Injectables in diabetes

- GLP-1
  - Lixisenatide (Lyxumia)
  - Liraglutide (Victoza)
  - Exenatide (Byetta)
  - Once weekly exenatide (Bydureon)
  - Once weekly dulaglutide (Trulicity)

- Insulin

GLP-1 Effects in Humans



Adapted from [1]Nauck MA, et al. *Diabetologia* 1993;36:741–744; [2]Larsson H, et al. *Acta Physiol Scand* 1997;160:413–422; [3]Nauck MA, et al. *Diabetologia* 1996;39:1546–1553; [4]Flint A, et al. *J Clin Invest* 1998;101:515–520; [5]Zander et al. *Lancet* 2002;359:824–830.

Nice Recommendation GLP-1

- Consider adding GLP-1 2nd or 3rd line if patient

  HbA_{1C} ≥ 58mmol/mol (7.5%)

  BMI >35.0kg/m^2

  BMI< 35.0kg/m^2 where insulin is unacceptable because of occupational implications or weight loss would benefit other significant obesity – related co mobidities

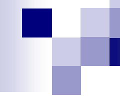
NICE Recommendation

Only continue GLP-1 therapy if the person has had a beneficial metabolic response

“a reduction of at least 1.0% (11mmol/mol) in HbA1c & weight loss of at least 3% of initial body weight at 6 months.”

Lixisenatide

- Once daily injection, before breakfast
- 10mcgs for 2 weeks then 20mcgs thereafter
- **1st choice GLP-1**
- Add on to insulin



Liraglutide(Victoza)

- Prefilled, disposable pen for s.c. injection
- Contains 18 mg liraglutide in 3 ml

- Once-daily s.c. injection
- Select dose (0.6, 1.2 or 1.8 mg)
- Inject at any time, independent of mealtimes (preferably same time each day)
- Start with 0.6mgs for 1 week increasing to 1.2 mgs thereafter
- Licence with basal insulin

Victoza® Summary of Product Characteristics

Bydureon

- Once weekly
- 2mgs once weekly
- Now in a disposable device
- No licence with insulin

Contraindications of GLP-1

- Not recommended in severe renal impairment eGFR <30
- Pregnancy/breast feeding
- Type 1 Diabetes
- Pancreatitis
- Risk of hypoglycaemia in combination with sulphonylurea

Patient Education for GLP-1

- Management of potential side effects
- Hypoglycaemia management ?
- Blood glucose monitoring ?
- Injection technique/ safe use of sharps
- Expectations of therapy, know when to stop

Considerations / barriers

- Weight loss
- Minimal titration
- Less considerations re driving/employment
- Side effects
- Contra Indications
- NICE recommendations for continuation
- Follow- up

What's next ?

Xultophy

- 1mL solution = 100 units Degludec + 3.6 mgs Liraglutide

Insulin

When to initiate insulin.

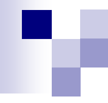
- If other measures fail to keep desired HbA1c <58 mmol/mol (7.5%)
- Max dose of tolerated treatment – usually triple therapy
- Consider in dual therapy when significant hyperglycaemia in preference to adding further drug to control blood glucose unless true justification not to.
- OHA not tolerated/contra-indicated
- Symptoms related to poor glycaemic control
- Other medication causing temporary raise in blood glucose levels.
- The aim of the treatment is to improve glycaemic control and quality of life.

Before insulin therapy

- Reinforce dietary advice and discuss lifestyle issues and employment i.e. smoking and physical activity
- Check ability to administer own insulin / carers district nurse involvement
- Patients should be taught home blood glucose monitoring - advise to monitor blood glucose at different times.

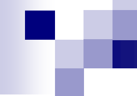
Structured programme

- Structured education
- Continuing telephone support
- Frequent self monitoring
- Dose titration to target
- Dietary understanding
- Management of hypoglycaemia
- Management of acute changes in glucose control



Which?

Basal Insulin with oral hypoglycaemic agents	Pre-mixed insulin with oral hypoglycaemic agents	Basal Bolus Regime consider referral to Community diabetes Team to initiate this regime
•First line choice •Overweight BMI >26 •Reluctance to start insulin •Unable to inject themselves	•HbA1c > 75 mmol/mol (9%) •Regular lifestyles •Symptomatic •Carbohydrate consistency	•On daily/bd insulin regimes without optimal control •Requiring flexibility due to an erratic lifestyle •Shift work •Regular travel across time zones •Regular sport •To optimise blood glucose control because of complications



Common options for intensifying basal insulin regimens

Basal insulin

Switch to twice-daily premixed insulin

Intensify with an additional injection

Add three times daily prandial insulin with meals (basal-bolus)

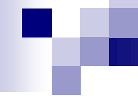
Add once-daily prandial insulin with the largest meal (basal-plus)

