Ultimate guide to mealtime insulin dosing with Type 1 Diabetes

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Type 1 Diabetes since 2008

(Watch me)

Contents

Abbreviations

AA = Amino Acid

ADP = Adenosine Di Phosphate

ATP = Adenosine Tri Phosphate

AUC = Area Under the Curve

BCAA = Branches Chain Amino Acids

Ca = Calcium

CGM = Continuous Glucose Monitoring

FFA = Free Fatty Acid

FPU - Fat and Protein Units

GDH = Glutamate Dehydrogenase.

GI = Glycaemic Index

GL = Glycaemic Load

GLP-1 = Glucagon-like peptide-1

GIP = Gastric Inhibitory Polypeptide

GPCR = G-Protein Coupled Receptor

I:G = Insulin to Glucagon ratio

ICR = Insulin to carbohydrate ratio

MDI = Multiple Daily Injections

MUFA = Monounsaturated Fatty Acids

KATP = ATP-regulated potassium channel

mTOR = mammalian target of rapamycin

SFA = Saturated Fatty Acid

TCA = Tri-Carboxyl-Acid cycle

Introduction

After being diagnosed with Type 1 diabetes, your first job is to get over the initial shock, because a month ago you felt in great shape.

You're then told your B-Cells has been attacked by your own immune system. Nobody knows exactly why, but your pancreas will never produce sufficient insulin again.

Then the big bomb. You need to inject or pump insulin into your body. Not just that, but in the exact amounts your B-Cells would have delivered, if they were working effectively!

Why?

To keep your blood glucose level between 4.0 - 7.0mmol/l (70 - 120mg/dl), so that you stay healthy now, and in the future.

Then it dawns on you:

> **"To deliver the right amount of insulin, my decisions must match that of my B-Cells."**

This realisation seems daunting at first, but then you get a lot of education (hopefully) to help you make those decisions.

Education such as:

- Carbohydrate counting
- How to use an insulin to carbohydrate ratio (ICR)
- Exercise management
- Maybe some information of Glycaemic Index (GI)
- Maybe some information on meal planning

The education does the trick. Your blood glucose levels stay in target, and you are super motivated. Then Boom, reality hits! The remaining B-cells are killed off, and your motivation waivers. The honeymoon is over, and you start to notice a few things:

- Carbohydrate counting does not always work. Despite counting to the gram, your blood glucose goes high when eating:
    - Pizza
    - Cheesy pasta dishes
    - Traditional English fry ups (toast, sausage, beans, bacon, egg)
    - Takeaways and fast foods meals
    - Three course meals with a big tasty dessert at the end

- When you have salad with a large protein source, your blood glucose level goes high despite having no carbohydrate on the plate.

- When you have carbohydrate only meals, such as fruit, you go hypo

What do you do next?

Ask your diabetes team, Dr. Google, or the diabetes online community?

A mixture of all three most likely. This leads to a variety of different answers and solutions. sound familiar?

- You must not be counting your carbs correctly, get weighing again. Most often from your Diabetes Team. This is not disrespecting diabetes teams, as I am diabetes dietitian by trade, and I USED to say that all the time!

- You need to count every gram of protein and fat and adjust insulin according. Have you not heard of the Warsaw method?

- You need to match your insulin delivery to the insulin demand for the whole meal. Have you not heard of the Food Insulin Index (FII) and Food Insulin Demand (FID) system?

- Take the low carbohydrate approach, which comes in different guises:

    - Cut your carbohydrate to a lower amount,50-200g per day, and up your protein and fat.

    - The Dr Bernstein approach (Bernstein, 2011). Cut your carbs right down to under 50g (ideally no more than 24g), up the protein considerably, and have moderate fat.

- Stop being a sugar burner, become a fat burner, **Keto is the only way!** Cut carbs to less than 50g per day, small to moderate protein, and fat should make up 70-80% of total energy intake.

What advice should you take?

This is the million-dollar question. Unfortunately, there is no simple answer that applies to everyone.

Some questions that are good to ask yourself;

- What impact will a certain type of diet have on my overall health in the long-term, even if it does improve my diabetes control?

- Does the diet provide my body with all the vitamins and minerals it needs to sustain my overall health?

- Can I honestly see myself sticking to the suggested food choices?

- Can I follow this when I socialise with friends?

- What insulin dosing strategy do I need use to get in target blood glucose levels with this type of diet?

- If I choose one diet today, does that mean I need to follow that for the rest of my life?

- Can I switch between different types of nutritional intake from meal to meal, day to day, week to week?

Today there is a wealth of information on the internet, and no shortage of people telling you there is only one way, THEIR WAY.

Some of the approaches are first class, some are money making scams, and others are promoted by people who have had enormous personal success, and think everyone should follow their approach.

The challenge is deciphering the Wheat from the Chaff.

I posed the above questions to myself nearly ten years ago. This led me to trying all approaches to see what works. It was a fun and challenging journey, but looking back, I realise I missed the most important questions:

- How much insulin do the B-Cells release after eating different combinations and amounts of carbohydrate, fat and protein?

- How much insulin is needed after eating for key metabolic processes, such as growth and repair?

- How much insulin is needed after eating to balance the effect of Glucagon, which is released from the A-Cells?

- Does it matter that I inject insulin, rather than having it delivered direct from the B-Cells?

- Are there any other hormones released from the B-Cells that need to be considered?

Answering these questions gave me the ability to match what my B-Cells would have done, if they were fully operational. If you invest the time to gain this knowledge, you can be very flexible with your dietary approach, whilst still achieving first class diabetes control.

Within these pages I have condensed ten years of research, clinical practice and experimentation:

- How the pancreas behaves after eating to keep blood glucose levels in target.
- What is different for people with Type 1 Diabetes.
- How the gap can be bridged with novel insulin dosing strategies.

Once you're comfortable with the this, we will move on to critique the commonly used insulin dosing strategies.

Finally and most importantly, we will discuss which insulin dosing strategies best fit the different nutritional approaches**. This flips the current way of thinking on its head**. The traditional approach is;

> "Here is your insulin dosing strategy, carbohydrate counting and an ICR, now fit your diet around it."

Imagine if it was the other way round;

> "Choose the diet that best suits you and your goals, then select an insulin dosing strategy that matches it."

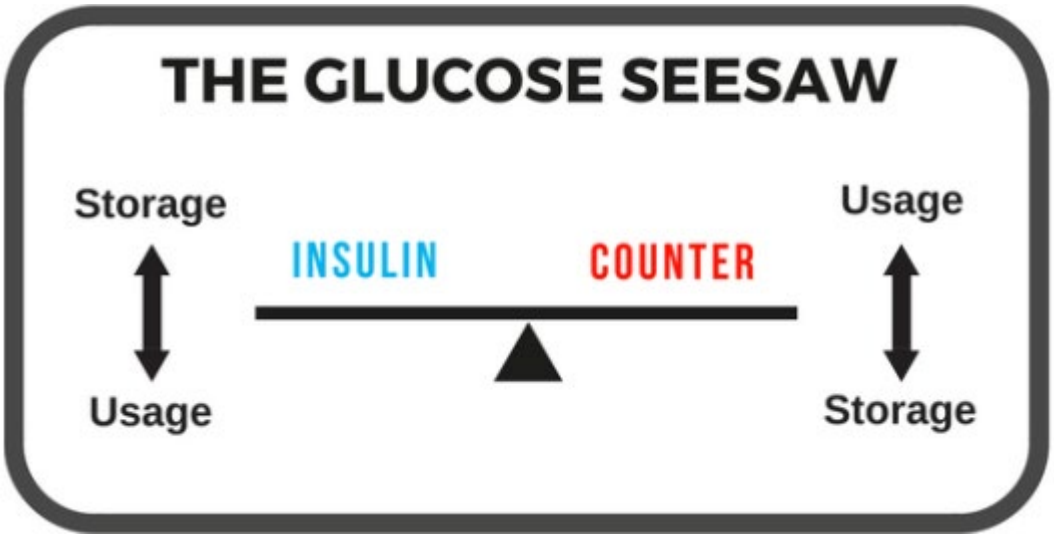
Before we get stuck in, I have to tell you there is some in-depth discussion regarding the physiology and nutritional biochemistry. If deep is not your thing, go straight to the summary sections for the highlights. If you love detail, you will love the full experience, Enjoy!

Do you have time and want a deep understanding into all this stuff? If so, go and read this PhD thesis, what I consider the bible by Kristine Bell (Bell, 2014). You will recognise a lot of my summaries contain the essence of Kristine's work. Please understand what you about to read is heavily influenced by Kristine's work! Why re-invent the wheel when someone has already made 22-inch alloys!

The main research group providing the key insights for insulin dosing strategies are from the University of Newcastle, New South Wales, Australia. You could look at the research profiles of Doctor Carmel Smart or Doctor Kirstine Bell to get the latest in this area.

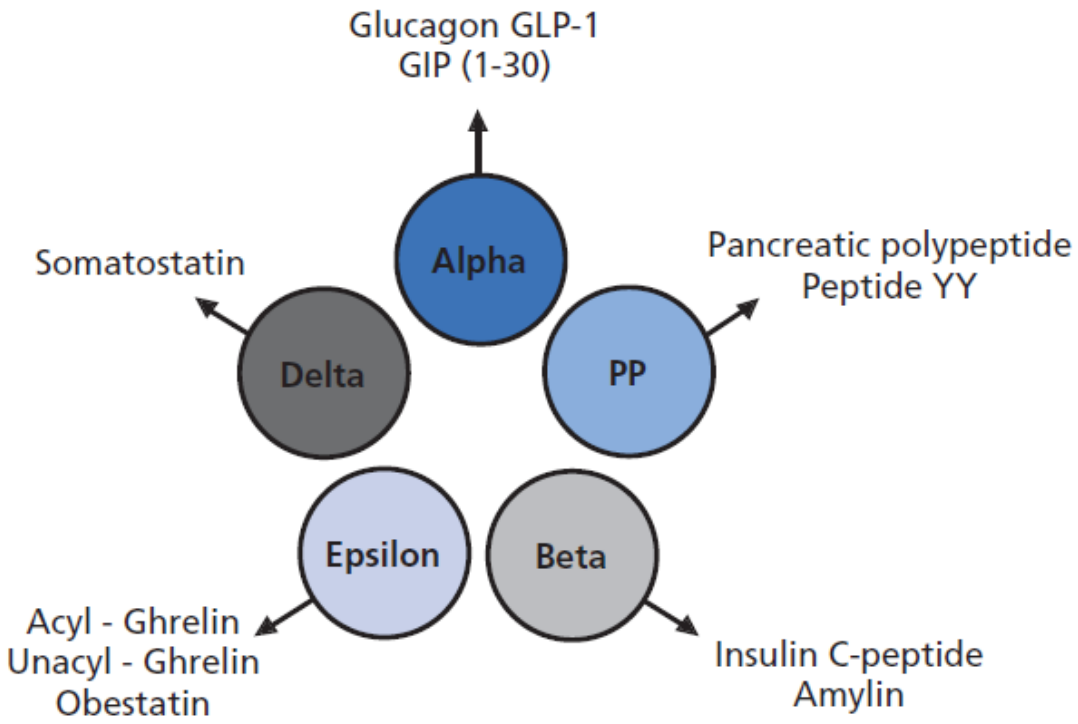
The insulin to glucagon ratio (I:G)

After eating your blood glucose level is mainly determined by two hormones that are secreted by the pancreas, Insulin and Glucagon. An easy way to remember the basic principle is to think of a Seesaw. When your INSULIN is high and glucagon (glucagon is one of the COUNTER-regulatory hormones, along with Cortisol and adrenaline) low, you have a high I:G,and your body is in energy storage mode. When your I:G is low, your body is in energy usage mode.



It is a little more complex, that's why we must consider all the hormones secreted by the pancreas cells.

Before going on I encourage you to go and get this MUST READ (Hughes and Narendran, 2014). I have summarised the key information, but there is no substitute for reading the source.



Adapted from (Hughes and Narendran, 2014)

At this stage you just need to recognise the different types of cells, and what hormones they secrete. We will move into why these are important, and under what circumstances they get secreted later.

Our main focus is discovering what happens when the I:G changes, and understanding the blood glucose consequences .

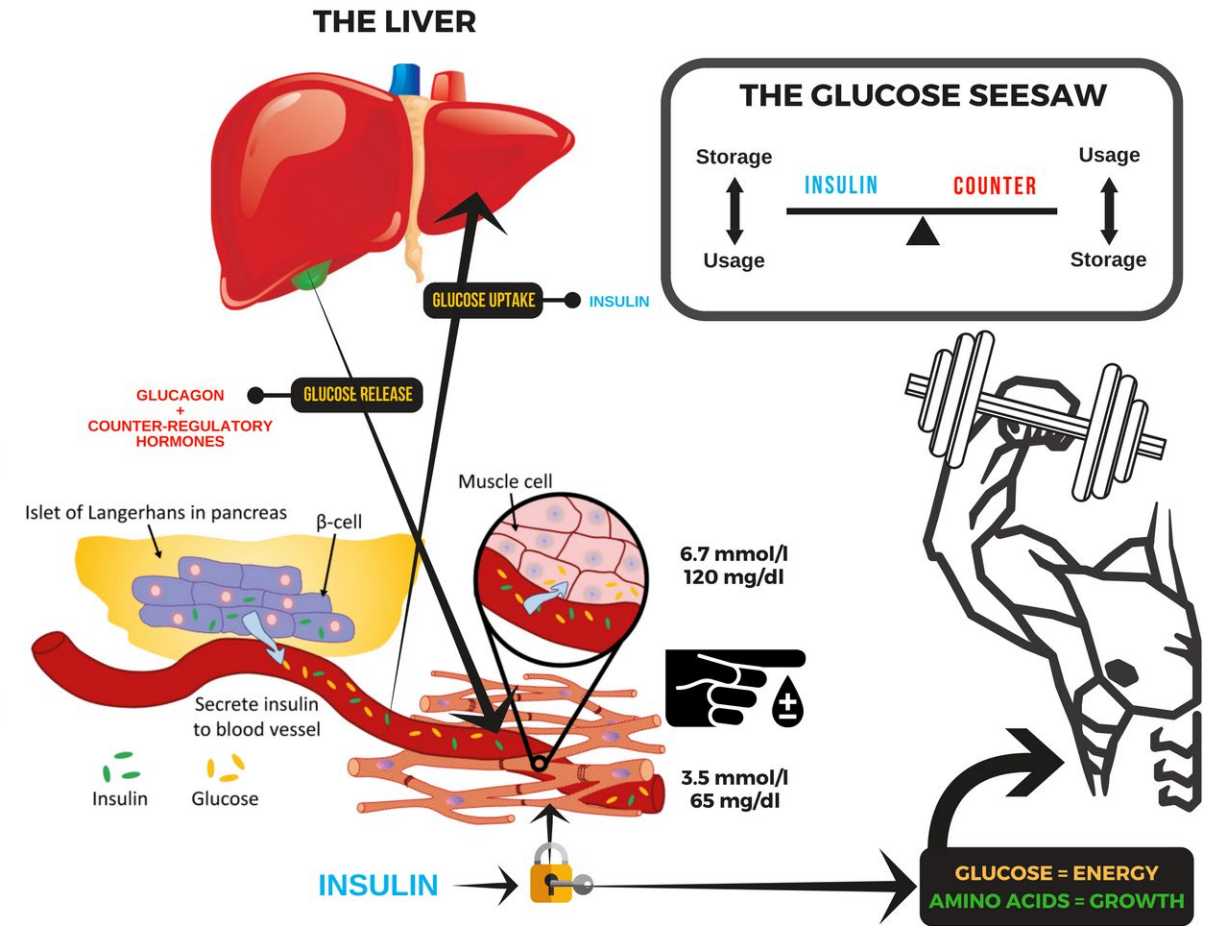
Let's get started with Insulin.

Insulin

Insulin is the main hormone secreted from the B-Cells of the pancreas. Insulin has an enormous number of direct and indirect effects on metabolism. We shall focus our discussion on the main ones of:

- Anabolism: using AA (amino Acids) for the synthesis of more complex molecules, mostly for growth and repair.
- Energy storage: Glucose as Glycogen and Free Fatty Acids (FFAs) as Fat.
- Energy production: the movement of Glucose into cells to be used as fuel.

Insulin moves glucose and AA from the blood into the cells of the body. Consider insulin as a key that unlocks the body's cell doors to allow glucose and AA to enter, a bit like a bouncer on a club door. See the below diagram for an overview. The next sections discuss what happens to the glucose and AA once they have been transported into the body's cells.

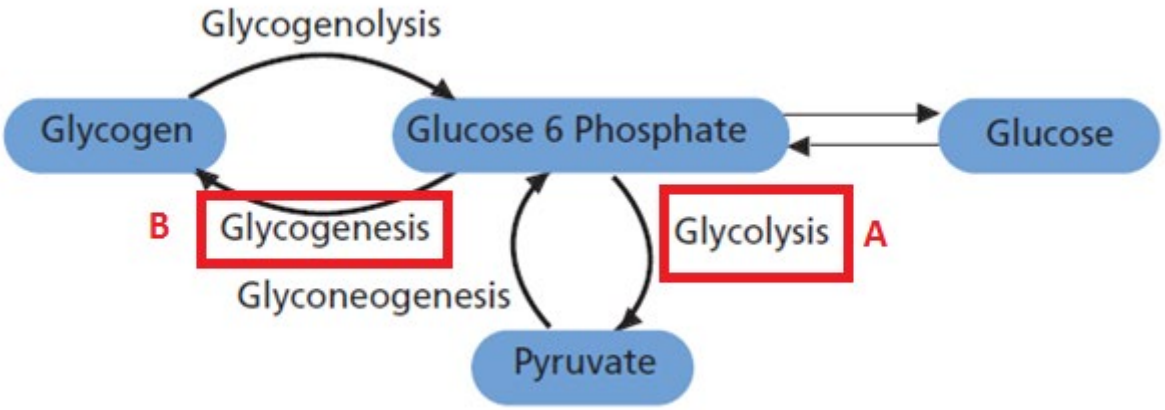


Glucose

Once glucose is transported into the cells by insulin, it can take several paths depending on the energy state of the cells:

A. **If the cells have a low energy state**, glucose will be metabolised immediately to produce energy, by a process called glycolysis.

B. **If the cells have a medium to high energy state**, glucose will be stored glycogen, which is a collection of glucose molecules bonded together, by a process called glycogenisis. This happens in the liver cells first, and later in the muscle cells.



Adapted from (Hughes and Narendran, 2014)

C. **If the cells have a very high or excess energy state**, glucose can be converted into fat in the liver cells, by a process called lipogenisis, the creation of new fat. You have to be continually overfeeding for this to happen. But as half of the population is overweight or obese, it's happening far more frequently than it should!

Amino Acids

Once AA's are transported into cells by insulin, they can take several paths depending on the energy state of your cells.

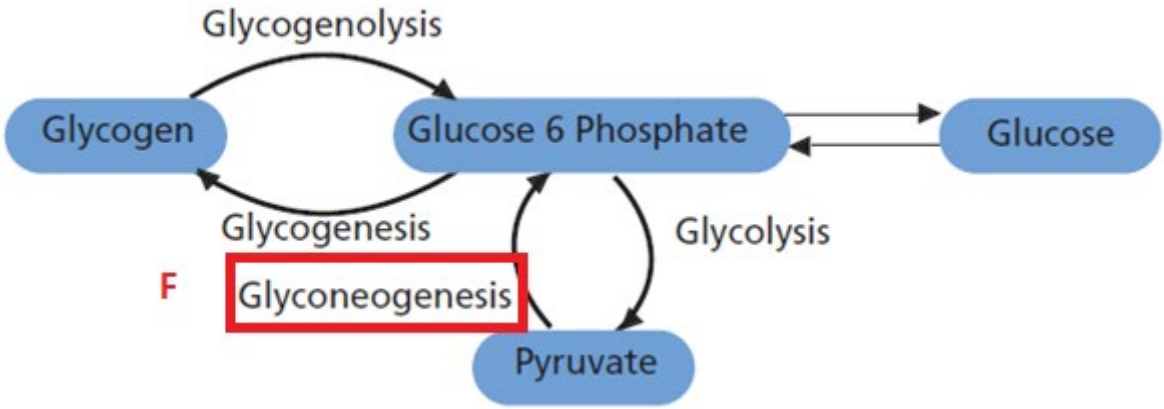
D. **If the cells have a low energy state**, AA can be converted into substrates for the production of energy from glycolysis. Think of substrates as an assembly line worker needed to produce car part. The worker is not the car part, but he is needed to ensure the process is done quickly and efficiently.

E. **If the cells have a medium to high energy state,** AA's will be used as building blocks for a massive array of metabolic processes that allow repair, regeneration and growth. Some of the more important ones are:

   - **Anabolism**: muscle protein synthesis allows your muscles to adapt and remodel in response to the daily stresses.

   - **Enzyme production** to ensure all the metabolic processes that are essential to sustain life run smoothly.

F. **If cells have a very high or excess energy state**, the AA not used as building blocks will be used for future energy production.
   - Excess AA's can be used as substrate to increase glycogen by a process call Glyconeogenisis.



Adapted from (Hughes and Narendran, 2014)

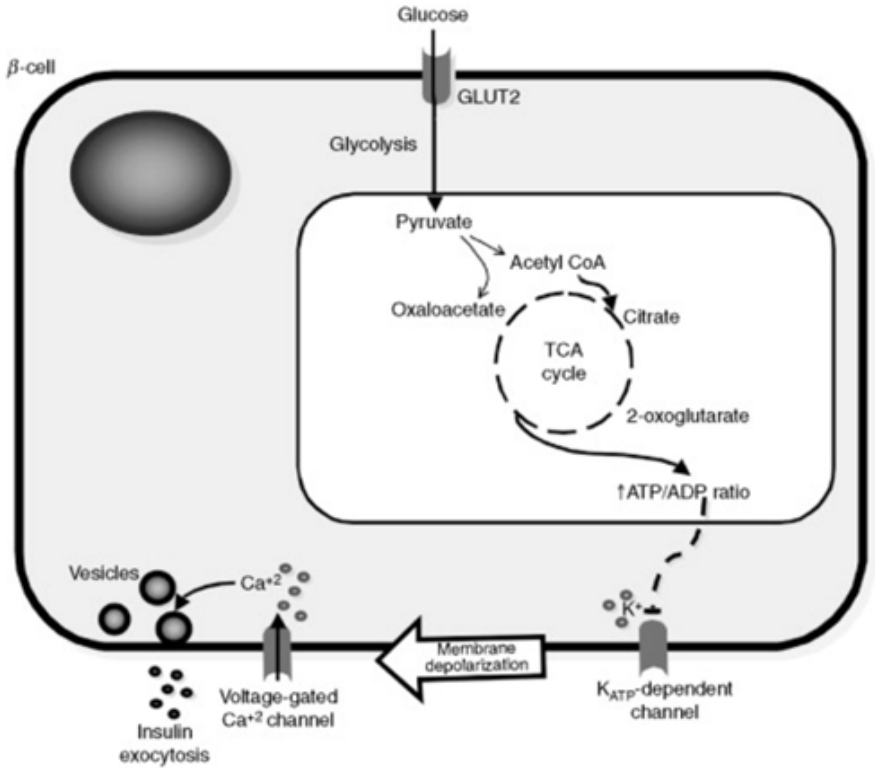
   - Or AA will be converted into new glucose that is delivered into the blood stream by a process called Gluconeogenisis. This basically means the creation of new glucose.

The regulation of insulin secretion

The regulation of Insulin secretion is very complex, and not yet fully understood. However, the key-regulators are well documented and are presented here.

Glucose

The major positive regulator that stimulates insulin secretion is an elevation of glucose in the B-Cell, as shown below by the diagram below.



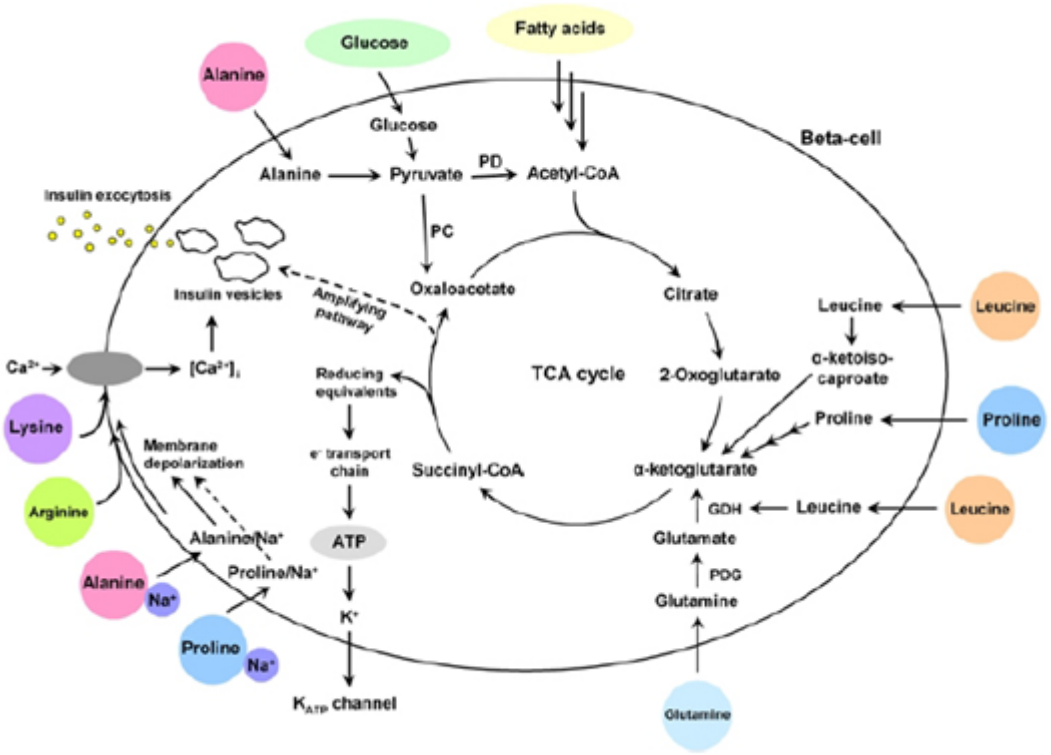
Adapted from (Bell, 2014)**:** The high energy state of the cell (high ATP/ADP ratio), from increased glucose availability and glycolysis, leads to depolarisation of the B-Cell membrane. The membrane depolarisation increases in-flux of Ca (Calcium), leading to insulin exocytosis from the form the vesicles into the blood stream.

Put simply, the B-Cell increases its energy state due to increased glycolysis and stimulates insulin secretion in dose-dependent manner.

Amino Acids

AA's can stimulate insulin secretion from the B-Cell by providing substrates to the Tri-Carboxyl-Acid cycle (TCA). The increase substrate availability speeds up energy production and increases energy state of the cell, a high ATP:ADP ratio. This elevation of energy state causes B-Cell membrane depolarization and insulin exocytosis. The speed and frequency of membrane depolarisation from elevated AA's in the B-Cell compared to glucose, is much slower and lower.

The below graphic shows where the different AA provides substrate for the TCA cycle to increase the ATP/ADP ratio. The graphic also shows the synergistic metabolic pathways that allow specific AA's to stimulate insulin secretion.



Adapted from (Bell, 2014)

Arginine

Arginine is the most potent stimulator of insulin release in the presence of glucose in the B-Cell when given intravenously. It directly increases Ca stimulated insulin secretion by depolarising the membrane. However, when Arginine supplements are consumed orally, it is not possible to get a high enough blood level to stimulate insulin secretion without causing diarrhoea (Gannon, Nuttall and Nuttall, 2002). Making it practically insignificant.

Leucine

Leucine when given intravenously is a very potent for increasing insulin secretion (Floyd *et al.*, 1966). This has been confirmed when ingested orally in combination with carbohydrate. Leucine was significantly correlating with the two hour postprandial insulin response (Van Loon *et al.*, 2000).

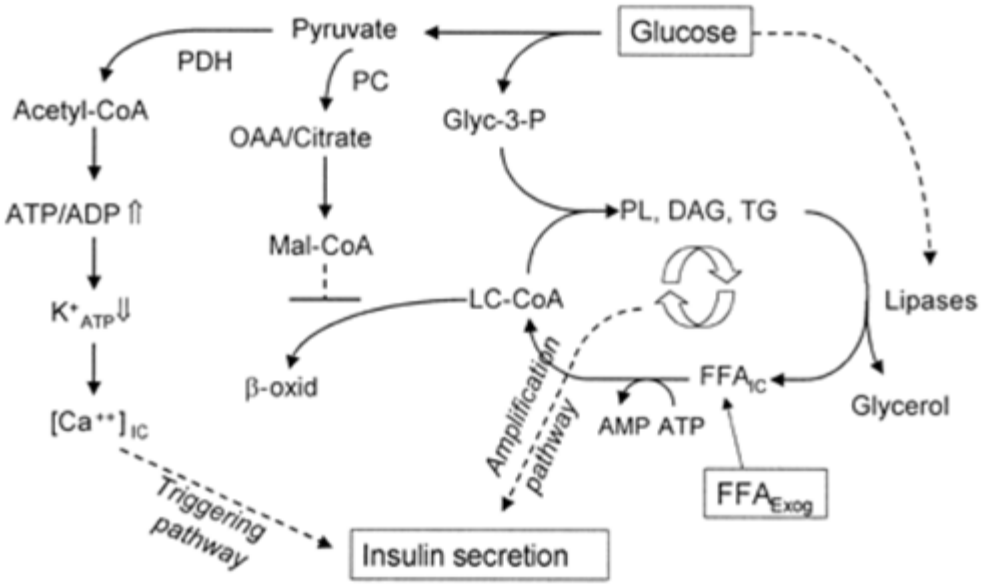
B-Cell studies have shown that Leucine activates glutamate dehydrogenase (GDH) in the B-Cell, therefore acting as both a substrate and positive regulator. GDH is a key enzyme controlling AA metabolism in the B-cells. GDH activation increases glutaminolysis and causes a subsequent increase in the TCA cycle activity, inhibition of the ATP-regulated potassium (KATP) channel activity, and thus enhanced insulin secretion (Yang *et al.*, 2010).

Another mechanism by which Leucine may stimulate insulin secretion is through the activation of mammalian target of rapamycin (mTOR). Activation of mTOR significantly increases gene transcription and protein synthesis in pancreatic B-cells, which in turn increases insulin secretion (Yang *et al.*, 2010).

Dairy products, particularly whey protein, are well-known to increase insulin secretion despite their low glycaemic impact. The increase secretion has been attributed to the high Leucine content. The rapidly available Leucine in the blood from quickly digested Whey elicits a stronger insulin response compared to casein. This is because although casein has high Leucine content, the proteins are coagulated, therefore blood Leucine concentration does not rise as rapidly (Van Loon *et al.*, 2000).

Free Fatty Acids

FFA's do not stimulate insulin release directly, however their presence is essential for glucose stimulated insulin secretion. A high FFA level amplifies the glucose stimulated insulin response (Poitout, 2003). The diagram below shows an abundance of FFA changes the metabolic flux to promote glycolysis, which drives membrane depolarisation, and subsequent insulin secretion.



Adapted from (Bell, 2014)

Fat ingestion also increase GLP-1 (Glucagon-Like-Peptide 1), which directly stimulates insulin release (Poitout, 2003). Acute FFA stimulates insulin secretion, however chronic exposure to high FFA levels leads to B-Cell death (Poitout, 2003).

Incretin Hormones: GLP-1 & GIP

GLP-1 and Gastric Inhibitory Polypeptide (GIP) are the two incretin hormones that are secreted by enteroendocrine cells in the intestine. GLP-1 is synthesised in the L-cells of the intestines and the A-Cells of the pancreas. GLP-1 has the most potent positive regulation on insulin secretion of the incretin hormones. GIP is synthesised in the K Cells and is weaker stimulating insulin secretion when compared to GLP-1. GIP is more potent at stimulating Glucagon secretion from the A-Cells, which we will discuss later. The picture below that shows the incretin hormones dynamic relationship, among many other signalling pathways of the B-Cell. The solid line represents positive regulation, the dashed line represents negative regulation.

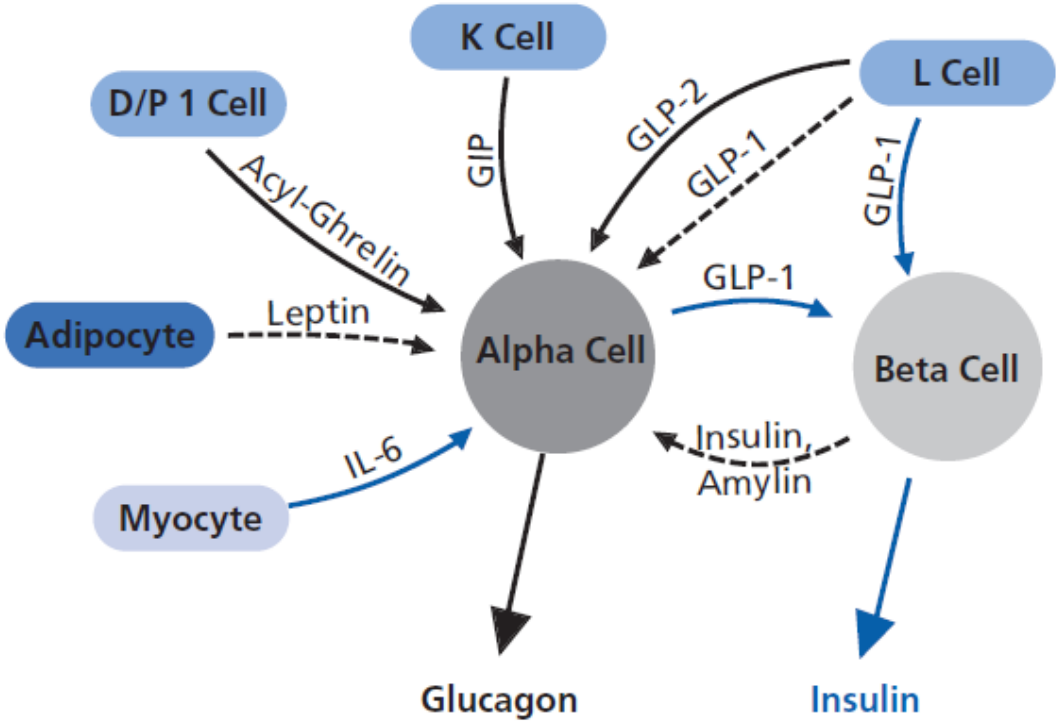
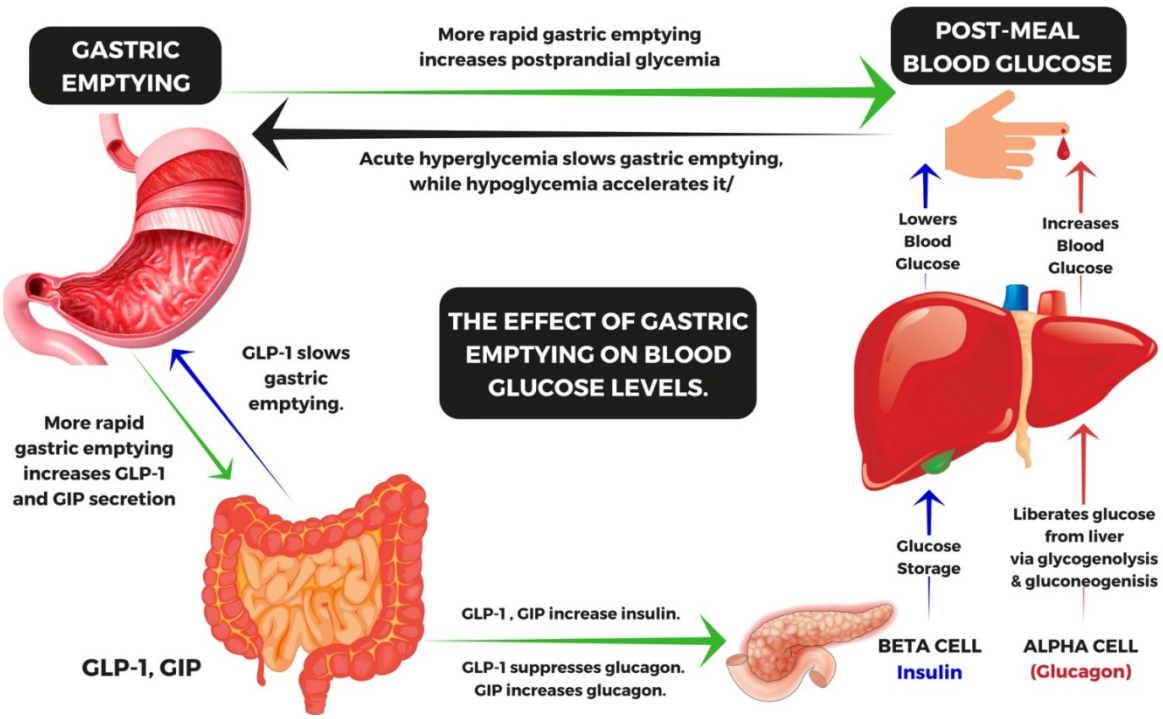


Figure Copied from (Hughes and Narendran, 2014)

The diagram below shows that GLP-1 and GIP play a major role in the speed of stomach emptying. It also highlights their regulatory effect on the B-Cells and A-Cells of the pancreas.



GLP-1 and GIP release follows a biphasic pattern, early release within 5 to 15 minutes, and a prolonged release follows within 30 to 60 minutes. The early phase release is likely due to neural signals from food anticipation, because the nutrients cannot have reached the K and L Cells by that time. The latter phase is when glucose, FFAs and AAs reach the L and K Cells.

The incretin hormones cause insulin secretion by binding to their specific receptors, GIPR and GLP-1R, on the B-cell. This activates a host of metabolic processes resulting in closing the KATP channels, elevation of the intracellular Ca concentration, increasing mitochondrial ATP synthesis, all of which ultimately enhance exocytosis of insulin.

This GLP-1 positive regulation of insulin secretion is dose-dependent, and often accounts for half of the total insulin secretion. GLP-1 is most strongly secreted in response to ingestion of glucose and least by the ingestion of FFA's, while AAs are an intermediate stimulus (Carrel *et al.*, 2011). **This point is crucial to remember, write it down.**

Summary **(Watch me)**

There are multiple regulators of insulin secretion from the B-Cells, if the B-Cells are functioning normally. The key ones stimulating insulin secretion by positive regulation are:

- Glucose
- AA, especially Leucine
- GLP-1

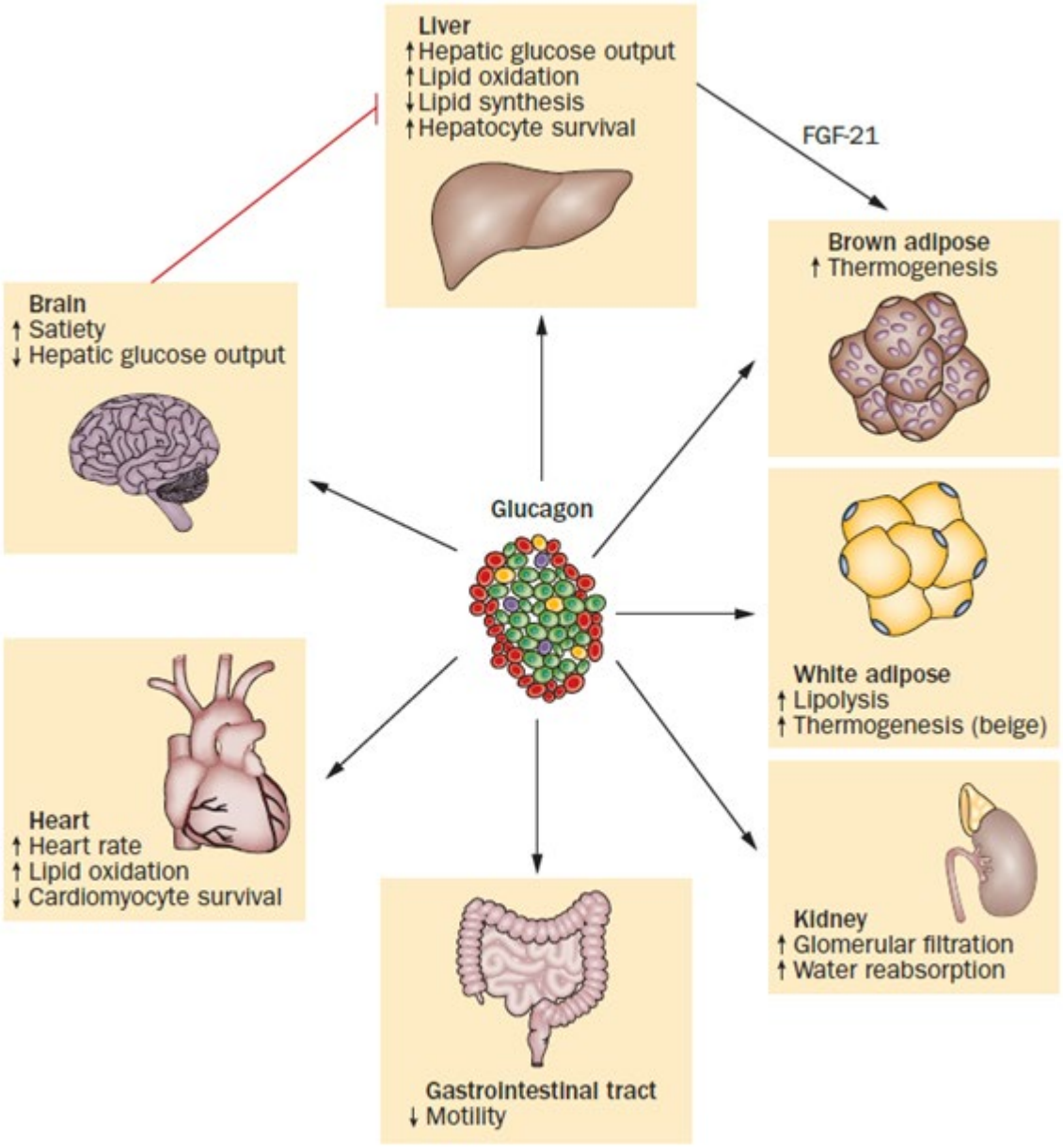
When the B-Cells have been destroyed, as happens with Type 1 Diabetes, all these signals are lost. Therefore, the job of a person with Type 1 Diabetes is to match insulin delivery to what the B-Cells would have secreted in response to the meal composition, so that:

  - Glucose can be transported from the blood into the cells for usage via glycolysis, and storage as glycogen.

  - AA can be transported into cells for protein synthesis, enzyme re-generation, and to provide substrate for glucose metabolism.

Glucagon

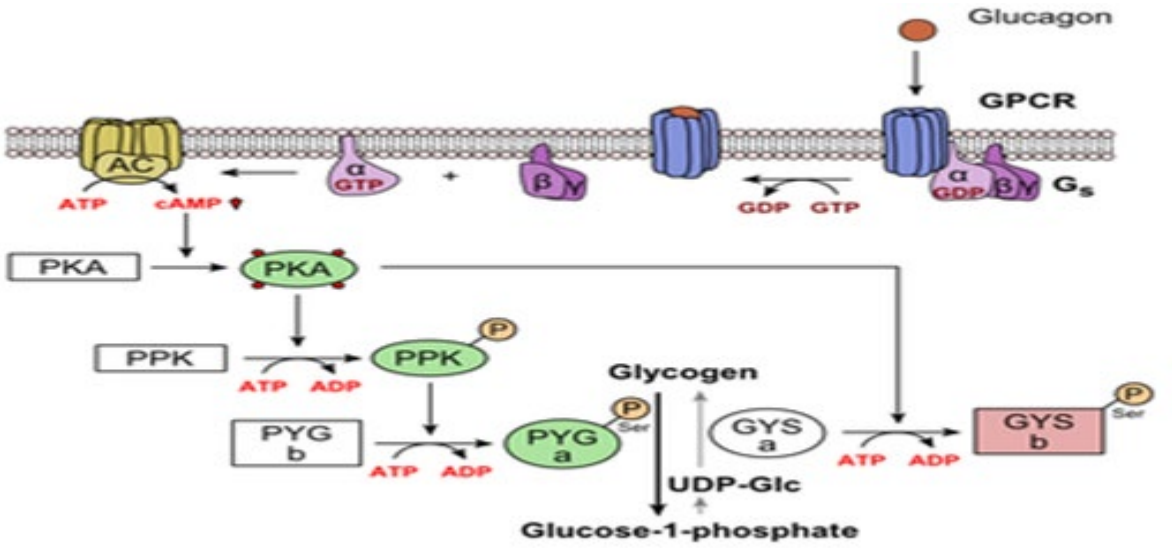
Glucagon is the main hormone secreted from the A-Cells of the pancreas. It has many functions in catabolism**,** the breaking down of more complex molecules, which include glucose liberation, glucose creation, and energy production. The diagram below shows the sites glucagon exerts an effect, and the number of different metabolic processes it initiates.



Adapted from (Hughes and Narendran, 2014)

For the purpose of our discussion, the main focus is glucose liberation, which is achieved through the G-Protein Coupled Receptor (GPGR). GPCR is a single G protein-coupled receptor expressed in the liver as well as multiple tissues, such as the brain, heart, kidney,

gastrointestinal tract and adipose tissues. Once Glucagon hits the GPCR, you can see in the below diagram the cascade of metabolic processes, leading to increasing glucose availability from glycogen.

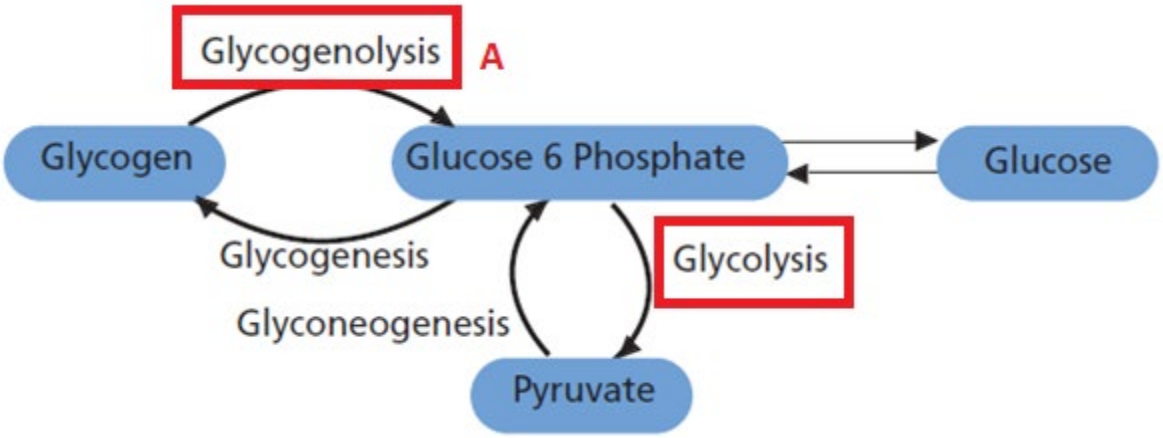


Adapted from https://en.wikipedia.org/wiki/Glucagon

The metabolic processes glucagon initiates depends on the energy state of the cells it binds to:

1) **If the cells have a low energy state or the I:G is low,** Glucagon will ramp up energy production and glucose availability for usage by;

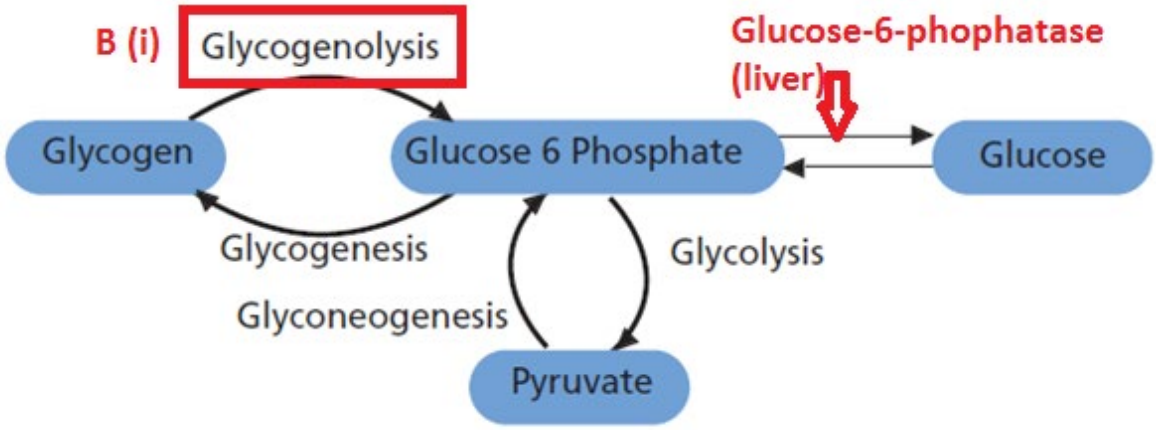
    a) Glucagon will liberate glucose from glycogen, by a process called **glycogenolysis**, simply the breakdown of glycogen to free glucose. The glucose will be metabolised to produce energy via glycolysis



Adapted from (Hughes and Narendran, 2014)

b) Glucagon will ensure the blood glucose level is maintained by acting primarily in the liver:

i) Liberating glucose from liver glycogen, by a process called **liver glycogenolysis,** so it can be pushed into the blood to supply the body's cells with glucose. Glucose-6-phophate from liver glycogenolysis can be metabolised to glucose by the enzyme Glucose-6-phosphatase. The glucose can then freely move from the liver cells into the blood. This cannot happen in the muscle cells, because they lack the Glucose-6-phosphatase enzyme.