Additional prandial injections can be added

Adapted from Barnett A et al (2008) *Int J Clin Pract* **62**: 1647–53

Basal Human Insulin

- NPH first line choice (NICE)
- Starting with a dose usually before bed
- Titrate in line with fasting blood glucose levels
- Continue with OHA to help control day time blood glucose levels
- May be given twice daily if blood glucose levels indicate it
- Associated with less weight gain and hypos

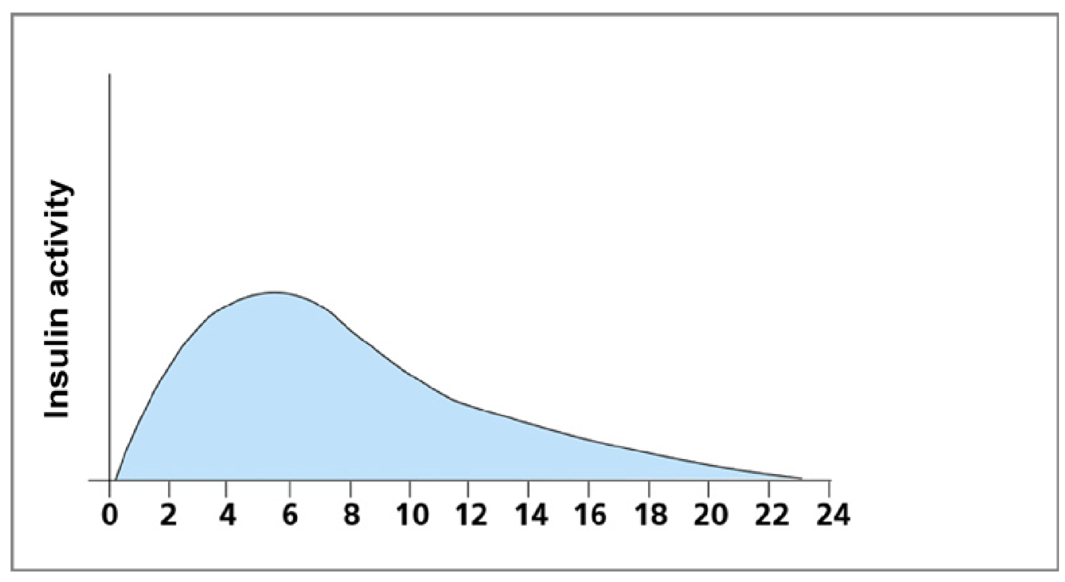


Basal Human Insulin

Humulin I

Insulatard

Insuman Basal

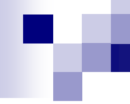


Getting started

- Commence once daily basal insulin in the evening - 10 units start dose
- Continue Metformin if tolerated
- Consider continuing sulfonylureas
- Teach the patient to titrate insulin dose by 2 - 4 units every 3 - 5 days
- Aim for fasting blood glucose of 5 – 8 mmol/l

What are the choices?

- Humulin I –
  - Kwikpen
  - 3ml Cartridges (Savvio Pen)
- Insulatard –
  - Innolet
  - 3ml Cartridges (Novopen 4)
- Insuman Basal
  - Solostar pen
  - 3ml Cartridges (Clikstar pen)



Basal Analogue

Lantus or Levemir

Consider:

- If person needs assistance from a carer or healthcare professional to inject insulin and therefore reduce the frequency of injections
- Hypoglycaemia is a problem with NPH

What are the choices?

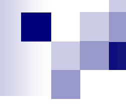
- Lantus
  - Solostar
  - 3ml Cartridges (Clikstar pen)

- Levemir
  - Flexpen
  - Innolet
  - 3ml Cartridge (Novopen 4)