Adapted from (Hughes and Narendran, 2014)

ii) A low I:G is needed for the liver to release glucose (Nuttall, Ngo and Gannon, 2008). This is important for people with Type 1 Diabetes for two reasons:

(1) When insulin delivery is too high, this stops glucagon liberating glucose from the liver when needed. This results hypogylcaemia.

(2) When insulin delivery is too low, or non-existent, the influence of Glucagon in the liver is exaggerated. This results in increasing glucose levels.

iii) Glucagon will start a cascade of events that creates new glucose from AA, this process is called **Gluconeogenisis,** basically the creation of new glucose.

(1) A massively important point here is that the rate of Gluconeogenesis is very stable on a day to day basis, regardless of diet type. A comprehensive research review shows that Gluconeogenesis is a demand driven process. In the normal person who is not fasting, the demand stays extremely stable, so

production remains unchanged (Nuttall, Ngo and Gannon, 2008). So simply providing more AA will not increase new glucose production. The authors concluded:

> **" the rate of Gluconeogenesis remains remarkably stable in widely varying metabolic conditions. The mechanism by which Gluconeogenesis remains relatively constant, even in the setting of excess substrates, is not known. One interesting speculation is that gluconeogenic substrates substitute for each other depending on availability. Thus, the overall rate is either unaffected or only modestly changed."**(Nuttall, Ngo and Gannon, 2008)

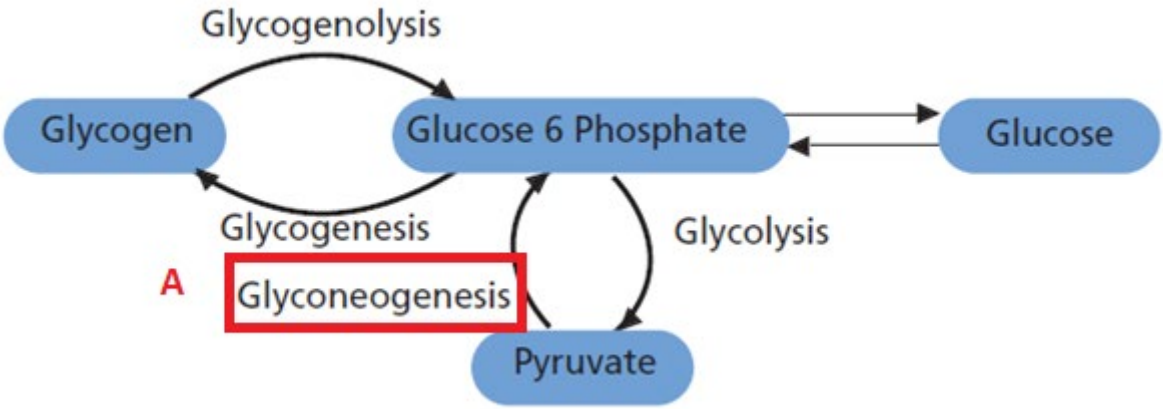
(2) This is a very important point to remember when we move into talking about Type 1 Diabetes and insulin needs later, **so take note.**

iv) Glucagon will start a cascade of events in the cells to liberate FFA from fat stores to produce energy. This reduces the usage of glucose and helps maintain the blood glucose level (Gromada, Franklin and Wollheim, 2007).

2) **If the cells have a medium to very high energy state**, generally the I:G will be high. Therefore, the body will be in anabolism and energy storage mode. However, when a high protein low carbohydrate meal is consumed, both insulin and glucagon are elevated. Why?

a) Glucagon will ensure the blood glucose level is maintained whilst insulin moves AA and glucose into the body's cells for anabolism. Glucagon stimulates liver glycogenolysis, to maintain the blood glucose level.

- We have already discussed that Gluconeogenesis is a demand driven process, and is not stimulated by excess substrate supply such as AA (Nuttall, Ngo and Gannon, 2008). This was shown neatly in a study where 50g of protein (beef) was consumed to see the fate of the AA. The amount of AA converted into glucose was 11-13g, but only 2g ended up in the blood supply. Therefore 9-11g were stored in the liver as glycogen, by process called glyconeogenisis (Gannon *et al.*, 2001). Glucogenic AA can be metabolised into TCA cycle substrates, and then into pyruvate. Pyruvate can then be metabolised into glycogen, as can be seen from the diagram below.



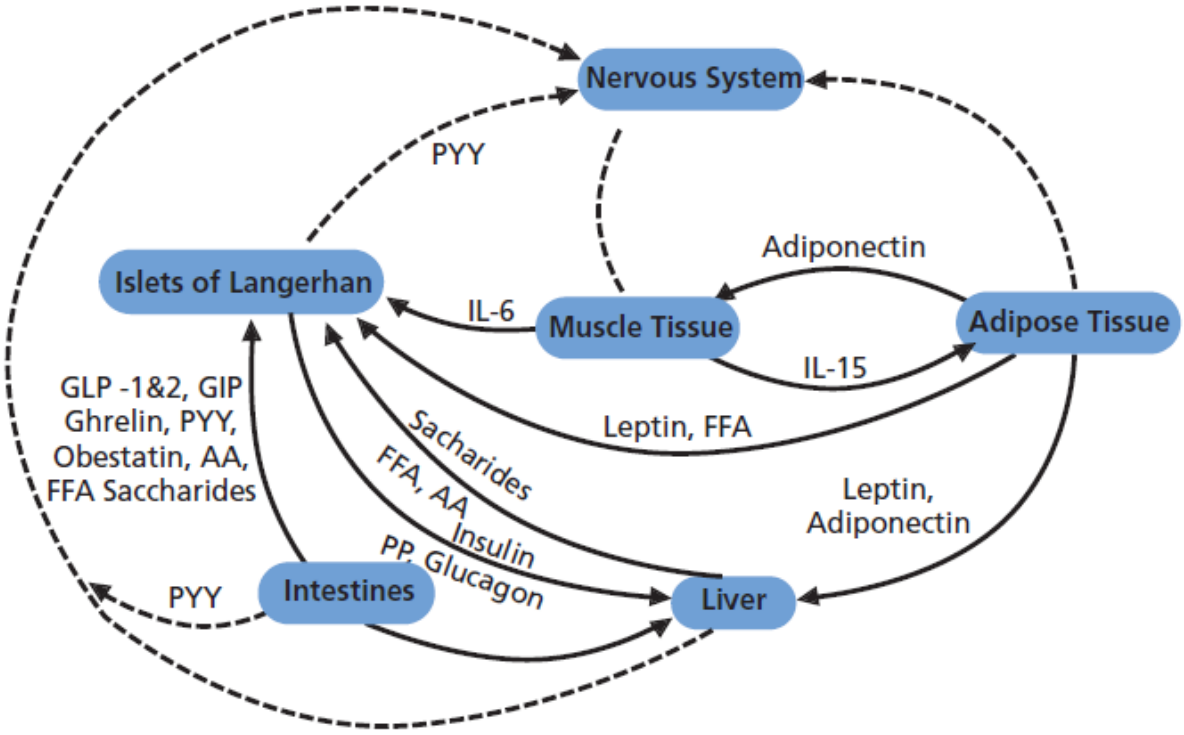
Adapted from (Hughes and Narendran, 2014)

The above discussion shows the importance of Glucagon in maintaining the glucose level, and how the I:Gis the major determinant. You can imagine how easy it is to disrupt the I:G by delivering insulin in the wrong amounts.

Therefore, understanding the regulation of glucagon secretion is a very important part of the puzzle. Let's take a deeper look.

The regulation of Glucagon secretion

The regulation of glucagon secretion from the A-Cells is very complex, and is less well understood than insulin regulation. To put the complexity into perspective, cast your eyes on the diagram below.



Adapted from (Hughes and Narendran, 2014)

This diagram shows the complex network of hormonal, neural, endocrine, muscle and adipose tissue signals communicating pancreatic islets of Langerhans cells. It is way beyond the scope of this article to cover all of these in detail. I refer you to two excellent reviews for exploration (Gromada, Franklin and Wollheim, 2007; Hughes and Narendran, 2014). The highlights are:

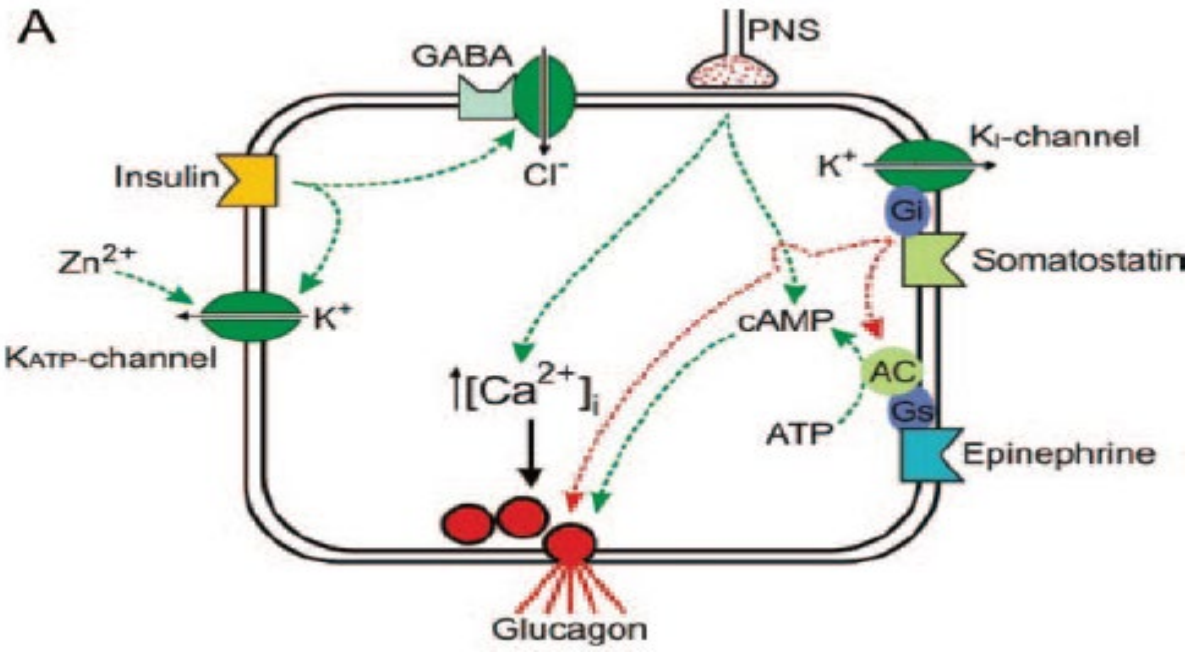
- The central nervous system stimulates Glucagon release:
    - Low blood glucose is detected in the hypothalamus leading to central nervous system activation. The end results is adrenaline release which positively regulates A-Cell secretion of Glucagon.

    - Parasympathetic stimulation of the vagus nerve leads to acetylcholine release that stimulates both B-Cells and A-Cells, but B-Cell stimulation is predominate. However, in Type 1 Diabetes where the B-Cell insulin secretion does not happen, A-Cells glucagon secretion predominates from parasympathetic stimulation.

- Leptin increase negatively regulates A-Cell secretion of Glucagon. Essentially the more satiated you are the lower Glucagon release.

- Arginine is a potent stimulator of Glucagon secretion.
- IL-6 from exercise increases Glucagon secretion

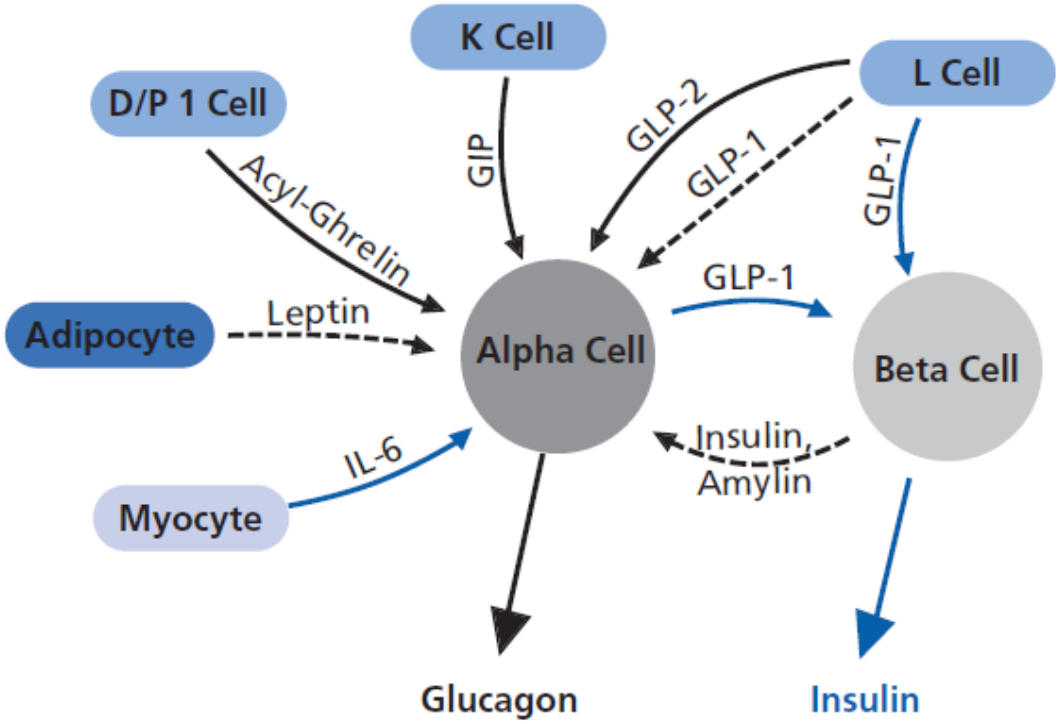
The diagram below shows how different signals regulate Glucagon secretion. The main stimulation is achieved by changing the cellular energy level, and elevating substrate availability.



Adapted from (Gromada, Franklin and Wollheim, 2007)

For this discussion we will take a deep dive into what is currently known about the key regulators that are influenced by digestion of carbohydrate, fat and protein.

The below diagram shows there are large number of hormonal regulators on A-Cell secretion of Glucagon. The dashed lines indicate negative regulation, and the solid lines indicated a positive regulation.



Adapted from (Hughes and Narendran, 2014)

Let's breakdown how these different hormones regulate A-Cell Glucagon secretion (Meier *et al.*, 2003):

- Intestinal K Cell secretion of GIP:
    - Positive regulation of glucagon. In healthy people GIP has a dose-dependent relationship with glucagon secretion.

- Intestinal L Cell secretion GLP-1 & GLP-2:
    - GLP-1: negative regulation of Glucagon
    - GLP-2: positive regulation of Glucagon

- B-Cell secretion of Insulin:
    - Strong negative regulation of Glucagon. The most potent of all the negative regulators.

- D-Cell Somatostain Secretion
    - Negative regulation of Glucagon

Summary (Watch me)

There are multiple regulators of glucagon secretion from the A-Cells. The key ones stimulating secretion by positive regulation are:

- GIP
- CNS via adrenaline

The key ones inhibiting secretion by negative regulation are:

- Insulin
- GLP-1

When the B-Cells have been destroyed, as happens with Type 1 Diabetes, the negative regulation signals are lost. Therefore, the job of a person with Type 1 Diabetes is to match insulin delivery to what the B-Cells would have secreted in response to the meal composition, so that:

  - Glucagon can be suppressed from rising too high after eating high protein and fat meals. If this does not happen Glucagon will increase liver output of glucose too much, causing hyperglycaemia.

  - Glucagon is not suppressed too much by delivering an incorrect large bolus of insulin. If this happens glucagon will not be released to prevent hypoglycaemia.

Insulin and Glucagon Summary (Watch me)

Let's simplify this, Insulin is the **big brother and master** in this hormonal relationship. Insulin trumps the action of other hormones when it comes to regulating Glucagon secretion. A high I:G will prevent glycogenolysis and gluconeogenisis, whilst simultaneously increasing glycolysis, glycogenisis and anabolism (Ramnanan *et al.*, 2010).

This works beautifully when the B-Cells of the pancreas are in full working order, and the adjustments are automatic. However, when you have Type 1 Diabetes, insulin secretion is not automatic, you must learn to be the master controller!

When B-Cells are working normally, if the glucose level starts to drop and is heading toward 3.5mmol/l (65mg/dl), there are multiple signals that stop insulin secretion. Simultaneously

there are multiple signals that increase Glucagon secretion, which stimulates liver glycogenolysis and glucose release. Result, hypo prevented. But when too much insulin has been administered for a meal, the I:G is way too high and there is no off switch for insulin action. The result is a hypo, and potentially a nasty one if the insulin dose was way too high.

This was borne out is the landmark trial, the DCCT, In this trial the intensification of insulin treatment in the experimental group massively improved their HbA1c and future health (Nathan, 2014). This trial is the reason why the holy grail is getting a HbA1c <6.5% (<48mmol/mol). However, the experimental group administered more insulin every day, increased their weight, and unsurprisingly had more hypos and severe hypos, 200-300% more.

Why?

The intensification of insulin dampened the response of Glucagon to pending hypoglycaemia.

Further evidence of this comes from studies conducted on adults and children with T1DM using a dual hormone pump. The dual pump infuses both insulin and glucagon. Glucagon infusion is triggered and insulin stopped when the CGM detects a dangerous downward trend in glucose. The dual infusion pump has recorded positive early results in reversing the frequency and severity of hypoglycaemia (El-khatib *et al.*, 2010; Russell *et al.*, 2014).

So, it's a big responsibility for the person with type 1 diabetes to use this trump card at the right time, and in the right amounts!

We have now built a foundational knowledge of the functions of insulin and Glucagon, and understand their key regulators. Let's move onto seeing how this hormonal relationship works after eating different types of meals. This will provide the model that people with Type 1 diabetes need to follow when delivering insulin for their meals.

To gain a full understanding we must ask extremely specific questions. What does the pancreas do to maintain blood glucose level, and what is different for the person with Type 1 Diabetes?

- When carbohydrate only is consumed?
- When protein only is consumed?
- When fat only is consumed?
- When carbs and protein and consumed?
- When carbs and fat and consumed?
- When fat and protein are consumed?
- When carbohydrate, fat and protein are consumed?

Here is where the real fun begins!

What does the pancreas do when carbohydrate only is consumed?

Insulin

Put simply, the B-Cells secrete extra insulin into the portal vein to move the glucose from digested carbohydrate into the liver for storage as glycogen. Glucose not stored as liver glycogen enters the circulation, and insulin moves the glucose from the blood into body's cells for energy production and storage as glycogen. All the signals that control insulin secretion have been discussed previously, but the most important ones when carbohydrate only is consumed are:

- Intestinal Y cells release GLP-1 which is a strong positive regulator of B-Cell insulin secretion, accounting for up to 50% of insulin secretion (Herrmann *et al.*, 1995).

- Increased glucose uptake by the B-Cells increases the energy state which causes insulin secretion.

Glucagon

Put simply, the A-Cells reduce secretion of Glucagon when carbohydrate only is consumed. The I:G increases ensuring the body moves into energy storage mode. All the signals that

control glucagon secretion have been discussed previously, but the most important ones when carbohydrate only is consumed are:

- Intestinal release GLP-1 is correlated with the suppression of A-Cell Glucagon secretion (Herrmann *et al.*, 1995). However, the suppression of Glucagon is mainly a secondary action of GLP-1 increasing insulin from the B-Cell. It is insulin that mainly inhibits Glucagon release (Campbell and Drucker, 2015).

- It is a common belief that the increasing glucose level from digested carbohydrate directly reduces A-Cell Glucagon secretion, by negative regulation. However, research using people with Type 1 Diabetes who consume a carbohydrate meal with no insulin does not support this (Pörksen *et al.*, 2007). In this study the increase glucose levels to 10 - 20mmol/l (180 - 360mg/dl) increased Glucagon release. Just like with GLP-1, it is the increased insulin secretion from the B-Cell in response to the rising glucose that negatively regulates the A-Cell. Therefore, it is the secondary action of glucose increasing insulin via the B-Cell, not glucose directly (Greenbaum, Prigeon and D'Alessio, 2002).

The above two points are essential to consider for a person with type 1 diabetes.

Why?

The automatic negative regulation of the A-Cell is not provided by B-Cell secretion of insulin. They must deliver insulin in the correct amount to not only move glucose and AA into cells, but also to elicit the inhibition of Glucagon secretion.

Consider this situation;

Not enough, or no insulin is delivered for a carbohydrate only meal, such as fruit or sweets. There is a double effect;

- Not enough insulin to move glucose from the blood into the cells, therefore the blood glucose level rises.

- Not enough insulin to negatively regulate A-Cells to stop glucagon production. Glucagon slightly increases, liver glycogenolysis increases, blood glucose increases further.

Summary (Watch me)

Very simply, when carbohydrate alone is consumed at 50g, the I:G ratio increases putting the body into storage mode. This is regulated by an increase in GLP-1 and glucose stimulating insulin secretion, and the consequent direct negative regulation of Glucagon release. The job of the person with Type 1 Diabetes is to match the amount of insulin the B-Cells would release for carbohydrate only. Too little leading to hyperglycaemia, too much leading to hypoglycaemia.

From this point forward, I want you to consider the insulin response to 50g of carbohydrate alone as 100% over 5-6 hours. Also consider the Glucagon response as a reduction on 20% over 5-6 hours.

Why?

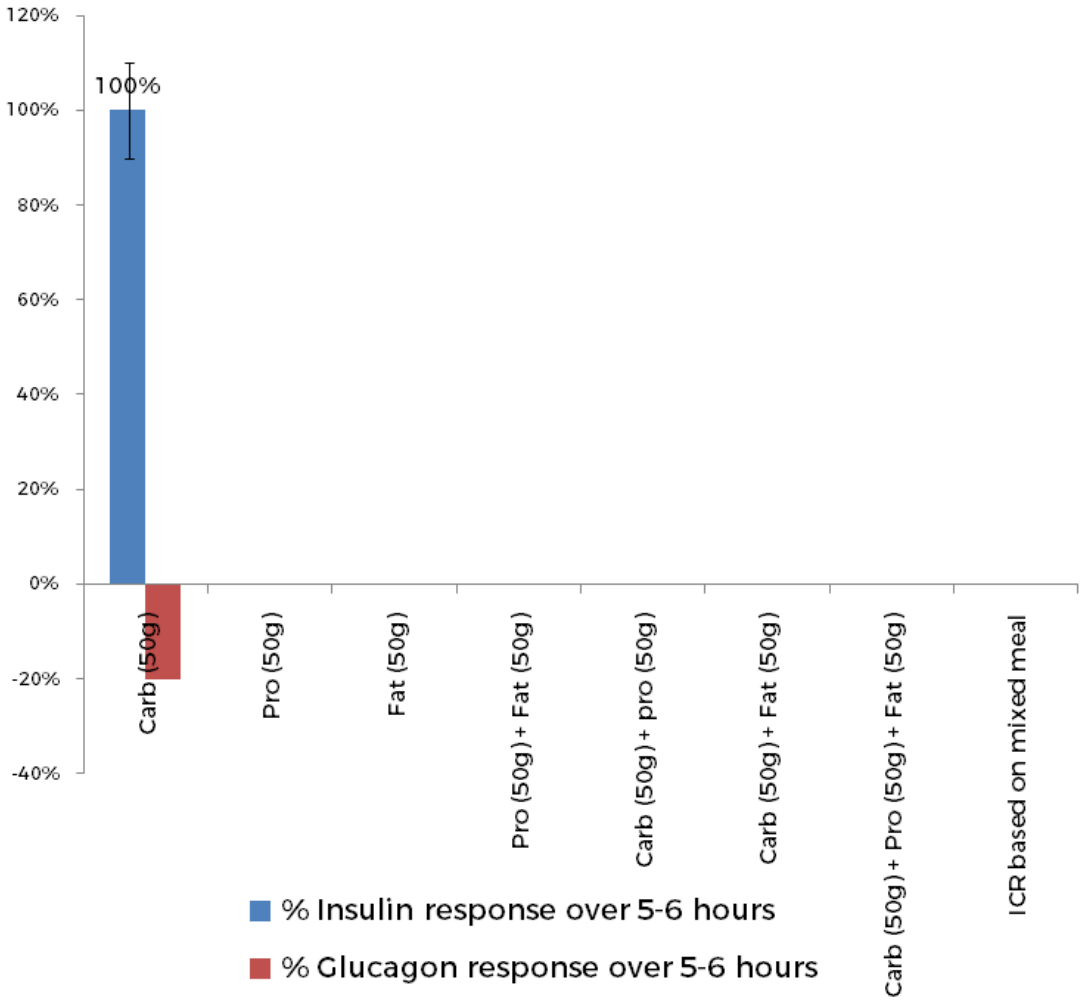
I want you to be able put the insulin and glucagon response for protein, fat, and their combinations with carbohydrate into context, relative to carbohydrate alone.

Please note this to help create a mental model and the numbers are not exact.

The below graph will be built upon to model the insulin and glucagon response required for the macronutrients singularly, and in combination. This will help put the insulin and glucagon response into perspective and identify the challenge a person with type 1 diabetes has to match it. This graph is not a perfectly scaled, therefore it is not 100% factually correct, but it will prove valuable to help you model and more importantly explain to people with diabetes.

It uses a dose of 50g of the macronutrients to compare and contrast the insulin response over 5-6 hours. The 50g dose was chosen because most studies have used that amount as the standard measure, and this often reflects real life consumption (Krezowski *et al.*, 1986). The time period of 5-6 hours was chosen because that is the post-meal monitoring duration of most studies (Krezowski *et al.*, 1986). Once we have worked through all the

macronutrients and their combinations, the graph will help determine which insulin dosing strategies will be most useful for certain diet or meal types.



The graph starts showing 50g of carbohydrate elicits a 100% insulin response over 5-6 hours, to serve as the reference. The graph also has error bars of 10% to show the effect of GI. If the 50g carbohydrate is high GI it may elicit a 110% response, if low GI only 90%. This highlights the first challenge of the person with type 1 diabetes when determining an insulin dose. The graph also shows Glucagon decreases by 20%.

To calculate the amount of insulin required for 50g carbohydrate, you would need to count every gram.

Insulin load = carbohydrate (g)

What does the pancreas do when protein only is consumed?

Insulin

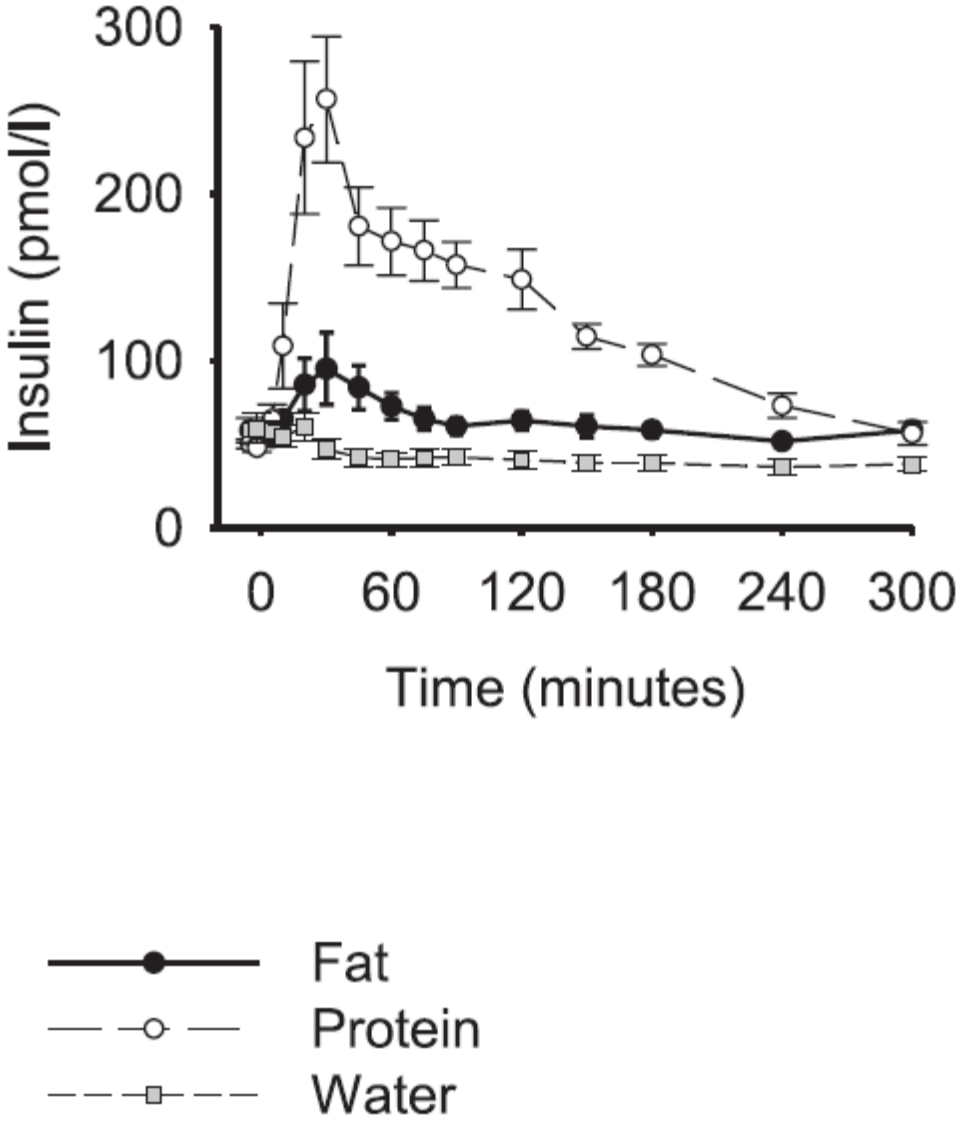
Put simply, the B-Cells secrete extra insulin into the blood to move the AA from digested protein from into the body's cells for anabolism. This has been proven by an increase in non-oxidative Leucine flux (Charlton, Adey and Nair, 1996). The increase insulin also moves glucose from the blood into the cells for usage and storage as glycogen.

The main signals that control insulin secretion are:

- Intestinal Y cells release GLP-1 which is a strong positive regulator of B-Cell insulin secretion (Herrmann *et al.*, 1995). The level of GLP-1 response to AA is much lower than that exerted by glucose (Carrel *et al.*, 2011).

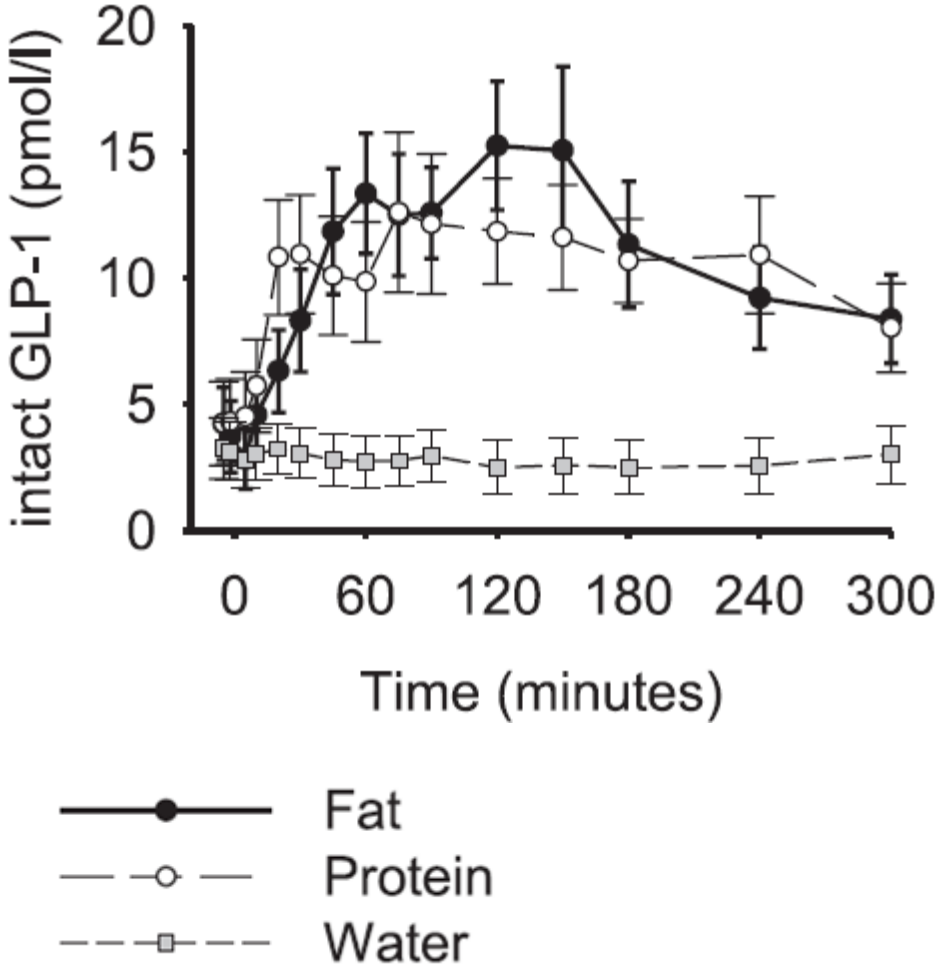
- Increased AA uptake by the B-Cells increases the energy state leading to insulin secretion. The AA increase the energy state by providing substrates for glycolysis, but not direct fuel like when glucose is consumed. Therefore, the insulin response is much lower for AA compared to glucose.

Research on healthy adults consuming protein only (2g/kg, 560kcal), shows the insulin levels begin to increase at 15minutes post-ingestion, and remains elevated up to 240 minutes compared to water (Carr *et al.*, 2008). When compared with fat (0.88g/kg, 560kcal), protein exhibited a much stronger Insulin response, as shown clearly from the below graph from the study. At 30 minutes the insulin concentration had increased more than fivefold from baseline. The graph below vividly shows the increase in insulin secretion over six hours. One thing to bear in mind is that protein at 2g/kg is a very large amount, an average 140g protein meal in this study. A usual meal maximum would be 1g/kg at the extreme!



Why the increase in Insulin from protein ingestion?

The graph below from this study showed the secretion of intact GLP-1 from the L-Cells of the intestine matches the insulin secretion (Carr *et al.*, 2008). This confirms what has been previously discussed, that dietary AA plays a major role in insulin secretion though GLP-1.



The important point to consider for people with Type 1 Diabetes is that the GLP-1 increase from the L-Cells of the intestine will not lead to insulin secretion. Therefore, the missing insulin secretion must be matched by the person with type 1 diabetes, by delivering the exact amount insulin required for the protein consumed.

Glucagon

Put simply, the A-Cells secrete extra Glucagon into the blood to prevent hypoglycaemia from the concurrent increase in insulin. The main signals that control glucagon secretion are:

- K-cells located in the small intestine respond to dietary AA and release GIP. GIP positively regulates the A-Cell to increase of Glucagon secretion.

- The drop in glucose level from the increase insulin secretion is detected in the hypothalamus. This stimulates adrenaline release that positively regulates Glucagon secretion (Campbell and Drucker, 2015).

- The AA from protein digestion increase GLP-1 secretion from the L-Cells of the intestine. This positively regulates B-Cell secretion of insulin, which in turn negatively regulates A-Cell Glucagon secretion. The GLP-1 secretion due to AA ingestion is moderate compared to glucose, but it still has an important impact.

It has been shown clearly that an increase in blood AA increases Glucagon secretion, but when this is not accompanied by an increase in insulin, the body moves into a catabolic state rather than the anabolic state. This was confirmed with non-oxidative Leucine flux studies (Charlton, Adey and Nair, 1996).

People with Type 1 diabetes do not have this automatic secretion of insulin from GLP-1 regulation when they consume protein. Therefore they have to balance delivering just enough insulin to allow anabolic activity, whilst not delivering too much causing hypoglycaemia.

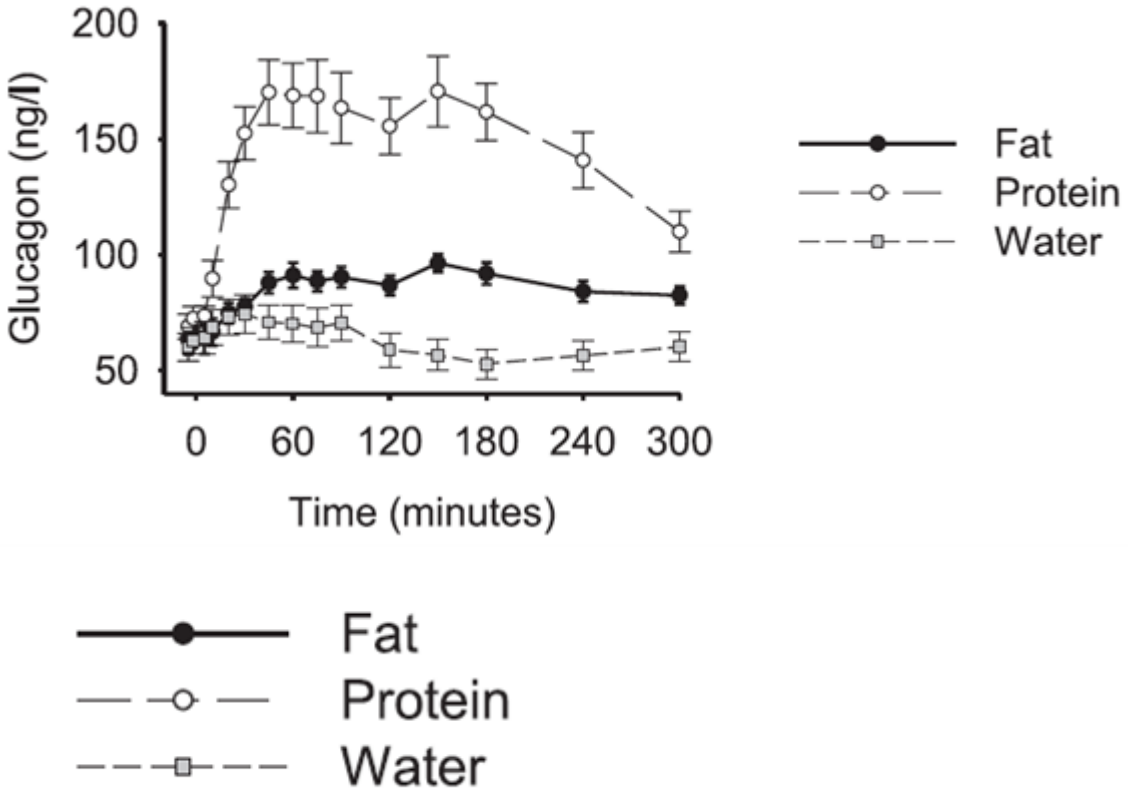
Consider this situation:

Not enough, or no insulin is delivered for protein only meals, you get a double whammy;

- Not enough insulin to move AA into the cells for anabolism. You miss out on growth and repair.

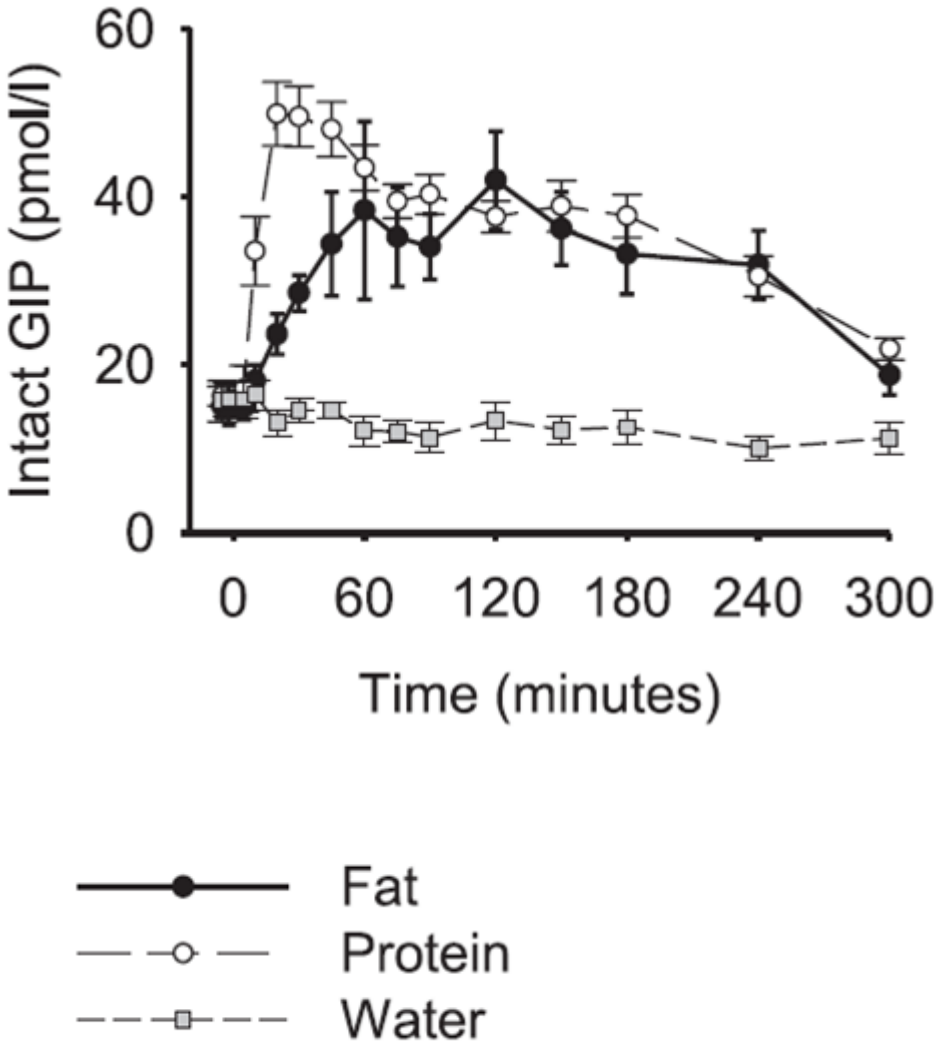
- Not enough insulin to A-Cells to stop glucagon secretion. Glucagon increases liver glycogenolysis leading to a steady and persistent rise in glucose after eating protein with no insulin.

Research on healthy adults consuming protein only (2g/kg, 560kcal) shows Glucagon levels increase fivefold at 30 minutes post-ingestion, and remain significantly elevated to 240 minutes (Carr *et al.*, 2008). When compared with fat alone (0.88g/kg, 560kcal), protein exhibited a much stronger Glucagon response, as shown clearly from the below graph from the study (Carr *et al.*, 2008). The Glucagon increase from baseline following protein only comes in a biphasic way. Initial bust after 30 minutes, a dip at 120 minutes, followed by another increase between 120-180 minutes before falling to 240 minutes.



Fat
Protein
Water

The study showed the secretion on intact GIP from the K-Cells of the intestine stimulated by AA plays a key role in Glucagon secretion. Interestingly the graph below shows the biphasic release of intact GIP, with a surge at 30minutes, followed by another burst between 120 - 180 minutes. However, statistical analysis did not find the relationship between GIP and Glucagon to be resoundingly strong (Carr *et al.*, 2008).



A recent review paper has highlighted there are different forms of GIP. Some that stimulate insulin secretion and other forms that stimulate Glucagon secretion (Campbell and Drucker, 2015). The lack of statistical finding in this study may be measurement error, or it speaks to the complex neural and hormonal signals that regulate Glucagon secretion previously discussed (Gromada, Franklin and Wollheim, 2007; Hughes and Narendran, 2014; Campbell and Drucker, 2015)

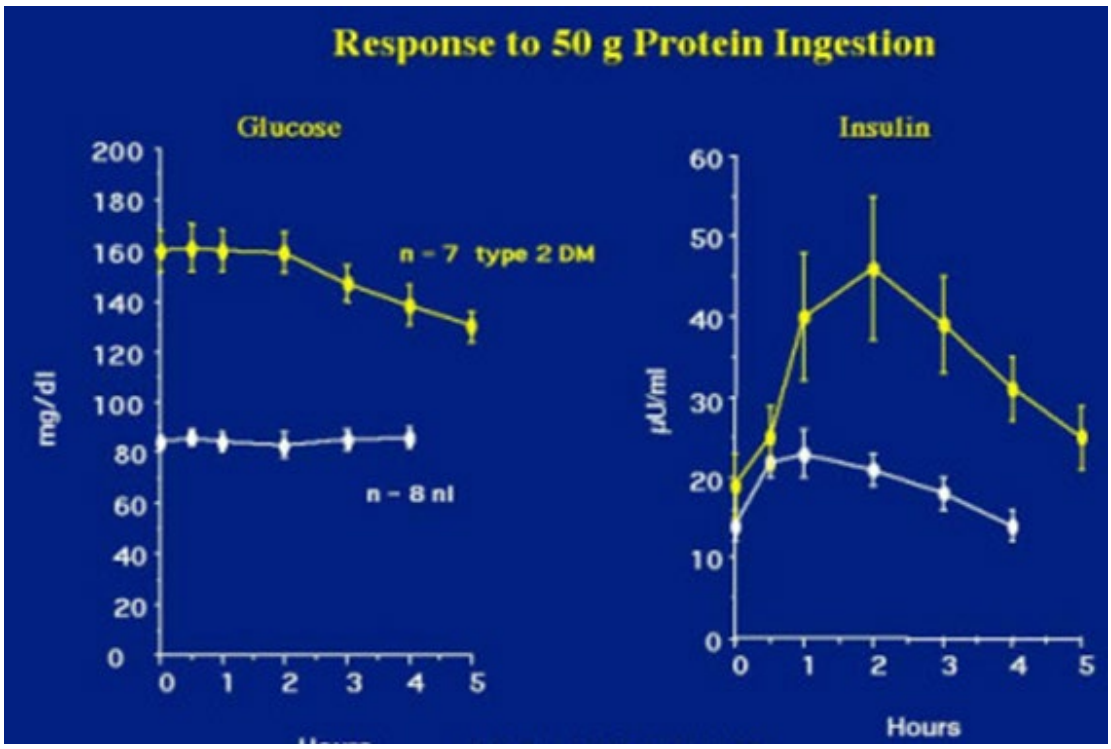
Research

In healthy subjects, ingestion of 50 g of protein as lean beef elicited a significant increase in insulin over four hours (Krezowski *et al.*, 1986). The amount required was 28% of that required for 50g of pure glucose. Similarly Berger found that ingestion of 50-100g protein elicited 21% of the insulin response of 100g glucose (Berger, S.; Vongaraya, 1966). Taken together this suggests the insulin requirement for 50 grams of protein is 20-30% of the requirement needed for 50g glucose.