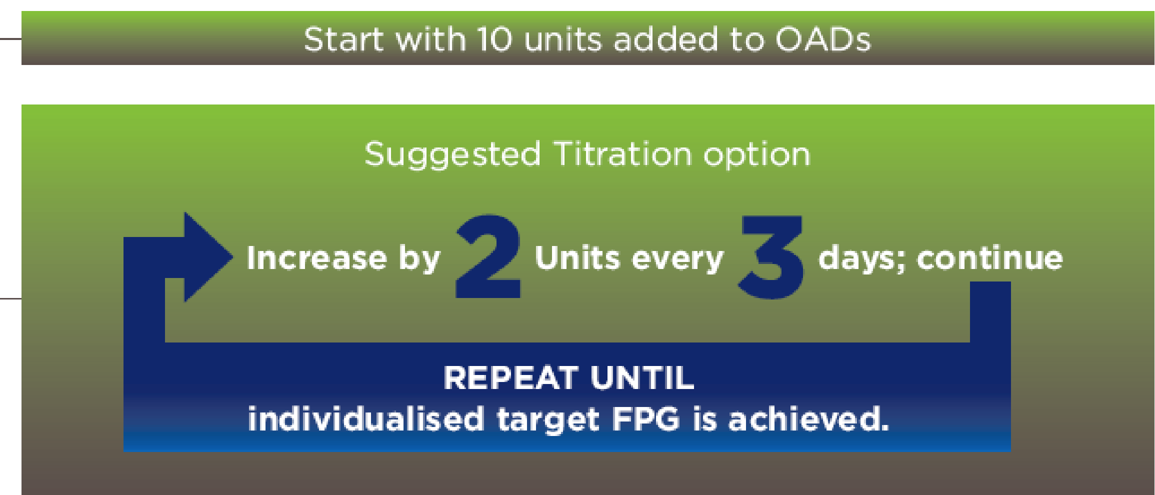
Human Basal V Basal Analogue

Basal analogue

0 2 4 6 8 10 12 14 16 18 20 22 24



Example algorithm for titrating human basal insulin from a randomised controlled trial



Exceptions to algorithm:

1. No increase in dose if fasting plasma glucose ≤4 mmol/L is documented at any time in the preceding week
2. Small insulin dose decreases (2-4 unit/day per adjustment) are allowed if severe hypoglycaemia (requiring assistance) or a fasting plasma glucose of 3.1 mmol/L is documented in the preceding week

Yki-Jarvinen H et al (2006) *Diabetologia* **49**: 442–51

Titration guidelines

Fasting blood Glucose mmol/l	Action
>10	Increase by 4 units
8 – 10	Increase by 2 units
5 - 7	No change
3 - 5	Reduce by 2 units
<3	Reduce by 4 units

Patient 1

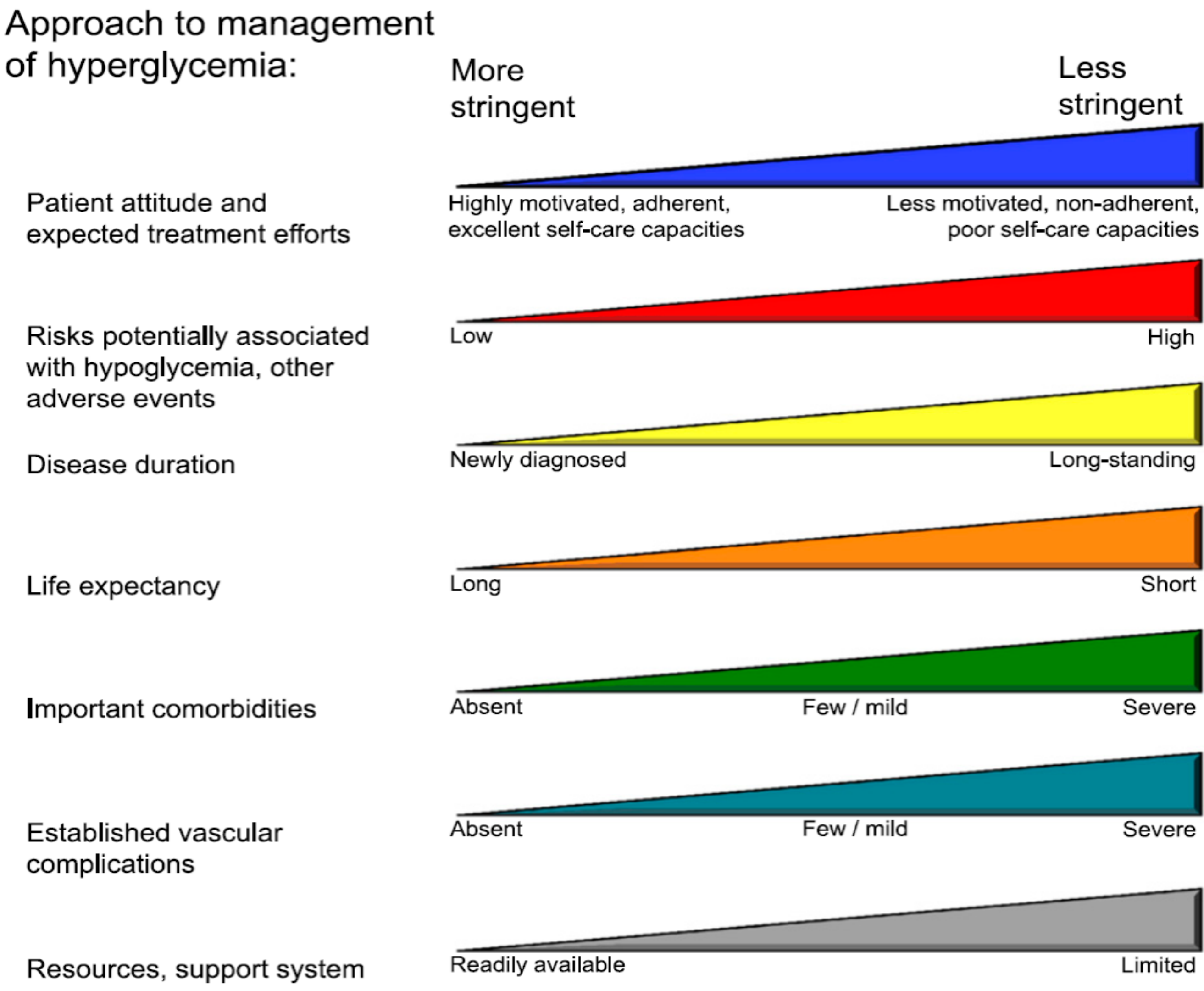
Breakfast	Lunch	Tea	Bed
14.4		12.9	
	17.2		10.3
13.6		10	
			12
	16.2		14.3

57 year old man, HbA1c 71 mmol/mol, BMI 28

Lives with wife, usually quite well but symptomatic

- Metformin 1g BD
- Gliclazide 160mgs BD
- Sitagliptin 100mgs OD

An Aid to Decision Making in Type 2 Diabetes

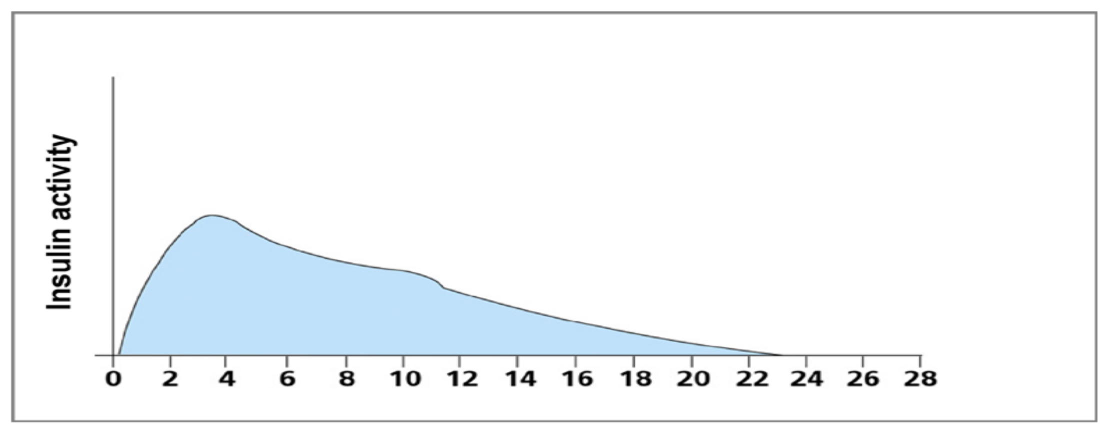


Patient 1

- Commence once daily Isophane insulin
  - Humulin I – Kwikpen
  - 10 units at bed time
- Stop Sitagliptin
- Continue on Gliclazide
- Titrate basal dose on fasting blood glucose levels, aiming for fasting 5-7 mmols.

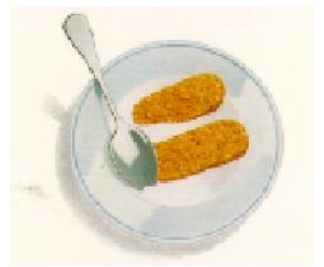
Twice Daily Biphasic Human insulin

- Consider if HbA1c ≥ 75mmol/mol (9%)
- If unable to achieve control on basal insulin
- Regular lifestyle
- Increased risk of weight gain / hypoglycaemia than with basal insulin
- NICE recommend Human Mixtures



BD Pre Mixed Human Insulin

6 7 8 9 10 11 12 1 2 3 4 5 6 7 8 9 10 11 12 1 2 3 4 5


Breakfast

Lunch

Evening Meal

Sleep

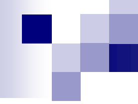
What are the choices?

- Humulin M3
  - Kwikpens (disposable device)
  - 3ml cartridge

- Insuman comb 15 / 25 / 50
  - 3ml cartridge
  - Solostar pen (disposable device) 25 mix only

Getting started

- In insulin naive patients usually start with:
  - 12 units am & 8 units pm or
  - 16 units am & 12 units pm in very overweight patients
- If switching from once daily basal insulin:
  - Consider reducing dose by 10 -20%
  - 2/3rds am 1/3 evening
- Need to be injected 30 – 40 mins pre meal
- Continue with metformin
- Continue the sulfonylurea initially, but review and discontinue if hypoglycaemia occurs.