It is worth noting that 50g of protein is much more like the amount that would be eaten for a normal protein only meal. Unlike the 140g protein meal eaten in the study discussed earlier (Carr *et al.*, 2008).

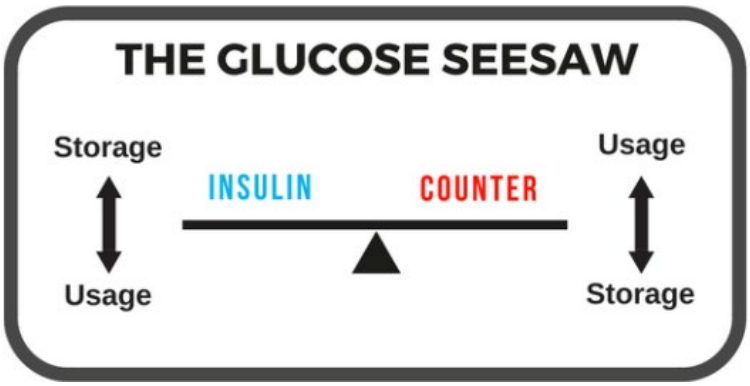
Interestingly Berger (Berger, S.; Vongaraya, 1966) investigated people with Type 2 Diabetes alongside the healthy cohort discussed above, and found a very different insulin responses. The insulin response for the people with Type 2 Diabetes to 50g protein was 80% of that of 50g pure glucose, a four-fold increase compared to healthy volunteers.

This graph from another type 2 study reported similar studies comparing the insulin response to 50g pure protein in healthy men (white line) to those with type 2 Diabetes (yellow line) (Gannon *et al.*, 2003) . You can see the peak rise in insulin is delayed but achieves a much greater concentration for the people with type 2 diabetes. Also, the rise in insulin is persistent for much longer for the people with Type 2 Diabetes.



This suggests the more insulin resistant you are, the greater the effect protein has on insulin secretion. Something to bear in mind for people with Type 1 who are insulin resistant.

Protein ingestion has also been shown to consistently increase Cortisol levels . Cortisol is another counter-regulatory hormone that increases liver Glycogenolysis early after eating, and gluconeogenesis later after eating (Slag *et al.*, 1981). Thinking back to our Seesaw you can see the increase in Cortisol will push the body into energy usage mode.

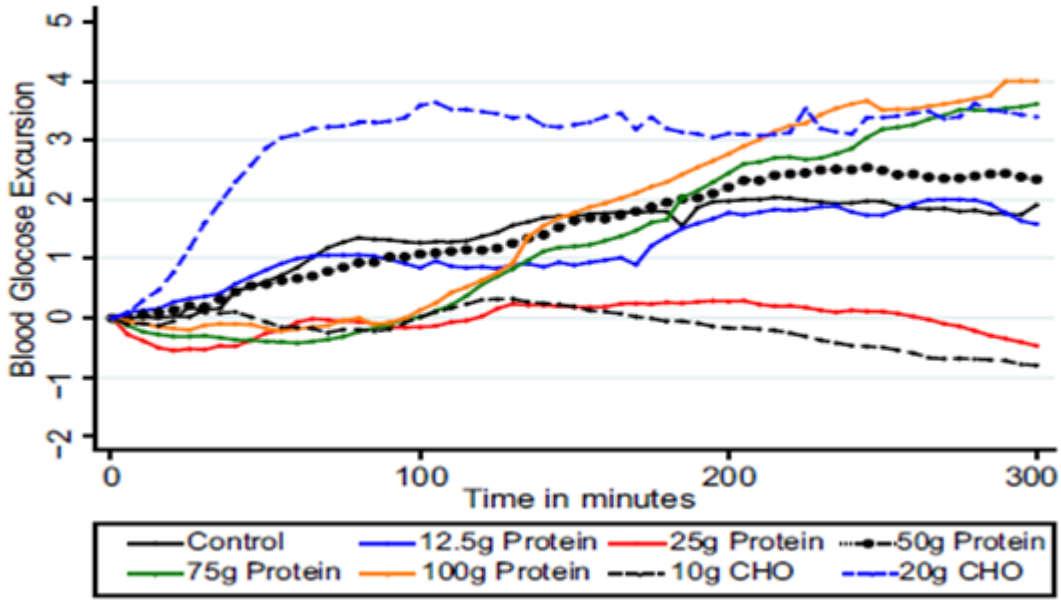


What about high protein meal research for people with Type 1 Diabetes?

The influential group from New South Wales studied the ingestion of pure whey isolate protein in the amounts of 12.5g, 50g, 75g (replicating a 230g steak), and 100g (replicating a 350g steak) and the effect on glucose level over five hours in 27 people with type 1 diabetes aged 7-40years old (Paterson *et al.*, 2014). They also used the same 27 subjects to study the effect of 10g and 20g glucose. No insulin was administered for any of the protein or glucose intakes, they just had their usual background insulin working.

What did the results show?

The graph below shows whey protein loads of 12.5g and 50 g did not result in significant post meal glycaemic excursions compared with water throughout the five hour study period. Whey protein loads of 75 and 100 g resulted in lower glycaemic excursions than control in the first 60–120 min, but higher excursions after 180–300 min when compared to water. The researchers reported that over five hours the effect of 75g and 100g protein was equivalent to 20g glucose. This idea of 20-30% again. But no effect of 12.5g or 50g protein.



Adapted from (Paterson *et al.*, 2014)

The eagle eyed among you will have noticed a few things from this graph:

- The control (water) had a glucose rise of 2mmol/l after 120minutes and stayed there until 300 minutes. This suggests the background insulin rates were not set correctly.

- The 10g carbohydrate and 25g protein tests had significantly lower glucose levels at 120min than water, and this continued all the way to 300min. This suggests a large number of the 27 people still had significant residual B-Cell function. Why? We know Whey protein is very high in leucine that stimulates the B-Cells to produce insulin and cause glucose and amino acids to be taken up by the cells (Van Loon *et al.*, 2000). Only measurement of C-peptide would give a clear answer to that.

So. what does all this research mean for people with type 1 Diabetes. Should they give insulin for protein only?

In my opinion YES. Here are a few reasons why:

- We know AA increases Glucagon secretion, but when this is not accompanied by an increase in insulin, the body moves into a catabolic state rather than the anabolic state, confirmed with non-oxidative Leucine flux studies (7).

- Insulin delivered in small but adequate quantities is needed to transport the AA for growth and repair, but this will start to decrease the blood glucose level. This blood glucose drop will be sensed by the hypothalamus leading to central nervous stimulation of the A-Cell by adrenaline (Hughes and Narendran, 2014; Campbell and Drucker, 2015). Therefore, hypoglycaemia will be prevented, but only if the insulin delivered is not too much! How much is too much, we will find out.

- Critique of the Whey protein study (Paterson *et al.*, 2014) suggests the participant's basal rates were not optimised, and there could have been people with significant residual B-Cell function. One key point to consider is just because the glucose level did not rise for Whey given at 12.5g and 50g, it does not mean insulin was not needed to transport AA for anabolism. It is likely some participants had residual B-Cell function given they glucose level dropped with the 12.5g and 50g conditions.

Put simply there are two very good reason for delivering insulin for pure protein meals:

- First, to ensure the AA's are used for anabolic activity.

- Second, to prevent glucagon from slowly increasing liver glycogenolysis and Gluconeogenisis and raising the blood glucose level.

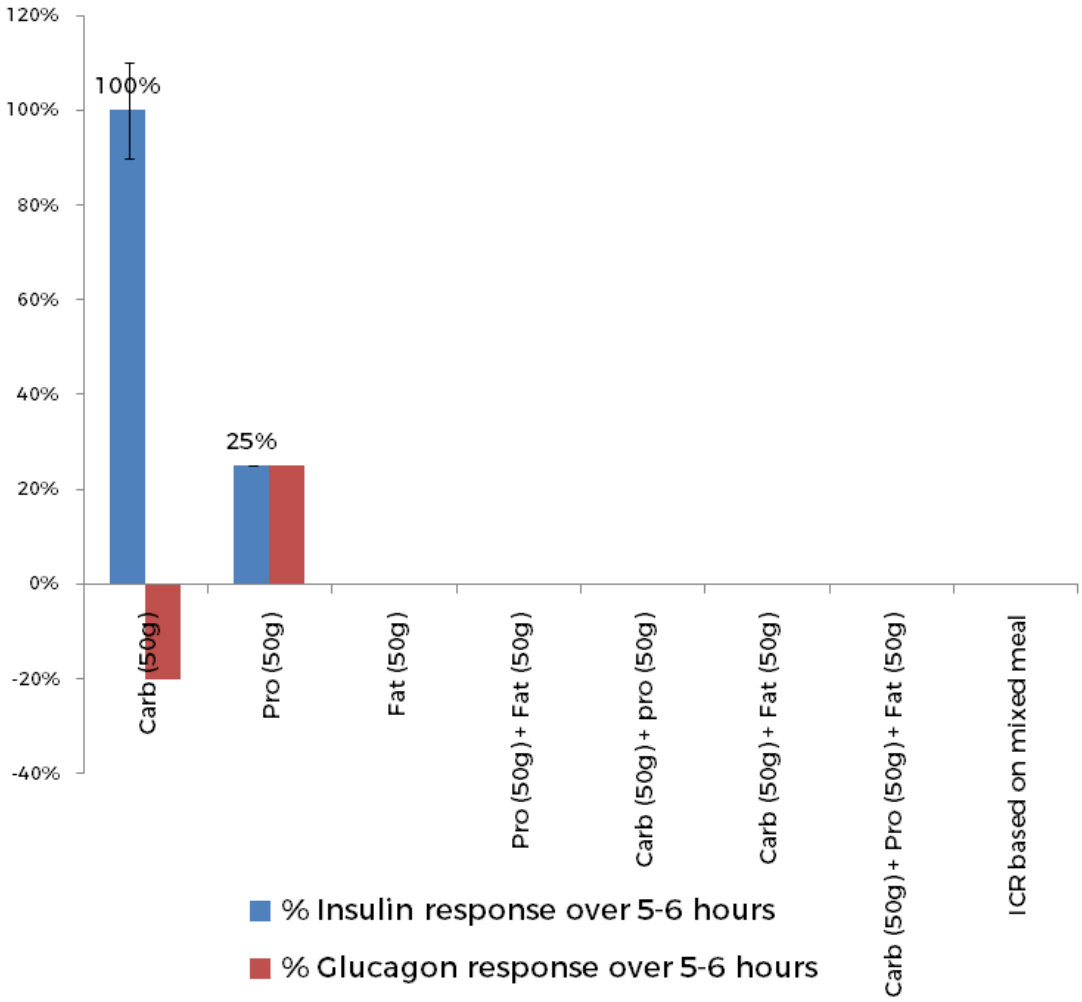
Summary (Watch me)

When protein alone is consumed at 50g, both Insulin and glucagon increase, therefore not altering the I:G. This allows AA to be used for anabolism whilst maintaining the glucose level. The increase GLP-1 stimulates insulin secretion, whilst the increase GIP and central nervous system activity stimulate glucagon secretion.

The job of the person with Type 1 Diabetes is to match the amount of insulin the B-Cells would release for protein only. Too little leading catabolism and hyperglycaemia, too much leading to hypoglycaemia.

How much insulin to deliver for protein on a gram basis?

Not an easy question to answer, but from the research above it would seem sensible to suggest that protein when ingested alone, elicits about 25% of the insulin response needed for carbohydrate alone. I have shown this graphically below in comparison to carbohydrate alone and have included the equal increase in Glucagon response.



If you counted 0.25g of every gram of protein and used the insulin ratio for the pure carbohydrate, you would not be too far off. For protein only meals the equation that would work out the insulin load is:

Insulin load = protein g x 0.25

Why do most people with type 1 diabetes not know or do this?

Most people with Type 1 diabetes who carbohydrate count do not see the effect of protein only on blood their glucose level for a few reasons:

- They rarely eat pure protein.
- If they do, they very rarely go more than 3-4hours without eating again, so the effect of the steady Glucagon rise 4-8hours after protein consumption is covered by the next meals insulin dose.

Times when it will be noticed:

- Having a Whey protein isolate shake or tin of low-fat fish such as Tuna. Usually reserved for people looking to build muscle. People following a low carb diet rarely eat protein in isolation, it is mixed with fat e.g. nuts, eggs, meat salad and olive oi.

Bonus: Do all amino acids behave the same?

This is a fascinating question and allows you to get your nerd hat on and get deep into the weeds of the research.

Gannon and Nutall (Gannon and Nuttall, 2010) reported on a series of intriguing research studies where they measured blood markers, Glucose, AA level, insulin & Glucagon, of healthy males over three hours, after ingesting 25g of individual AAs. They compared the results to water ingestion, and they also repeated the studies adding 25g of glucose to the AA, but we will discuss those in the relevant section.

What did they find in the 25g AA studies?

1) The below graph shows all AA levels in blood increased. No surprises that the BCAA (branch chain amino acids), isoleucine, leucine, and valine had the highest blood levels, because their uptake by the liver is the least. Whereas the AA used immediately for metabolism in the intestinal cells increased only slightly in the blood, namely Glutamine, Aspartate, Arginine.

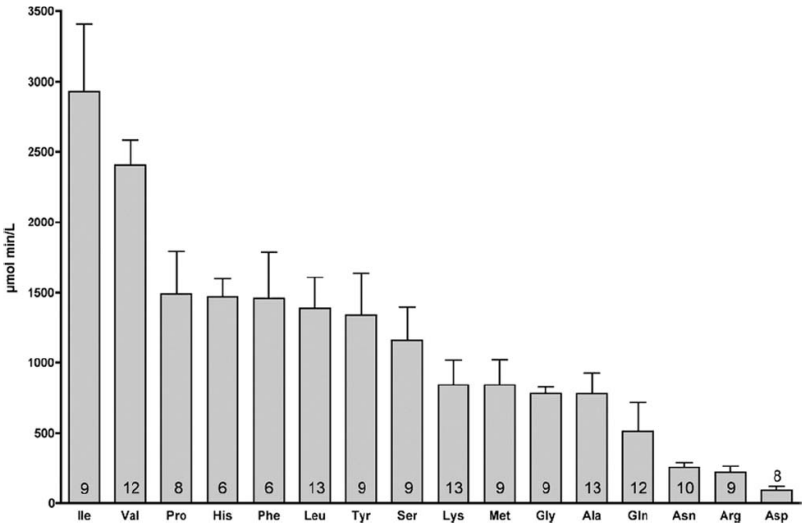


Figure 1. Amino acid area response following ingestion of individual amino acids. Bars indicate mean + SEM. Numbers within the bars indicate the number of subjects studied.

Adapted from (Gannon and Nuttall, 2010)

2) The below graph shows almost all AA elicited an insulin response. Some of the AA's were more portent in stimulating insulin secretion. This mirrors the early work showing , Glycine and phenylalanine are the most potent insulin secretagogues when had in the absence of carbohydrate (Floyd *et al.*, 1966). The practical significance of the difference elicited by AA on their own is truly little, because they are rarely consumed singularly in the diet. The main point is that AA show a robust and repeatable insulin response.

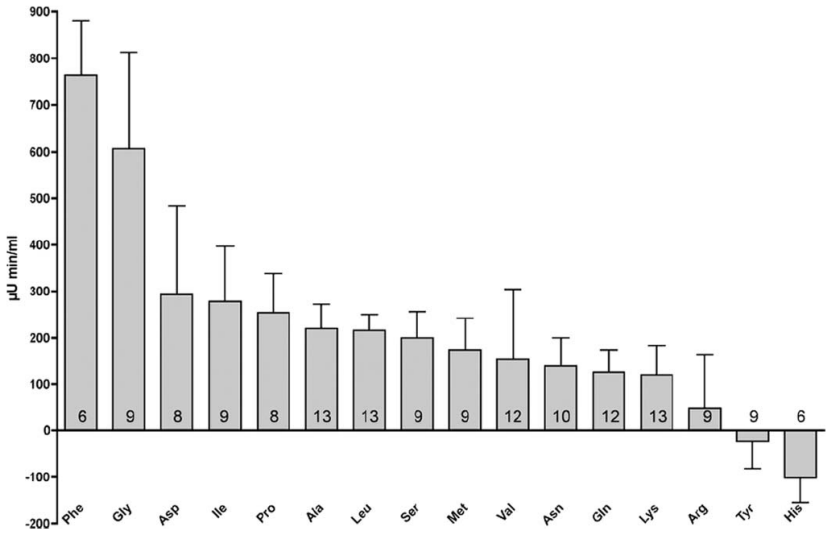


Figure 2. Insulin area response following ingestion of individual amino acids. The insulin area response to water only (control) was subtracted from the area response to the amino acid to give a net area. Bars indicate mean + SEM. Numbers indicate the number of subjects studied.

Adapted from (Gannon and Nuttall, 2010)

3) The below graph shows almost all AA elicited a Glucagon response. Some of the AA's elicited a greater response of Glucagon secretion. The practical significance of the difference elicited by AA on their own is little, the main point is that AA show a robust and repeatable Glucagon response.

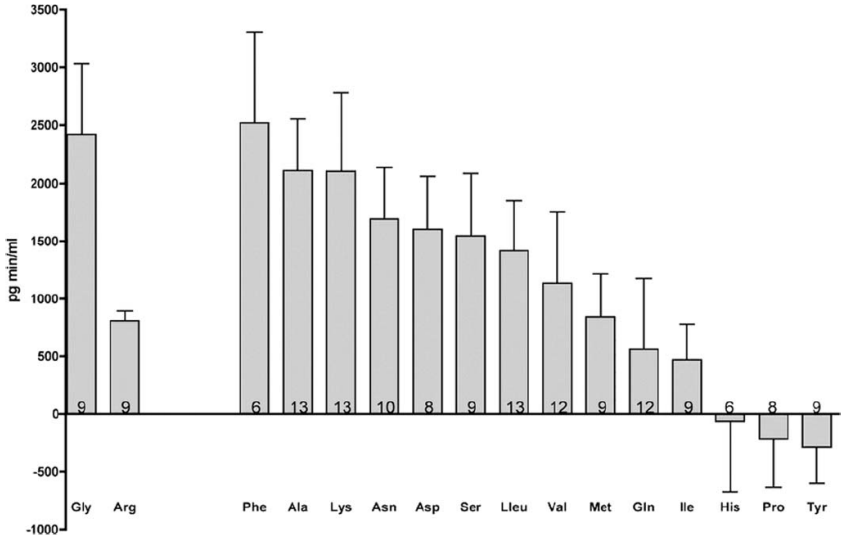


Figure 3. Glucagon area response following ingestion of individual amino acids. The data for glycine and arginine were obtained using a different assay, so the data are not directly comparable. The numbers on this graph for Gly and Arg should be multiplied by 10 to obtain the correct area response obtained with the former glucagon assay. Bars indicate mean + SEM. Numbers within the bars indicate the number of subjects studied.

Adapted from (Gannon and Nuttall, 2010)

What does the pancreas do when fat only is consumed?

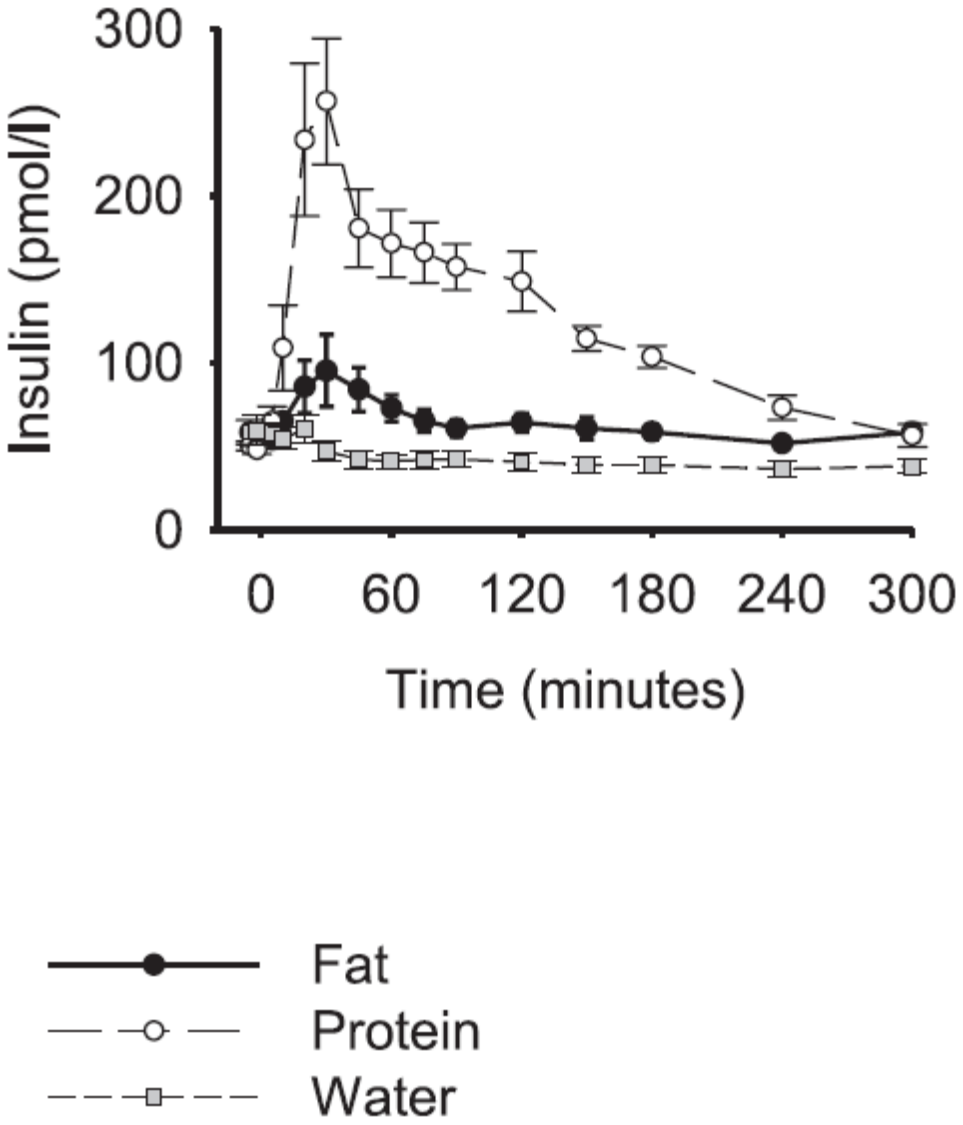
Insulin

Put simply, the B-Cells secrete a little extra insulin into the blood to promotes storage of FFA in the fat tissue. There are a lot of signals that regulate insulin secretion, but the main and most important ones are:

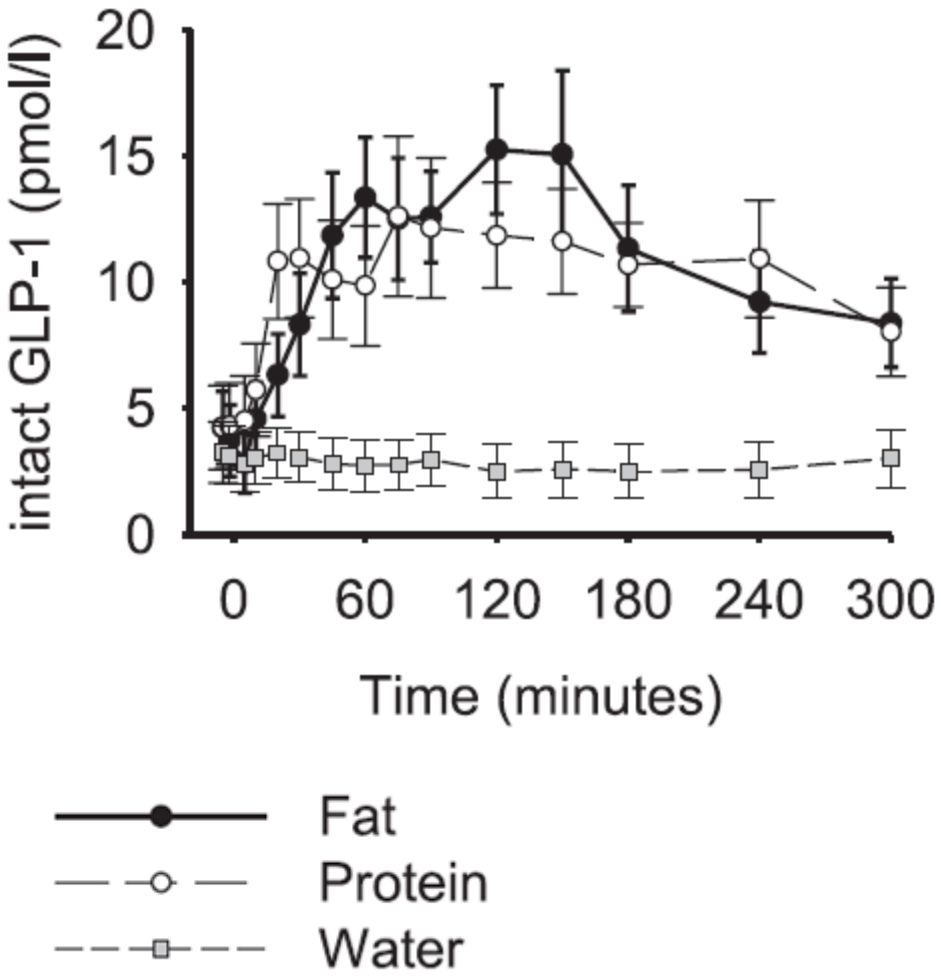
- Intestinal Y cells release GLP-1 which is a strong positive regulator of B-Cell insulin secretion (Herrmann *et al.*, 1995). The level of GLP-1 response to FFA is the similar to that of AA (Carrel *et al.*, 2011).

- Increased FFA uptake by the B-Cells increases the energy state leading to insulin secretion. This effect is much weaker than that of AA (Turner, N., Cooney, G.J., Kraegen, E.W., Bruce, 2014)

Research on healthy adults consuming fat only (0.88g/kg, 560kcal) show the insulin level begins to increase at 30minutes post-ingestion, and remains elevated up to 240 minutes (Carrel *et al.*, 2011). At 30 minutes the insulin concentration doubles, but this is a much lower response of the fivefold increase in response to the same kcal volume of protein. Granted having a pure fat meal of 62g on its own is unlikely in one sitting!



As discussed earlier and shown in the graph below from the same study, the secretion on intact GLP-1 from the L-Cells of the intestine due to dietary FFA plays a major role in insulin secretion.



Glucagon

Put simply, the A-Cells secrete a little extra glucagon into the blood to promote FFA oxidation and glycogenolysis. There are a lot of signals that regulate Glucagon secretion, but the main and most important ones are (Hughes and Narendran, 2014):

- G cells located in the small intestine sense the FFA and release GIP. GIP positively regulates A-Cell Glucagon secretion.

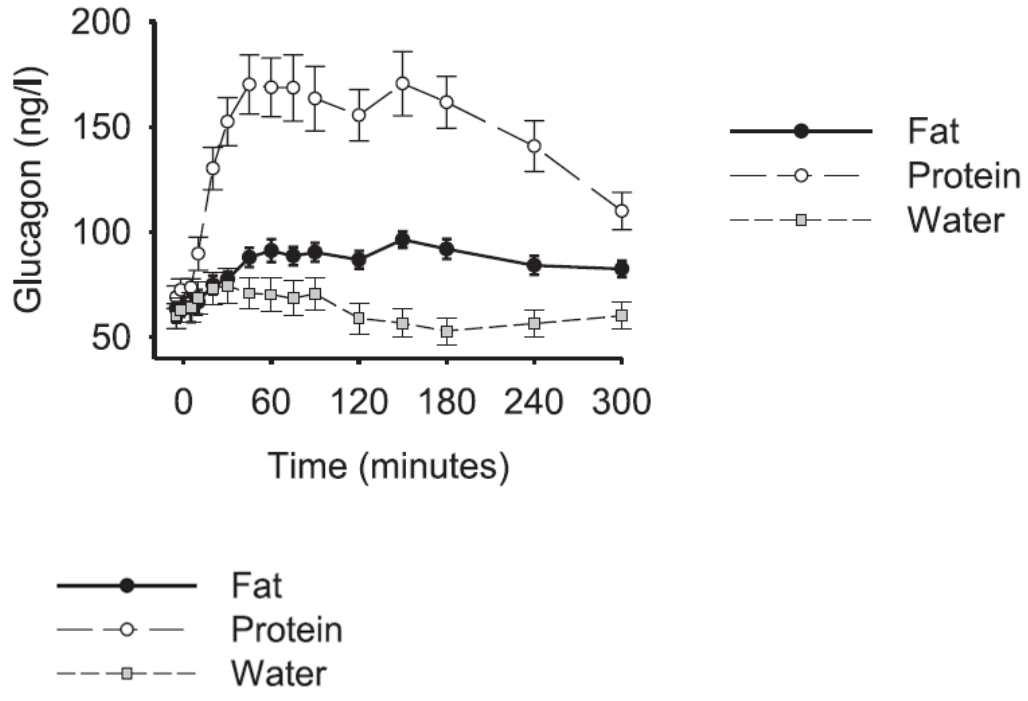
- The FFA from fat digestion increase GLP-1 secretion from the L Cells of the intestine. This positively regulates B-Cell secretion of insulin, which in turn negatively regulates

A-Cell Glucagon secretion. However, the GLP-1 secretion is moderate compared to when glucose is ingested, and the positive regulation by GIP leads to a net Glucagon increase after fat is consumed.

People with Type 1 diabetes do not have this automatic secretion of insulin from the B-Cells in response to GLP-1 when they consume fat. Consider this situation, it may explain a few things:

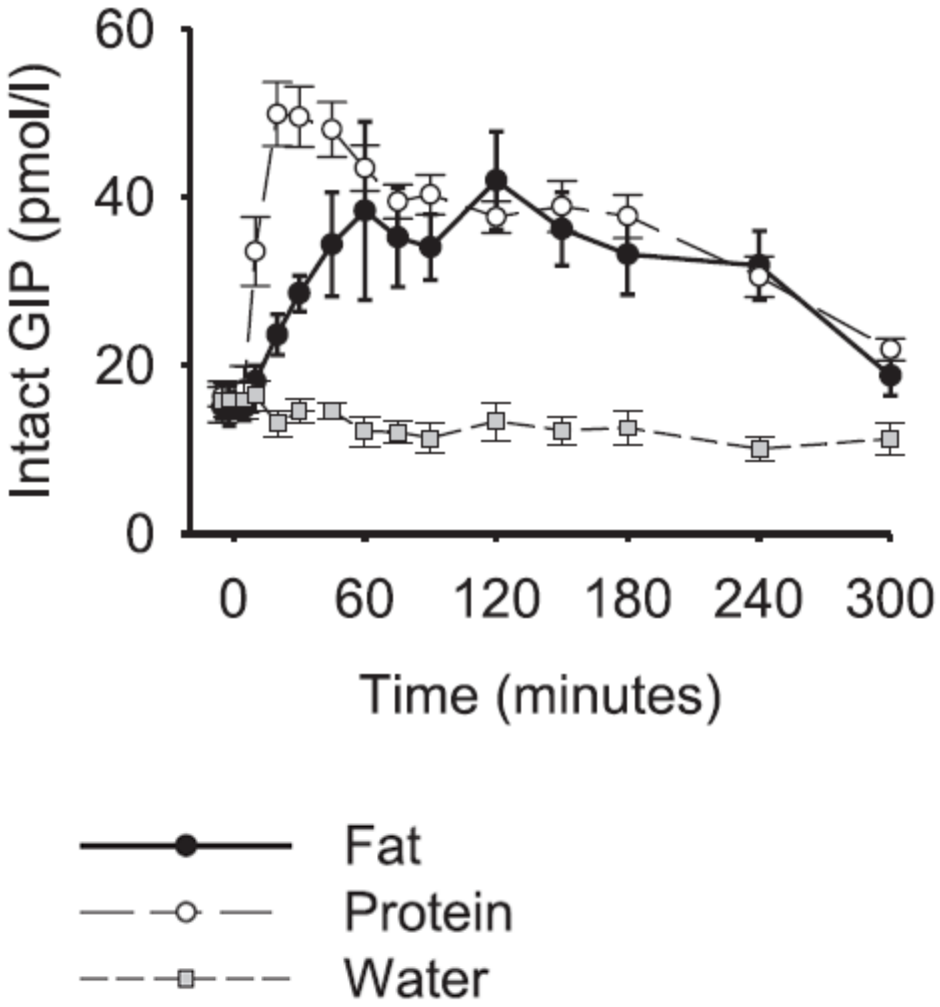
- If you have not provided enough, or any insulin for a fat only meal, the unchecked Glucagon will mildly elevate liver glycogenolysis and Gluconeogenisis. This could lead to a late rise in glucose after eating fat only meals.

Research on healthy adults consuming fat only (0.88g/kg, 560kcal), shows Glucagon levels increase two fold at 120 minutes post-ingestion, and remain at that level until 300 minutes (Carrel *et al.*, 2011). This point is particularly important, because as shown in the above insulin graph, the insulin does peak at 30 minutes, but then drops close to baseline by 300 minutes. Therefore, glucagon will take the predominant role in FFA oxidation, liver glycogenolysis, and potentially Gluconeogenesis after 120 minutes. This research stopped and 300 minutes, therefore it's difficult to know how long this elevation would have lasted.



As discussed earlier and shown in the graph below from the same study, the secretion on intact GIP from the K-Cells of the intestine, due to dietary FFA plays a role in Glucagon secretion. Interestingly you can also see the late peak of intact GIP is at 120 minutes, the time when Glucagon rises after fat ingestion. However, statistical analysis did not find the relationship between GIP and Glucagon to be resoundingly strong.

A recent review paper has highlighted there are different forms of GIP, some that stimulate insulin secretion and other forms that stimulate Glucagon secretion (Campbell and Drucker, 2015). This may be measurement error, or it speaks to the multitude of complex neural and hormonal signals that regulate Glucagon secretion discussed in the Glucagon section) (Gromada, Franklin and Wollheim, 2007; Hughes and Narendran, 2014; Campbell and Drucker, 2015).



Summary (Watch me)

Very simply, when fat alone is consumed at 50g, both Insulin and glucagon slightly increase, therefore not altering the I:G. This allows insulin to promote FFA to be stored as fat, which is positively regulated by an increase in GLP-1. This allows glucagon to increase FFA oxidation and liver glycogenolysis for energy production, which is positively regulated by GIP.

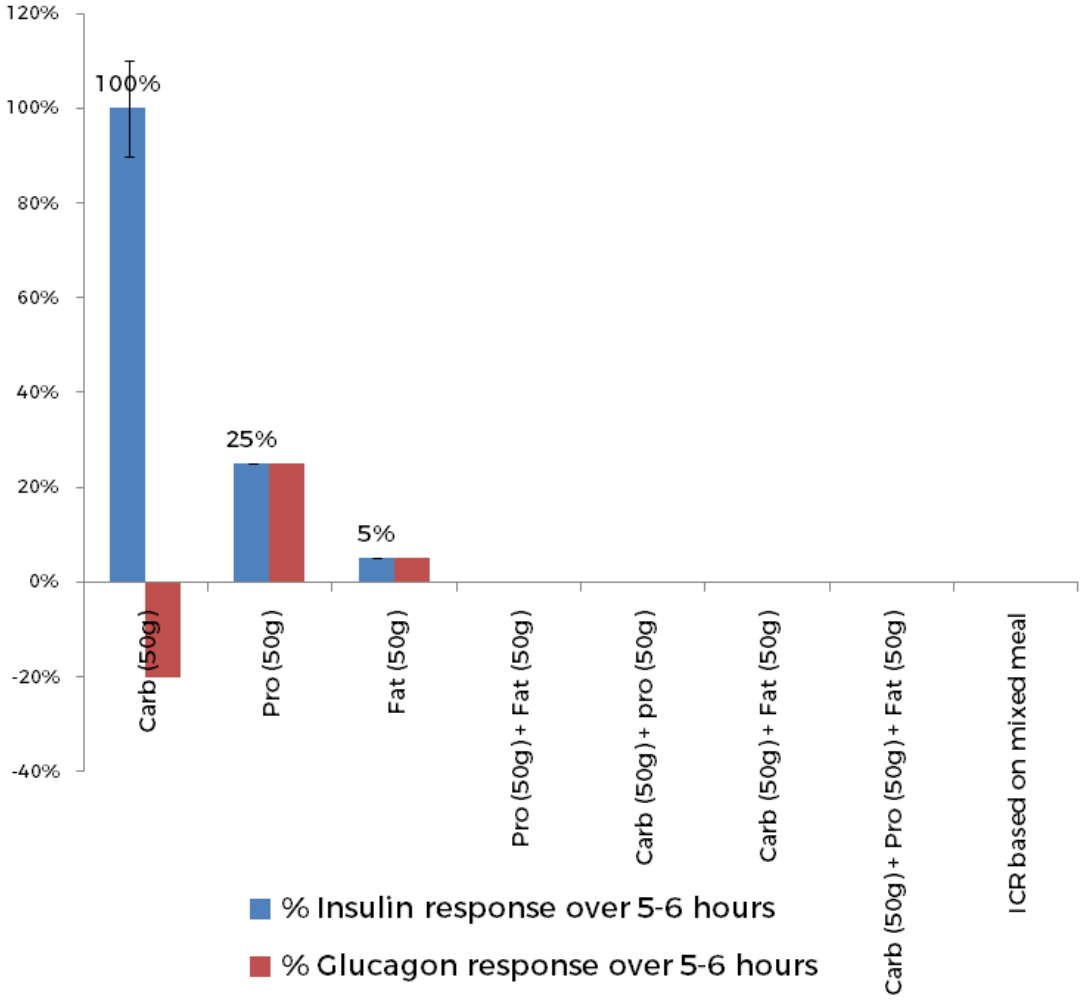
The job of the person with Type 1 Diabetes is to match the amount of insulin the pancreas would release for fat only. Too little leading to potential slight hyperglycaemia, too much leading to hypoglycaemia.

How much insulin to deliver for fat on a gram basis?

There is little research on the insulin requirement for fat alone over 5-6 hours for people with Type 1 diabetes. Therefore, we can use the above study which compared 560kcal of fat and protein (Carr *et al.*, 2008). The insulin and glucagon response to fat was only 20% of that of protein. Considering protein alone has an estimated 25%insulin response compared to carbohydrate alone, this puts the insulin and Glucagon response for fat compared to carbohydrate at 5%.

There is some evidence that corroborates this 5% effect. The Food Insulin Index (FII) group assessed the insulin requirement of 27g of fat from butter and olive oil, and 25g fat from Avocado. They found a 2%, 3%, and 4% insulin response respectively, when compared to glucose over two hours (Bell, 2014).Granted this was only over two hours, but it does paint a consistent picture.

The graph now shows 50g fat alone has a 5% insulin requirement of 50g pure glucose.



If you counted 0.05g of every gram of fat and applied the insulin ratio for pure glucose, you would not be too far off. So simply, for fat only meals this equation would work out the insulin load:

Insulin load = fat (g) x 0.05

The average person with type 1 Diabetes will rarely encounter this issue for a number of reasons:

- They rarely drink 50mls of olive oil just for kicks.

- Even if they do, they are generally eating in the next 3-4 hours so will not encounter the later raise in glucagon, and covered in next meal time insulin dose.

The only people this may apply to are those on a ketogenic diet who consume 70-80% of their energy intake as fat. Generally, they have a slightly higher background rate of insulin to cover this and often do not even bolus at meal times.

Summary of pancreatic response to single macronutrients?

You now have a good understanding of what happens when the macronutrients are consumed individually. But rarely do we eat these macronutrients on their own, we usually eat mixed meals.

It would be nice if insulin requirement was just simply the addition of the individual macronutrient insulin requirements. For example, if someone had a 1unit to 10g ICR:

- Carbohydrate at 100g, count 100% = 10units
- Protein at 30g, count 25% (7.5g) = 0.75 units
- Fat at 50g, count 5% (2.5g)= 0.25 units
- Then a meal of 100g carbohydrate, 30 grams protein and 50g fat would obviously need 11.0units of insulin! Simple!

If only it was that simple! Unfortunately, it is not. We need to look at what happens in real life, when the macronutrients are consumed together.

What does the pancreas do when protein and fat are consumed?

Insulin

Put simply, the B-Cells secrete extra insulin to move AA into the cells for anabolism, and promote FFA storage. The same regulators of B-Cell insulin secretion that have already been detailed are at play here. Most notably the increase inGLP-1, and the increased substrates for B-Cell glycolysis.

The big difference here is that the increase insulin requirement is not as immediate, it is more gradually over time. The stomach empties at a constant energy rate (8.4 kJ/min), therefore because fat is very energy dense, gastric emptying and consequent insulin signalling is delayed (Carbannel *et al.*, 1994).

Glucagon

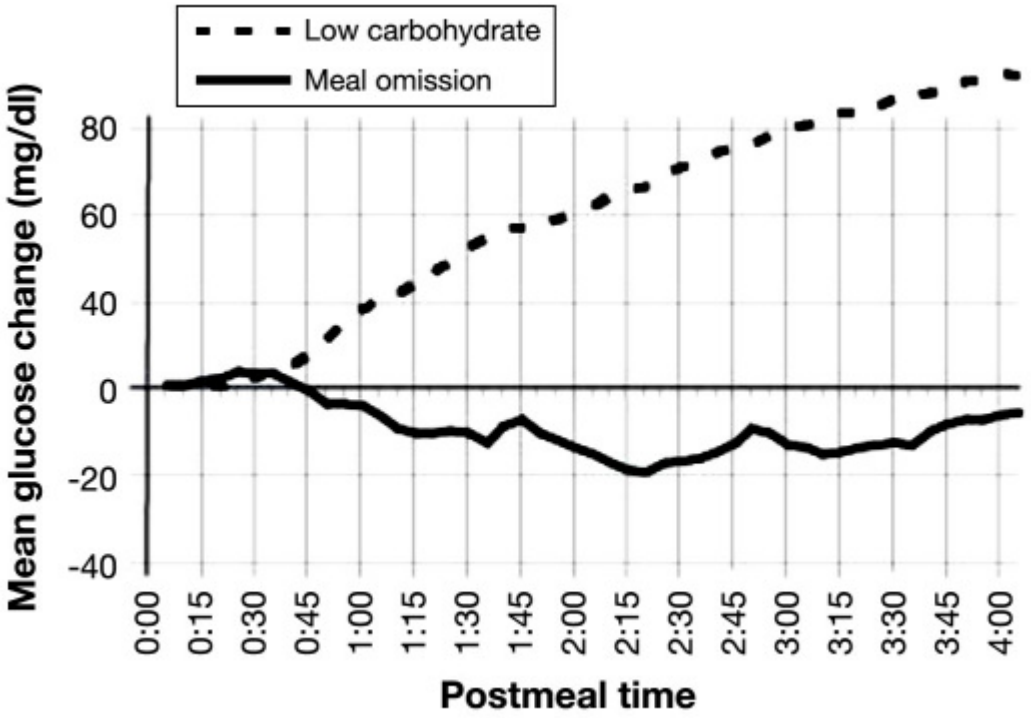
Put simply, the A-Cells secrete extra glucagon to prevent hypoglycaemia, and later to stimulate FFA oxidation and gluconeogenesis. The same regulators of A-Cell glucagon secretion that have already been detailed are at play her. Most notably the increased positive regulation from GIP, and negative regulation from insulin.

For the person with Type 1 diabetes, if no insulin is administered for a fat and protein meal, the I:G will drop leading to liver glycogenolysis and Gluconeogenesis. Also, the AA's will not be used for anabolism.

Research

In 2010 a study assessed the effect of low carb meals with no bolus insulin vs meal omission on ten males with type 1 diabetes (Uthoff *et al.*, 2010). The three carb free meals all consisted of <3g carbohydrate, 32-34g protein and 48-52g fat, 580-612kcal. They first did a fasting test to ensure the background insulin was set appropriately. The glucose level stayed stable over the four hour fasting test (7.2 - 6.8mmol/l), suggesting adequate background insulin. This would have been useful in the whey protein critiqued study earlier (Paterson *et al.*, 2014).

For each carb free meals, there was a consistent glucose rise of more than 3mmol/l (56mg/dl) over four hours. The researchers showed the glucose would have highly likely kept rising if the study continued to measure past four hours, possibly up eight hours. This is supported by the consistent observation of the late post-prandial hyperglycaemia effect of fat in type 1 diabetes (Smart *et al.*, 2013; Wolpert *et al.*, 2013)



Adapted from (Uthoff *et al.*, 2010)

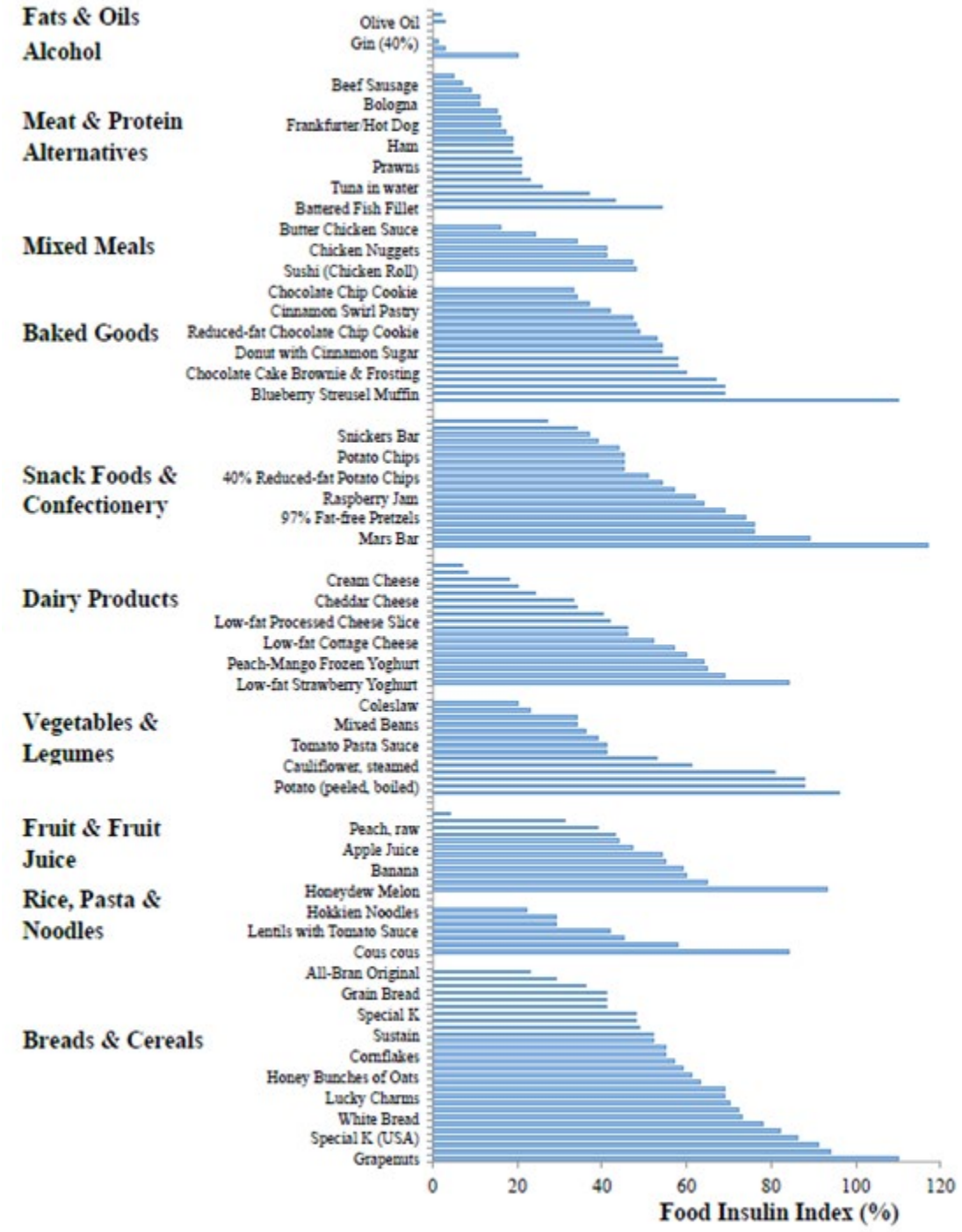
What about Type 1 diabetes studies where insulin was delivered for fat and protein meals?

First, we need to understand the Food Insulin Index (FII).

> The FII is a measure based of the insulin response to a fixed 1000kj portion of food over two hours, performed on 10 healthy men aged 18-65yrs. The insulin response elicited by glucose is given a score of 100% as the reference.
>
> So far 147 foods have been tested over 20 years. Each food has been given a FII score based on the percentage of incremental area under the curve of plasma insulin compared to that elicited from glucose (Bell, 2014). The FII is unique in that it

measures the insulin response to foods, therefore measures exactly what the person with Type 1 Diabetes needs to administer.

The FII produced some very interesting and unexpected results. For example 1000kj of Tuna (FII=23) produced a very similar insulin response to 1000kj of porridge (FII=29) over two hours. See the below graphic to see the different FII scores.



Adapted from (Bell, 2014; Bell, Petocz, *et al.*, 2016)

It must be highlighted the FII only measures insulin response over two hours, therefore it will likely underestimate the insulin requirement for protein and fat over 5-6 hours. However, the FII does show the importance of considering the insulin requirement for foods as a whole over two hours after eating. Rather than just considering the carbohydrate content.

Interestingly when the FII researchers isolated low carbohydrate (<10g) foods, they found protein was the strongest predictor of insulin response, explaining 54% of the variance in those foods (Bell, Petocz, *et al.*, 2016).

A study on 11 people with Type 1 Diabetes to determine if a new insulin dosing algorithm based on the Food Insulin Index (FII) would achieve better blood glucose control than carbohydrate counting over three hours, for commonly eaten high protein foods (K. J. Bell *et al.*, 2014).

Each study participant ate six different high protein foods (Beef steak FII 37, battered fish FII=54, poached eggs FII=23, low fat yoghurt=84, baked beans FII=88 and peanuts FII=15) on two occasions. On the first occasion they gave insulin for the food based on counting the carbohydrate and apply their ICR. On the second occasion they gave an insulin dose based on the FII score, but adjusted for the portion size to give an insulin dose based on a Food Insulin Demand (FID) score. Each participant had a unique FID ratio. The effect on blood glucose was measured over the next three hours.

The table below shows the insulin doses delivered for the same food, using the different methods. You can see the FID insulin doses were significantly higher than carbohydrate counting alone.

Table 4.1: Nutritional information and serving size for the six test foods

Food	Weight (g)	Energy (kJ)	Fibre (g)	Fat (g)	Protein (g)	CHO* (g)	Avg Insulin Dose using CHO (units)	FID†	Avg Insulin Dose using FID (units)
Beef Steak	225	1350	0	11.4	59.8	0	0.0	31	3.7
Battered Fish	105	945	1.0	14.3	12.4	14	1.6	31	3.7
Poached Egg	180	1080	0	20.3	23.6	2	0.1	15	1.8
Low-fat Strawberry Yoghurt	300	1200	1.2	5.8	13.8	45	5.4	57	6.9
Baked Beans	330	990	16.0	1.9	15.0	36	4.3	49	5.9
Salted Peanuts	150	3900	7.9	78.9	39.5	19	2.4	35	4.2

* CHO, available carbohydrate including sugars and starch and excluding fibre.

† FID, Food Insulin Demand. (FID = FII x kJ in food portion /1000) scaled using the FID and carbohydrate content of 1000 kJ of glucose powder (100/59)).

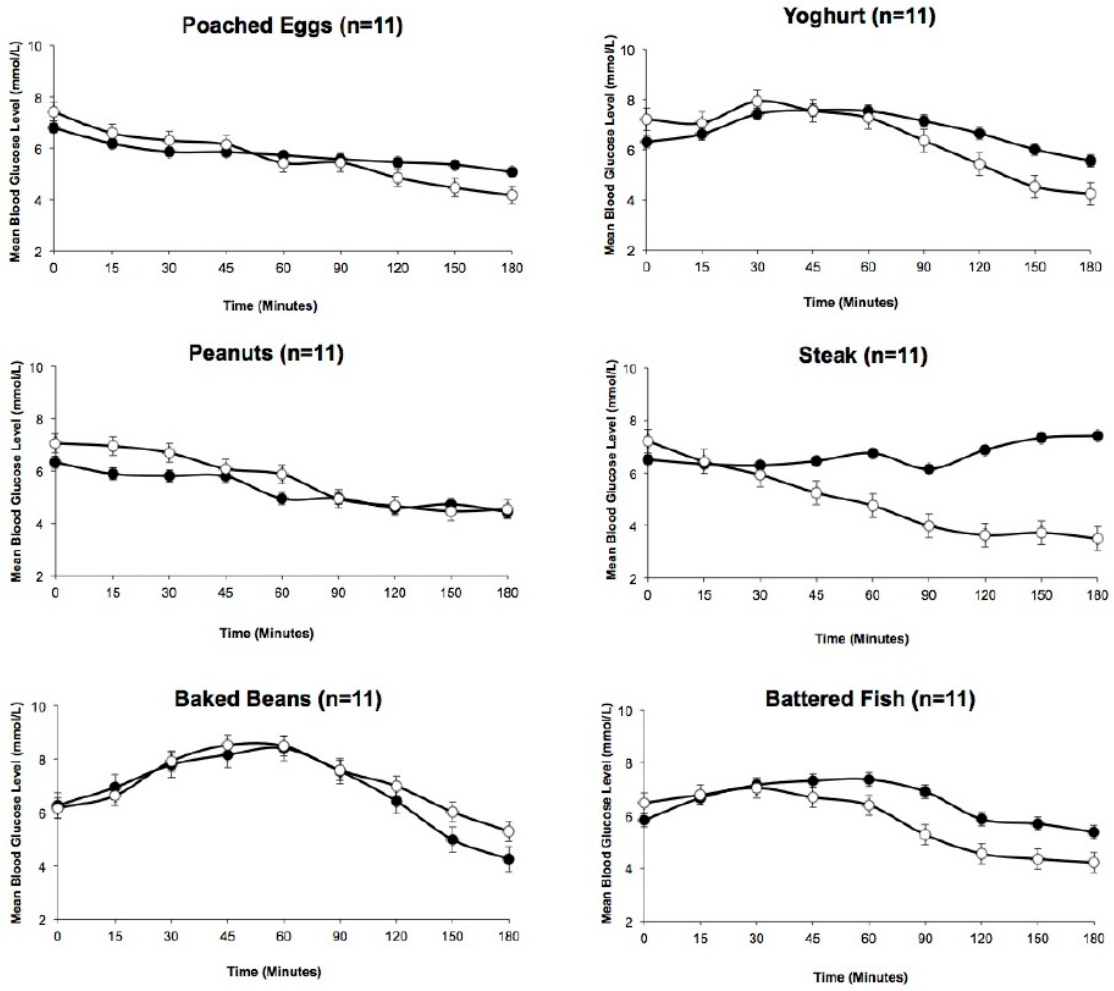
Adapted from (K. J. Bell *et al.*, 2014)

The focus of this section is high protein fat foods with low carbohydrate. From the table above you can see the difference in insulin doses:

- Three poached eggs, 0.1units from carb counting vs. 1.8units for FID
- Huge 225g Beef steak, 0.0 units for carb counting vs. 3.7units for FID.
- Peanuts, 2.4 units for carb counting vs. 4.2 units for FID

So what happened to the blood glucose levels when all this extra insulin was given?

In the three hours after eating, the average blood glucose was significantly lower in the FID group (5.7mmol/.l vs. 6.5mmol/l). The rate of hypoglycaemia between the two different methods was not significantly different. Take a look at the profiles over three hours for the individual foods in the below graphs. The blood glucose profiles of the carb counting group are the black dots, and FID group in white dots.



Adapted from (K. J. Bell *et al.*, 2014) **FID white circles, carb counting black circles**

The FID Beef Steak group had a lot more hypos, with 8 of the 11 people going low after bolusing on average 3.7units vs. 0.0units for carb counting, where only two participants went hypo.

However, If you exclude the beef steak example, you can see that extra insulin is required for people with Type 1 Diabetes when consuming high protein high fat foods. Certainly much more than just carb counting alone would suggest. The peanuts and eggs had a perfect profile with the FID insulin dose.

This adds credence to the fact that people with Type 1 Diabetes need insulin to transport AA for protein synthesis when high protein high fat meals are consumed. Also the risk of hypoglycaemia will not be increased with the extra insulin, unless the amount delivered is extremely high, as it was for the Beef Steak example!

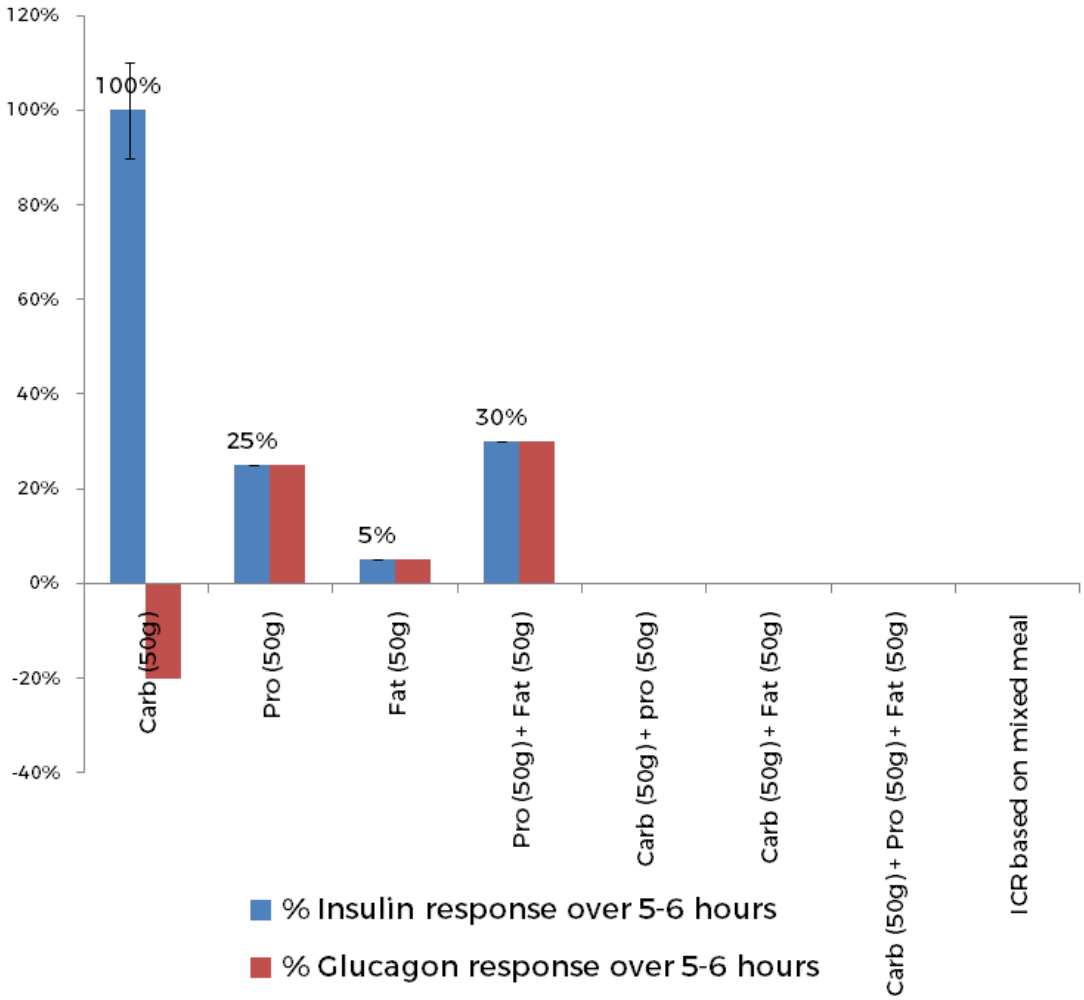
Summary (Watch me)

Very simply, when protein and fat are together both at 50g, both Insulin and glucagon increase, therefore not altering the I:G. This allows AA to be used for anabolism, FFA to be stored as fat or used for oxidation, all whilst maintaining the glucose levels. This is regulated by an increase in GLP-1 stimulating insulin secretion, and an increase in GIP stimulating Glucagon secretion.

The job of the person with Type 1 Diabetes is to match the amount of insulin the pancreas would release for protein and fat combinations. Too little leading catabolism and hyperglycaemia, too much leading to hypoglycaemia.

How much insulin to deliver for protein and fat on a gram basis?

Taken together these two studies discussed strongly suggest protein and fat together require insulin. It would seem protein exerts the majority of the insulin response initially, with fat becoming more prevalent later. The graphic includes an expected response of 30% for both insulin and Glucagon.



In terms of delivering insulin for high protein and fat meals, it is likely more insulin is needed upfront to cover the protein. An extended bolus on a pump or second small injection may be justified to cover the late glucose rise from fat. This may not be practical for most people, and they may choose to have a slightly elevated background insulin to deal with the late rise.

Insulin delivery options:

Initial bolus.

Insulin load = protein (g) x 0.25

Later extended bolus over 2-5 hours or second injection in 60-90 minutes, if background insulin not increased.

Insulin load = Fat (g) x 0.05

The average person with type 1 Diabetes will rarely encounter this issue for a number of reasons:

- They rarely have large carb free meals
- Even if they do, they are generally eating in the next 3-4 hours so will not encounter the later raise in glucagon, and covered in next meal time insulin dose.

Times when the person with Type 1 Diabetes will have encountered this:

- Change of breakfast on a Sunday from usual cereal with milk, to a protein and fat breakfast (bacon, egg, sausage). Result, high glucose level.
- Large carb free meal before bed without injection, probable high glucose on waking.

What does the pancreas do when carbohydrate and protein are consumed?

Insulin

Put simply, the B-Cells secrete extra insulin to move AA and glucose into the cells for anabolism and storage. More insulin is secreted than you would expect from their individual insulin secreting effects. The same signals that were discussed above are in play here. But one of the key factors that increases insulin more than expected are.

- Blood glucose and AA level starts to increase, therefore more glucose and AA enters the B-Cell. The B-Cell now has abundant glucose to speed energy production through glycolysis, and more AA substrates to ensure glycolysis runs at full capacity. Therefore, the B-Cell energy state is very high, leading to rapid insulin secretion.

Glucagon

The A-Cells also increase Glucagon secretion, which is the opposite to the decrease caused by carbohydrate alone. The same signals that were discussed above are in play here for Glucagon. But one of the key factors to be mindful here of is.

- Insulin is the trump card! Although the GIP increases A-Cells secretion of Glucagon, the negative regulation from the high level of insulin dampens the glucagon rise compared the protein only.

If this increase requirement is not met by the person with Type 1 Diabetes, what are the consequences?

- Lack of insulin to move the necessary glucose from the blood into the cells.

- The negative regulation of insulin on the A-Cells will not be as high as it should be. Therefore, higher glucagon levels will increase liver glucose output, especially after 3-4 hours after eating when the administered insulin is wearing off.

- Combined this means a glucose level that goes high initially and stays high.

Research

In healthy subjects, ingestion of 50 g of protein as lean beef and 50g of pure glucose elicited a significant increase in insulin over four hours (Krezowski *et al.*, 1986). The amount required was 127% of that required for 50g of pure glucose over four hours. Another study compared the insulin response when adding different protein sources (milk, cod, whey, and others) to white bread (100%). They found the increase in insulin response varied from 124-190% extra. Another study found the addition of protein to carbohydrate elicited 166% of the insulin response compared to carbohydrate alone (100%) (Esteves de Oliveira, Pinheiro Volp and Alfenas, 2011).

This evidence is strongly suggestive that when protein is added to carbohydrate, the increase in insulin requirement is higher than you would expect than just carbohydrate alone. The evidence suggests for healthy people the requirement for carbohydrate and protein combined, compared to carbohydrate alone (100%) is in the region of 130-190% over 5-6 hours.

A consistent finding in the research is that people with insulin resistance have an even greater synergistic effect compared to healthy people. One study took seventeen people

with type 2 diabetes and got them to consume 50g of glucose as a baseline, and measured the insulin response over the next five hours (Gannon *et al.*, 1988). They repeated the experiment several times, but added 25g of different proteins (beef, turkey, gelatin, egg white, cottage cheese, fish, and soy). The insulin secretion for glucose (50g) & cottage cheese (25g protein) was 360% vs. 100% for glucose alone. The lowest increase was that of egg white at 190%.

The person with type 1 diabetes who has also experiences insulin resistance needs to be mindful of this.

What about research on people with Type 1 Diabetes?

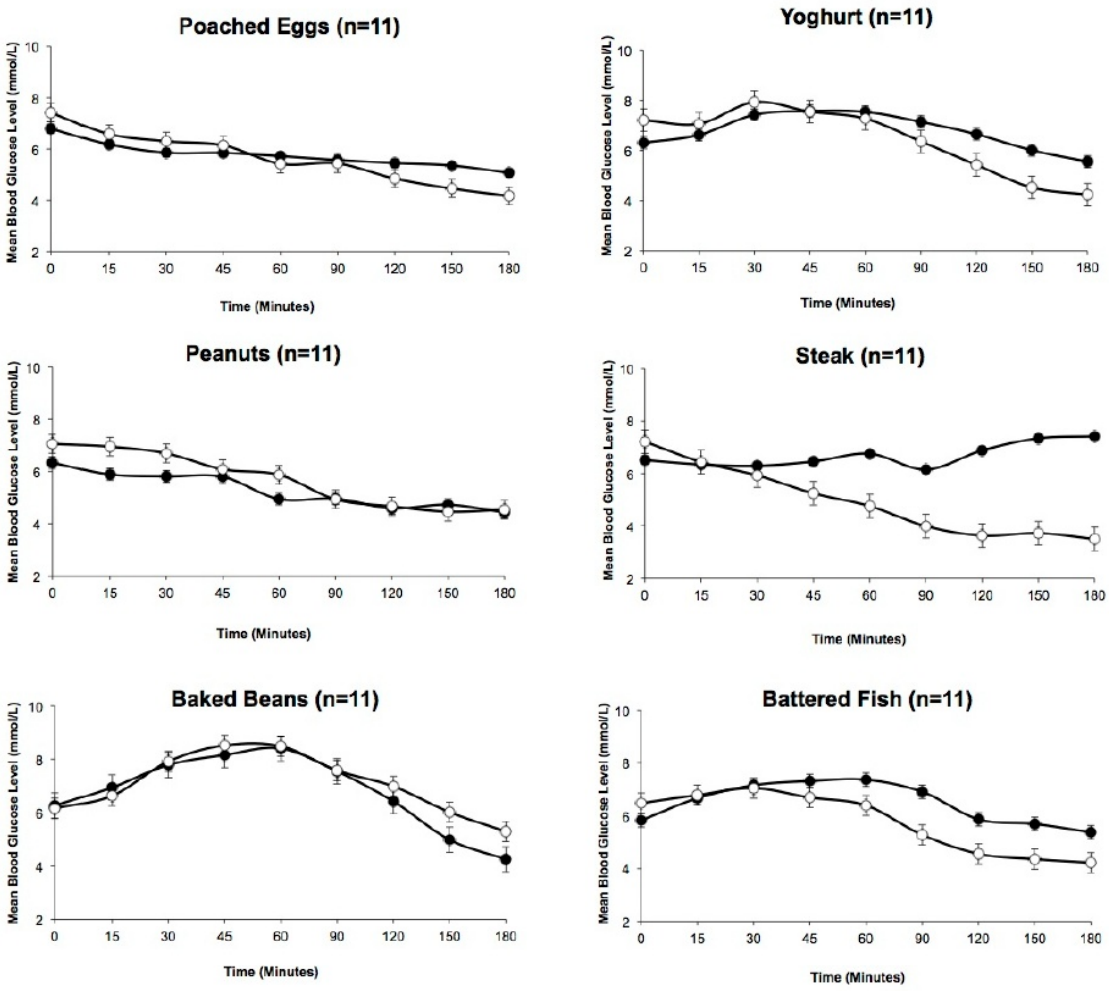
Research on children with Type 1 diabetes shows increasing protein from 5g to 40g protein for a 30g carbohydrate meal increased the glucose level at three hours by 2.4mmol/l. The glucose level stayed elevated at five hours by 2.6mmol/l, when compared to 30g of carbs alone (Smart *et al.*, 2013). This suggests that extra insulin was needed in the first three hours.

Other studies report similar effects, where meals containing 28-57 g of additional protein have demonstrated significantly higher postprandial glycaemic excursions and insulin requirements in the two to five hour postprandial period in type 1 diabetes (Winiger *et al.*, 1995; García-López *et al.*, 2013).

As discussed in the fat and protein section, the FII study grouped looked at insulin dosing for high protein high carb foods. They compared the insulin dosing of carbohydrate counting vs. FID. The doses suggested are presented below, along with the percentage extra suggested by the FID (K. J. Bell *et al.*, 2014):

- Low fat straw yoghurts, 5.4untis for carb counting vs. 6.9units for FID (28% extra).
- Baked beans, 4.3 units vs. 5.9units for FID (37% extra).
- Battered fish, 1.6units vs. 3.7units for FID (130% extra).

The results showed the FID insulin dosing had significantly lower average glucose level over three hours, with no difference in hypoglycaemia. The graphs below confirm 28-130% extra insulin is needed for high protein and carbohydrate foods compared to carb counting alone.



Adapted from (K. J. Bell *et al.*, 2014) **FID white circles, carb counting black circles**

The FII group (K. J. Bell *et al.*, 2014) used commercially available nutritional information to calculate the most effective algorithm for predicting the insulin response over two hours. A multiple regression algorithm was used on the 147 FII foods. The strongest performing formula could explain 50% of the insulin variance. That formula was:

FII = 10.4 + (1.0 Carbohydrate) + (0.4 Protein)

One must remember the FII only measures insulin requirement over two hours, and we know the effect of protein lasts much longer than that. Therefore, this is likely a substantial underestimation.

Summary (Watch me)

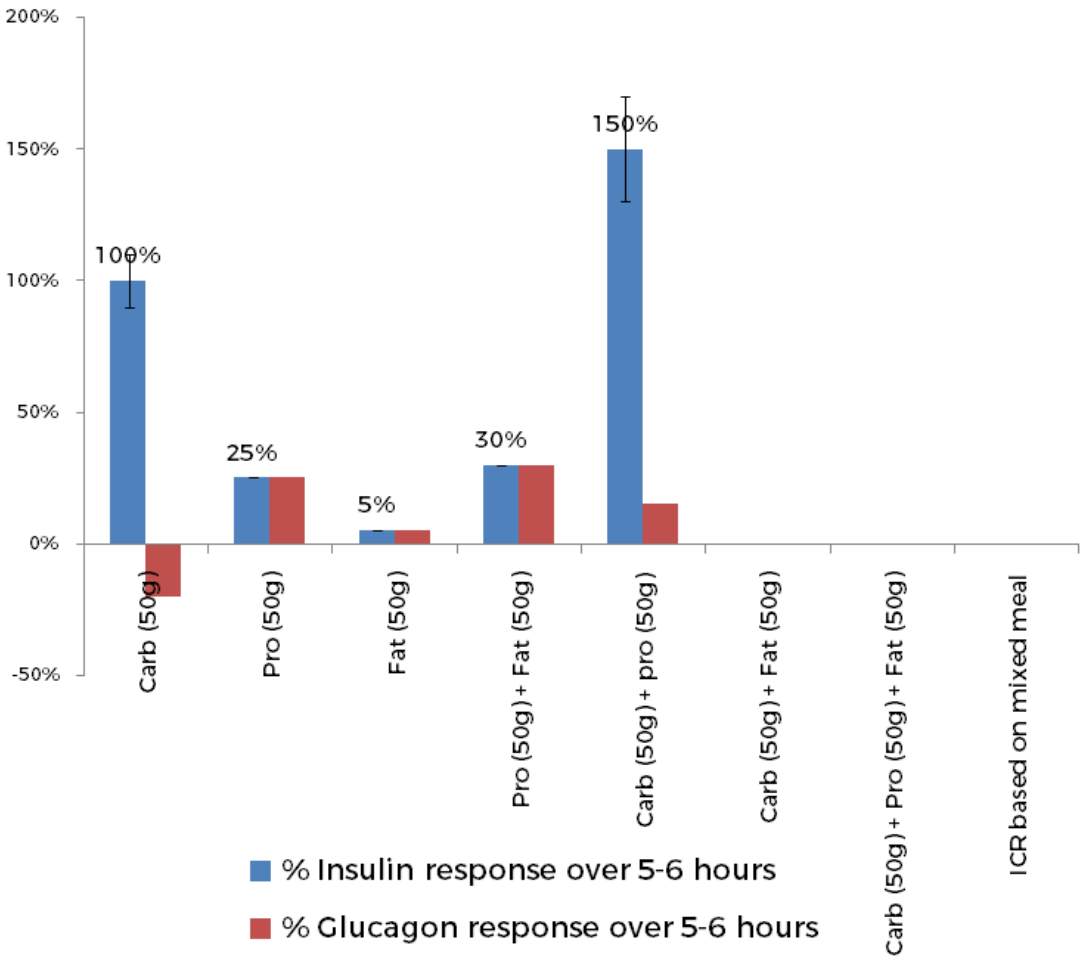
Very simply, when carbohydrate and protein are consumed both at 50g, the insulin increases more than would be predicted from their individual effects. The main factor is the synergy of AA and glucose in the B-Cell leading to an extremely high energy sate and insulin secretion. Glucagon only slightly increases, therefore the I:G is increased significantly. This allows anabolism and glucose storage as glycogen.

The job of the person with Type 1 Diabetes is to match the amount of insulin the pancreas would release for carbohydrate and protein. The main risk is too little leading to substantial hyperglycaemia, but too much would cause hypoglycaemia.

How much insulin to deliver for carbohydrate and protein on a gram basis?

The research suggests compared to carbohydrate alone (100%), the insulin requirement for carbohydrate and protein together is between 130-190%, dependant on type of protein. The FII data over two hours suggests you need to account for 40% of each gram of protein, but this is likely an underestimation of the total requirement over 5-6 hours.

The data suggest the average insulin requirement is about 150% for carbohydrate and protein, when compared to carbohydrate alone. For Glucagon, a slight increase from baseline of about 15%. Both are represented in the graph below. There is a 20% error bar included to accommodate the discussion on type of protein in the coming section. To keep it simple, dairy protein that is high in Leucine requires more insulin that foods lower in leucine.



For carbohydrate and protein meals, the best fit equation seems to be:

Insulin load = (protein (g) x 0.5) + (g) carbohydrate

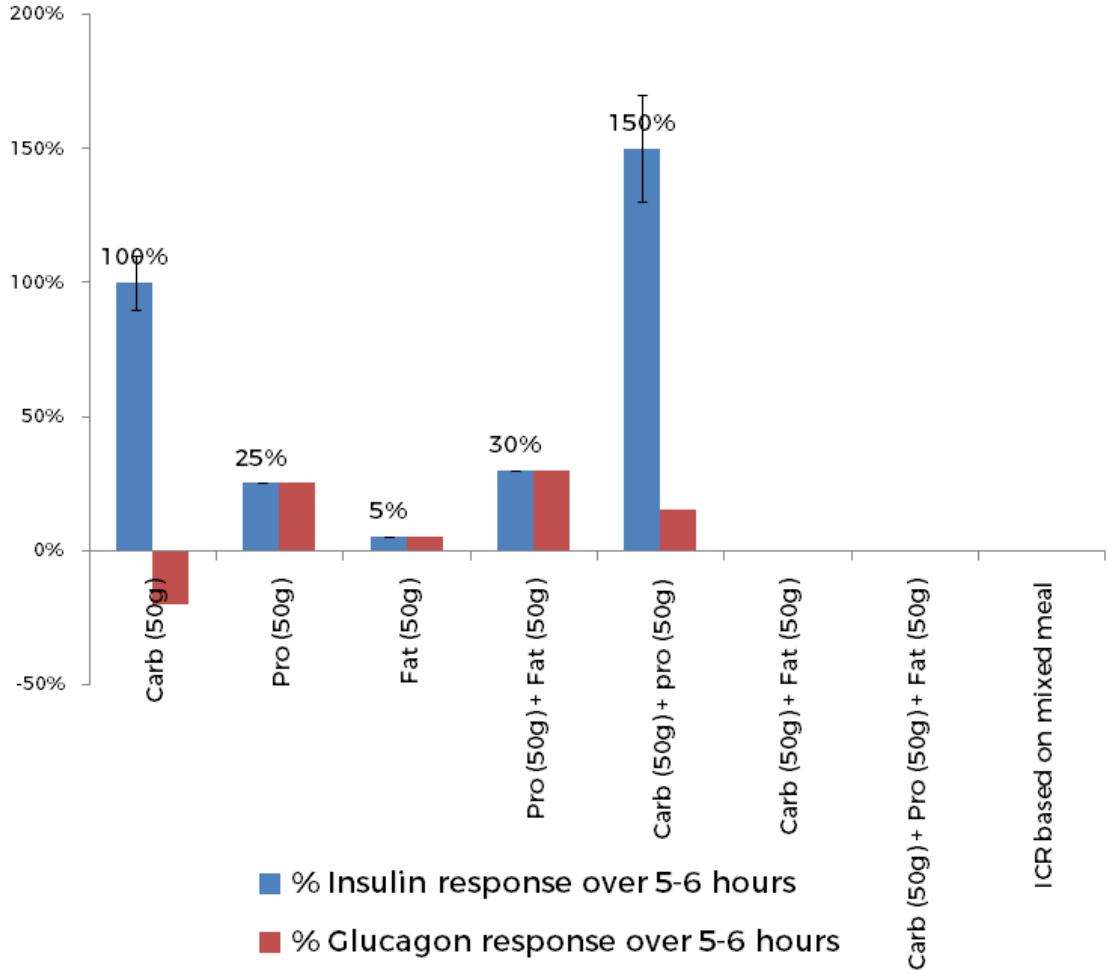
The Type 1 Diabetes research discussed above suggests the increase insulin requirement when protein is added to carbs is mostly in the first three hours (Smart *et al.*, 2013). Therefore it would not appear necessary to split or delay the insulin delivery.

Why do most people with type 1 diabetes not do this?

Most people with Type 1 diabetes who carb count do not see the effect of usual protein intake on blood glucose level for a very important reason you **MUST** understand:

- When they work out there ICR, it is always on a mixed meal that contains their usual amount of carbs, protein, and fat. Unfortunately they believe they are only giving insulin to cover the effect of the carbohydrate. Whereas, they are covering the effect of their usual mixed macronutrient meals. Have you ever tested and ICR using only bread? or did you have meat, fish, cheese, or butter on it?

- To help you picture this, look at the graph below. We will discuss later why the ICR covers about 130% of the effect of carbohydrate only. Just realise the ICR is more like a usual mixed meal ratio, that is mostly influenced by carbohydrate.



Times when protein and carbohydrate combinations present a problem:

- Change breakfast on a Sunday from typical cereal to a full English breakfast (Toast, Beans, mushrooms, sausage, eggs, bacon). Give the insulin for the toast only and end up with a very high glucose level.

- Large Steak with potatoes and bread

Bonus: Do all amino acids behave the same when combined with carbohydrate?

Certain AAs have been shown to have a more potent effect on increasing insulin secretion than others, when combined with carbohydrate. Leucine has consistently been shown to increase insulin secretion more than any other AA. In their series of studies Gannon and Nutall (Gannon and Nuttall, 2010) showed a marked increase in insulin response for Leucine.

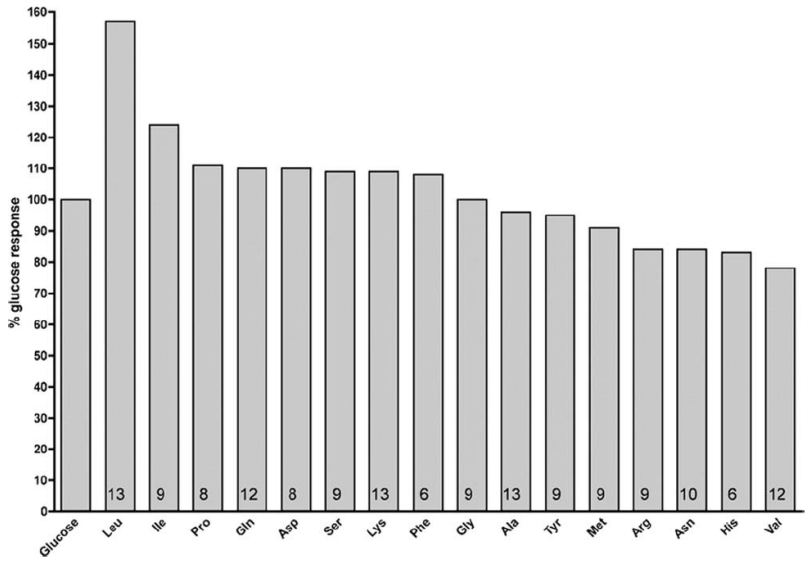


Figure 5. Insulin area response. % Individual amino acid + glucose compared to glucose alone. The mean insulin area response to glucose was set at 100%. The mean insulin area response to ingestion of the amino acid + glucose was divided by the mean area response to glucose alone to give a percentage. Numbers within the bars indicate the number of subjects studied.

Adapted from (Gannon and Nuttall, 2010)

The mechanisms by which Leucine increases insulin secretion have been discussed previously. To jog the memory:

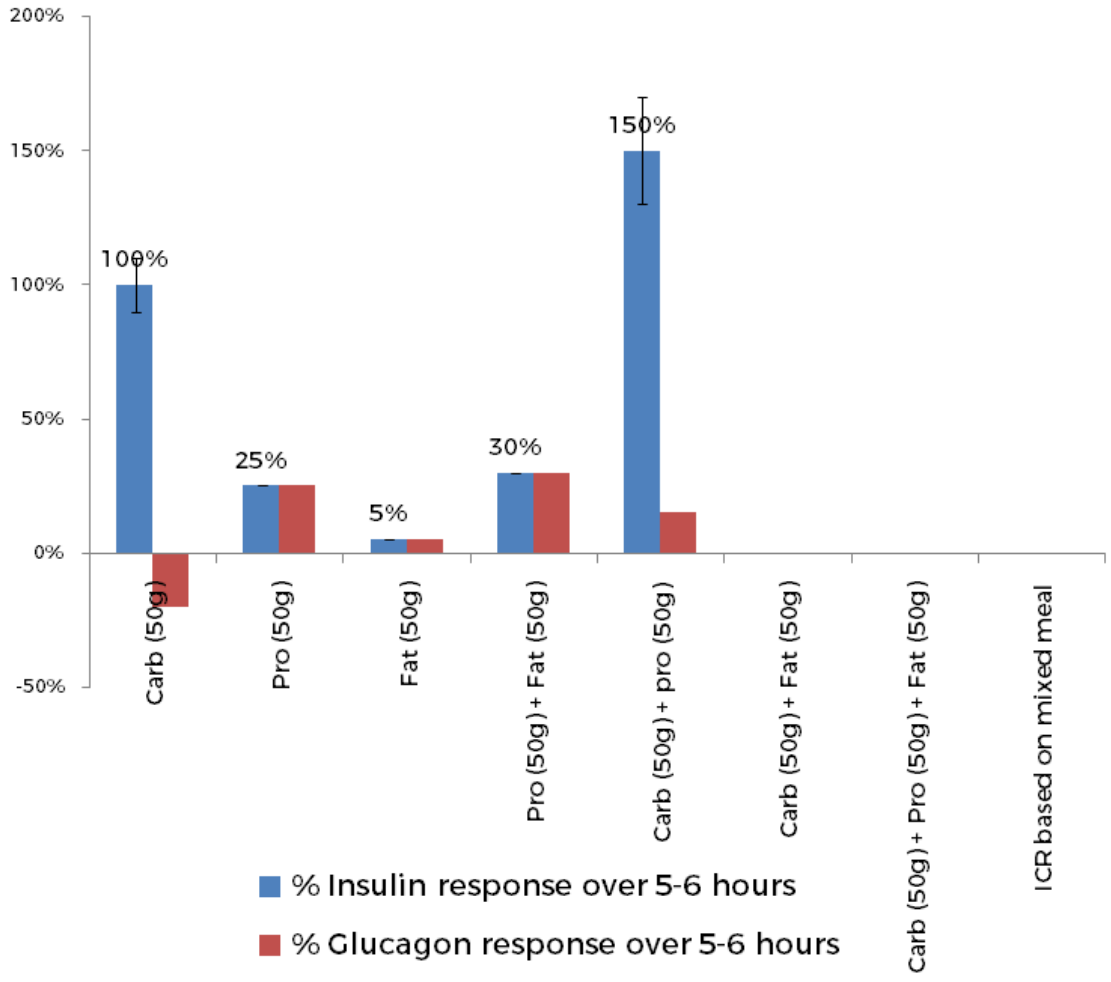
- Activating GDH in the B-Cell (Van Loon *et al.*, 2000)

- Activation of MTOR in the B-Cell (Yang *et al.*, 2010).

This helps explain why studies show whey protein, due to its rapidly absorbable Leucine, increases insulin secretion much higher than other protein sources (Nilsson *et al.*, 2004). This may also explain the high FII scores for low fat dairy foods, such as of low fat yoghurt and skim milk. Analysis of the FII data reported that compared to all the AA, Leucine had one of the strongest correlations with insulin secretion (Bell, Petocz, *et al.*, 2016).

This helps explain why people with type 1 diabetes often complain of very high post-prandial high glucose levels after breakfast cereal with milk (high in leucine).

If you consume a diet that is high in milk based dairy products, or have a lot of whey protein, you may need to increase your insulin dose a little higher. This is represented in the 20% standard deviation bar shown that was added to the model we are building.



What does the pancreas do when carbohydrate and fat are consumed?

Insulin

Put simply, the B-Cells secrete extra insulin to move glucose into the cells for storage, and promote FFA storage as fat tissue. The same regulators of B-Cell insulin secretion that have already been detailed are at play here. Most notably the increase GLP-1, and the increased substrates for glycolysis in the B-Cell.

The big difference here is that the increase insulin requirement is not as immediate, it rises more gradually over time. The stomach empties at a constant energy rate (8.4 kJ/min), therefore because fat is very energy dense, gastric emptying will be delayed (Carbannel *et al.*, 1994). In healthy individuals the addition of fat to a carbohydrate meal delayed both the glycaemic and insulin responses (Welch McL. *et al.*, 1987).

Glucagon

Put simply, the A-Cells secret a little extra Glucagon to increase FFA oxidation. The same regulators of A-Cell Glucagon secretion that have already been detailed are at play here. Most notably the increased GIP to positively regulate, and increased insulin to negatively regulate.

One study confirmed that when adolescents with type 1 diabetes consumed a high fat high carbohydrate meal, GLP-1 and GIP both increased significantly (Lodefalk, M.; Carlsson-Skwirut, C.; Holst, J.J;. Aman, J.; Bang, 2010). This suggested the expected physiological changes occur in people with Type 1 Diabetes.

Research

In one study it was shown that giving eleven type 1 adults an additional 50g of fat to high carbohydrate low fat (96g carb& 10g fat) meal, increased the insulin requirement by 42% on average (Wolpert *et al.*, 2013). The 42% increase was determined by closed loop CGM

insulin delivery. The 42% was still not enough, as the glucose results after the meal with added 50g fat were on average higher than the 96g carb and 10g fat meal. Interestingly the extra requirement ranged in participants from -17% to 108%. The extra insulin was needed up to 5-10hours after ingestion, confirming the delayed gastric emptying effect.

A study on children with Type 1 diabetes also showed the glucose raising properties of fat when combined with carbohydrate over 5 hours (Bell *et al.*, 2020). This graph shows when the carbohydrate is fixed at 45g and protein is constant, adding additional fat increases the glucose level in a dose dependent manner over 5 hours. It also shows meal with 0g fat will lead to hypoglycaemia and 60g will lead to hyperglycaemia. This suggests the carb ratio can accommodate 20-40g of fat.

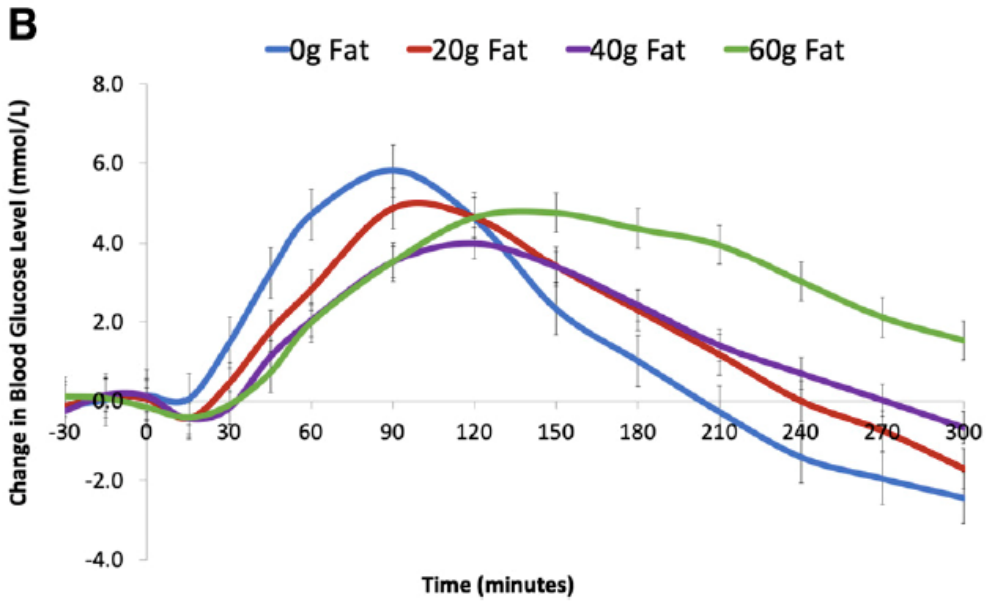
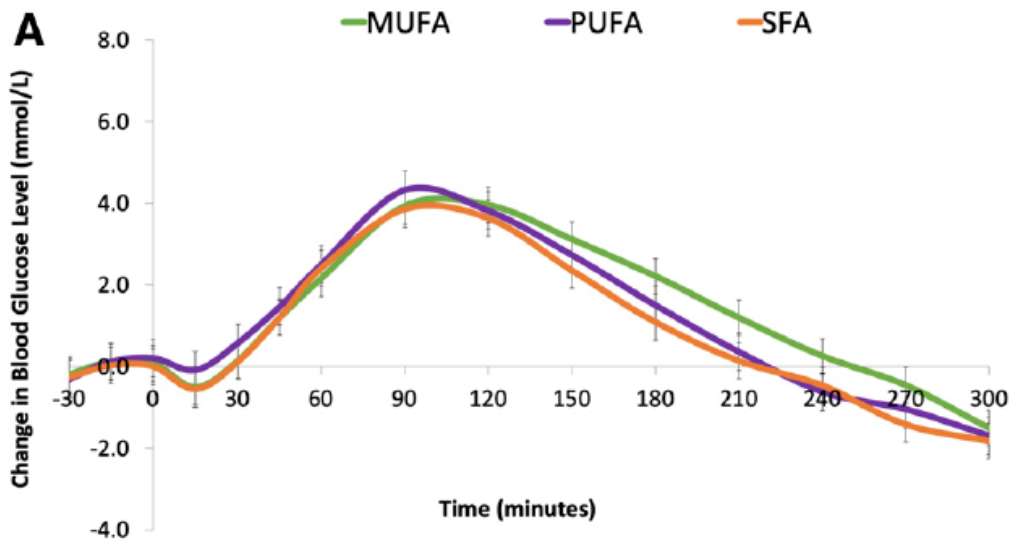


Figure 1—Postprandial glucose profiles for varying types (*A*) ($n = 16$) and amounts of fat (*B*) ($n = 15$) in adults with T1D using insulin pump therapy with insulin dosed according to individualized ICR as dual-wave 50/50% over 2 h.

The same study also shows that type of fat did not significantly impact the after meal glucose level for 5 hours, as shown below (Bell *et al.*, 2020).



The same study determined how much extra insulin was needed and how it should be spread with a dual/extended wave on a pump to cover increasing levels of fat on top of 45g carbohydrate, using 0g fat as the baseline condition (Bell *et al.*, 2020). For 20g fat it was +6% insulin, 74/26% over 73 minutes, 40g fat it was +6% insulin, 63/37% over 75 minutes, and for 60g fat it was +21% over 49/51% 105 minutes.

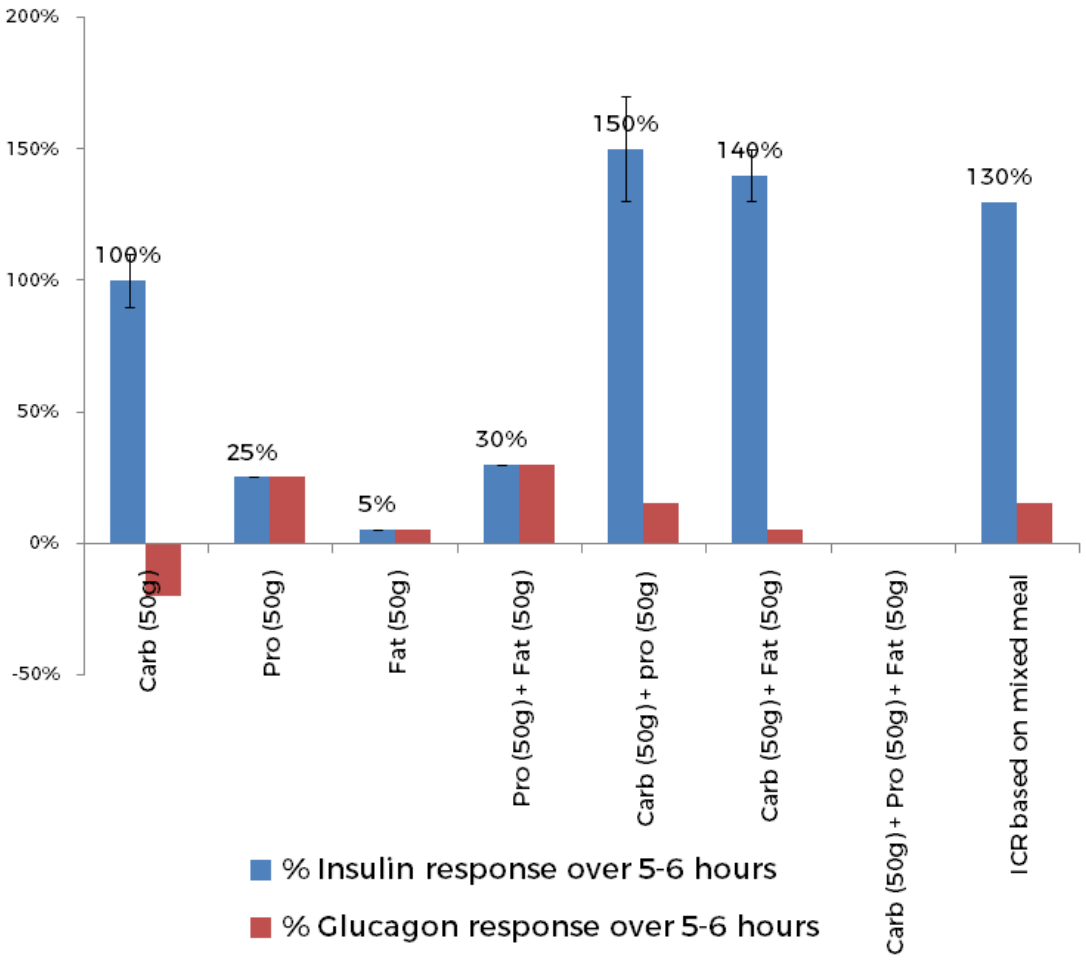
Summary (Watch me)

Very simply, when carbohydrate and fat are consumed both at 50g, the Insulin increases more than would be predicted from their individual effects on insulin. The main factor is the synergy of FFA and glucose in the B-Cell leading to a very high energy sate and insulin secretion. Glucagon only slightly increases, therefore the I:G is increased significantly. The increase in insulin is not as immediate when compared to carbohydrate and protein, due to the delayed gastric emptying from the high fat intake. This change in I:G promotes glucose storage as glycogen, and FFA storage as fat over a prolonged period of time.