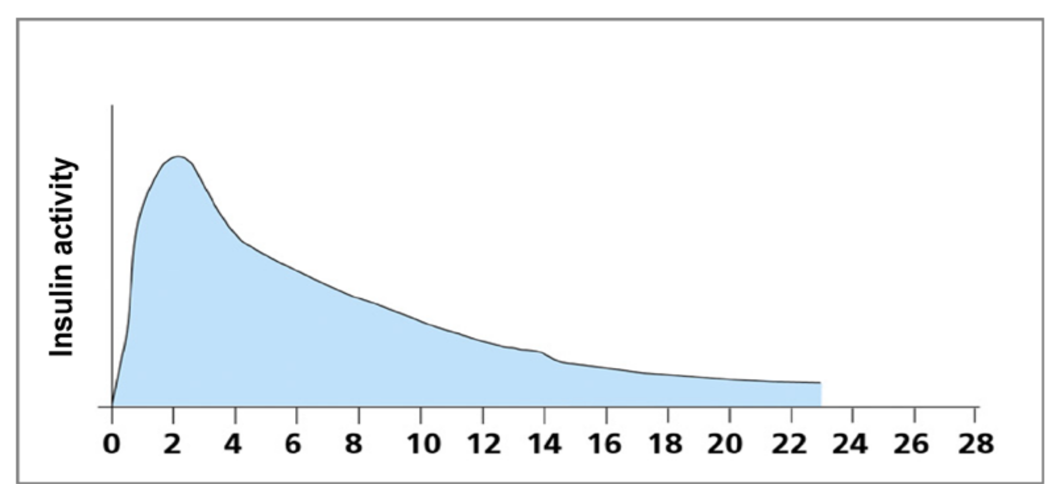


When to consider an analogue mix?

- Analogue mixtures provide a quicker onset of action and offer some advantage in people with post-prandial (after-meal) rises.
- May also help prevent hypoglycaemia in between meals due to shorter action of rapid insulin
- Injection timing an issue

Insulin Analogue Mixtures

- Inject twice daily, within 0 to 15 minutes before or after meals.
- Useful in rapid post prandial rise as works quicker



Humalog Mix25, Mix50

Novomix 30

What are the choices?

- Humalog Mix 25, 50
  - Kwik pen
  - 3ml cartdriges (Savvio pen)
- Novomix 30
  - Flexpen
  - 3ml Cartridges (Novopen 4)

Patient 2

- 63 year old lady, able to give own insulin
- Humulin I – 40 units before bed
- Metformin 1g BD
- Gliclazide 160mg BD

Breakfast	Lunch	Tea	Bed
6.5	12.5	16	17.6
8.5	9.0	12.5	15
7.6	7.9	11	10.5
8.2	8.2	12.3	13.0

Example 2

FBG satisfactory

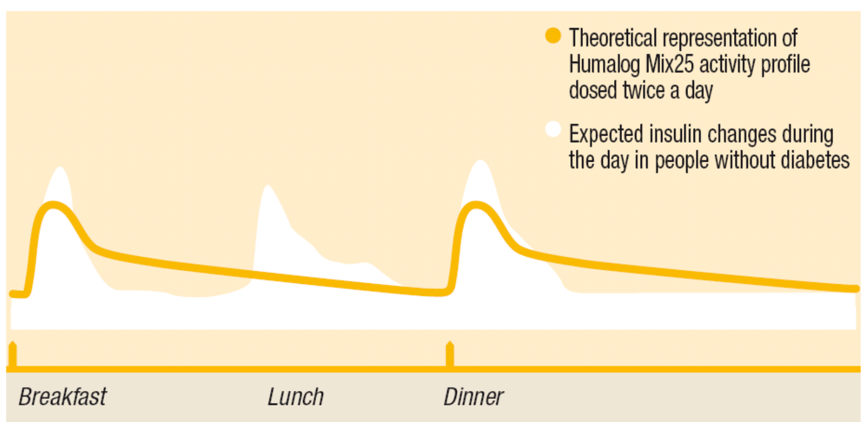
Main problem is elevation of levels during the day

Review HbA1c,

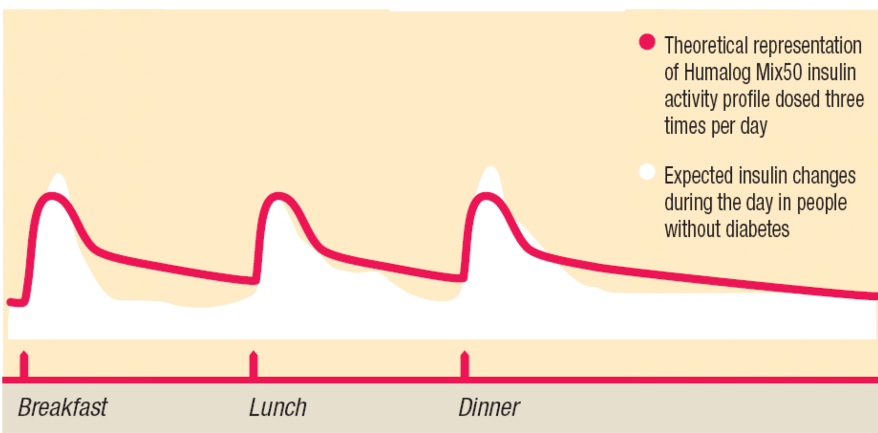
- Consider adding a dose of Humulin I with breakfast and titrate inline with blood glucose levels during the day – usually start with 10 units – may need to reduce bed time dose
- Switch to BD Mixed insulin – stop SU
- Reduce dose by 10% 2/3 AM, 1/3 Pm