The job of the person with Type 1 Diabetes is to match the amount of insulin the pancreas would release for carbohydrate and fat. The first risk is too much insulin too early causing hypoglycaemia. But later on, after about three hours has passed, the big risk is not having enough insulin leading to significant hyperglycaemia.

How much insulin to deliver for carbohydrate and fat on a gram basis?

The research suggests compared to carbohydrate alone (100%), the insulin requirement when adding 50g fat is 121-142%.vThis is much greater than if just added the fat only response to the carbohydrate only response, that would have only been 105%. Also the interindividual variability is -17-108% (Wolpert *et al.*, 2013). For Glucagon, a slight increase from baseline about 5%, as represented in the graph below.



The equation for working out the insulin load from fat and carbohydrate:

Insulin load = (fat (g) x 0.4) + (g) carbohydrate

The Type 1 Diabetes research discussed suggests the extra insulin requirement for fat in this combination mostly happens after 210 minutes (Paterson *et al.*, 2014). Therefore, the extra insulin delivered to account for the fat must be given by splitting the injection, or using the

extended bolus options on a pump. This would prevent going hypoglycaemic initially, and prevent hyperglycaemia later.

The current suggestion from a research review, a MUST READ is (Bell, Smart, *et al.*, 2015) suggests;

- If on a pump, split the total dose 50% upfront and 50% spread over two and a half hours, via an extended wave.

- If on MDI, give 50% upfront and the other 50% in 60-90minutes time.

This could now be updated following the recent fat dosing study (Bell *et al.*, 2020):

- Only increase the dose if fat is >40g
- Start by increasing the dose by 20%
- Split the dose 50/50
- Spread the second 50% over 100 minutes

Why do most people with type 1 diabetes not take this into account?

Most people with Type 1 diabetes who carb count do not see the effect of usual fat intake on blood glucose level for a few reasons:

- As discussed in the carbohydrate and protein section, the ICRis tested on a mixed meal that contains their usual meal amounts of carbs, protein and fat. Therefore, it already accounts for some of the fat effect by covering 130% of the effect of carbohydrate alone.

- They very rarely go more than 3-4hours without eating again, so the effect of rising glucagon 4-8hours after fat is covered by the next meals insulin dose.

Times when they will really notice it, and probably avoid these situations as a consequence:

- Have a very heavy chocolate cake that is very high in carbohydrate and fat. Way above the usual that the ICR caters for.

- A bag of chips (large fried potato chunks!) for the chippy, that is loaded with fat in amounts much higher than the ICR is tested on.

- Going on a donut and biscuit raid. The amount of fat is much more than the usual ICR is ready to deal with.

Bonus: Do all free fatty acids behave the same?

Animal research has shown the more saturated the fatty acid is, the greater the release of Somatostain, a pancreatic hormone that positively regulates A-Cell release of Glucagon. Therefore, Glucagon is secreted at a higher rate, leading to increase liver glucose output (Olofsson *et al.*, 2004).

The FII (Bell, Petocz, *et al.*, 2016) analysed the effect of different fatty acids on the insulin requirement over two hours. They showed of the FFAs, MUFA was most strongly correlated with to the lowest insulin response, and SFA the highest insulin response.

The research shows clearly total fat is the most important parameter(Bell *et al.*, 2020), but if you were looking to reduce insulin dose, you may want to choose MUFA options, such as olive oil, avocado etc.

What does the pancreas do when carbohydrate, fat and protein are consumed?

Insulin

Put simply, the B-Cells secrete a lot more extra insulin for anabolism, glucose storage, and FFA storage. All mediated by the regulators discussed previously. The most important factors being the positive regulation by GLP-1, and the extremely high energy state of the B-Cell.

Glucagon

Put simply, the A-Cells secrete slightly more Glucagon to promote FAA oxidation and gluconeogenesis later on. All mediated by the regulators discussed previously. Positive regulation by GIP, and negative regulation by insulin.

If the person with type 1 diabetes does not deliver the extra insulin required there will be serious hyperglycaemia that is prolonged.

Research

We have already discussed the value of this MUST READ (Smart *et al.*, 2013) meal study, which looked at the effect of adding protein and fat to carbs. However, this study did the tri-factor, it also studies when both fat and protein is added to carbs. Let's take a detailed look at this study.

This study first looked at what happens when you give the insulin dose suggested by the ICR for a moderate carbohydrate low fat low protein meal. Then using that same insulin dose, what happens to the glucose level when the other macronutrients are increased in a stepwise manner. I have put the macronutrient profile of all the different pancakes used in the study:

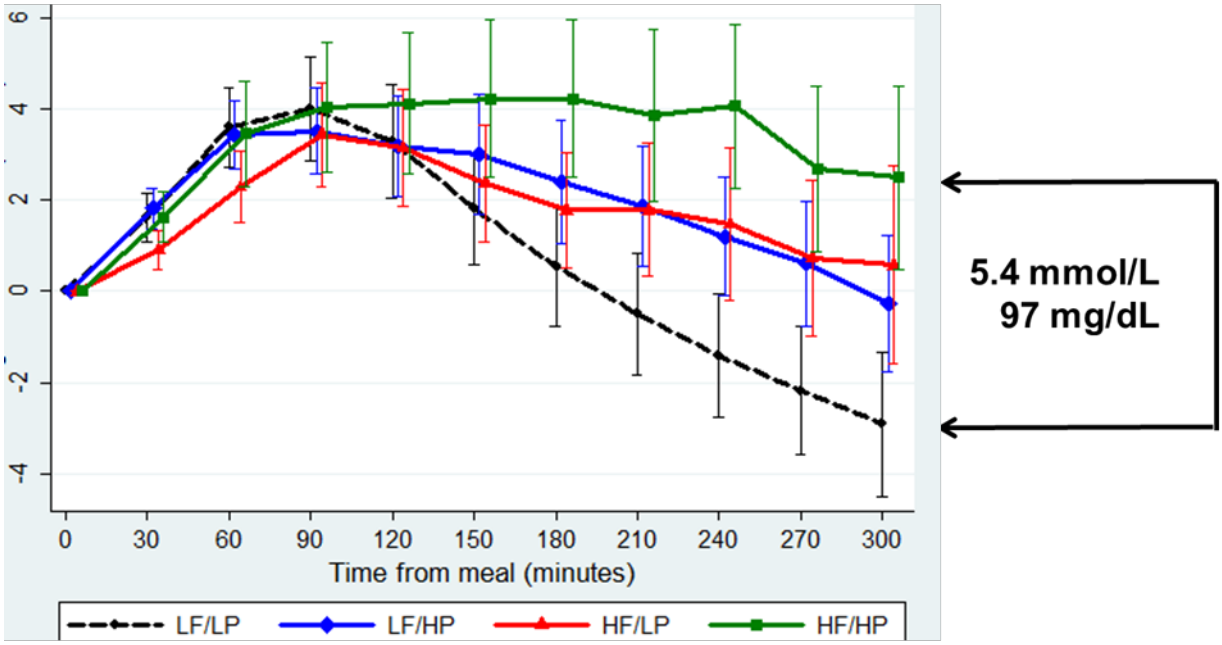
- Low Fat Low Protein (LF/LP) meal:
    - 30g carbohydrate, 4g fat, 5g protein, 176kcal

- Low Fat High Protein (LF/HP)
    - 30g carbohydrate, 4g fat, 40g protein, 316kcal

- High Fat Low Protein (HF/LP)
    - 30g carbohydrate, 35g fat, 5g protein, 446kcal

- High Fat/High Protein (HF/HP)
    - 30g carbohydrate, 35g fat, 40g protein, 595kcal

The graph below shows what happened to the thirty-three adolescents blood glucose profiles after consuming each of the four meals.



Adapted from (Smart *et al.*, 2013)

What have you noticed?

This study really helps bring together what we have been building towards.

What does the ICR cover?

If you use your ICR and give insulin according the carbohydrate in the meal, what happens when:

- That meal is LFLP: You will go hypo! In this study the glucose level was on average 2.9mmol/l (52mg/dl) lower after five hours compared to baseline. This speaks to the fact that when you work out your ICR it is based on your usual mixed meals, not just the carbohydrate content! You can see by 300 minutes both LFHP and HFLP are back to baseline level, -0.3mmol/l (-5mg/dl) and +0.6mmol/l (11mg/dl) respectively. This just goes to show your ICR accounts for the insulin response needed for a mixed meal, not just carbohydrate.

- After 180 minutes the HPLF meal glucose level is significantly higher than the LFLP meal, whereas the HFLP was not. This is just a reiteration of an earlier discussion, that the increase in insulin for protein needs to be delivered before the meal. This will stop the rise at 180minutes.

- After 210 minutes the HFLP becomes significantly higher than the LFLP, and stays higher up to 300 minutes. Therefore the increase in insulin for fat needs to be delivered later on, and delivered as a spilt injection or extended wave on a pump.

- When HPHF was consumed there was a cumulative effect of adding both protein and fat to LFLP. At 180minutes HFHP was 3.7mmol/l higher than LFLP, and by 300 minutes that increased to 5.4mmol/l higher. The differences at 180minutes and 300minutes were almost a perfect addition of the individual effect of LFHP and HFLP. Basically showing that both fat and protein need accounting for when insulin dosing, and they are cumulative.

Let's bring this closer to home. Bell and colleagues in 2016 (Bell, Toschi, *et al.*, 2016) used a closed loop insulin dosing method to find out how much insulin was needed when comparing a pizza base (50g carbs, 4g fat, 9g protein, 273kcal) with a cheese pizza (50g carbs, 44g fat, 36g protein, 764kcal) over six hours. Nine men and one woman with Type 1 Diabetes undertook the pizza challenge.

How much extra insulin do you think was needed?

A whopping 65% extra insulin on average. Not only that, due to the high fat content, the insulin needed to be spread out, 30% upfront and 70% over 2.5 hours via an extended wave on a pump.

Did all ten type 1 pizza addicts need 65% extra?

One person only needed 24% extra, whilst one person needed a massive 124% extra. This is not surprising when you consider the evidence we discussed earlier showing people with insulin resistance have exaggerated insulin requirements for high protein and fat (Berger, S.; Vongaraya, 1966)

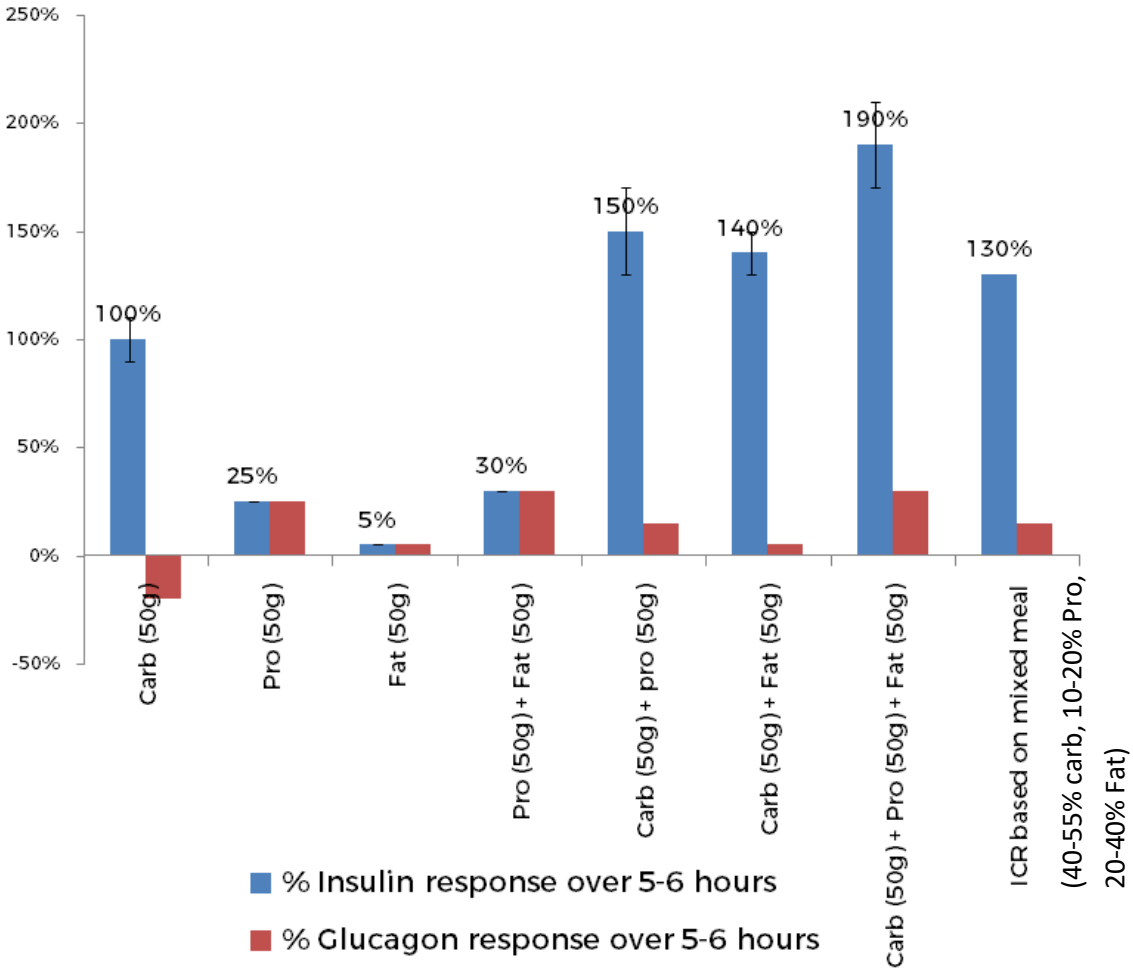
Summary (Watch me)

Very simply, when carbohydrate, fat and protein are consumed all at 50g, the extra Insulin required compared to carbohydrate alone is equal to adding the extra needed for both carbohydrate plus protein, and carbohydrate plus fat. The main factor is the synergy of glucose, AA, FFA in the B-Cell leading to a very high energy sate and insulin secretion. Glucagon only slightly increases, therefore the I:G is increased significantly. The increase in insulin is both immediate due to AA, and delayed due to FFA. This allows AA to be used for anabolism, glucose to be stored as glycogen, and FFA to be stored fat.

The job of the person with Type 1 Diabetes is to match the amount of insulin the pancreas would release for this tri-factor. The main risk is not enough insulin leading to early and persistent hyperglycaemia. The risk of hypoglycaemia is very low when a meal as large as this is consumed.

How much insulin to deliver for carbohydrate, protein and fat on a gram basis?

This research suggests when adding protein and fat to carbohydrate, the increase in insulin requirement is cumulative. Therefore, following our graphical model, we need to add the extra 50% and 40% together, to get a 190% requirement in comparison to carbohydrate alone. We also need to add a 30% error bar to include the type of protein and fat. With a meal high in Leucine (Dairy) and SFA (Butter, cheese, cream) having a higher requirement.



For a carbohydrate, protein, fat meals the best fit equation for insulin load is:

Insulin load = ((protein (g) x 0.5) + (fat (g)x 0.4))+ g carbohydrate)

The Type 1 Diabetes research discussed suggests the increase insulin requirement for protein and carbs is mostly in the first three hours, and the additional requirement for fat would be from three to six hours (Smart *et al.*, 2013; Wolpert *et al.*, 2013; Bell, Toschi, *et al.*, 2016). Therefore, a split dose or extended wave would be needed for a high carb, fat and protein meal.

Why do most people with type 1 diabetes not do this?

Most people with Type 1 diabetes who carb count only do not see this effect, Why:

- As discussed ICR accounts for 130% of the effect of glucose, therefore there will be no issue as long as carbohydrate stays within 40-55% of total mela kcal. within 10-20% and fat within 20-40%, which is a **usual meal for most people.**

- Why 130% for the ICR?

- Smart and colleagues (Smart *et al.*, 2013) showed the ICR worked perfectly for a 30g carbohydrate meal with high fat low protein (35g, 5g) and low fat high protein (5g, 40g). But the ICR gave too much insulin for the 30g carb low fat low protein (5g,5g) meal. Finally, the ICR did not give enough insulin for the 30g carb high fat high protein (35g, 40g) meal. It would therefore seem sensible that ICR accounts for about 130% of the effect on carbohydrate alone. **This is obviously an approximation and heuristic but helps put the insulin dosing strategies into context.**

However, when they venture outside the normal fat and protein in meals, they have an issue:

- Very high glucose levels after Pizza, Cheesy pasta, large meals with fancy desserts, BBQ.

- Hypoglycaemia when carbohydrate only meals are consumed and matched with insulin using the ICR. Meals such as fruit only.

If the person with type 1 diabetes wanted to use this very labour-intensive approach of counting all macronutrient grams, they would have to consider a few things.

- First: Count every gram of carb, fat and protein, and apply the below formula to get the insulin load. But they must remember to relax their carb ratio by about 60%. For example, a 1u:10g would change to a 1u:16g. Also, you would probable want to change the term to a meal ratio rather than carb ratio.

    - Insulin load = ((protein (g) x 0.5) + (fat (g) x 0.4))+ g carbohydrate

- Second, when the fat amount gets high (>40g) to split the insulin 50/50 by a second injection in an hour's time on MDI, or an extended wave for 2.5 hours if pump.

Now we have a good understanding of what the pancreas would do, let's see if the currently available insulin dosing strategies are fit for purpose.

Current available insulin dosing strategies

We have developed a good understanding of the hormonal interplay required to maintain a stable blood glucose level after eating. We have also highlighted the unique challenges a person with Type 1 Diabetes faces. We are now in a fantastic position to evaluate the most popular insulin dosing strategies.

Let's have a look at the current insulin dosing strategies to;

- Appreciate their benefits and draw backs
- Know when they will work and when they will not
- See what diet types they fit best
- See if we can swap and change strategies depending on meal composition

Carbohydrate counting (Watch me)

This method is based on counting the carbohydrate content of a meal, then applying an ICR to determine the insulin dose. For example, if you have a ratio of 1unit for 10g carbs and eat 30g, that's 3 units, simple!

Carbohydrate counting is the gold standard method for determining meal time insulin dose recommended by the main regulatory bodies (Smart *et al.*, 2018; ADA, 2020).Therefore you would assume there is a solid evidence base on carbohydrate counting's effectiveness.

Carbohydrate counting became the gold standard approach following the DCCT results. The DCCT (DCCT Research Group, 1993) found intensive insulin treatment by MDI or pump therapy, combined with regular follow-up, aiming to get HbA1c to 6% (42mmol/mol), significantly reduced HbA1c compared to two injections per day. On average the intensive group had 6.5 years of improved HbA1c control, where their Hba1c was on average 2% lower. This led to a huge relative risk reductions in microvascular complications at 6.5 years:

- 76% reduction in eye disease
- 50% reduction is kidney disease
- 60% reduction is nerve disease

It was too soon to determine the effect on cardiovascular health, after only 6.5 years. Therefore the research group followed up 90% of the DCCT trial patients for the EDIC study (Nathan, 2014). The intensive groups HbA1c drifted back up to the two injections per day group almost as soon as the 6.5 years were up. The EDIC study found what is to be known as "metabolic memory". This is where the period of 6.5 years improved control by 2% lead to persistent microvascular benefits, but not just that, massive macrovascular health relative risk reductions also:

- 42% reduced risk of a cardiovascular event
- 57% reduced risk of non-fatal heart attack, stroke, or death from cardiovascular causes

This landmark trial was the clear evidence that certified HbA1c as the crucial marker for monitoring diabetes control. Also that intensive management of Type 1 Diabetes is necessary to achieve a lower Hba1c that is sustained.

Most people assume the intensive group in the DCCT used carb counting to determine meal time insulin dosing. However, when you look into the DCCT trial (DCCT Research Group, 1993), the insulin dosing strategies used at mealtimes was different at each of the 29 American Centres participating. The strategies used can be grouped into three main categories:

- Food exchanges, where the person can exchange, starchy, dairy, protein, and fruit and veg portions. In some centres the insulin was adjusted based on the amount of different foods groups at the meal time. In other centres the participants were given fixed meal insulin dose, then they could exchange the food groups to meet the dose.

- Total available glucose (TAG). This method counted every gram of each macronutrient and then used a proportion of each gram to determine the insulin load grams. They would then apply an insulin load ratio, which works on the same principle as an ICR. The breakdown of the maths is below.
    - Every gram of carbohydrate as 1g
    - Every gram of protein as 0.5g
    - Every gram of fat as 0.1g

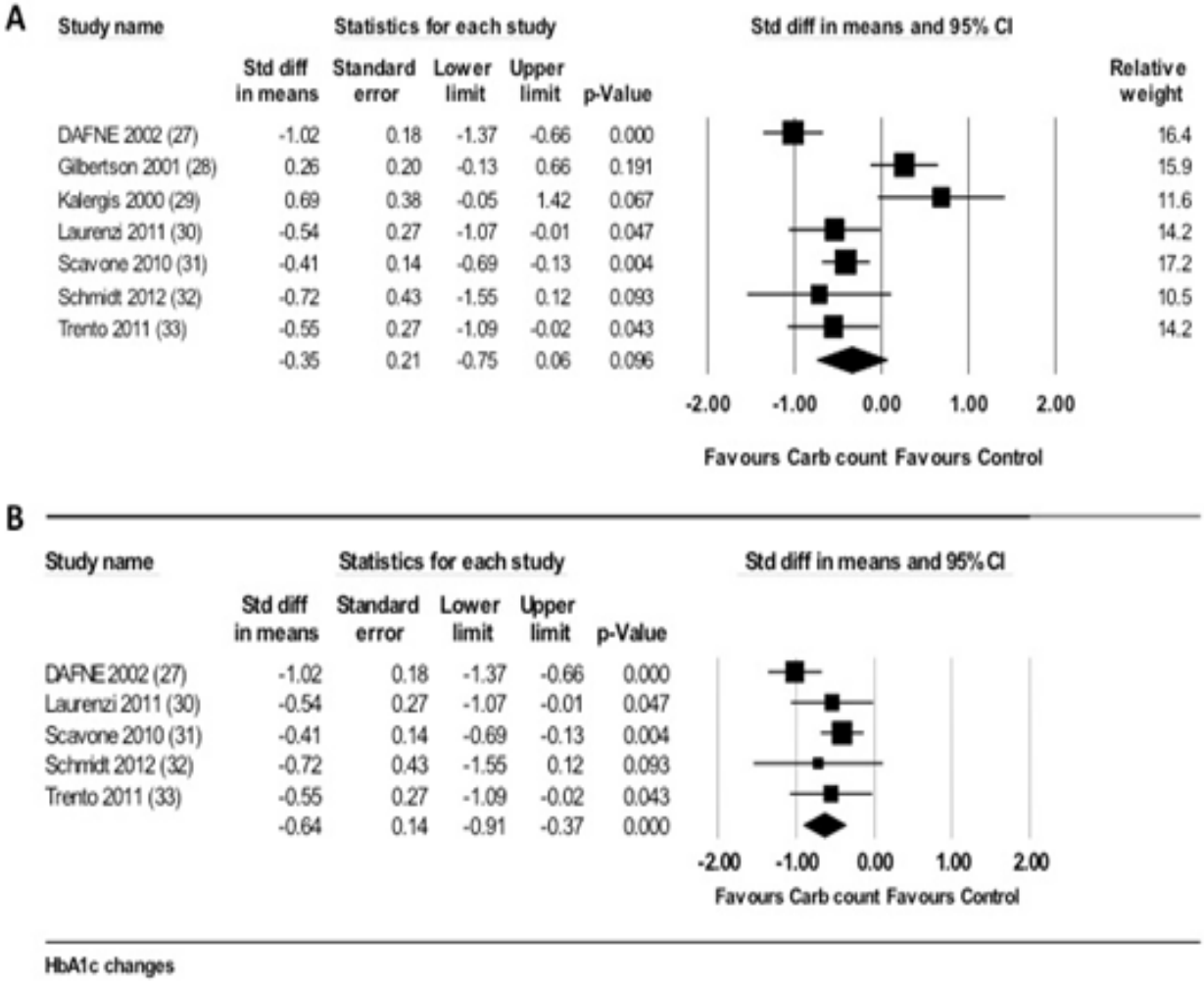
- Carbohydrate counting and applying an ICR.

What does the research say about carbohydrate counting?

The only high quality meta-analysis performed on the effectiveness of carbohydrate counting was performed 2014 (Kirstine J. Bell *et al.*, 2014). Only seven (5 adult and 2 paediatric) out of 311 studies passed the inclusion criteria, highlighting the poor quality of research studies on carbohydrate counting,

What did they find?

Figure A below shows a HbA1c reduction of only 0.35% in three months or longer, which was not statistically significant. Figure B shows sub-group analysis of those studies running parallel design, where a 0.64% reduction was found, which was both statistically and clinically significant. Carbohydrate counting was only found to be beneficial for adults (-0.4%), but not for children (Kirstine J. Bell *et al.*, 2014).



Adapted from (Kirstine J. Bell *et al.*, 2014)

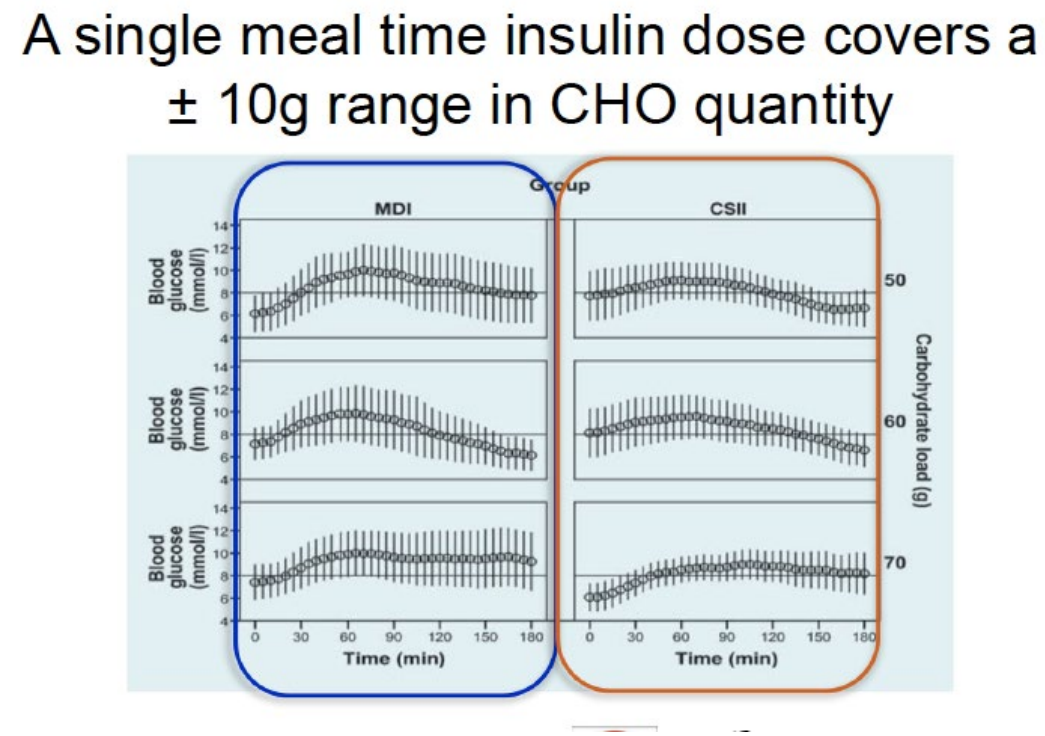
Why is that?

Accuracy is one issue. It has been shown those families in the top 25% of counting accuracy have a 0.8% lower HbA1c than those in the bottom 25% (Mehta, Quinn, *et al.*, 2009).

So, if accurate then all good right, but how accurate do you need to be?

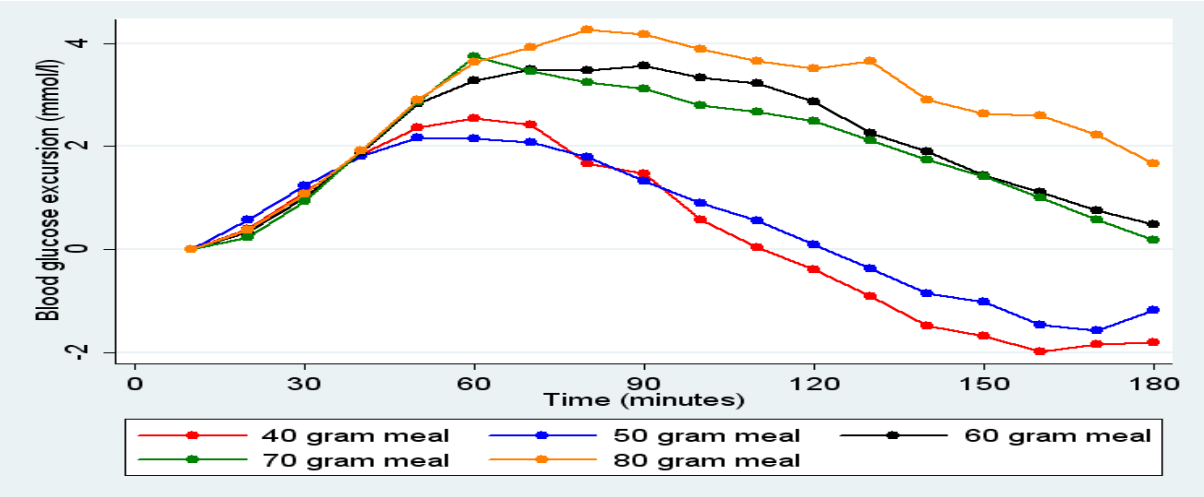
An innovative meal experiment has shown that counting accuracy only needs to be within ±10g of the actual amount of carbohydrate on the plate, to calculate an effective insulin dose (Smart *et al.*, 2009). The meal was a ham sandwich with cereal bar (55% carbs, 12%

protein, 33% fat) – **Notice how this meal fall within the ICR for mixed meals (40-55% carbs, 10-20% protein, 20-40% fat)**



Adapted from (Smart *et al.*, 2009).

When the it goes to ±20g there is hypos and hypers as shown by the same research group where the insulin dose was for 60g carbohydrate (Smart *et al.*, 2012). **This was another test meal that fall within the ICR for mixed meals (40-55% carbs, 10-20% protein, 20-40% fat)**



Can people count carbohydrate within a 10g accuracy?

Carb counting accuracy within 10-15g can be achieved by 50-80% of motivated parents, under experimental conditions in the lab, but for adolescents, only 23% achieve the necessary level of accuracy (Bishop *et al.*, 2009). For adults, the research consistently shows 50% achieve an accuracy within 10-15g (Nebel *et al.*, 2002).

So if you are within 10-15g accuracy, all is good right?

No quite. We have discussed carbohydrate counting and applying an ICR work when **the meal falls within 40-55% carbs, 10-20% protein, 20-40% fat**. When a person has a low fat and protein meal and applies their ICR, they go on average 2.9mmol/l lower from where they started at five hours. Conversely when they add a large amount of fat and protein to a meal and apply their ICR, the blood glucose is on average 2.3mmol/l higher at five hours (Smart *et al.*, 2013).

When a person has meals way outside their norms, there are blood glucose consequences. Bell (Bell, Toschi, *et al.*, 2016) showed on average 65% extra insulin (24-124%) was needed for a heavily cheesed pizza, compared to when just ate the pizza base. Both meals contained 50g of carbohydrate.

Taken together this research shows:

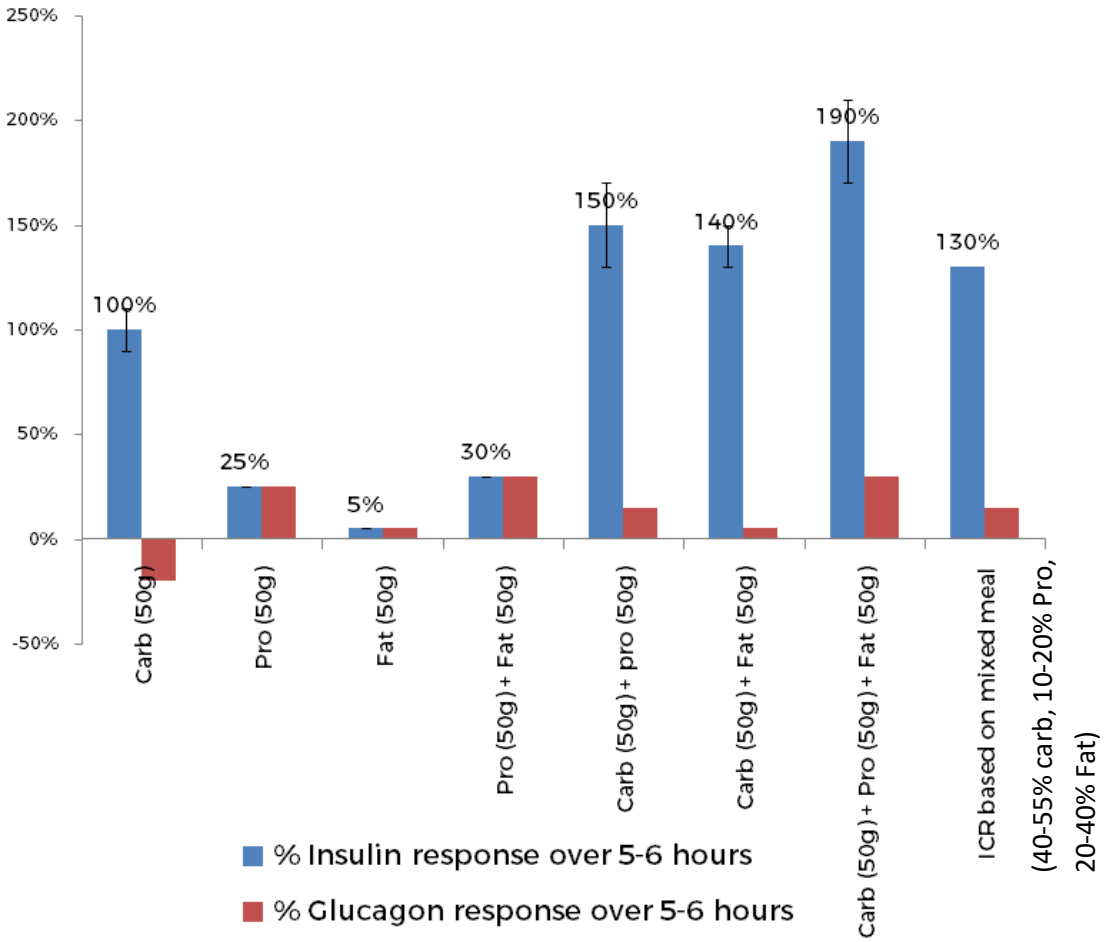
> **If you keep the meal within 40-55% from carbs, 10-20% from protein, 20-40% from fat then the carb counting accuracy only needs to ±10g**

This is of massive practical significance because most people who carbohydrate count believe as long as their accuracy is within 10g, all will be good. However, if they change their usual fat and protein amounts, all good will not be good!

As discussed earlier, ICR's are tried and tested eating usual mixed meals, therefore they already take into account the glucose raising effect of your usual protein and fat intake. So really it's not an ICR, it's a usual mixed meal ratio using carbohydrate as the main

determinant when the energy content is **40-55% from carbs, 10-20% from protein, 20-40% from fat**

This point is shown schematically in the graph we have built throughout this document. When people work out their ICR it's based on their usual mixed meal, and that is actually covers about 130% of the insulin response needed for the 100% carbohydrate. The other 30% is the insulin required for the protein and fat content of that meal. Therefore, as long as the meal stays withing **40-55% from carbs, 10-20% from protein, 20-40% from fat**, the ICR will work because the carbohydrate is the main determinant of the insulin response needed.



If no fat and protein are eaten with the carbs, for example three pieces of fruit, and then ICR is applied, a hypo is likely, as there will be 30% too much insulin. On the reverse, if a high fat and high protein meal is eaten the extra 30% covered by the ICR will not be enough, another 60% would be needed, and some portion of the extra insulin delayed.

Carbohydrate counting can lead to a reliance on packaged food and a disregard for a healthy balanced nutritional intake (Mehta, Haynie, *et al.*, 2009).

Fat and Protein Units (FPU) - Warsaw Method (Watch me)

The Warsaw FPU (Pańkowska *et al.*, 2009) method acknowledges fat and protein have an effect on post-prandial blood glucose level, and require insulin to mitigate. The FPU methods assumes that 100kcal of either fat (11g) or protein (25g) has the same insulin requirement as 10g carbohydrate. So if the person has a 1u:10g ICR, then 100kcal of fat and protein requires 1 unit of insulin, called 1 FPU. If ICR is 1u:20g, then 100kcal of fat and protein needs 0.5 units insulin, 0.5FPU.

How that FPU insulin is delivered is unique. The insulin for the carbohydrate is always given before eating. Then the insulin required for the FPU is then spread out using and extended bolus over a number of hours via a pump. The length of extension for the FPU is determined by the total FPUs:

- 1 FPU = 3 hours
- 2FPU = 4h hours
- 3FPU = 5 hours
- >3FPIU = 8 hours

Potential issues:

- This method assumes fat and protein have similar effect on insulin requirement, regardless if they are consumed on their own or in combination. Our discussion has shown that fat and protein alone require less insulin than when they are combined carbohydrate. Also that protein has a greater insulin requirement than fat on a gram by gram basis.

- The FPUs are delivered over a extended bolus, regardless of if the FPUs are due to protein or fat. The research discussed shows the protein portion needs to be delivered before eating, and the fat portion later (Smart *et al.*, 2013). There is a big chance of mis-matching the insulin dose to the food.

- The extension times suggest 3-8hours depending on the FPU. This leaves lots of active insulin working when people do physical activity many hours after eating, leading to hypos.

What does the research say about the Warsaw FPU method?

Research has shown following the FPU system caused a lot of hypoglycaemia when compared to carbohydrate counting (Pańkowska *et al.*, 2009). This potentially could have been reduced if the ICR was made less aggressive before the group started the FPU system.

There did not appear to be an understanding that the current ICR takes into account 30% of the response of usual fat and protein. If they reduced the FPU ICR by 60% before starting, they may have had better results.

We must considering the maths involved. We already discussed the most motivated groups only count carbohydrate with 50-80% accuracy, adults 50%, and adolescents at 23%. What would happen if they also needed to count fat and protein grams and apply formulas?

Personal and clinical experience has taught me it does not work for the vast majority! Obviously APP's and new technology may make this easier to use in practice.

Food Insulin Index (FII) and Food Insulin Demand (FID) (Watch me)

The FII was developed by measuring the incremental area under the plasma insulin curve observed by a 1000 kJ portion of a test food, expressed as a percentage of the response to a 1000 kJ portion of the reference food (glucose) within a lean, healthy subject (Bell, Petocz, *et al.*, 2016).

The final FII of a food is calculated as the average FII in 10 subjects.

Food Insulin Index (FII) =

(120min AUC Insulin for 1000 kJ test food / 120min AUC Insulin for 1000 kJ reference food) x 100

Therefore instead of measuring the glucose response, like the GI, it measures the insulin requirement, which is much more useful for people with Type 1D.

The FII database has been added to over 20 years and has 147 foods, some singular foods, other mixed meal foods (Bell, Petocz, *et al.*, 2016). The FII is a percentage insulin response over two hours compared to 100% of Glucose, a summary is presented below in the table.

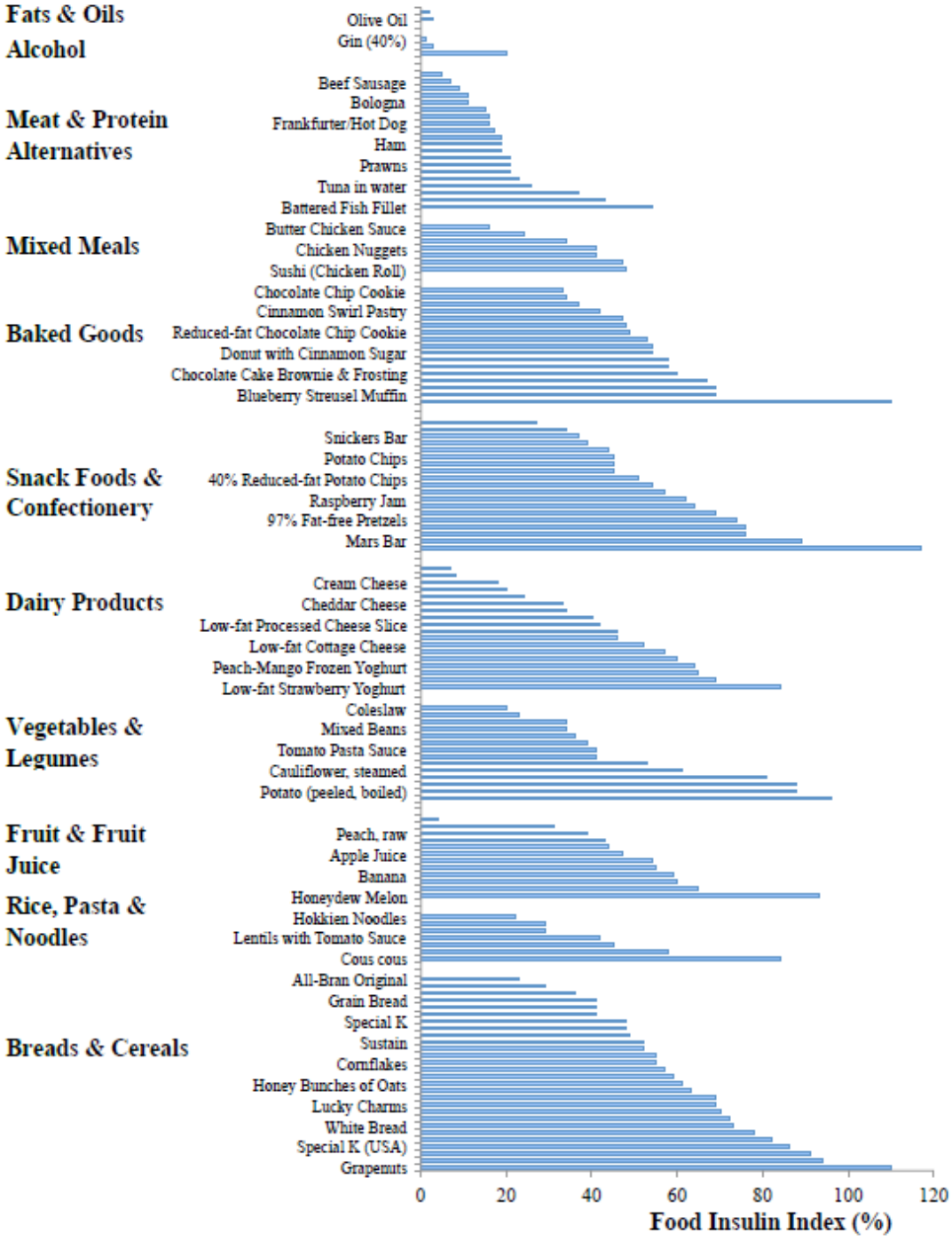


Figure 3.3: Observed insulin responses of 147 single foods, relative to an isoenergetic reference food (FII) arranged by food group.

Adapted from (Bell, Petocz, *et al.*, 2016)

The researchers (Bell, Petocz, *et al.*, 2016) completed a lot of statistical analysis to determine the strongest predictors of insulin response. From their analysis they found the best fit formula could predict 78% of the variance in insulin response:

FII = - 4.2 + (0.9 x Glucose Score) + (0.3 x Sugar (g)) + (0.5 Protein(g)) + (0.4 Fat (g))

Glucose score can only be determined by assessing the food individually using the FII protocol, therefore it cannot be applied to commercially available nutritional information. The best fit for commercially available information was using carbohydrate and protein. This below formula explained 50% of the insulin variance over two hours.

FII = 10.4 + (1.0 x Carbohydrate (g)) + (0.4 x Protein (g)

Using this FII for each of the 147 foods, the researchers developed a Food Insulin Demand (FID) score, with the below formula (Bell, Petocz, *et al.*, 2016).

FID = FII x kJ per serving /1000

This allows an FID score to be generated for the 147 foods, accounting for portion size. A FID ratio can then be given to an individual to be used in the same way as the ICR. Obviously this somewhat restricts people to only 147 foods, but it is based on the insulin response over two hours.

What does the research say about the Food Insulin Index (FII) method?

The researchers assessed the FID vs. carbohydrate counting in a one meal study. They found the FID insulin dose improved time in glucose target range over 5hrs by 31%. This improvement was not at the cost of any increased risk of hypoglycaemia (Bell, 2014).

The big question is could this one meal study translate into real life. To answer this question the researchers conducted a three months RCT of FID vs. carbohydrate counting.

The FOODII study tested the FID vs. carbohydrate counting in 26 patients with T1D over three months (Bell, Gray, *et al.*, 2016). The team developed resources, a SMART phone APP, and other educational materials equivalent to those available for the carb counting. If you want to take a look, you can find them in part 2 of Bells Thesis (Bell, 2014):

> If you are going to try this method, please note you will need to relax your carb ratio by 60% to prevent hypos. So for example if your ICR is 1u:10g, you will need to change it to 1u:16g. all you need to do is apply the formula, ICR x 1.6.

After three months they found no difference in HbA1c between the FID and carb counting groups. They did find a trend towards a reduction in hypoglycaemia in favour of the FID. The FID counters reported after the first couple of weeks learning it was easy to follow, certainly not more difficult than carb counting.

The FID in principle sounds like it should have improved HbA1c, why did it not show clear benefit in glycaemic control?

- When combining FID scores of individual foods, the insulin requirement for high fat foods will very likely be underestimated. For example, the FID for individual components such as Olive oil (FII 3) and butter (FII 2) will be very low, suggesting little insulin required. This is correct if they are had on their own. But when you combine them with bread, the synergy of carbohydrate and fat increases the insulin demand more than just adding the individual components together.

- The FID score only accounts for two hours insulin demand. To measure true insulin requirement, a period of 5-8 hours is needed. Again this likely means the insulin demand for mixed meals is massively underrepresented.

- It's a new system with limited food choices that would take some time to get used to. Whereas the carb counters are used to this approach and the carbohydrate info is everywhere, for every food!

To assess if the FII could be useful for people with Type 2 Diabetes, the research team brought 10 people with Type 2 diabetes into the lab on two separate days (Bell, Bao, *et al.*, 2015). On day one they consumed a diet of high FID, and on the send visit a diet low in FID. Important to note that both diets were equal in macronutrient profile and kcal. The results showed clearly the low FID diet resulted in much lower blood insulin levels, 41% lower,

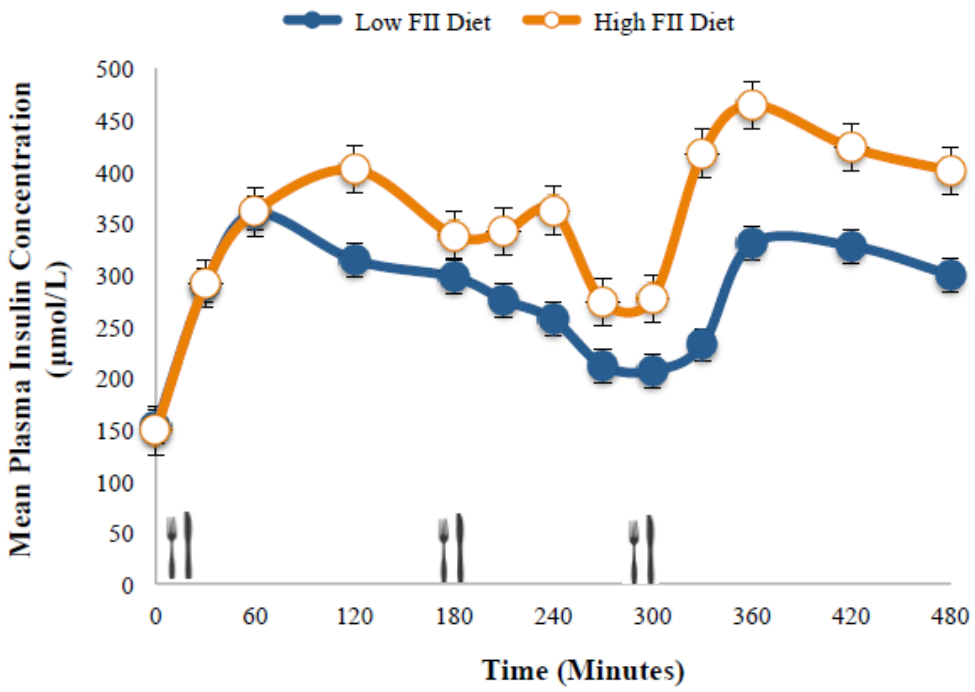


Figure 6.1: High FII vs Low FII Diet over 8 hours on the Mean Plasma Insulin Profile in Adults with Type 2 Diabetes (n=10)

Adapted from (Bell, Bao, *et al.*, 2015)

As expected the blood glucose level was not different on the two occasions, essentially showing the pancreas has to work much harder to secrete enough insulin to keep up with a high FID diet. This may have some application for the insulin resistant person with Type 1 Diabetes.

Summary

If you are thinking none of the current insulin dosing systems are full proof, you are correct. But at least you now understand the pro's and con's of each approach, and how different macronutrients require a different insulin response depending if they are eaten singularly or combined.

Rather than choosing an insulin dosing strategy and trying to make you diet fit around it. Why not choose the type of nutritional intake that best suits your lifestyle, food preferences, and goals in life. Then choose an insulin dosing strategy that best suits that nutritional intake.

First ask yourself these questions:

What diet do I currently follow, and what is the macronutrient split?

Do I keep my macronutrient split consistent at meal times, and from day to day?

Do I want to go low carb, medium carb, high carb?

Do I change my nutritional intake depending on the phase of physical training I am in?

Take inventory of what you regularly consume. Then decide what diet approach will suit you best. You can apply the best fit insulin dosing strategy. Don't be afraid to experiment, that's when you learn the most!

We will evaluate the most common dietary approaches, and see which insulin dosing strategy fits best.

Government and Diabetes Associations nutrition recommendations Watch me

The ADA (ADA, 2020) and ISPAD (Smart *et al.*, 2018) recommend a nutritional intake of:

- 40-55% carbohydrate
- 30% fat
- 20% protein
- Low GI
- Starchy wholegrain foods
- At least five fruit & vegetables a day
- Choose MUFA and keep SFA low
- Keep sugar less than 5-10% of total energy

The reason why all the governments and agencies promote this type of intake is because:

> **The wealth of research evidence resoundingly supports that this type of intake gives the best chance for a healthy disease-free life.**

If you were to believe the "guru bloggers", you would think all the governments and diabetes associations are conspiring against people with type 1 diabetes. Reality check! This type of intake is based on very sound evidence. It is not a conspiracy, it's sound science.

A diet that is 40-55% carbohydrate will provide the necessary fast burning fuel to optimally power:

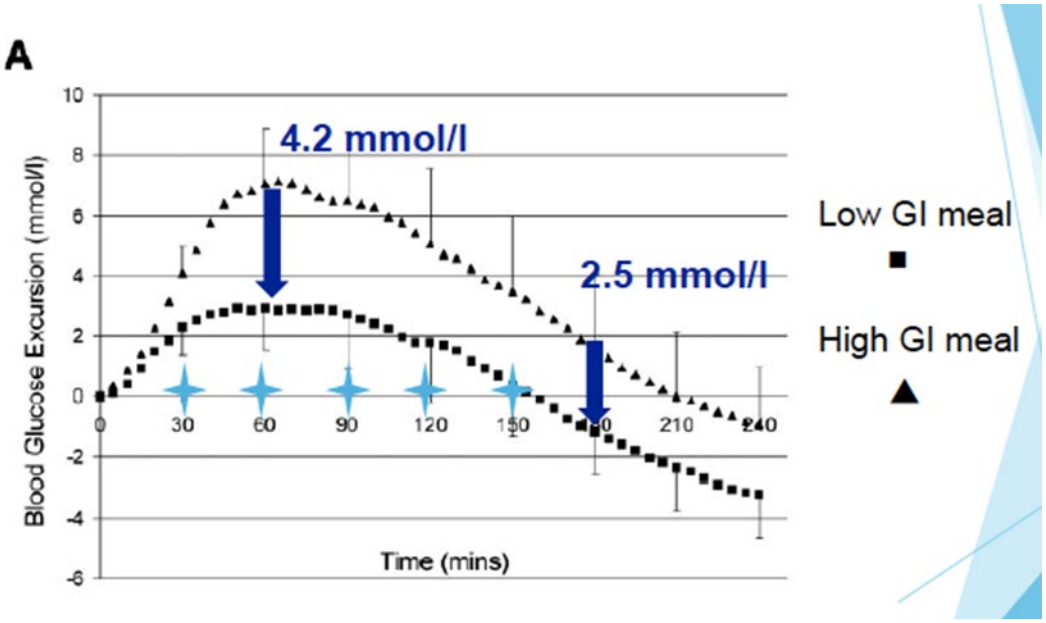
- Fast paced sports activities such as football, basketball, rugby, netball, tennis, rowing.
- Resistance exercise to promote strength and muscle growth.
- Endurance activity where optimal performance is the main goal. Events such as competitive running, triathlon and swimming.
- Recovery from exercise.

That being said, it is challenging to attain a HbA1c of <6.5% (48mmol/l) eating 40-50% of energy intake from carbohydrate. It can be done if you follow these tips;

Top tips for preventing after meals highs with a 40-55% carbohydrate diet

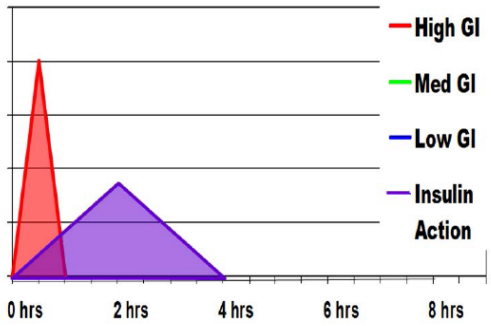
Choose mainly low GI options

One important note is that not all carbohydrate elicits the same insulin response. Studies using people with Type 1 Diabetes investigated what happens if you deliver the same insulin dose for a low GI meal and high GI meal, whilst keeping the carbohydrate, fat and protein content exactly the same. It has been shown found for low GI meals there is a lower after meal rise but more hypoglycaemia after 5 hours, shown in the figure below (Ryan *et al.*, 2008).

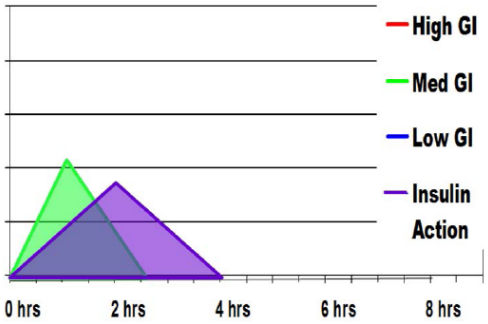


This beneficial effect of following a low GI diet on glycaemic excursions has been replicated (Lafrance *et al.*, 1998; Nansel, Gellar and McGill, 2008). This could mean if there is a change in nutritional intake to be lower in GI, the mealtime insulin doing may need decreasing.

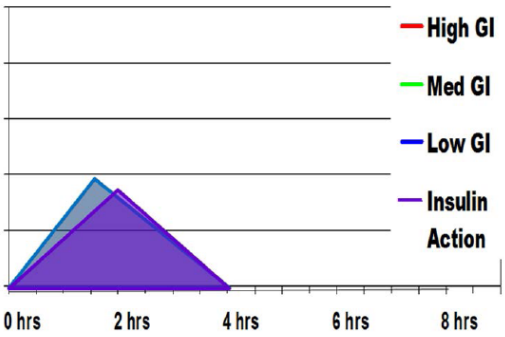
This concept can be explained simply with some easy to understand pictures, like this.



High GI foods such as sugary cereal or drink gets absorbed into the blood stream very quickly, making it very difficult to match with insulin. Mixing high GI with low GI foods is therefore very important to control blood glucose levels.



Medium GI foods get absorbed into the blood stream slower than high GI foods, but their absorption time is still slightly quicker than the insulin time. Injecting for these foods 15 minutes before eating is essential to achieve more in target glucose readings.



Low GI foods get absorbed into the blood stream almost identically matches insulin action when given 15 minutes before eating, and hence keeps the glucose level very stable. Aim to include a variety of these foods in your diet.

You can lower GI in two ways. First, simple swaps as in this table.

Low GI cereals	Medium GI cereals	High GI cereals
All bran	Muesli (no added sugar)	Cornflakes
Oat bran	Mini wheats	Instant porridge
Porridge (whole oats)	Rolled oats	Coco Pops
Special K	Sultana bran	Weetabix
Oatibix	Shredded Wheat	Rice Krispies
Readybrek	Fruit and Fibre	Cheerios
		Bran Flakes
Low GI Breads	**Medium GI Breads**	**High GI Breads**
Sourdough bread	Oatmeal	White bread
Soya & Linseed	Pitta bread	French baguette
Granary	Wholemeal bread	Flatbread
Tortilla wrap	Chapatti	
Muffins (for toasting)	Bagel	
Low GI Starchy Foods	**Medium GI Starchy Foods**	**High GI Starchy Foods**
Pasta /Spaghetti (not overcooked)	Boiled potato	Mashed potatoes
Gluten free pasta	Sweet Potatoes	Baked potato
Cheese Tortellini	Easy cook	Thai rice (Jasmine)
Yam	American rice	Glutinous rice
Rice noodles	Wild rice	
Quinoa, pulses	Couscous	
Basmati rice		
Brown rice		

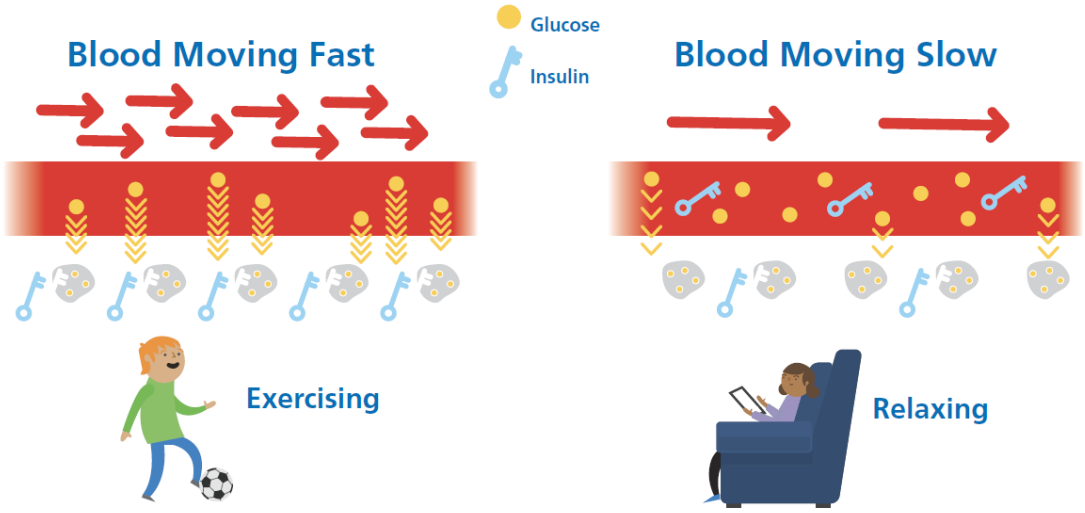
Secondly, you can exchange some carbs for fat and protein if the meals are high carb. This table has some examples.

Meals high in carbohydrate and low in fat and protein that can make the glucose spike 1-2 hours after eating	How you exchanges some of the carbohydrate for fat and protein glucose spiking by adding fat and protein
Breakfasts	
Large Breakfast cereal with skimmed or semi skimmed milk	Medium breakfast cereal with full cream milk and a boiled egg.
Two toast with spread and jam or honey	One toast with spread and scrambled egg or mackerel or cheese spread
Croissant with Jam	Croissant with cream cheese
4 pieces of fruit	2 pieces of fruit with normal yoghurt
Lunches	
Two ham sandwich with low fat yoghurt and fruit	One cheese sandwich with full fat yoghurt
Tomato soup with 2 slices white bread and rice cakes	Tomato soup with one wholemeal bread with spread on small bag of crisps
Baked potato with spaghetti hoops	Sweet potato with spread and cheese
Evening meal	
Large white rice with curry	Basmati rice with curry and vegetables
Baked potato with beans - no spread	Baked potato with tuna mayonnaise
Mashed potato, baked beans and waffles	Mashed potato with sausages, vegetables and baked beans
Snacks	
3 Rice cakes	Small bag Corn or tortilla chips
Low fat snack bars	Nut based snack bars
Dried fruit	Nuts

At least 10 minutes movement after meals.

It is now clear the rate limiting step of insulin action is the passive diffusion of insulin across the endothelial membrane, the barrier from the blood to the cells (Williams *et al.*, 2018). Therefore, by speeding up blood flow and the passive diffusion is accelerated and insulin action is much sooner (Wagenmakers *et al.*, 2016). This is especially important for people with type 1 diabetes because the insulin injected of infused goes into the outer blood circulation rather than directly into the portal vein when it comes from the pancreas. This means the chance to store a lot of the digested carbohydrate in the liver is missed and glucose gets out into the outer circulation rapidly.

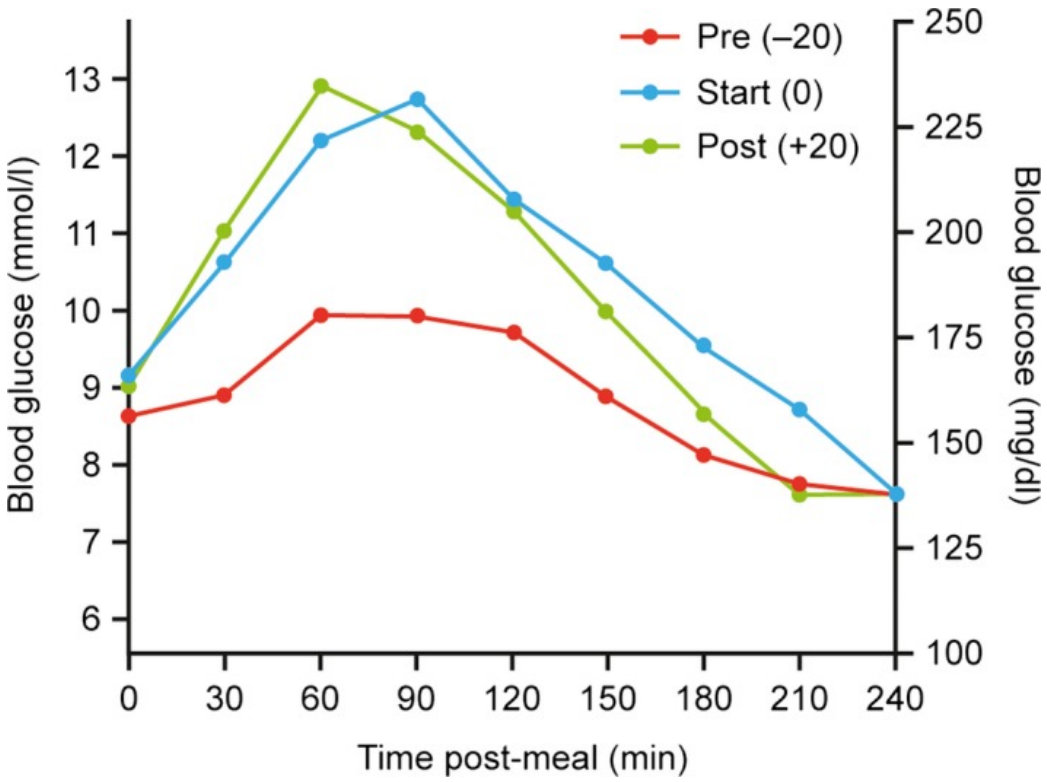
This diagram shows that by being active for 10 minutes after eating there is increase blood flood flow to the muscles to increase insulin passive diffusion. There is a double positive effect as there is less blood flood to the gastro-intestinal tract to slow food digestion.



Keep it simple, do 10 minutes of moderate activity after each meal to stop glucose spikes!

Deliver mealtime insulin 20minutes before meals

A comprehensive review of evidence shows fast acting insulin should be administered 20 minutes before eating to reduce after meal glucose spikes (Slattery, Amiel and Choudhary, 2018). This graph from a classic study illustrates the point (Cobry *et al.*, 2010).



Obviously, this advice needs to be moderated with fussy eaters, gastroparesis and possibly very high fat foods. BUT, the default should be insulin 20 minutes before meals.

Now people have CGM. the pre-meal timing can be changes based on glucose value and trend arrow. This is an example of what Birmingham Children's Hospital use in their CGM Academy that has a evaluation of the first 50 patients under review.

Sensor glucose Levels	Trend arrow	Minutes to bolus before meal
4.0 - 5.9 mmol/l		Prevent hypo
		Prevent hypo
		Prevent hypo
		15
		20
		25
		30
6.0 - 9.9 mmol/l		0
		10
		15
		20
		25
		30
		35
10.0 - 14.0 mmol/l		15
Watch Yusuf		20
		25
		30
		35
		40
		45
More than 14.0 mmol/l	 OR 	25
		30
		40
		45
	 OR 	50

Use activity to lower after meals highs

If you have not given insulin 20 minutes before eating is likely you will go high 1-2 hours after eating and come back down. You cannot give a correction, otherwise you will go low 2-3 hours later. The only option is to get the insulin working faster by a short burst of activity to increase blood flow to the muscles so the insulin can get to work quicker.

It is much safer to do this with a CGM as you can keep an eye on the effect and are protected if you have over done the exercise. This table is a guide that is used in the Birmingham Children's Hospital CGM Academy.

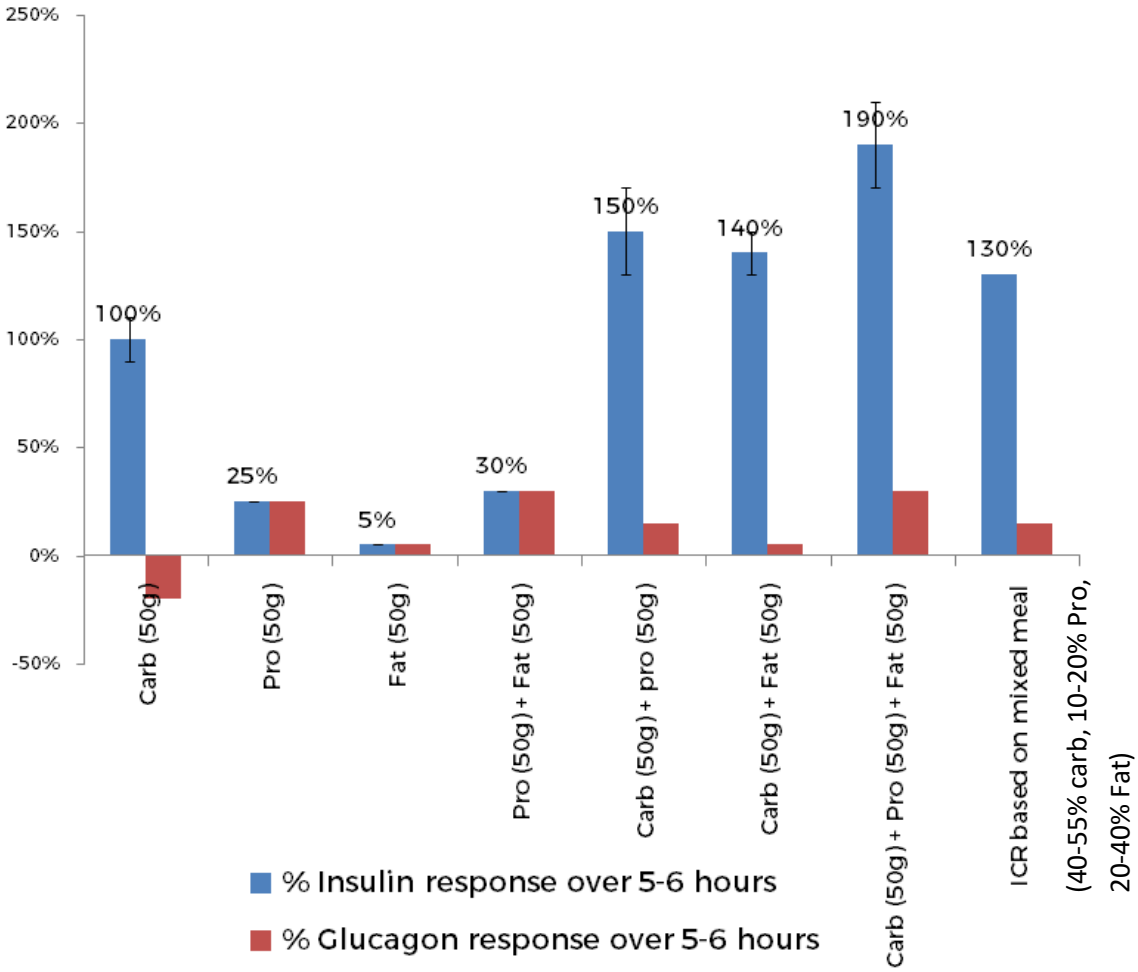
Practical tip: use short bouts of activity if your glucose level is spiking **1-2 hours after eating**

Dexcom sensor glucose Levels	Trend arrow	How many minutes of activity
8.0 - 10.0 mmol/l		5
		10
		15
10.0 - 14.0 mmol/l		15
		20
		25
		30
More than 14.0 mmol/l		15
		20
		25
		30
		40

This is an action video to illustrate the point

Consistency in meal carbohydrate, protein, and fat amounts

Consistency is the key to getting good diabetes control when carbohydrate counting. Keep your macronutrient split and amounts consistent, then just count the carbohydrate and give the insulin based on your ICR. Remember from the graph below that usual mixed meal ICR accounts for about 130% of the effect of carbohydrate.



- Working out your ICR for your usual mixed meals of 40-55% from carbohydrate, 10-20% from protein, 20-40% fromFat.
    - **Breakfast:** If you calculate your ICR for cereal with milk, which is usually about 50g carb, 15g protein, 10g fat, the ICR will work for breakfasts of that composition. If you change to fry up that is 20g carbohydrate 30g protein, 30g fat, you will certainly have a high glucose reading if you only bolus for the carb amount using your ICR!

- **Lunch:** If you calculate your ICR for sandwich, yoghurt, crisp, which is usually 50g carb, 20g protein, 20g fat. The lunch ICR will work for meals very similar to that. When you change to salad with a lot of protein and fat dressing (Caesar Salad), which is 10g carbohydrate, 30g protein, 20g fat, you have the same problem as breakfast.

- **Evening meal:** If you calculate your ICR for meat, potatoes and vegetables, which is usually 50g carb, 25g protein, 20g fat. When you change to heavily cheesed pizza, which is 50g carb, 35g protein, 40g fat, you can expect very high reading for a prolonged time. The other way round, what happens if you establish your ICR on consuming high protein and fat foods for evening meal such as Pizza, Lasagne, Cheesy pasta. When you decide to go for the meat, two vegetables and potatoes you go hypo!

- **Snacks:** If you calculate your ICR for snacks on a breakfast bar or crisps, which is usually 15g carb, 1-5g protein, 10g fat. When you change to fruit only, which is 10-15g carb, 0g protein, 0g fat, you can expect a hypo if you use that ICR.

Here are some simple pictures to drive home the point.

When carbohydrate counting works well

- When you weigh foods regularly.
- When you convert weighed portions into household measures - saves time!
- When you give insulin 15 minutes before eating.
- When you plan ahead before eating out.
- When you eat your usual well-balanced meals.

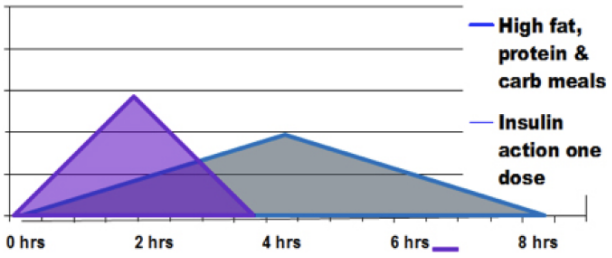
The secret to keeping your glucose levels in target after eating is to choose meals that have a similar amount of carbs, a palm size protein option and plenty of vegetables or salad.

When carbohydrate counting is not effective

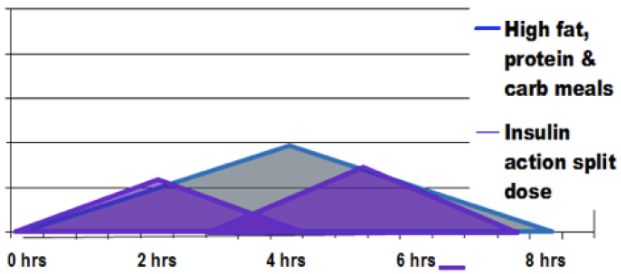
- When you eat meals that are **high in fat and protein**, much higher than your usual well-balanced meals.

Your insulin to carbohydrate ratio will calculate an accurate insulin dose to cover your usual well-balanced meals. But it will not calculate enough insulin if your meal is very high in fat and protein.

High fat and protein meals



High fat, protein and carb meals such as pizza get absorbed slower than usual meals. Also, the high fat and protein content requires extra insulin. If all the insulin is given in one dose before the meal, the glucose will often go low first, then very high later.



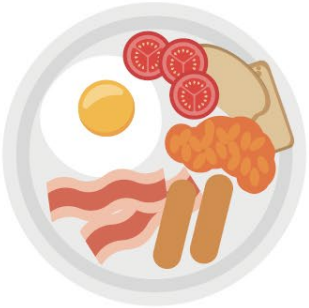
There is a two-step process to prevent the glucose level going down then up for high fat, protein and carb meals. First, increase the total amount of insulin to cover the impact of the high fat and protein. Second, split the insulin dose into two separate parts.

Normal meal

High fat and protein meal

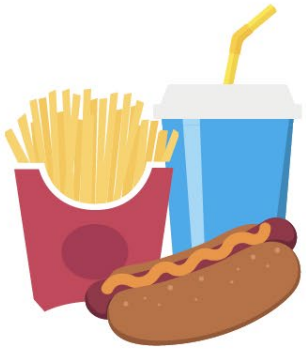
When Carbohydrate Counting Works
Well-balanced breakfast

When more insulin is needed
High fat and protein breakfast



Well-balanced lunch

High fat and protein lunch

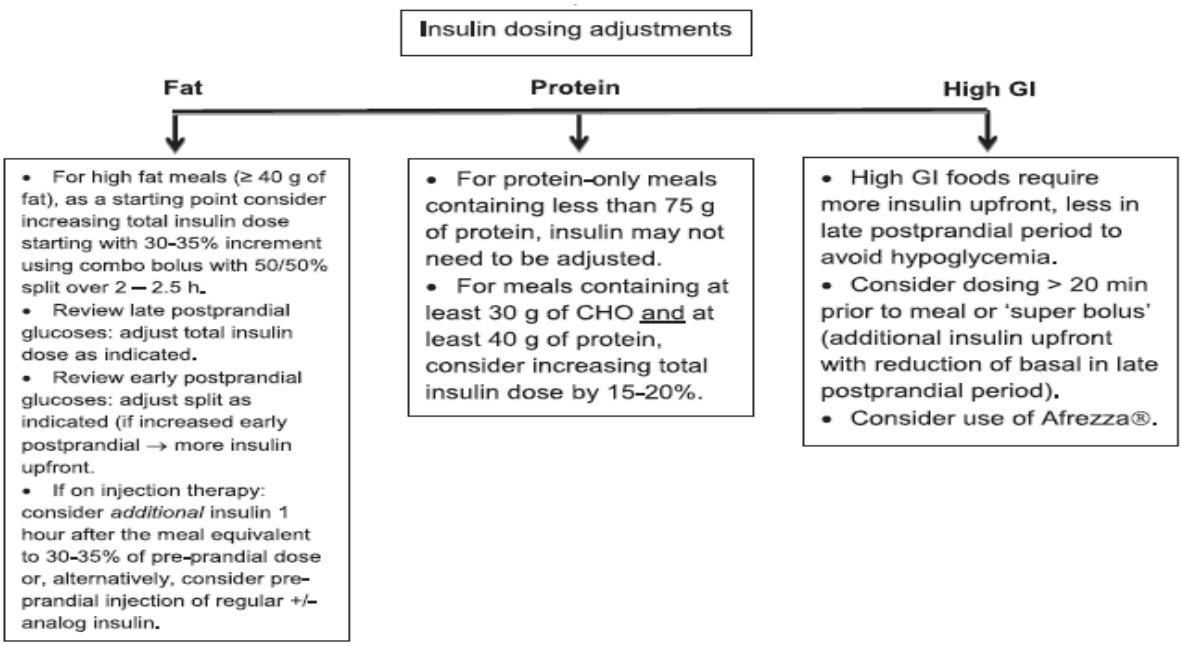


Well-balanced evening meal

High fat and protein evening meal

Extra insulin spread out for high fat and protein meals

If you decide to change the fat and protein amounts significantly, you must expect high and low blood glucose levels, unless you make allowances. Use this algorithm to help guide you (Bell, Smart, *et al.*, 2015).



- What do you do when you go outside the norm with high fat and protein?

    - If protein is 40g or more and carbs are at least 30g, add an extra 15-20%insulin and give before meal.
        - So, a 10 unit bolus would become a 12unit bolus.
        - Easy equation, insulin dose x 1.20

    - When a meal is more than 35g fat and is at least 30g carbohydrate, add 30-35% extra insulin, and spread the insulin out, 50% upfront, 50% later.
        - So a 10 unit bolus would become a 13.0unit bolus. If on a pump use a dual/split/combo/multiwave wave bolus. If injections give one injection of 7units before eating, followed by another of 6.5unit injection in one hours time.
        - Easy equation, insulin dose x 1.3 then divide by 2
        - Remember that for high fat there was a large variability for person to person -17% to 108% extra insulin (Wolpert *et al.*, 2013), **so do not expect this work perfectly!**

    - When you have a meal than is at least 30g carb, at least 40g protein, and at least 35g fat, you need to add 50% extra insulin and spread the insulin out, 50% upfront, 50% later.

- So a 10 unit bolus would become a 15unit bolus. If on a pump use a dual/split/combo/multiwave wave bolus. If injections give one injection of 7.5units before eating, followed by another of 7.5unit injection in one hours time.
- Easy equation, insulin dose x 1.5 then divide 2
- Remember that for high fat and protein pizza there was a large variability for person to person 24% to 124% extra insulin (Bell, Toschi, *et al.*, 2016)**so do not expect this work perfectly!**

- Birmingham Children's Hospital Diabetes Team have developed the Keep it Simple & Safe method (KISS) (Pemberton, Leal and McCoubrey, 2018). You start by increasing the insulin does by 20% for high fat and protein meals and split the dose 50% upfront and 50% over 2.5 hours pumps. Extra insulin spread out was shown to be effective for people on injections when the dose determined from carb content is given before, with an extra 30% 3 hours after eating for a high fat meal (Campbell *et al.*, 2017). The KISS system is not perfect but it's a good place to start that does not require complicated maths. Here it is and watch this video for a clinical audit on the results:

Meal	Extra Insulin	Multiwave/Dualwave or split injection
Fish and Chips	25%	Pumps: 50% now, 50% over 2.5 hours Injections: 50% 15 mins before & 50% 60mins after
Indian Takeaway	25%	Pumps: 50% now, 50% over 2.5 hours Injections: 50% 15 mins before & 50% 60mins after
Pizza	25%	Pumps: 50% now, 50% over 2.5 hours Injections: 50% 15 mins before & 50% 60mins after
Chinese Takeaway	25%	Pumps: 50% now, 50% over 2.5 hours Injections: 50% 15 mins before & 50% 60mins after
Pasta with creamy sauce e.g. Macaroni cheese	25%	Pumps: 50% now, 50% over 2.5 hours Injections: 50% 15 mins before & 50% 60mins after
Fast food meals e.g. McDonalds, KFC	25%	50% 15 minutes before eating. 50% 60 mins after eating

How do I do this?

1. **Work out the total insulin dose and add the extra 25%:**
   - Set up a Health Event with +25% on the Expert meter

   Or
   - Multiply the insulin amount by 1.25 if not using and Expert meter
   - E.g. 8units x 1.25 = 10units

2. **Split the total dose in half and decide how to give depending if on a pump or injections. If using injections give half 15 minutes before eating and the other half 60 minutes after eating. If using a pump use a dual/extended wave give 50% now and 50% spread over 2 1/2 hours.**
   - For example
   - 10 units x 0.5 = 5 units
   - 5 units before and 5 units 60 minutes after (injections) or 5 units over 2 1/2hours (pump)

3. **Monitor glucose:**
   - Before
   - 2.5 hours after
   - 6 hours after

4. **Follow the guidance on the next page to see if you need to change the insulin doses for next time.**

Guidance on adapting insulin percentages from the 2.5 hours test

Two half hour test: Does the first insulin dose percentage need adjusting?

- If blood glucose at 2.5 hours is **more than 4mmol.l** higher than pre meal:
    - **Increase initial percentage** by 20% next time to:
    - 70% (multiply total insulin by 0.7) & 30% multiply total insulin by 0.3).
    - Give the 70% 15 minutes before and the 30% 60 minutes after or over 2 1/2 hours.
    - E.g. 10 x 0.7 = 7units & 10units x 0.3units = 3units.

- If blood glucose at 2.5 hours is **lower** than pre meal:
    - **Reduce initial percentage** by 20% next time to:
    - 30% (multiply total insulin by 0.3) & 70% multiply total insulin by 0.7).
    - Give the 30% 15 minutes before and the 70% 60 minutes after or over 2 1/2 hours.
    - E.g. 10 x 0.3 = 3units & 10units x 0.7units = 7units.

Guidance on if you need more than 25% extra insulin next time, from the 6 hour test

Six hour test - do you need more insulin?

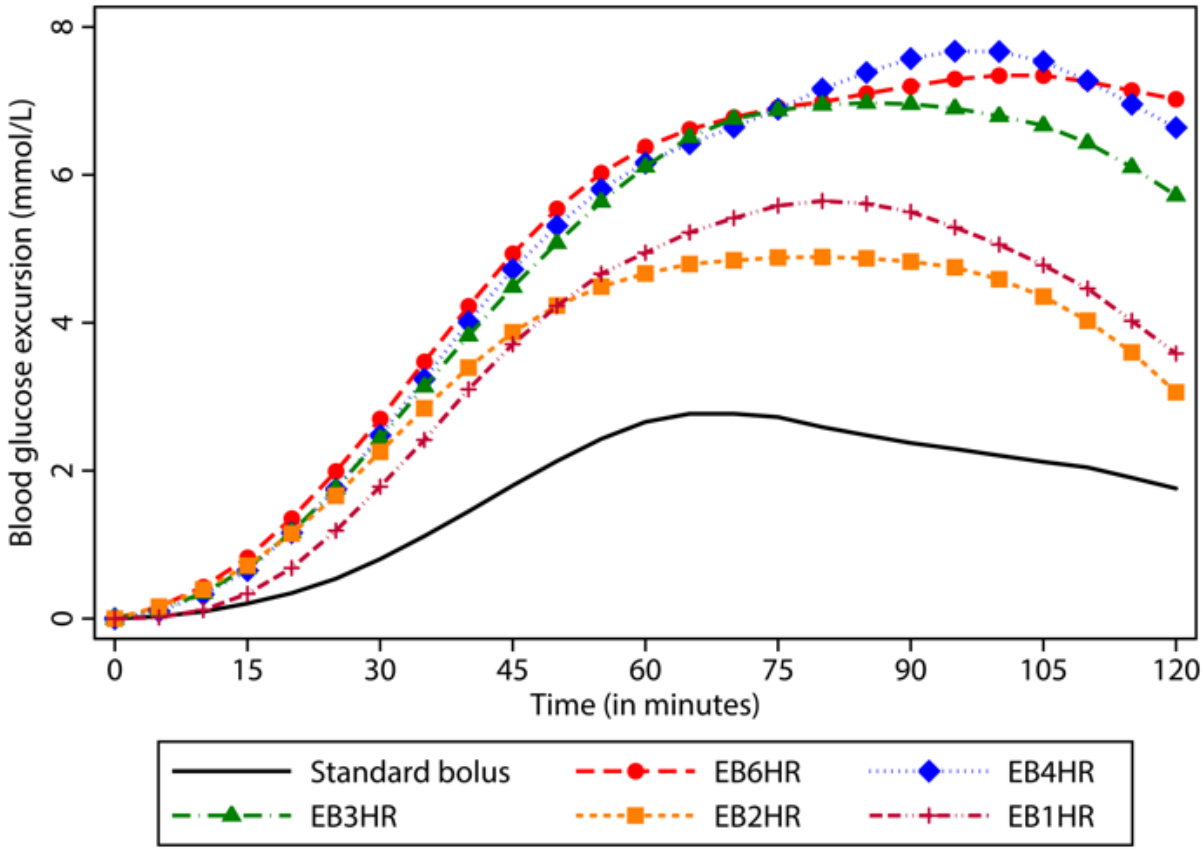
Guidance on adapting extra insulin:

- If blood glucose at six hours is **2 - 6mmol.l higher** than pre meal:
    - Increase the additional insulin by 10% so from 25% extra to 35% extra by:
        - **Set up health Event of +35% on Expert meter**
        - Or
        - Insulin dose x 1.35
        - E.g. 10 x 1.35 = 13.5

- If blood glucose at six hours is **more than 6mmol.l higher** than pre meal:
    - Increase the additional insulin by 20% so from 25% extra to 45% extra by:
        - **Set up health Event of +45% on Expert meter**
        - Or
        - Insulin dose x 1.45
        - E.g. 10 x 1.45 = 14.5

Should you use a dual/square/extended bolus or split injections for every meal?

For meals with usual amounts of fat and protein you should not delay the insulin going in as showed by this group of pumps users (Lopez *et al.*, 2014). They had a usual breakfast cereal, full cream milk and orange juice breakfast (60g carbs, 10g fat, 10g protein). They did this six times in the lab each time varying the bolus from normal bolus up to 6 hour extended bolus. It confirms a normal bolus is needed for most usual meals, especially breakfast.



However, when it's a high fat meal (40g) you need to increase the does and spilt it, but keep at least 50% in the first deliver, otherwise you will go high after eating. This was shown clearly in another high fat and protein pancake experiment (Lopez *et al.*, 2017). This study did not increase the total dose for the high fat and protein content and is most likely why all five of the six conditions ended up with a high and rising glucose level at 6 hours. If they would have added 25% extra insulin onto the dose, I predict most of the 6 hour results would not have been high.

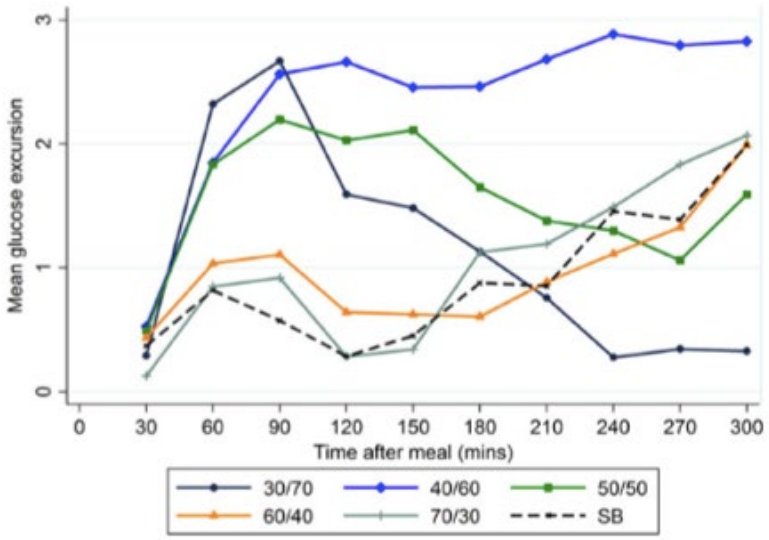
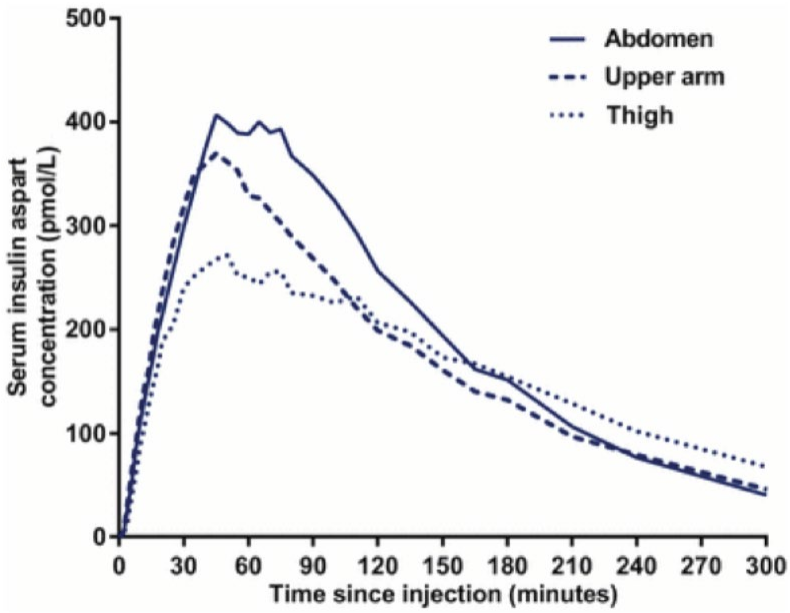


FIGURE 1 Glucose excursions for 300 min for a standard bolus (SB) and five different combination bolus splits after consumption of a high fat, high protein meal.

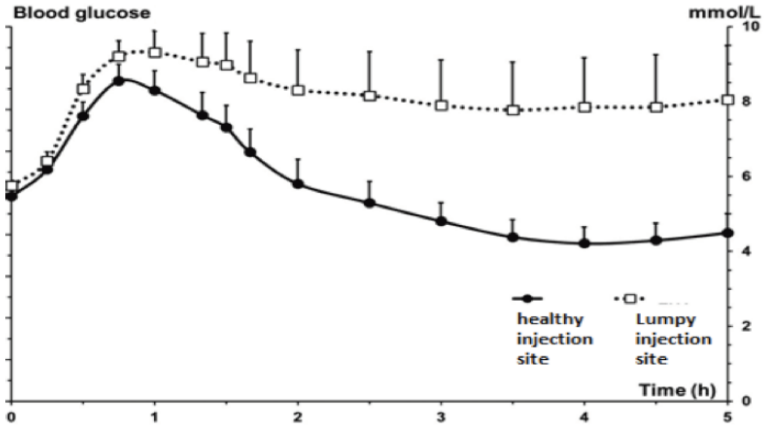
Speeding up the absorption of insulin

You can speed up the absorption of insulin in three main ways. First, inject mealtime insulin or place you pump cannula in the abdomen or arm – NOT THE LEG OR BUTTOCKS. See this graph from a classic study showing insulin absorption is fastest in the abdomen, followed by arm and slowest in the thigh. This review is a MUST READ to understand how insulin works (Gradel *et al.*, 2018)



Second, stay away from lumpy injections sites. This graphic shows why, another gen from the review paper (Gradel *et al.*, 2018).

Stay away from lumpy injection sites

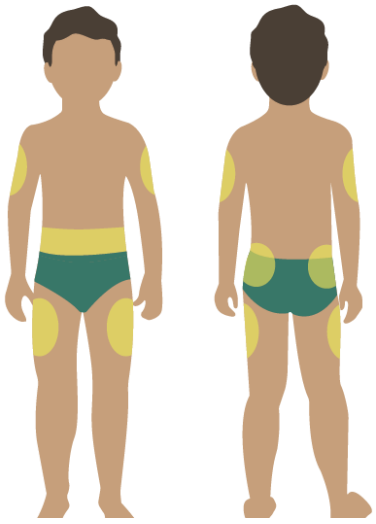


This graph shows the glucose level will be about 4mmol/l higher four hours after eating if the insulin is given into a lumpy injection site when compared to a healthy injection site. It is very important to check for lumps under the skin before inserting a new cannula or giving an insulin injection.

Check for lumps to avoid glucose bumps!

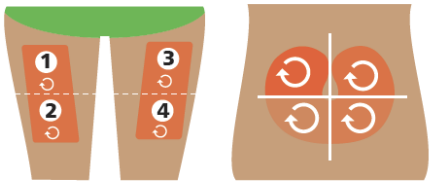
Injection sites

- If you inject into the same place a lot of the time, you are at risk of developing some lumps and bumps. The posh name for this is Lipohypertrophy.
- If you develop lipohypertrophy and inject your insulin into them, then your insulin won't be absorbed as effectively, this will lead to it working much faster on some days and much slower on others.
- In order to prevent this from happening it can be useful to have a plan of rotating your injection sites.

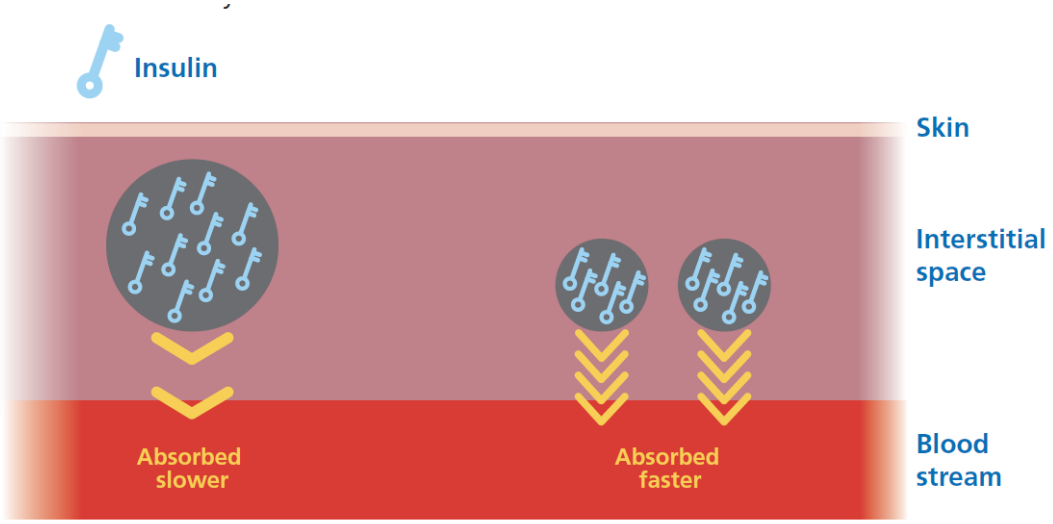


Top Tip

initial next to the insulin dose in your blood glucose diary where you have given your insulin
e.g LL = Left Leg, RL = Right Leg.