TDS Insulin Mixtures

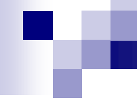
- ‘Humalog mix 50’or Novomix 30 generally ones of choice
- Higher amount of rapid acting insulin per dose
- Ideal for those with a high CHO intake with meals
- Generally given 3 times a day with meals
- Don’t usually use human mixed insulin due to the concerns re stacking of insulin and increased risk of hypoglycaemia



Theoretical representation of Humalog Mix25 activity profile dosed twice a day
Expected insulin changes during the day in people without diabetes
Breakfast
Lunch
Dinner



Theoretical representation of Humalog Mix50 insulin activity profile dosed three times per day
Expected insulin changes during the day in people without diabetes
Breakfast
Lunch
Dinner



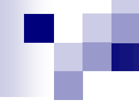
Basal plus

- Addition of prandial rapid acting insulin to basal insulin (Humulin I, Insuman basal, Insulatard)
  - Give rapid dose with main meal or highest post meal blood glucose level
  - Stepwise approach leading to injection with each meal
  - Usual starting dose 6 units
    - NovoRapid / Humalog / Apidra
- Continue on basal insulin

Patient 3

- 50 year old lady
- Humulin M3-36 units AM 24 units PM
- Metformin 1g BD

Breakfast	Lunch	Tea	Bed
6.5	7.5	15	8.2
7.5	8.1	12.5	9.5
6.9	6.5	14.3	8.5
8.0	6.9	15.5	10



Patient 3

- Elevated levels before evening meal
- Review diet
- Consider giving TDS mix 30 / 50 so lunch is covered with the quick acting component.

What else do we need to know?

- Blood glucose monitoring
- Hypoglycaemia management
- Illness management / sick day rules
- Injection rotation
- Driving
- Identification / insulin passport
- INSULIN TITRATION guidelines.

Blood glucose testing -

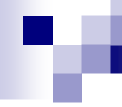
- Individual assessment based on
  - Number of injections
  - Occupation / driving
  - Treatment

- Consider post meal in patients who you suspect of post prandial hyperglycaemia.
- Meter standardisation in Type 2 diabetes
- Who to test, when to test

Treatment of hypoglycaemia

- Blood glucose below 4 mmol/l
  - 4- 5 glucotabs
  - 100mls lucozade
  - 3-4 jelly babies
  - 1x mini can of coca cola.

- RECOVERY 10 – 15 MINS
  - Longer acting Carbohydrate
  - 1 portion fruit / 2 plain biscuits / 1 slice of bread.

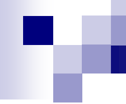


Sick day rules.

- Don't stop insulin
  - Blood glucose 13-17 mmol/L = 2 units extra
  - Blood glucose 17-22 mmol/L = 4 units extra
  - Blood glucose more than 22 mmol/L 6 units extra

  (if on over 50 units a day double the adjustments)
- Increase blood glucose monitoring usually every 4 hours
- Drink fluids – 100mL/hour prevent dehydration

Managing diabetes during intercurrent illness in the community February 2013 NHS Diabetes