Last, split large doses of mealtime insulin to prevent insulin clumping together and slowing absorption (Mader *et al.*, 2013). This picture illustrates the point.



For people on injections, if you are happy to have two injections, you could consider:

- To split the fast acting insulin amount into two injections if it is above 10 units.
    - o For example, you could give two injections of 8 units in different sides of the abdomen if the total fast acting insulin amount was 16 units.
    - o If the total fasting acting insulin came to 18 units, how could you split the injections to speed up the absorption?

.....

For people on pumps you could consider;

- Using an extended/square bolus over 15minutes if the amount is above 10 units. This would keep the size of insulin ball under control over 15 minutes, instead of pumping in a large ball in less than 2 minutes.

Super bolus for insulin pumps

If you use an insulin pump you can use a super bolus by adding extra insulin to a bolus that you borrow from the basal. The Super bolus is very good for tackling the after breakfast glucose spike and for pregnant ladies (Ziegler, Freckmann and Heinemann, 2017).

Here is a video of how I teach at Birmingham, **watch me.** See the information below we give to the families.

Very simply...
A Super Bolus is where your borrow the basal insulin for two hours, and add it to the bolus insulin that is delivered 15-30 minutes before eating.

Why?
So that you get more insulin working in your blood when you need it the most. Which is just as you eat those foods that cause your blood glucose level to rise very quickly!

Lets take an example:
Craig has a basal rate of 1.00units per hour. He is eating 50g of carbohydrate (cornflakes) for breakfast and his ICR is 1unit:10g.

Normally he would bolus 5 units before breakfast.

What would be different with a Super Bolus?

- First, he would put a temporary basal rate of 0% on for 2 hours.
- Second, he would enter 50g carbohydrate into his bolus calculator, which would suggest 5 units of insulin.
- Finally, he would override the 5 units and increase it by 2 units, and he would deliver the 7 units before eating.

Would Craig not go hypo?

No because the total amount of insulin the pump delivers over the two hours after the bolus is exactly the same, 7 units. The only difference is he will be getting more of the 7 units working when he needs it the most, just after he eats his cornflakes.

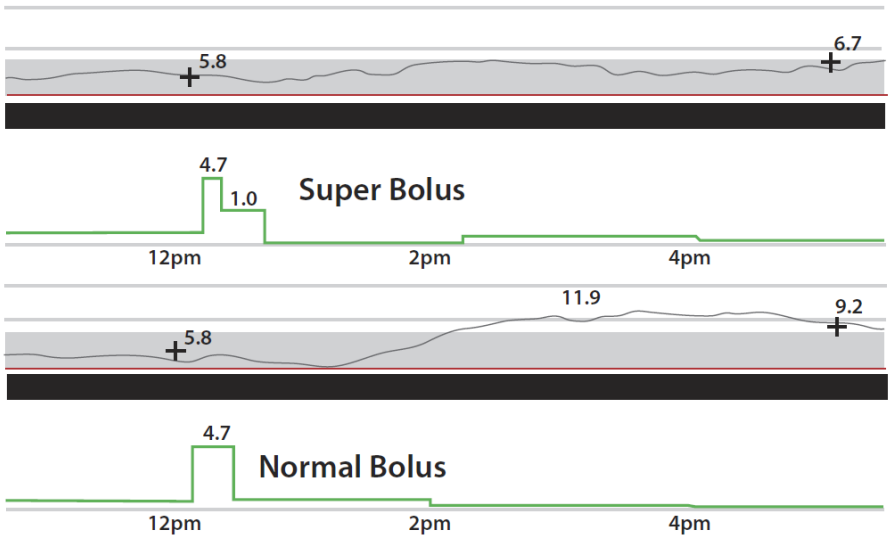
This will mean his blood glucose after two hours will be lower than usual, but his four hour glucose level will be the same, in target.

A Real life Super Bolus

Look at the picture below, this is a real life example of a young person with Type 1 Diabetes who used a Super Bolus for 57g of breakfast cereal on the first day, and then a normal bolus for the exact same meal the next day.

A few things to notice...

- On both days the amount of insulin for the cereal was 4.7units
- The basal rate must have been 0.5units per hour, because a temporary basal rate of 0% for two hours meant 1.0unit was added for the Super Bolus.
- After the Super Bolus the blood glucose never went above 7.7mmol/l.
- After the Normal Bolus the glucose level went up to 11.9mmol/l and took four hours to come back down to target.



How will you know if the Super Bolus has worked?

Test your blood glucose level:

- Before the meal.
- Two hours after the meal.
- Four hours after the meal.

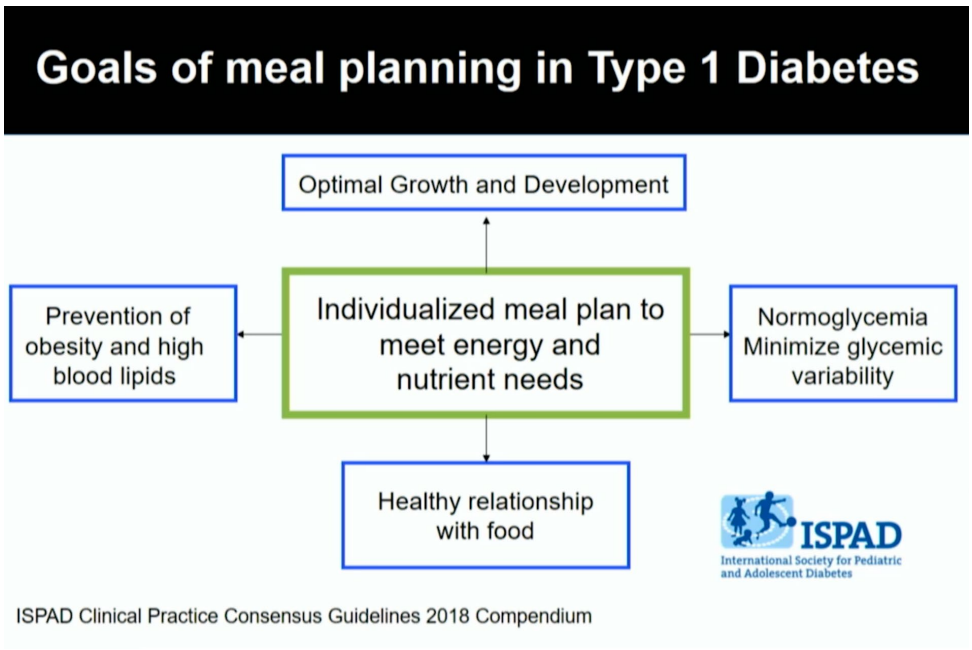
Ideally the blood glucose should not increase more than 4mmol/l from the reading before the meal at two hours, and be back into target by 4 hours.

- If it has increased more than 4mmol/l, you could try making the Super Bolus more aggressive by doing a temporary basal for 3 hours at 0% and adding the 3 hours of missed basal onto the bolus.
- So in Craig's example, he would bolus 8 units instead of 7 units, and he will have a temporary basal of 0% for three hours running, not two hours.

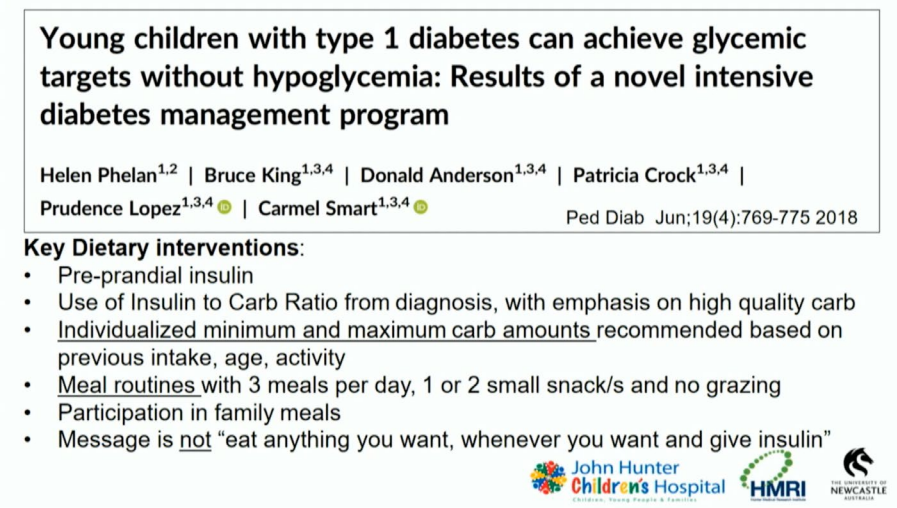
Limit snacking

Before reading this you MUST watch:

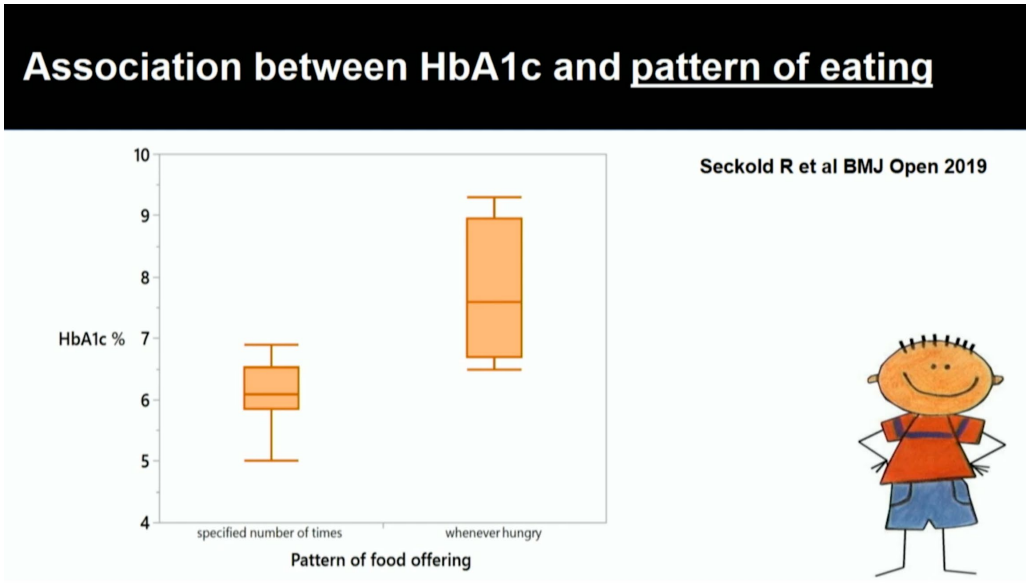
Dr Smart ISPAD Presentation on low carbohydrate diets



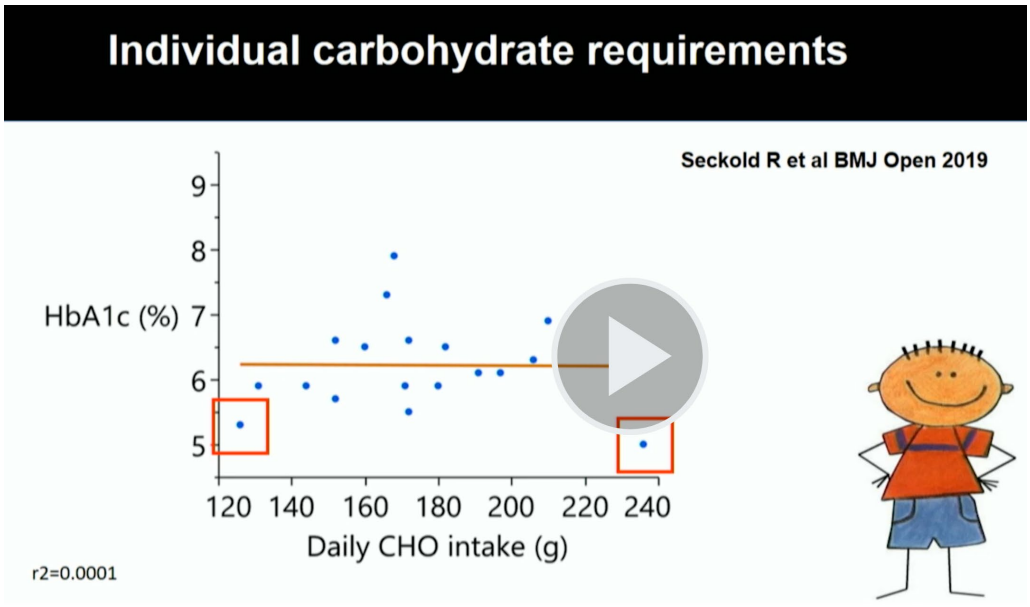
Screenshot from Dr Smart ISPAD Presentation on low carbohydrate diets



Screenshot from Dr Smart ISPAD Presentation (Phelan *et al.*, 2018)on low carbohydrate diets



Screenshot from Dr Smart ISPAD Presentation (Rowen Seckold *et al.*, 2019) on low carbohydrate diets

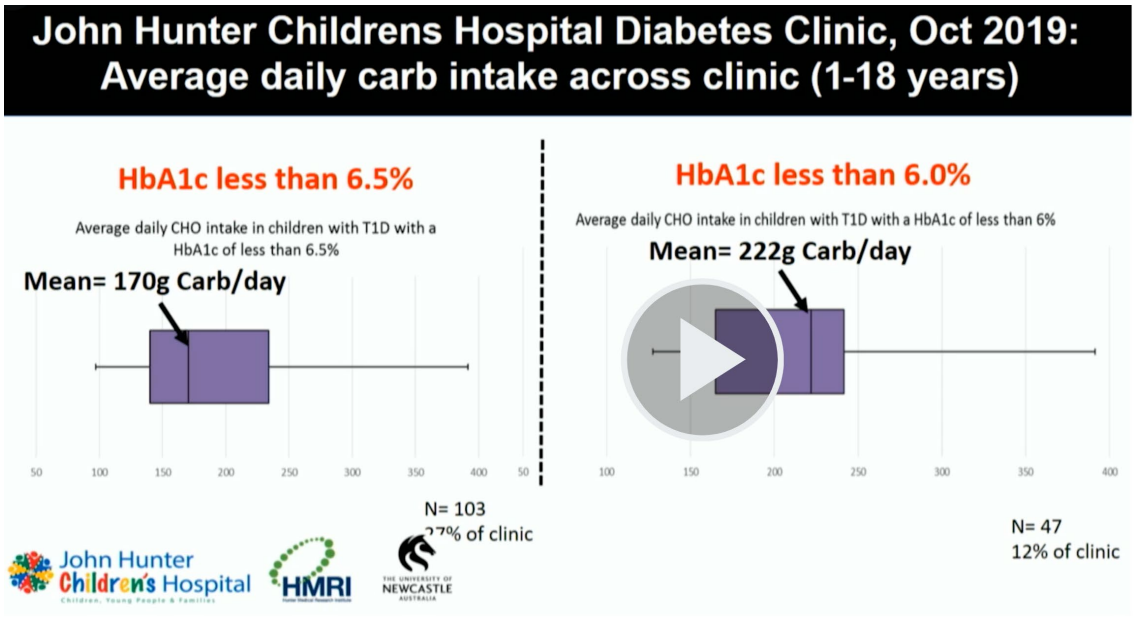


Screenshot from Dr Smart ISPAD Presentation (Rowen Seckold *et al.*, 2019) on low carbohydrate diets

Take home messages:

- Keep to 3-4 meals and limit snacks
- Meal pattern/consistency and limiting snacks is more important than carbohydrate amount, as long as carb amount is within 40-55%
- Promote structured meal plans with nutrient dense real foods and stop the message of “eat what you want just give insulin for it!”

Keep closer to the 40% than 55% carbohydrate



Screenshot from Dr Smart ISPAD Presentation on low carbohydrate diets

Key take homes:

- Target HbA1c can be achieved with at least 40% energy intake from carbohydrate
- At 170-222g per day that is closer the 40% than 55% of intake in well-controlled children and young people.

At Birmingham we have an emphasis on:

- A range from 40-55% of intake from carbs and define in actual amounts
- Split that into 3-4 CONSISTENT meals per day giving practical suggestions to keep kcal of meals to 40-55% from carbohydrate, 10-20% from protein & 30-40% from fat.
- Discourage grazing
- Focus on nutrient rich meals that are balanced in carbs, fat and protein.

See the below example for 5 year old boy using our workbook.

How much carbohydrate do I need?

Everybody needs carbohydrate for energy and the government recommendations are for you have 40% to 55% of energy from carbohydrate.

Age (years)	Average daily carbohydrate requirement in grams	
	Boys	Girls
1 - 3	70 – 145g	70 – 130g
4 – 6	140 – 195g	130 – 185g
7 – 10	165 – 250g	150 – 240g
11 – 14	215 – 330g	200 – 290g
15 – 18	280 – 400g	240 – 310g

To provide your body with a consistent supply of energy it's best to spread carbohydrate as equally as possible throughout the day. This is not possible every day but, a structure to your normal eating pattern would help your energy levels and blood glucose control.

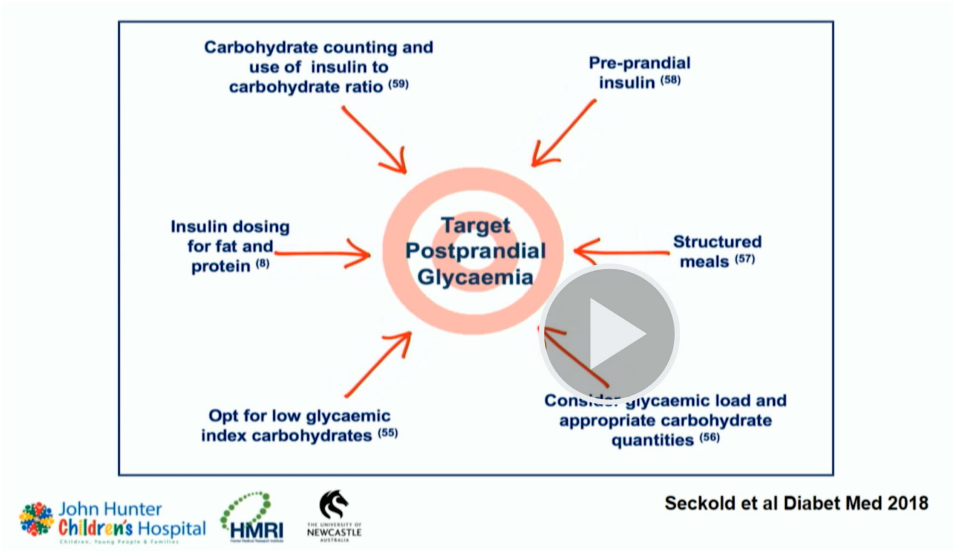
Watch me: How much carbohydrate

Your average daily carbohydrate requirement calculated with your Dietitian is:

Daily carbohydrate: 140 **g to** 196 **g**

Main meals carbohydrate: 34 **g to** 56 **g**

Summary



This Screenshot from Dr Smart ISPAD Presentation on low carbohydrate diets says it all!

Low carbohydrate and very low carbohydrate diets

Before reading this you MUST watch these two presentations from ISPAD 2019,

Dr Smart ISPAD Presentation on low carbohydrate diets

Dr Lennernez ISPAD Presentation on very low carbohydrate diets

This review is also a very good synopsis (R. Seckold *et al.*, 2019)

This review is an excellent overview of LCD and VLCD for T2D & T1D (Bolla *et al.*, 2019)

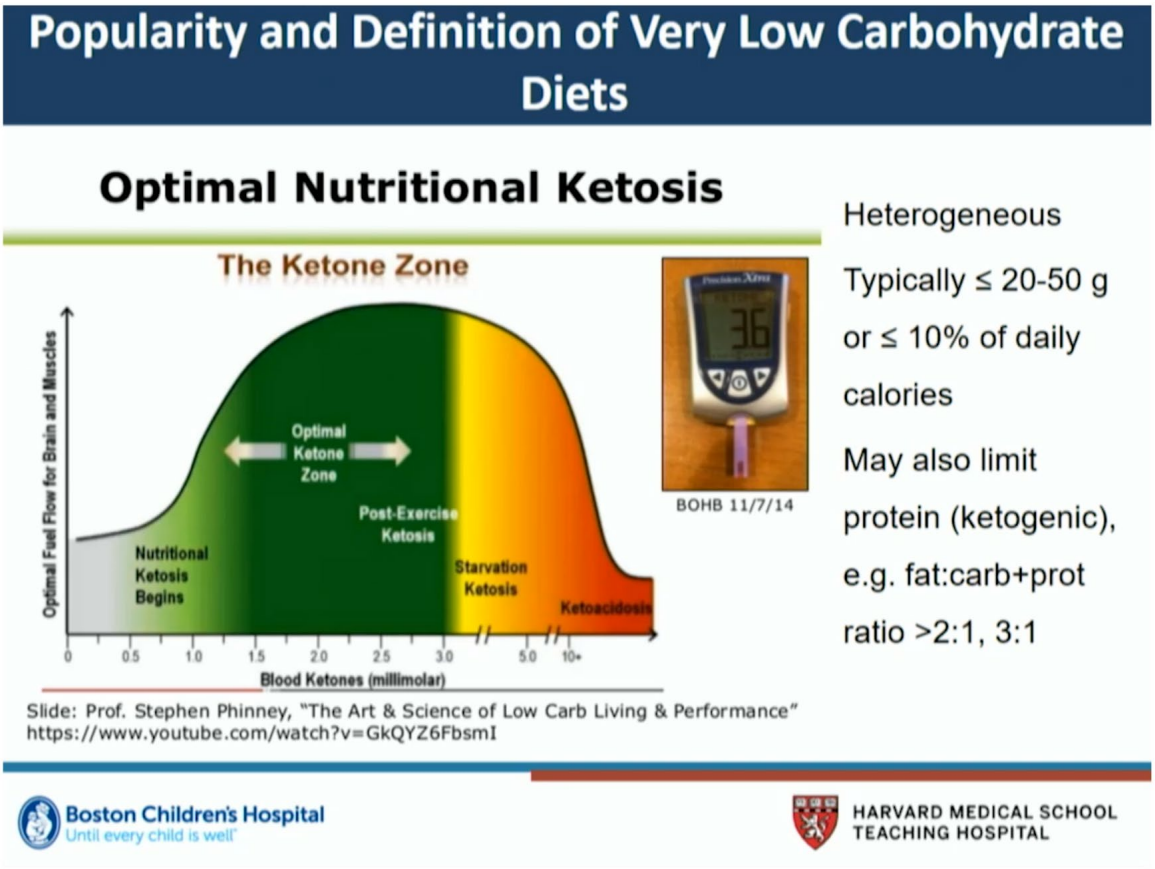
I have pulled out the key information with a dash of critical appraisal and practical implementation

VLCD and LCD definition and nomenclature

The definitions using percentage of energy intake seem the most sensible, especially in children.

% carbohydrate of average energy requirements for age	1-5 years	6-10 years	11-16 years	adults
55%	>170g	>230g	>320g	>280g
45%	140g	200g	280g	220g
Low carbohydrate Diet (LCD) 26%	<80g	<110g	<150g	<130g
Very low carbohydrate diet (VLCD) <10%	<30g	<40g	<60g	<50g

Adapted from (R. Seckold *et al.*, 2019) with thanks the Francesca Annan



Dr Lennernez ISPAD Presentation on very low carbohydrate diets

People following a very low carbohydrate (VLCD) approach generally in two camps:

- A nutritional ketosis approach which is much lower in protein, usually 0.6-1.2g/kg/day, and 70-80% of the total energy coming from fat. Protein is lower is to keep the insulin low. This allows the body to up regulate its metabolic machinery to oxidise FFA and ketones as the major fuel source. You must understand the difference between nutritional ketosis and diabetic ketoacidosis:
    - Nutritional ketosis is ketosis in the presence of insulin which is sufficient. Blood ketones will be 0.6-3.0mmol/L and glucose levels usually <8.0mmol/L because fat is being metabolised to ketones bodies to be used for fuel due to lack of glucose availability. There is adequate insulin to prevent unregulated ketone body production that results in DKA. This is a deliberate physiological state induced by consuming a diet that is 70-80% fat, 10-15% protein, 5-10% carbohydrate.

    - DKA is ketosis in the absence of or insufficiency of insulin. Blood ketones will normally be >3.0mmol/L and blood glucose normally >14.0mmol/l because there is insufficient insulin and fat is being metabolised to ketones bodies in an unregulated way which has the side effect of dropping the blood ph to a dangerous level. Just like at diagnosis or deliberate insulin omission.

- A Dr Bernstein (Bernstein, 2011) style approach, which is typically high in protein >2.0g/kg/day, carbs aiming for maximum 24g per day, and the rest made up with fat (50-60%). You are UNLIKELY to get into nutritional ketosis with this approach because the protein intake increases the insulin demand which in turn prevents nutritional ketosis.

The difference in protein levels between the two approaches is very important. The Dr Bernstein (Bernstein, 2011) style does not aim to achieve nutritional ketosis. It has a much higher protein intake aiming to stimulate anabolism by accompanying protein with insulin. Whereas nutritional ketosis has a much lower protein and insulin intake, with the aim of increasing production of ketone bodies by the liver. Therefore, very little opportunity for anabolism and this is a major concern for the growth of children.

Why is this important?

Nutritional ketosis is not recommended for people aged under 18 years. A research review on children in prolonged nutritional ketosis to treat refractory epilepsy reported (Martin *et al.*, 2016):

- Increase risk of faltering growth, that catches up when nutritional ketosis is stopped.

- Abnormal lipid profiles linked with increase risk of cardiovascular issues.

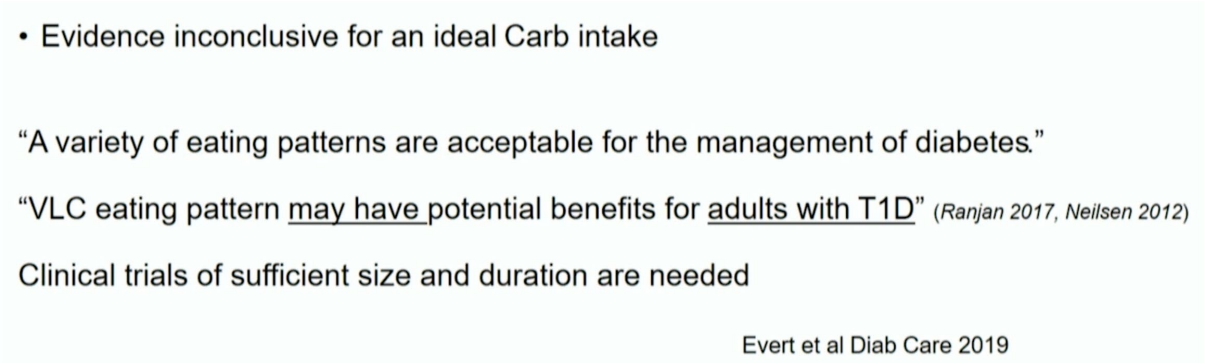
- Kidney stones and low bone mineral density.

Does this mean low carbohydrate diets should be avoided for people with type 1 diabetes?

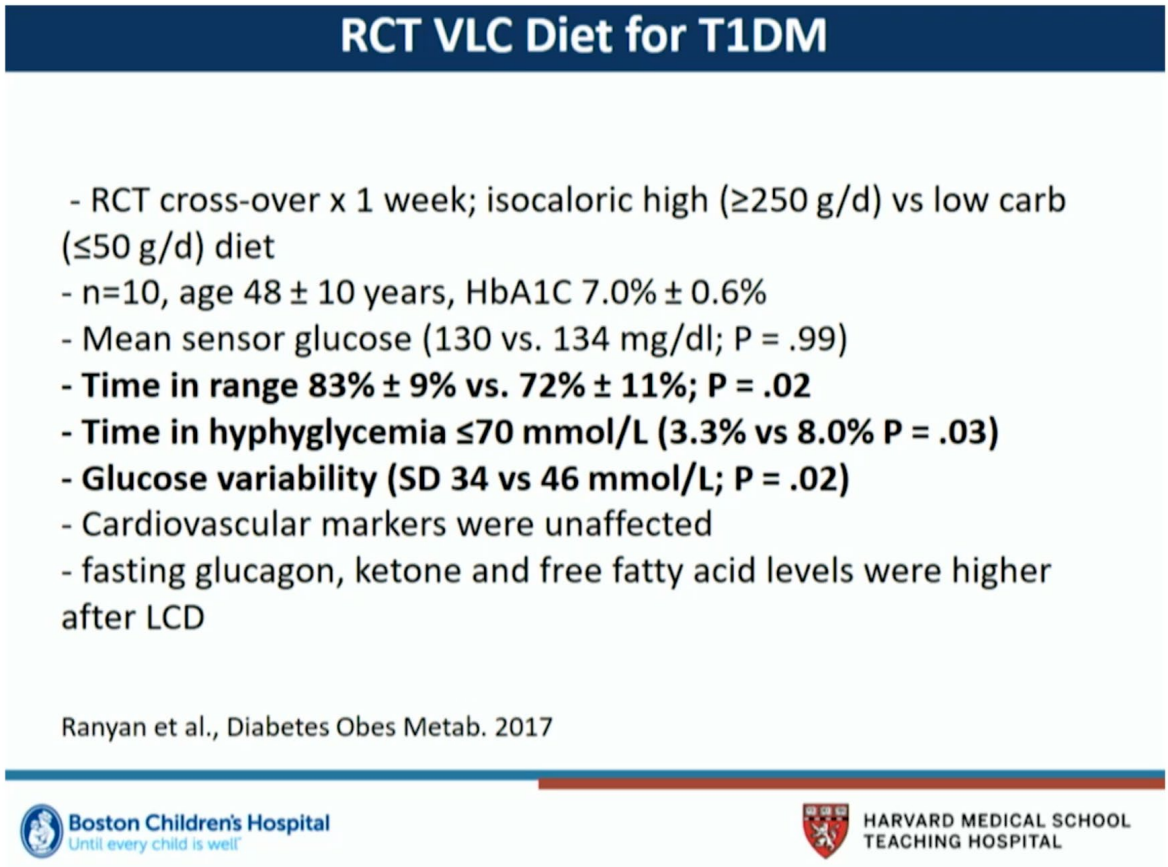
The evidence is sparse to say the least. Let's start with the adults.

Adult research on VLCD and LCD

ADA position statement for adults



Screenshot from Dr Smart ISPAD Presentation on low carbohydrate diets



Dr Lennernez ISPAD Presentation on very low carbohydrate diets

Study	Study type	Aim/intervention	Findings
Ranjan (2017)	Randomized cross-over (n=10)	>250g vs <50g Carb/day for one week each.	Time in range 83% vs 72% VLCD. Less insulin on VLCD. Cognitive scores were reduced on VLCD.
Nielsen (2012)	Retrospective audit of 48 adults who attended a VLCD course	<75g Carb/day for 4 years Adherence based on HbA1c changes	52% (n=25) non-adherent. A1c decreased: 7.6% to 6.9% (partly adherent)
Schmidt (2019)	Randomized cross-over (n=10)	>200g vs < 100g Carb/day for two weeks each	No difference in time in range 68% vs 65% VLCD. **Wt loss: 2kg LCD despite meal plans isocaloric**
Krebs (2016)	Random allocation to VLCD or usual carb (n=10) 5 adults in each group	"Usual" vs < 75g carb/day for 12 weeks	No difference in A1c 7.4% "usual" vs 7.2% VLCD. **Wt loss: 5kg VLCD**

Screenshot from Dr Smart ISPAD Presentation on low carbohydrate diets

Take Home for adult research

- One week study shows more time in range with VLCD (Ranjan 2017). Anyone can follow anything for one week, but it is a proof of concep.

- A diet of <75 per day if followed for 4 years suggest a much lower HbA1c and potentially lower cardiovasucal risk profile (Neilsen e al, 2012) see below for a deep dive.

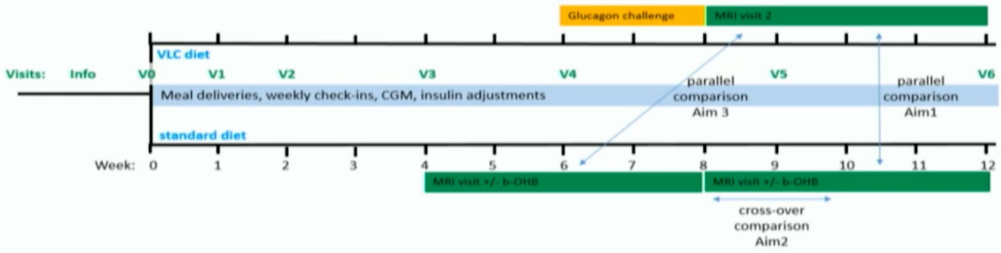
- When changing to a VLCD weight loss occurs. Unclear if this is water weight of lean tissue loss (Schmdit, 2019; Krebs, 2016). This raises concern for children and young peoples growth, as it can be hard to eat enough when you are not allowed to eat 80% of the foods normally available.

- VLCD may work well for adults if they can adhere to it and there is little concern with growth and development as there is for children.

We need an RCT, good job Dr Lennernez is conducting one. Keep an eye out for this in the future.

RCT

- N=32 males and females with T1DM, aged 18-30
- Food deliveries
  - VLCD - 5% carbohydrate, 75% fat, 20% protein
    < 23% sat fat, 5g salt
  - standard diet - 50% carbohydrate, 30% fat, 20% protein
    < 10% kcal sat fat, < 10% kcal added sugar, <2.3 g salt
  - Matched for vegetables, micronutrient sufficient
  - Supplemental MVI, omega-3, VLC also Mg, bouillon, fiber (PRN)



Dr Lennernez ISPAD Presentation on very low carbohydrate diets

RCT – Monitoring and Interventions (VLC)

Insulin:

- 50% reduction
- Carb bolus plus extended (2-3hr) protein bolus (3 g protein ~ 1 g carb) at beginning of meal
- Treat to Target Algorithm: fasting: 80-110 mg/dl, pre-meal 80-120 mg/dl

Monitoring:

- Know your baseline keone level
- Check BOHB if: BG >200 mg/dl in AM or for > 2 hrs during the day, or if having sx of nausea, abdominal pain, malaise or lethargy
- Call if: BG < 50 mg/dl, BOHB >3 mmol/L, feeling unwell
  → Physician to troubleshoot, hydrate, monitor
  → additional treatment for ketosis (carbs, insulin, ED) if feeling unwell per BOHB > 5 mmol/L

Hypoglycemia:

If BG **60-70** mg/dl, take ½ glucose tablet (2 g) and check again in 15 minutes.
If BG <60 mg/dl, take 1 full glucose tablet (4 g) and check again in 15 minutes
If under **75** mg/dl, repeat

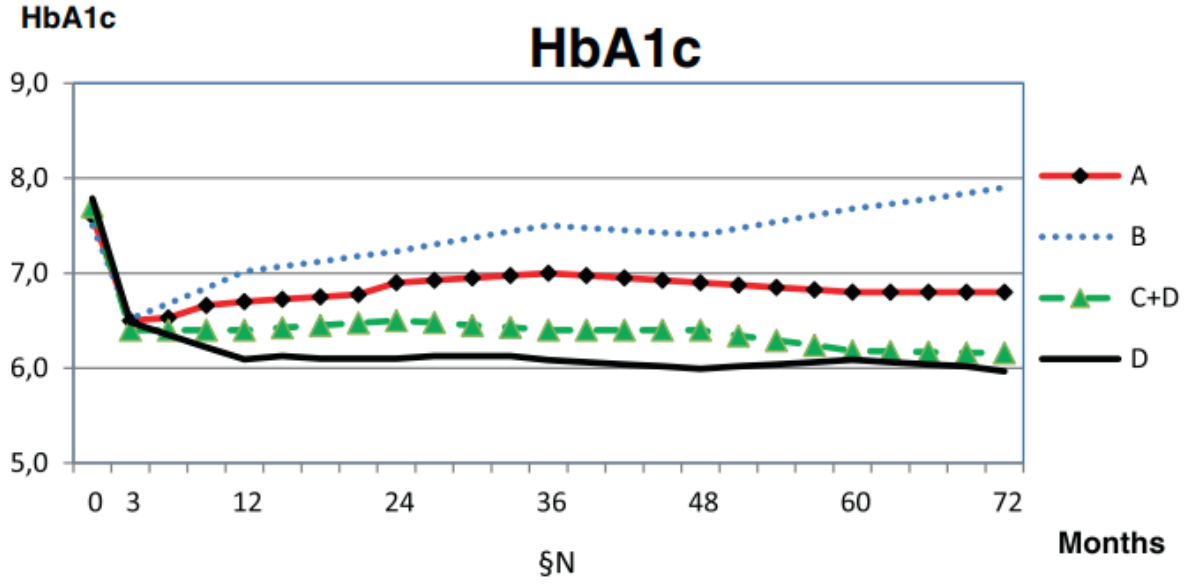
*) 1 gram ofc arbohydrate will raise blood glucose by ~5 mg/dl in a ~ 70kg person

Dr Lennernez ISPAD Presentation on very low carbohydrate diets

I promised a deep dive into the Nielsen study.

A group of 48 adults with type 1 diabetes were educated on how to safely consume a diet of less than 75g of carbohydrate per day (Nielsen *et al.*, 2012). They followed them up at 3 months, 3 years and 4 years. The below graph shows what happened to their HbA1c, depending on their adherence to the diet:

- A = All 48 people
- B = Non-adherent to <75g carbohydrate
- C = Partially adherent to <75g carbohydrate
- D = Adherent to <75g carbohydrate



A	48	23	7
B	25	10	3
C+D	23	13	4
D	13	8	3

Adapted from (Nielsen *et al.*, 2012)

The main points to understand from this study are:

- If you fully adhere or partially adhere to a low carbohydrate approach, you could get a sustained drop over four years in HbA1c of 1.8% and 0.7% respectively.

- Only 27% of people can fully adhere to low carb, whilst an additional 21% can partially adhere. More than 50% cannot do adhere to <75g.

- The 27% who fully adhered actually improved their lipid profile. A significantly better TC:HDL ,with no increase in other complications. The authors used microvascular and cardiovascular algorithms to predict the low carb adherers reduced their risk of both sets of complications by 20-40%. However, Apo-B is the best predictor of cardiovascular risk for people with type 1 diabetes as LDL particle size is usually smaller due to dysregulated glycaemia (Schofiled, J.; Ho, J.; Soran, 2019). The just is still out here.

- The low carbohydrate adherers reduced their total bolus insulin by 10units, but background insulin remained the same.

The very limited data suggests a few things. If you are an ADULT and you adhere to a low carb diet (<75g day) you will highly likely improve your HbA1c. This study does suggest there is an improvement in cardiovascular risk, however, we now know measuring Apo-B is much more effective in assessing cardiovascular risk for patients with type 1 diabetes as they are prone to smaller dense LDL particles (Schofiled, J.; Ho, J.; Soran, 2019).

Children and young people research on VLCD and LCD

A recent report on six children following a low carb diet concluded, children following a VLCD are at increased risk of (de Bock *et al.*, 2018):

- Faltering growth
- Cardiovascular disease profile risk increase
- Social/emotional issues

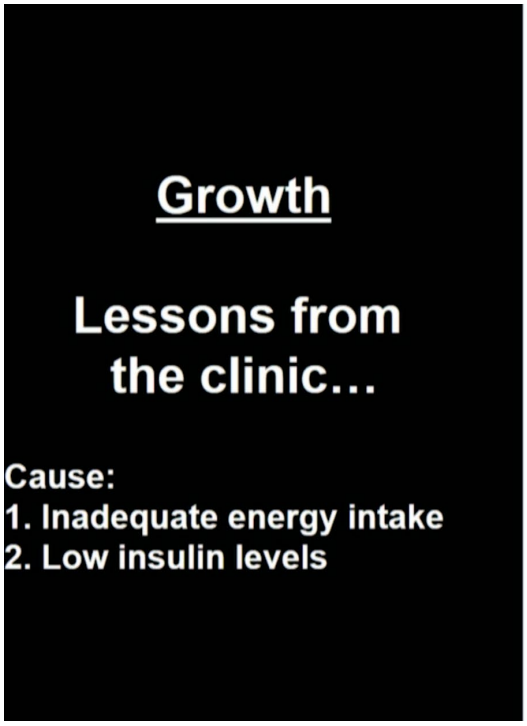
Case Series VLC Diet for T1DM

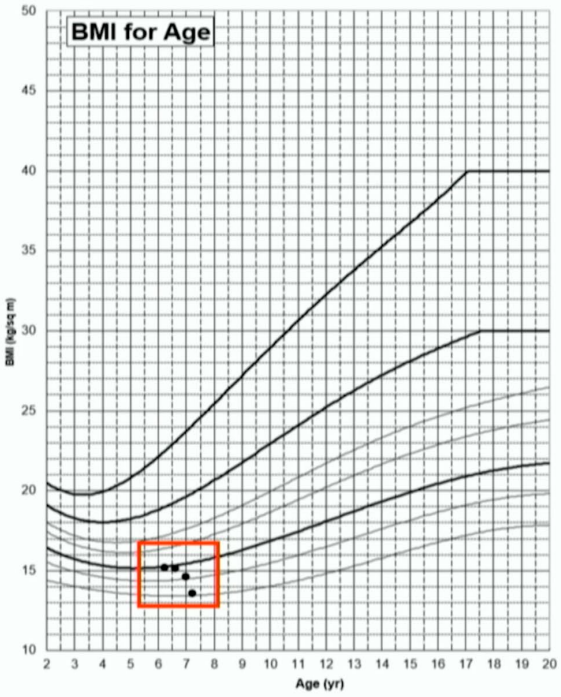
2017 - case series solicited from endocrinologists in Australia for concerning VLC effects

Age Dx	Age Diet	Carb	A1C	Anthro	Diet quality	Cho	Other concerns
12;1	13-15	60g	5.8-6%	poor wt gain	Hypocaloric, <70% RDI Ca, thiamin	5.5	fatigue
8;7	12-14	20g	6-8%	wt loss, (intent)	Hypocaloric, 50% RDI Ca	5.7	Insulin omission, low f/u amenorrhea
6;3	6.5-7	50g	7.9 %	wt loss	Hypocaloric, 30% RDI Ca	-	Hunger, insulin omission
4	4-11.5	40%	8.4-10.4 %	wt loss, poor growth	Hypocaloric, 47% RDI Ca, 70% Phos, 74% Mg	5.2	loss to f/u, insulin omission, mild-mod hyopoglycemia bone age -2 yrs
2	3-5	45g	4.9 %	wt loss, poor growth	Hypocaloric, 406% RDA NaCL, 50% RDI Ca	4.7	mild-mod hyopoglycemia; failed GH-stim (4.3mU/L)
0;22	7-7.3	40g	-	Wt loss	-	-	Hunger, low energy, poor variety

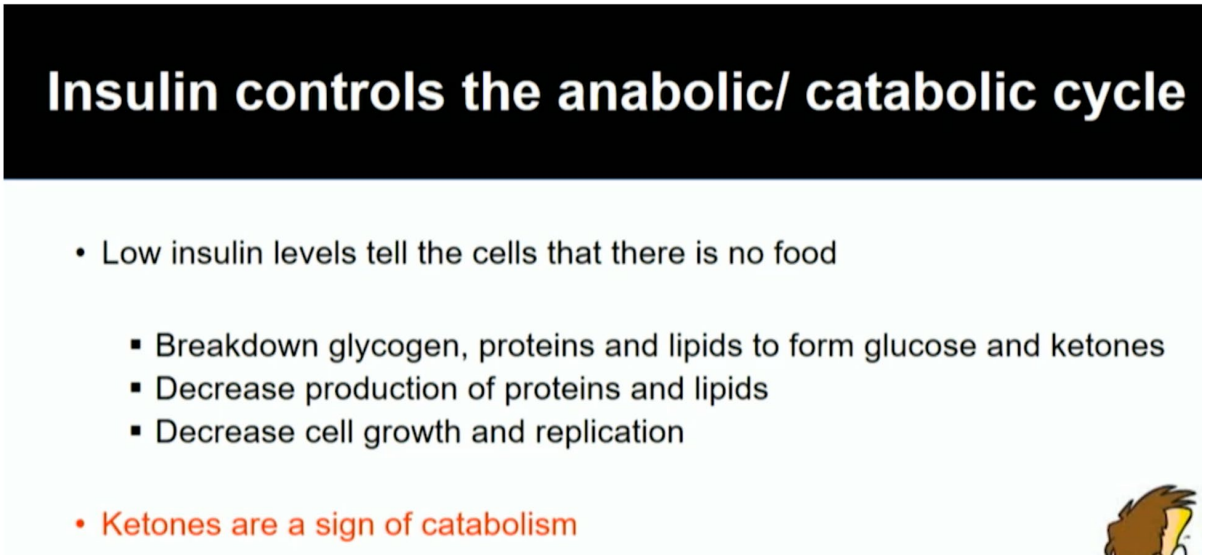
DeBock et al., Pediatric Diabetes. 2017

- Dr Lennernez ISPAD Presentation on very low carbohydrate diets





Screenshot from Dr Smart ISPAD Presentation on low carbohydrate diets



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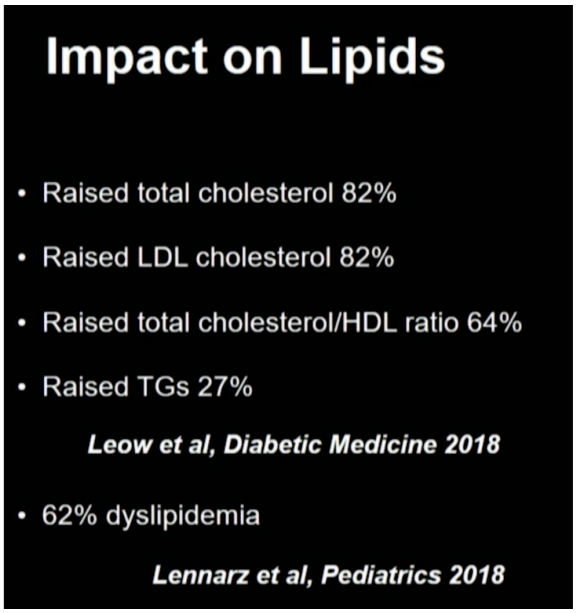


Screenshot from Dr Smart ISPAD Presentation on low carbohydrate diets

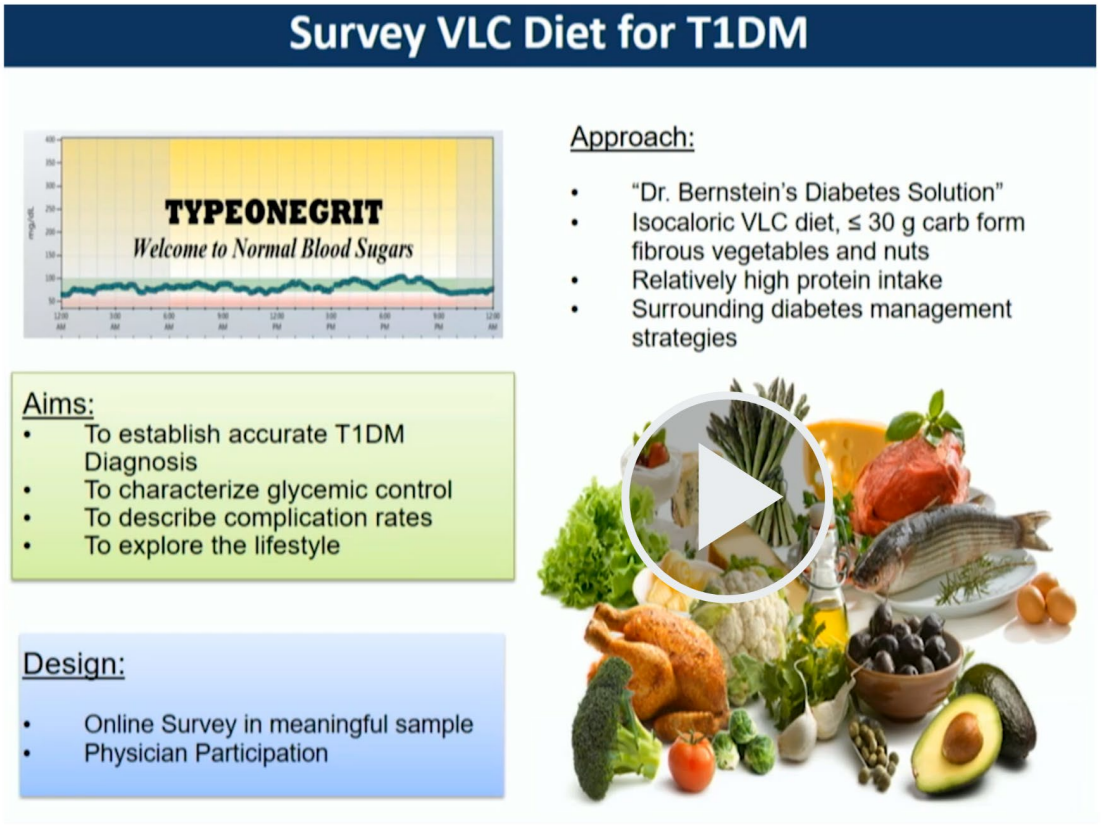
On reading the six case reports a few things became evident about the six children.