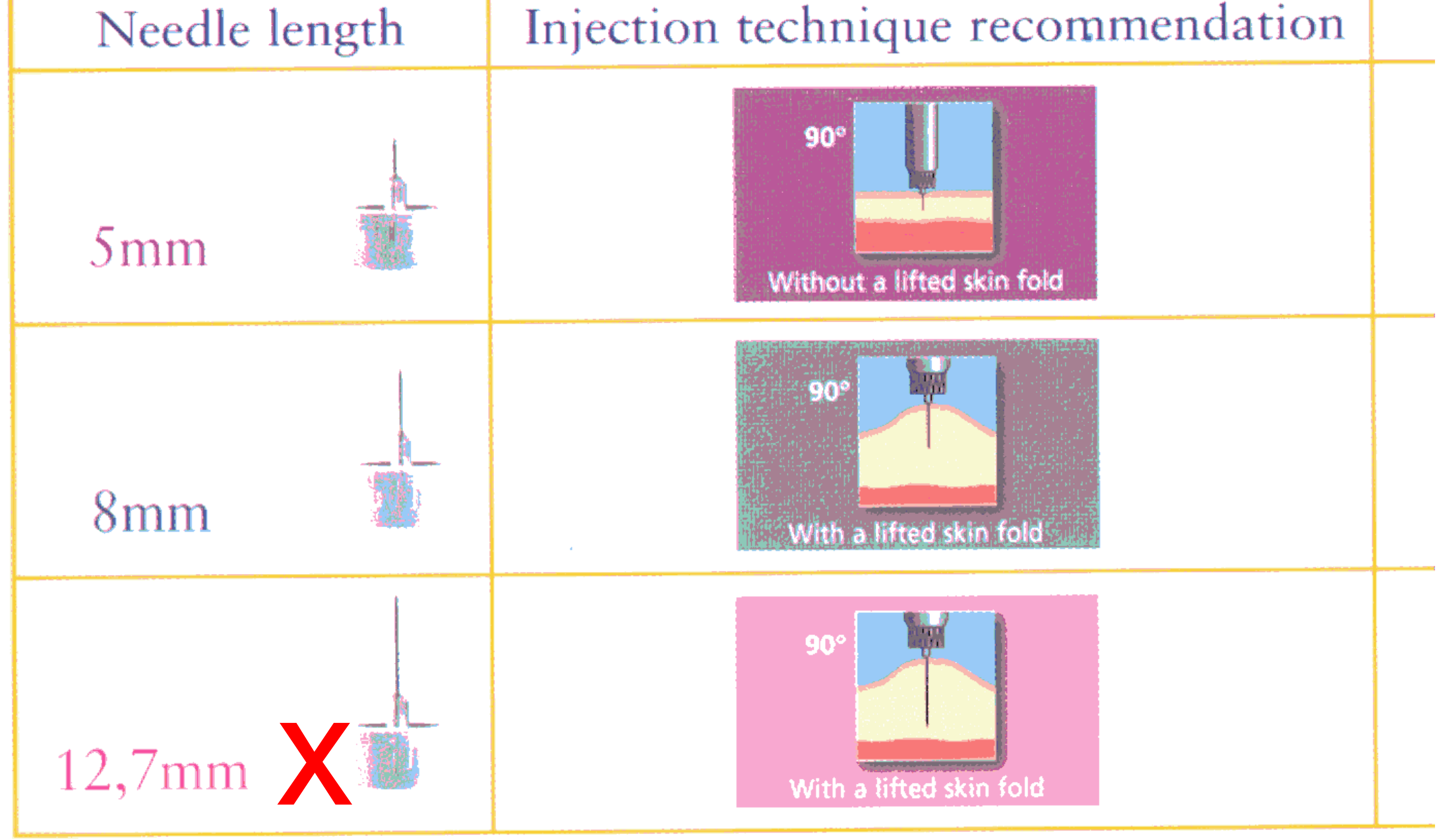


Travel

- Carrying insulin / frio packs
- Travel letter
- Time zones
- Foot care
- Identification
- Insurance

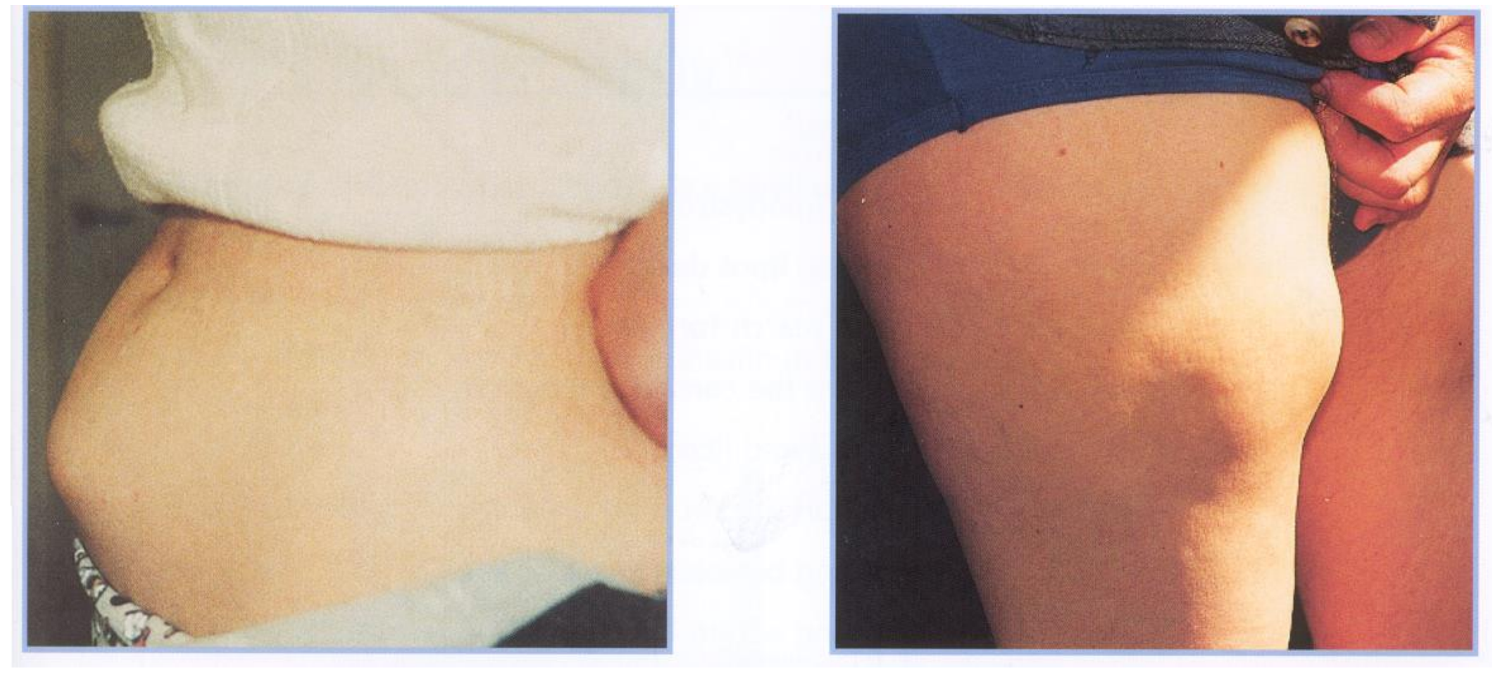
Needle size

4 or 5 mm needle length of choice



Needle length	Injection technique recommendation
5mm	90° Without a lifted skin fold
8mm	90° With a lifted skin fold
12,7mm X	90° With a lifted skin fold

Lipohypertrophy



DVLA requirements

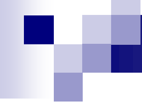
- Specific to insulin treated patients with group 1 entitlement
  - Must have awareness of hypoglycaemia
  - Must not have had more than one episode of hypoglycaemia requiring assistance of another person in the preceding 12 months
  - There must be appropriate blood glucose monitoring
  - Must not be regarded as a likely source of danger to the public while driving
  - The visual standards for acuity and visual field must be met.

What to include in the annual review!

- Understanding of:
  - Hypoglycaemia status and management
  - Sick day rules
  - Check for lipos
  - Injection technique – are they reusing needles!
  - Sharps removal
  - When to seek help and by whom
  - Dietary update
  - Driving status and DVLA recommendations
  - ID
  - How to titrate doses

Titration guidelines

Fasting blood Glucose mmol/l	Action
>10	Increase by 4 units
8 – 10	Increase by 2 units
5 - 7	No change
3 - 5	Reduce by 2 units
<3	Reduce by 4 units



Summary

- Consider human basal and human mixed insulin initially
- Analogue basal and analogue mixed insulin to be considered only when clinically indicated
- Take care with people taking animal insulins – they are most probably on these for a reason !!!
- Analogues are routinely used in the management of type 1 diabetes.

And finally !

- Stepwise approach to insulin regimes
- Newer therapies should be considered first especially if weight / hypoglycaemia risk is an issue
- No one insulin regime fits all
- Intensification necessary in majority of patients
- Individual assessment on most appropriate regimen is required

Cost comparison

based on prefilled disposable pens x5

	Basal	Biphasic
Lilly	**Humulin I** **£21.70**	**Humulin M3** **£21.70** Humalog Mix 25 / 50 £30.98
Novo Nordisk	**Insulatard** **£20.40** Levemir £42.00 Degludec £72.00	Novomix 30 £29.89
Sanofi Aventis	**Insuman Basal** **£19.80** Lantus £41.50	**Insuman Comb 25** **£19.80**

Insulin regimens for type 2 diabetes compared

Basal	BD Human Mixtures (30/70)	BD Analogue Mixtures	TDS Analogue Mixtures	Basal +,++,+++*	Basal Bolus
• 1 insulin • 1-2 injections	• 1 insulin • 2 injections	• 1 insulin • 2 injections	• 1 insulin • 3 injections	• 2 insulins • 2,3,4 injections	• 2 insulins • 4/5 injections
Pros • Simplicity • Once daily blood testing	**Pros** • Simplicity • Covers breakfast and evening meal	**Pros** • Simplicity • Inject and eat • Covers breakfast and evening meal • Maybe used where hypoglycaemia is a problem with human mixtures	**Pros** • Inject and eat • Covers breakfast, lunch and evening meal • Simple fixed mixture	**Pros** • Flexibility to have irregular meal times • Inject and eat	**Pros** • Flexibility to have irregular meal times Inject and eat
Cons • Controls background blood glucose only	**Cons** • Lack of flexibility • Regular meal patterns • Inject about 30 mins prior to meals • Regular snacks	**Cons** • Lack of flexibility • Regular meal patterns	**Cons** • Lack of flexibility • Regular meal patterns	**Cons** • Requires self titration and carbohydrate counting * + indicates the addition of a bolus insulin	**Cons** • Requires self titration and carbohydrate counting • Frequent blood glucose monitoring

LOW — Patient Skills and Capabilities — HIGH