- They all had inadequate energy intake
- It was not clear if they were in nutritional ketosis
- They were high concern patients across several different centres in Australia

The case reports show clearly that a poorly formulated low carbohydrate diet is a major issue for children, not unlike a ketogenic diet (Martin *et al.*, 2016). However, the case reports do not make clear if a high protein, adequate energy, and well formulated low carbohydrate diet is detrimental.

Let's take a look at an observational report suggesting VLCD has promise in children and young people with type 1 diabetes.

An observational study of the on the TYPE ONE GRIT, Dr Bernstein (Bernstein, 2011) approach, Facebook group was completed by Boston Children's Hospital team (Lennerz *et al.*, 2018).



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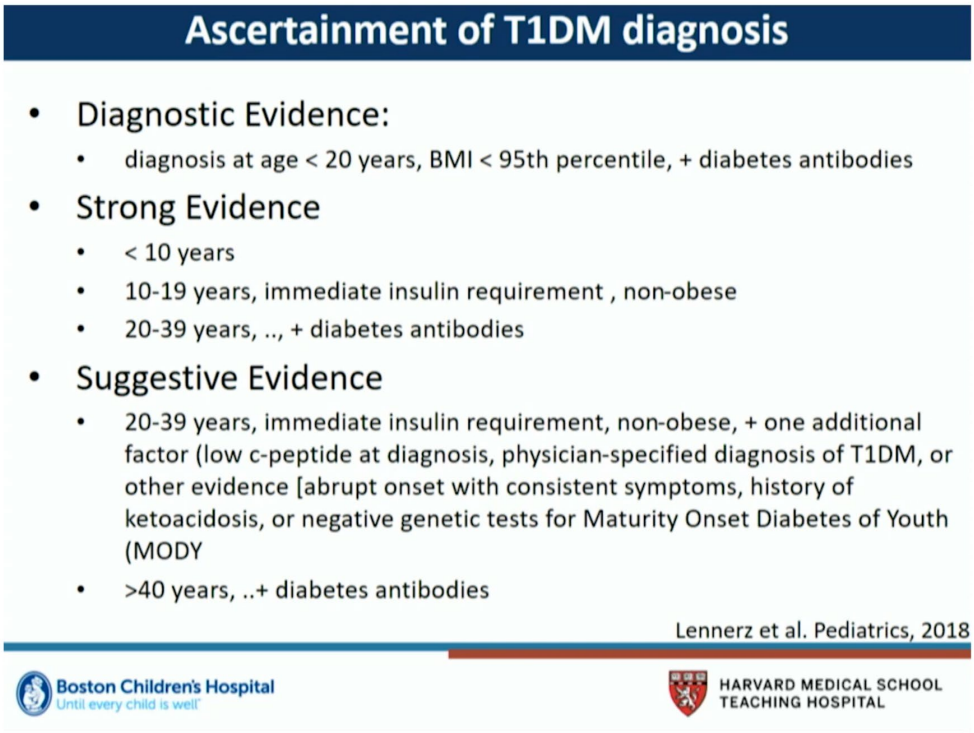

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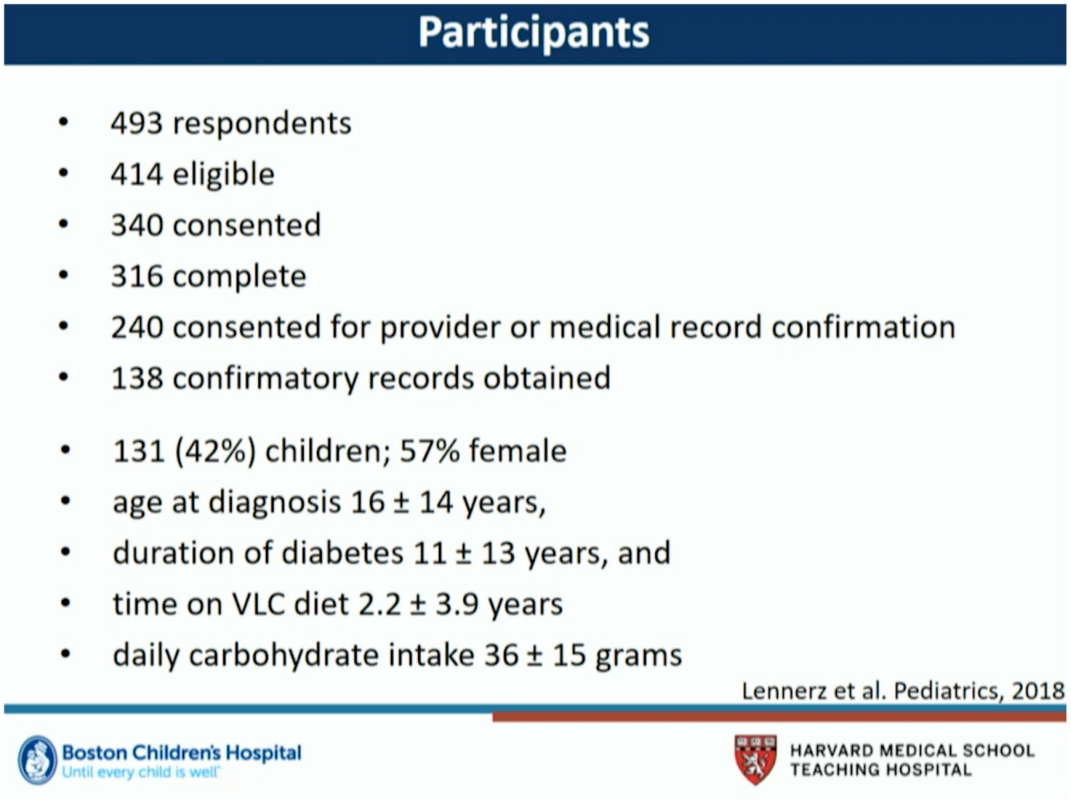

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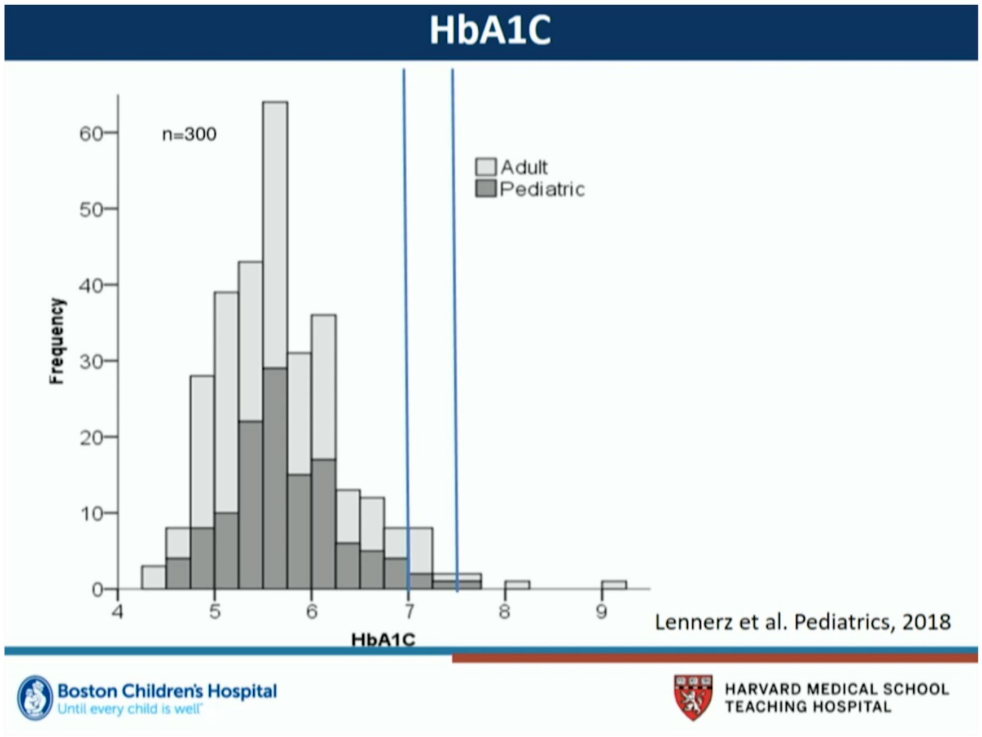
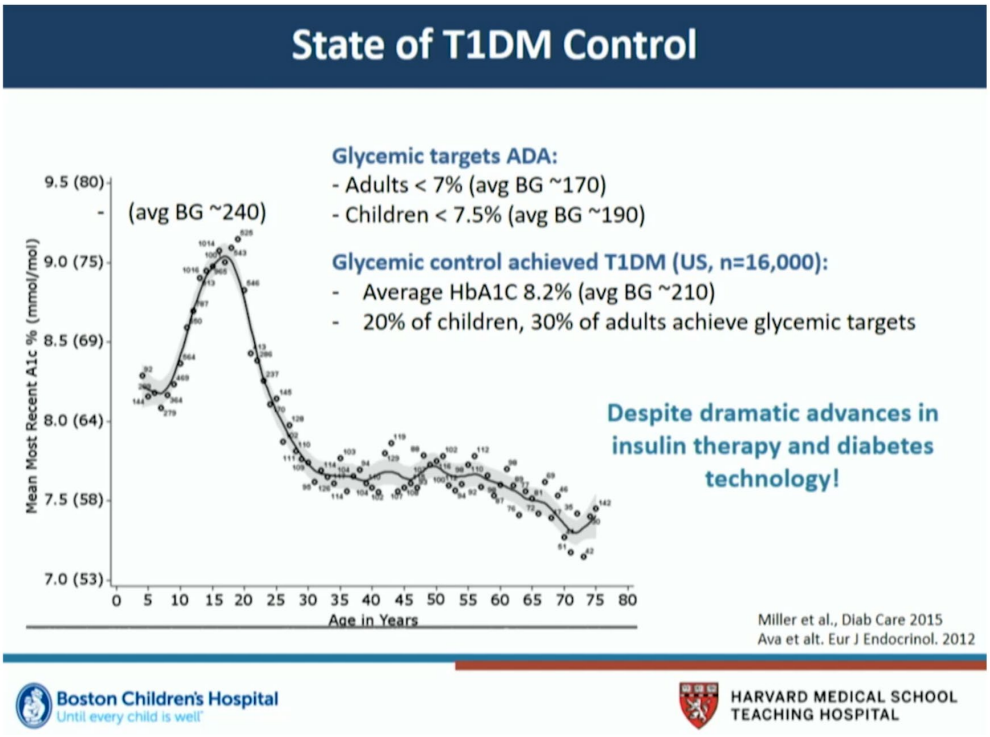


Dr Lennernez ISPAD Presentation on [very low carbohydrate diets]



Dr Lennernez ISPAD Presentation on [very low carbohydrate diets]

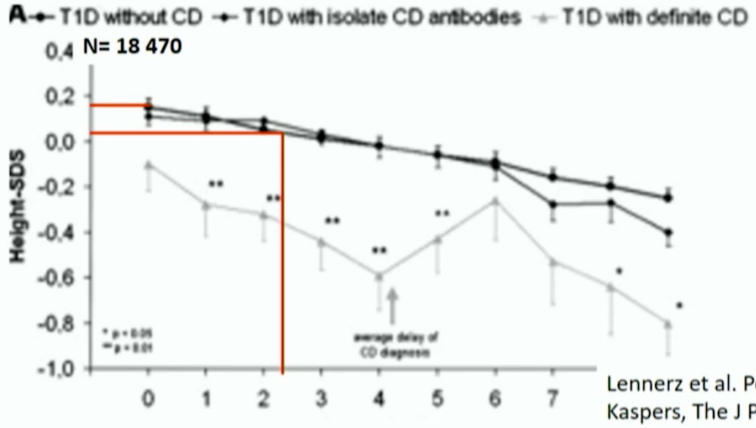
Clinical Variables	Mean (SD), No. (%)	No. Responses
Glycemic control		
HbA1C, mean (SD), %	5.67 (0.7)	300
Insulin daily dose, mean (SD), units/kg/d	0.40 (0.19)	282
Insulin percent basal, mean (SD), %	64 (21)	198
Complications		
Diabetes related hospitalizations, No. (%), persons per year [c]	7 (2)	300
DKA	4 (1)	
Hypoglycemia	2 (1)	
Other	4 (1)	
Hypoglycemia w seizure / coma, No. (%), persons per year	7 (2)	300
Hypoglycemia requiring glucagon	11 (4)	301
Monthly symptomatic hypoglycemic episodes, mean (SD), n	6.1 (8.5)	101
Lipids		
TC, mean (SD), mg/dl	234 (89)	79
LDL, mean (SD), mg/dl	147 (83	81
HDL, mean (SD), mg/dl	74 (21)	80
TAG, mean (SD), mg/dl	74 (37)	81

Lennerz et al. Pediatrics, 2018

Dr Lennernez ISPAD Presentation on very low carbohydrate diets

Growth

	N	Height z-score	Height z-score at dx	Time since dx	Time on diet
Self-reported	107	0.26 ± 1.21			
Provider-reported	34	0.20 ± 1.02	0.41 ± 1.27	2.3 ± 2.0	1.2 ± 0.8



Lennerz et al. Pediatrics, 2018
Kaspers, The J Peds, 2004

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Take homes:

- Average HbA1c of 5.7% with virtually all respondents <7.5% (58mmol/mol) is unprecedented results. We know HbA1c is the main risk factor for both micro and macrovascular complications (DCCT Research Group, 1993; Nathan, 2014) and the protective effect of a sustained HbA1c in this range must be considered strongly when balancing against theoretical risk.

- Mixed lipid profile results with TC and LDL increases suggesting increase risk but lower TG and higher HDL suggesting reduced risk. Atherosclerosis is a complex disease state of three main pillars; cholesterol, endothelial dysfunction and inflammation (Schofiled, J.; Ho, J.; Soran, 2019). People with type 1 diabetes are at much higher risk of cardiovascular disease primarily because of dysregulated glucose levels (Schofiled, J.; Ho, J.; Soran, 2019). Leaving the question, "does having a HbA1c at 5.7% override any risk of increased LDL and in particular Apo-B?".

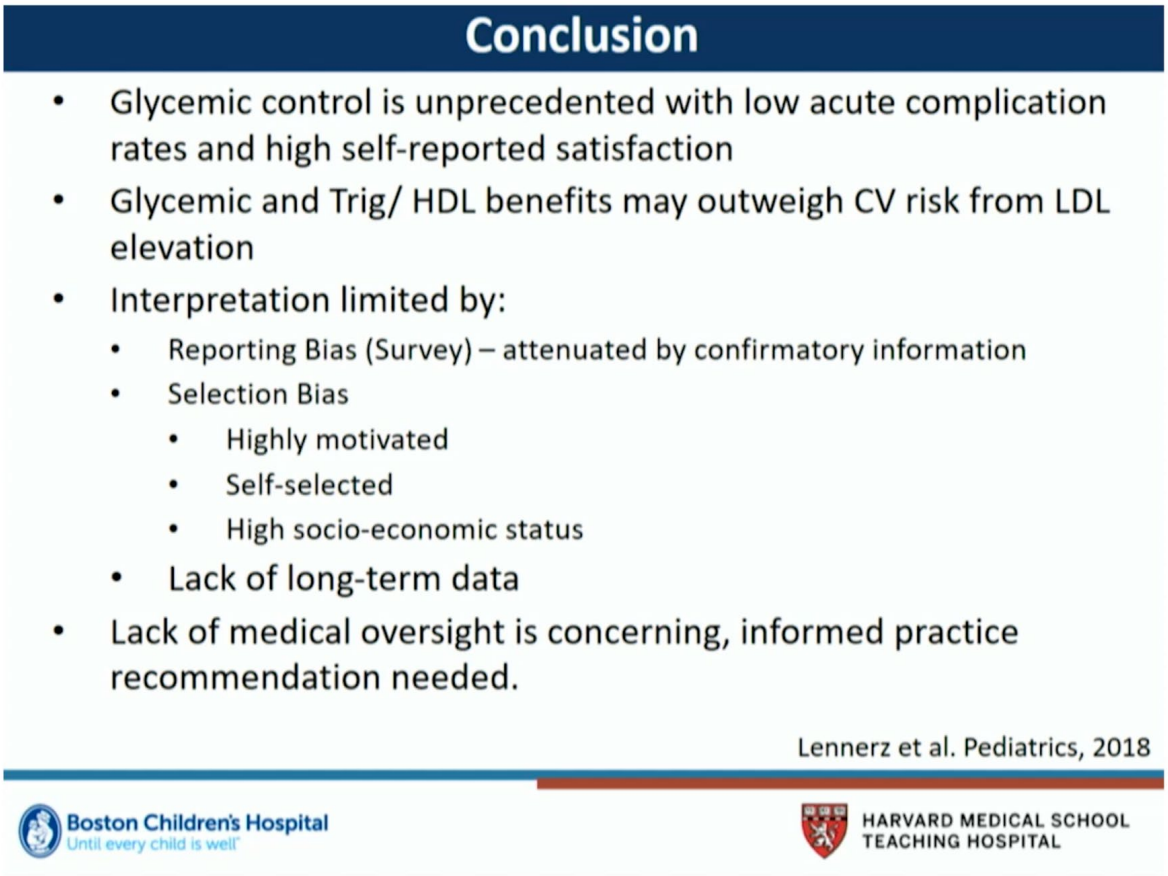
- A slight decrease of 0.2 in height Z score SDS in children 2.3 years post diagnosis (1.2 years from VLCD) is like 0.2 drop in the German DPV large data set assessing from diagnosis to 2.3 years. The study was unable to establish if the 0.2 drop came when on the VLCD diet, before the VLCD or equally spread out? This suggests growth concerns may not be as pronounced as theorised **IF** a well formulated adequate energy intake VLCD is maintained.

What should strike you from both these reports?

- They both cherry picked the most extreme cohort to report on, which suggests bias towards finding a positive.

- Both did not have any type of control group to assess the independent impact of VLCD.

A point acknowledged by Dr Lennernez



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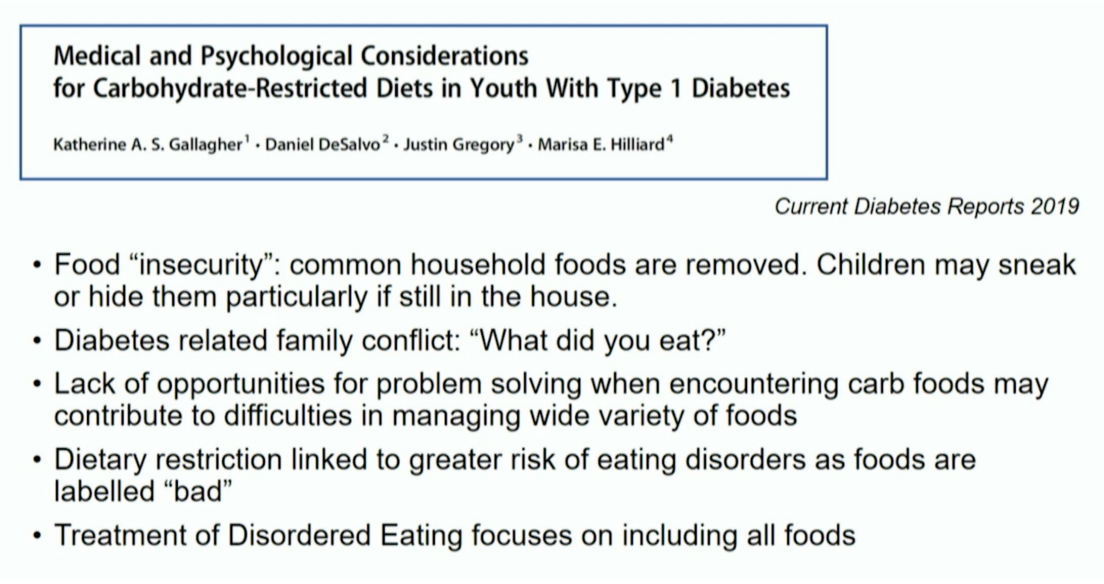
There are also psychological concerns for children and young people following carbohydrate restricted diet.



Screenshot from Dr Smart ISPAD Presentation on low carbohydrate diets

Summary: Considerations on a low carb diet

Nutrition	Insulin	Day to day
Degree of Carb restriction	Continue adequate insulin on diet commencement	Motivating factor for child/adolescent/parent
Monitor growth	Adjustment to ICR and basal as diet liberalised	Sick day management
B Vits, Calcium	Dose for protein and fat	Time and expense
Fiber intake	Aware of euglycemic DKA	Quality of Life for whole family
Monitor lipids	Hypo frequency	Preschool and School management
Change in eating pattern as transition to adult lifestyle or with co-morbidity ie. Coeliac	Glucagon action	Exercise adjustments

Screenshot from Dr Smart ISPAD Presentation on low carbohydrate diets

Controversy - Hopes and Concerns for VLC diets in T1DM

Hopes	Concerns
Low glycemic variability	Chronic ketosis may increase DKA risk
→ Beneficial effects on cognition	Inadequacy meeting brain glucose demands
→ Lower hypoglycemia risk	Higher hypoglycemia risk due to inadequate carbohydrate intake and glycogen stores
Reduced insulin exposure increases insulin sensitivity and metabolic health (decreased anabolic drive on adipocytes)	Adequacy of nutrition?
→ lower triglycerides and higher HDL	Increased saturated fat intake may lead to elevated total and LDL cholesterol
Improved quality of life, reduced anxiety	Restrictive lifestyle impairs quality of life and promotes eating disorders
Improved growth and development in children due to better glycemic control	Adverse effects on growth and development in children due to nutritional deficiency

Boston Children's Hospital
Until every child is well

HARVARD MEDICAL SCHOOL
TEACHING HOSPITAL

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Research questions to answer

There are a few big questions that require answering with research.

- Is faltering growth an issue with adequate energy high protein VLCD that DO NOT aim for nutritional ketosis?

- Are there detrimental lipid profile changes, especially Apo-B (Schofiled, J.; Ho, J.; Soran, 2019), or is it beneficial?

- If the lipid profile is slightly deranged and/or height z-score SDS negatively impacted, is that off-set by keeping HbA1c below 6% (42mmol/mol) for a lifetime with diabetes?

- What is the social impact?
    - Does restricting food choices have a negative impact on social development?

    - Does having excellent control with less hypos and more predictability improve confidence in living with diabetes?

    - Is there an acceptable off for the above two and should it be individuals choice?

I make sure I keep an open mind. It is easy to project our fears, concerns and misconceptions of evidence about low carb diets. It is impossible to be certain that VLCD are the best or worst for people with type 1 diabetes, especially children.

A LCD or VLCD diet will very likely improve glucose control for the average person with type 1 diabetes. However, it is important to consider other lifestyle factors when choosing a nutritional strategy. Some likely situations this type of approach diet will not be optimal for:

- Anyone who plays a sport that requires fast bursts of energy, such as football, basketball, HITT training etc. Notice it says OPTIMAL. You can do these activities on a low carb diet, you just will not be as explosive, and therefore as good.

- Anyone who wants to compete at their best in endurance events such as half marathon, triathlon and cycling races. Again, these activities can be done on a low carbohydrate diet, there is no doubt. A low carbohydrate diet will certainly achieve better blood glucose control during the activity. However, without adequate muscle

glycogen stores, the muscles will not be able to create energy at a high enough rate to perform optimally.

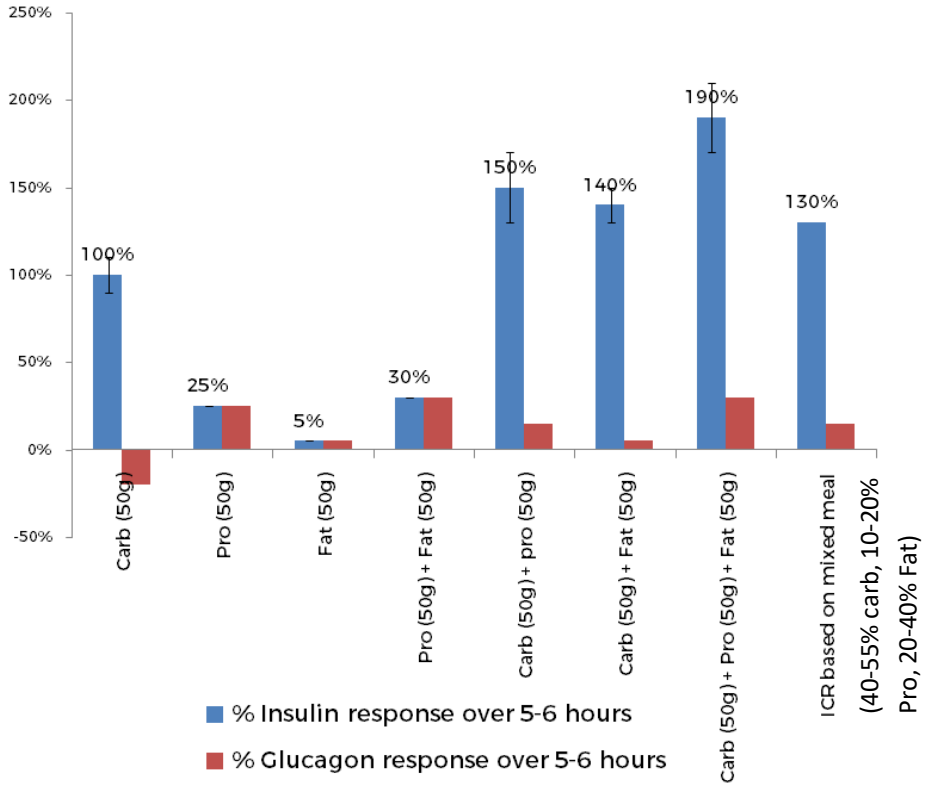
- Anyone wanting to gain significant amounts of muscle in a bulking phase. You need the insulin stimulus and glycogen stores for anabolism, and carbohydrate to fuel hard training, and support recovery (Riddell *et al.*, 2017).

- Anyone who likes to eat carbohydrate foods. They would find it very challenging in social situations. The low carb Dr Bernstein group call themselves GRIT for a reason, and that has to be understood and respected.

How to support a person choosing LCD or VLCD

If a person is going to follow a VLCD and you are supporting them you would want to ensure:

- How to insulin dose for the protein and fat content?



A formula that may be worth starting with is:

Insulin load = carbohydrate (g) + (protein (g) x 0.25)

You could then apply your ICR to get an insulin dose. The impact of fat is usually covered by a higher background insulin, although an older quick acting insulin like Actrapid may help.

What to monitor:

- Adequate total kcal intake for age and weight. They will not be eating 80% of the food choices normally available, this can make eating enough a challenge without good planning.

- Adequate protein intake for age and to prevent nutritional ketosis 1.5-2.0g/kg may be a place to start.

- Predominantly MUFA will help get some benefits of the Mediterranean diet.

- Adequate calcium intake by unsweetened nut milks and high fat yoghurts.

- Vitamin and mineral intake against reference nutrient intakes – An App called Cronometer is an effective way for self-monitoring. Watch out specifically for calcium, vitamin D, iron, magnesium and calcium

- Maximise the low carb greens such as spinach, broccoli, sprouts etc.. Supplement with fibre 5-10g per day. Keep an eye out for regular bowel movements

- Measure growth centiles very closely, especially height Z score SDS, but expect a 0.2 decrease from diagnosis from to 2.3years. Some initial weight loss is expected because as glycogen decreases so does water content. An initial drop of 1-4kg depending on the weight of the person is usual.

- Measure lipid profile (TC, LDL-C, HDL-C, Non-HDL-C., TG and especially Apo-B)

- Monitor emotional and social well-being. This approach takes serious GRIT by both parents and child. Equally they may be incredibly happy with not having to deal with constant fluctuating glucose levels. Be open minded!

- Adequate omega-3 (EPA/DHA) intake – choose oily fish or consider a supplement

Diabetes UK Position Statement

For the time being it is advisable to follow the precautionary principle sounded by the position statement from Diabetes UK (Diabetes UK, 2017):

- Low-carbohydrate diets can be safe and effective in the short term in managing weight, and improving glycaemic control and cardiovascular risk in people with Type 2 diabetes.

- People who chose to follow a low-carb diet should be supported to make changes to relevant diabetes medications and to monitor blood glucose to reduce the risk of hypoglycaemia.

- There is absence of strong evidence to recommend low-carb diets to people with Type 1 diabetes.

- There is evidence that low-carb diets can affect growth in children and should not be recommended.
- Whether people chose to follow a low-carb diet or not, they should be encouraged to include foods with good evidence to support health. This includes fruit and vegetables, wholegrains, dairy, seafood, pulses, and nuts

- People should be encouraged to reduce their intake of red meat and processed meat, sugar-sweetened foods, particularly sugar-sweetened drinks, and refined grains such as white bread.

It's a wrap (Watch me)

Here is what you should be taking into practice, as a minimum!

- Insulin is required to use nutrients from carbohydrate, protein and fat. Insulin allows glucose to be used and stored as energy, amino acids for growth and repair, and fatty acids to be stored in adipose tissue.
    - For people without diabetes insulin is delivered into the portal vein by the beta cells. This is driven by glucose, amino acids and fatty acids increasing the energy state (ATP:ADP) of the cell leading the membrane depolarization and insulin exocytosis. Also, all these nutrients increase GLP-1 output from the intestinal cells leading to direct stimulation of insulin release from the beta cells.
    - The job of the person with diabetes is to match what the beta cells would do with external insulin delivery from pump or injections.
- Glucagon is released in response to consumption of protein and fat. Glucagon initiates a metabolic cascade in the liver to release stored glucose into the blood stream.
    - For people without diabetes Glucagon is delivered into the portal vein by the alpha cells. This is driven by amino acids and fatty acids increasing the energy state (ATP:ADP) of the alpha cell leading the membrane depolarization and Glucagon exocytosis. Also, amino acids and fatty acids increase GIP output from the intestinal cells leading to direct stimulation of the alpha cells to release Glucagon. Insulin is released to act as a negative feedback loop if the glucose levels goes to high.
    - The job of the person with diabetes is to match what the beta cells would do with external insulin delivery from pump or injections to provide the negative feedback to the alpha cells.
- Most people with diabetes count carbohydrate and apply an insulin to carbohydrate ratio (ICR) to determine the dose. The mistake to is to believe the insulin determined this way is only covering the carbohydrate content. **The ICR is also covering the insulin requirement for fat and protein of their usual meals, based on the kcal from**

the meals keeping to 40-55% from carbohydrate, 10-20% from protein and 20-40% from fat.

- The carb counting and ICR method works well if the person is consistent in their usual carb, fat and protein intake from meal to meal. However, when they have high fat and protein meals, they will need more insulin spread out over a longer period. When they have meals with exceptionally low carb content, they may need to reduce their insulin dose.

- Achieving a HbA1c of <6.5% (<48mmol/mol) when consuming a diet that is 40-55% carbohydrate can be challenging. Glucose appearance in the blood from carbohydrate digestion is quicker than the onset of insulin action. This is made worse by the insulin being infused into the outer circulation and not the portal vein. The opportunity to dump most of the glucose into the liver is missed! This can be overcome by employing several strategies:

    - Low GI diet
    - Using 10 mins activity after eating
    - Giving insulin 20 minutes before eating
    - Administering meal-time insulin into abdomen or arm
    - Splitting large mealtime insulin doses
    - The Super bolus
    - Using exercise if did not bolus 20 minutes before meals
    - Consistent 3-4 meals per day with limited snacking
    - Staying closer to 40% than 55% of carbohydrate intake

- For high protein meals over 40g the insulin dose will need to be increased 20-25% and delivered by a normal bolus

- For high fat meals over 40g the insulin dose will need to be increased 20-40% split 50/50 over 100 minutes or split injection, one before the meal and the second 60 minutes after. But remember individual respond differently requiring from -17 to 108% extra insulin, so trial and error is needed.

- For high protein (>40g) and high fat meals (>40g) insulin dose will need to be increased 50% split 50/50 over 150 minutes or split injection, one before and one 75 minutes after. But remember individual respond differently requiring from 24% to 124% extra insulin, so trial and error is needed. Or you can use the simpler KISS method to start safe and build confidence.

- For protein only or protein and fat meals you could start by counting the protein grams of the meal, applying the ICR and then divide by 4 to get a starting dose.

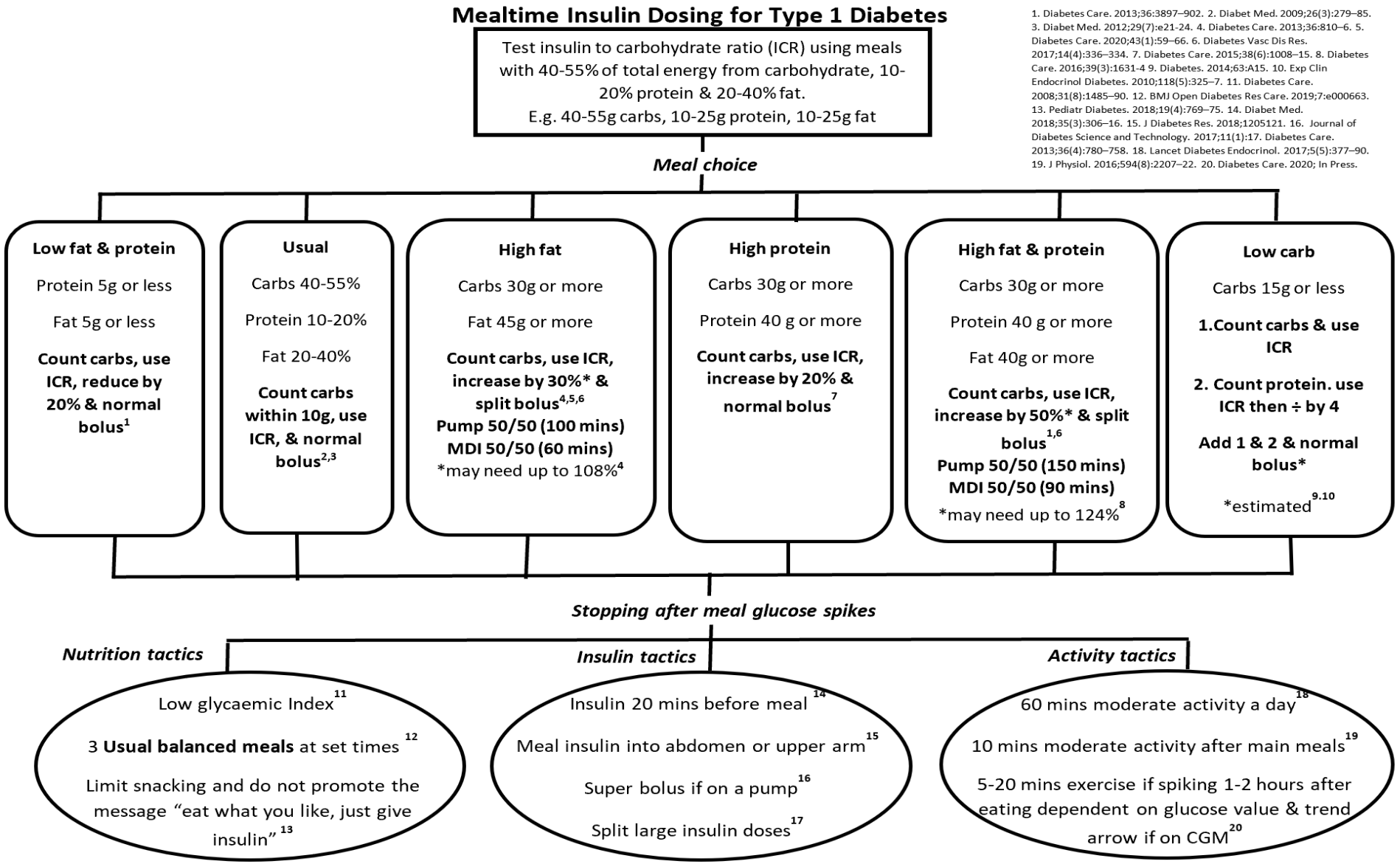
- VLCD and LCD have not been well studied. People following this approach will almost certainly improve glucose control but may carry unknown tail risks/benefits?

    - For children, a ketogenic (70-80% fat and <50g carbs) should be avoided at all costs due to the Epilepsy research showing obvious harm. For children following the Dr Bernstein method (Bernstein, 2011) there appears to be a clear glucose control improvement for those who can follow it. But there is mixed observation from case reports about growth, cardiovascular risk and social/emotional well-being. Until non-biased representative evidence is obtained one must apply the precautionary principle. If a young person is going to take this approach, close supervision and support should be provided.

    - For adults there is no growth and social/emotional concern and clinic audit data suggests those who can keep to <75g per day appear to benefit in diabetes control and possibly cardiovascular risk. Again, there is limited data and randomised control trial in the pipeline should answer some questions.

- This guide shows the level of trial and error tinkering a person with type 1 diabetes must do to mimic the pancreas. Knowledge provides opportunity but the rubber meets the road only by trying things out and learning from mistakes!

Infographic: Ultimate guide to mealtime insulin dosing for type 1 diabetes (Watch me)



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Mealtime Insulin Dosing for Type 1 Diabetes

NHS
Birmingham Women's and Children's
NHS Foundation Trust

Insulin to carbohydrate ratio (ICR)
covers the insulin requirement for balanced meals containing usual amounts carbohydrate, protein, and fat[1].

To get the right amount of insulin count carbohydrate within 10g accuracy and give a normal bolus 20 minutes before eating [2,3,14]

Balanced meals: 40-55% of total energy from carbohydrate, 10-20% from protein & 20-40% from fat. Examples:

Scrambled egg on toast: 20-30g carbs, 5-15g protein, 5-15g fat

Cheese sandwich & yoghurt: 40-55g carbs, 10-25g protein, 10-25g fat

Chicken, mash potatoes & veg: 60-75g carbs, 15-35g protein, 15-35g fat

Different meals

Low fat & protein meal

Protein 5g or less

Fat 5g or less

Count carbs, use ICR, reduce insulin by 20% & give a normal bolus 20 minutes before eating [3,14]

High fat meal

Carbs 30g or more

Fat 45g or more

Count carbs, use ICR, increase insulin by 30%* & use a split bolus[4,5,6]
Pump 50/50 (100 mins)
MDI 50/50 (60 mins)

*may need up to 108%[4]

High protein meal

Carbs 30g or more

Protein 40 g or more

Count carbs, use ICR, increase insulin by 20% & give a normal bolus 20 minutes before eating[7,14]

High fat & protein meal

Carbs 30g or more

Protein 40 g or more

Fat 40g or more

Count carbs, use ICR, increase insulin by 50%* & use a split bolus[1,6]
Pump 50/50 (150 mins)
MDI 50/50 (90 mins)

*may need up to 124%[8]

Low carb meal

Carbs 15g or less

1.Count carbs & use ICR

2. Count protein, ÷ by 4 & use ICR

Add 1 & 2 & give a normal bolus*

*estimated[9,10]

Stopping after meal glucose spikes

Nutrition tactics

Low glycaemic Index[11]

Three meals at set times [12]

Limit snacking and do not follow "eat what you like, just give insulin" [13]

Insulin tactics

20 mins[14] before or DynamicGM[20]

Meal insulin into abdomen or upper arm[15]

Super bolus if on a pump[16]

Split large insulin doses[17]

Activity tactics

60 mins moderate activity a day[18]

10 mins moderate activity after main meals[19]

DynamicGM short-burst of exercise if spiking 1-2 hours after eating [20]

1.Diabetes Care. 2013;36:3897–902 2. Diabet Med. 2009;26(3):279–85. 3. Diabet Med. 2012;29(7):e21-24. 4. Diabetes Care. 2013;36:810–6. 5. Diabetes Care. 2020;43(1):59–66. 6. Diabetes Vasc Dis Res. 2017;14(4):336–334. 7. Diabetes Care. 2015;38(6):1008–15. 8. Diabetes Care. 2016;39(3):1631-4 9. Diabetes. 2014;63:A15. 10. Exp Clin Endocrinol Diabetes. 2010;118(5):325–7. 11. Diabetes Care. 2008;31(8):1485–90. 12. BMJ Open Diabetes Res Care. 2019;7:e000663. 13. Pediatr Diabetes. 2018;19(4):769–75. 14. Diabet Med. 2018;35(3):306–16. 15. J Diabetes Res. 2018;1205121. 16. Journal of Diabetes Science and Technology. 2017;11(1):17. Diabetes Care. 2013;36(4):780–758. 18. Lancet Diabetes Endocrinol. 2017;5(5):377–90. 19. J Physiol. 2016;594(8):2207–22. 20. Diabetes Care. 2020; In Press.

Mealtime Insulin Dosing for Type 1 Diabetes

Birmingham Women's and Children's NHS Foundation Trust

ICR covers balanced meals NOT just carbs

Insulin to carbohydrate ratio (ICR) covers the insulin requirement for meals containing balanced amounts carbohydrate, protein, and fat[1].

1. **Count carbs (g) within 10g accuracy [2,3] & use ICR**
2. **Normal bolus 20 minutes before eating[14]**

What are balanced meals?

40-55% of total energy from carbohydrate, 20-40% from fat & 10-20% from protein[22,23].

Scrambled egg on toast: 20-30g carbs, 5-15g fat, 5-15g protein

Cheese sandwich & yogurt: 40-55g carbs, 10-25g fat, 10-25g protein

Chicken, mash potatoes & veg: 60-75g carbs, 15-35g fat, 15-35g protein

Different meals

High carb, low fat & protein

Carbs more than 55%, fat & protein less than 6g each[1]

Fruit, cereal, biscuits & bars, toast & jam, rice crackers

1. **Count carbs (g) & use ICR**
2. **Consider reducing insulin by 20%**
3. **Must be normal bolus 20 minutes before eating** [24]

High fat with at least 30g carbs

Fat more than 40g[4,5,6,7,8]

Pizza, takeaways, creamy curry, Sunday roast & pudding, English breakfast

1. **Count carbs (g) & use ICR**
2. **Increase insulin by 20-50%***
3. **Pump: 50% before, 50% over 120 mins[5], MDI: 50% before, 50% in 60 mins[6]**
4. **KISS method to adjust extra insulin & bolus split[21]**

*may need to increase by 17-124%[5,6,7,8]

Low carb

Carbs less then 15g

Meat & veg, eggs & mushrooms, cheese & salad

1. **Count carbs (g) & use ICR**
2. **Count protein (g) ÷ 4 & use ICR***
3. **Add calculated insulin from 1 & 2**
4. **Pump: Extended 1hr, MDI: Bolus after meal** estimated[9,10]

Stopping after meal glucose spikes

Nutrition tactics

Three balanced meals with minimal snacks[12]

Do not follow:
"Eat what you like, when you like, just give insulin" [13]

Low glycaemic Index carb choices[11]

Insulin tactics

20 mins[14] before meal or DynamicGM[20]

Meal insulin into abdomen or upper arm[15]

Super bolus if on a pump[16]

Split large bolus insulin doses[17]

Activity tactics

60 mins moderate activity a day[18]

10 mins moderate activity after main meals[19]

DynamicGM short-burst of exercise if spiking 1-2 hours after eating[20]

1.Diabetes Care. 2013;36:3897–902 2. Diabet Med. 2009;26(3):279–85. 3. Diabet Med. 2012;29(7):e21-24. 4. Diabetes Care. 2013;36:810–6. 5. Diabetes Care. 2020;43(1):59–66. 6. Diabetes Vasc Dis Res. 2017;14(4):336–334. 7. Diabetes Care. 2015;38(6):1008–15. 8. Diabetes Care. 2016;39(3):1631-4 9. Diabetes. 2014;63:A15. 10. Exp Clin Endocrinol Diabetes. 2010;118(5):325–7. 11. Diabetes Care. 2008;31(8):1485–90. 12. BMJ Open Diabetes Res Care. 2019;7:e000663. 13. Pediatr Diabetes. 2018;19(4):769–75. 14. Diabet Med. 2018;35(3):306–16. 15. J Diabetes Res. 2018;1205121. 16. Journal of Diabetes Science and Technology. 2017;11(1):17. Diabetes Care. 2013;36(4):780–758. 18. Lancet Diabetes Endocrinol. 2017;5(5):377–90. 19. J Physiol. 2016;594(8):2207–22. 20. Diabetes Care. 2020; In Press. 21. Endocrine Abstracts. 2018;58:P062. 22. Pediatric Diabetes. 2018;19(27):136-154. 23. Diabetes care. 2020;43(1):S163-182. 24. BMJ Open Diabetes Research andCare 2014;2:e000050

Mealtime Insulin for Type 1 Diabetes

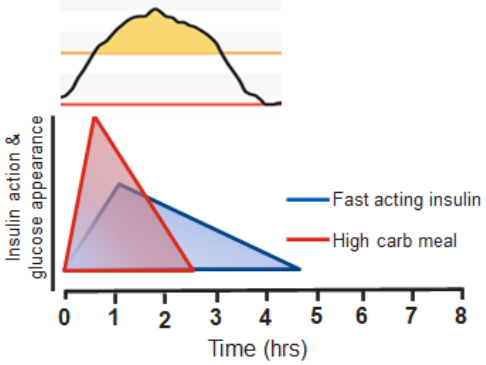
Birmingham Women's and Children's NHS Foundation Trust

What does the Insulin to Carb Ratio (ICR) actually cover?

Glucose from digested carbohydrate and the small amount of insulin required to use fat and protein effectively.

Fast acting mealtime insulin **peaks after 60-90 minutes and lasts 4-6 hours**

High carbohydrate meals



Glucose appearance peaks at 30-60 mins, lasts 3-4 hours

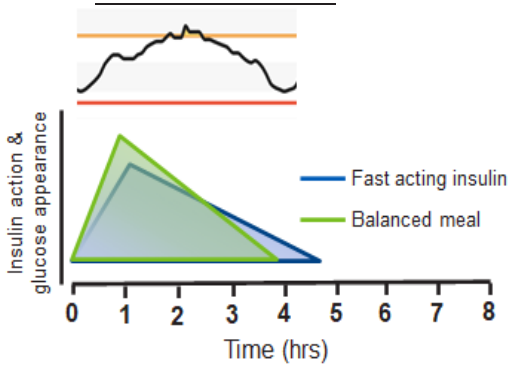
Carbs more than 55%

Breakfasts: Cereal with light milk, toast and jam, fruit bread
Meals: Jacket potato & beans, super noodles, waffles & hoops
Snacks: Cereal bars, biscuits, rice crackers, fat free yoghurt

How to better match insulin to a high carbohydrate meal?

1. Count carbs (g) within 10g accuracy & use ICR
2. Choose lower glycaemic index carb choices
3. Must be normal bolus 20 minutes before eating

Balanced meals



Glucose appearance peaks at 60-90 mins, lasts 4-5 hours

40-55% carbs, 20-40% fat & 10-20% protein

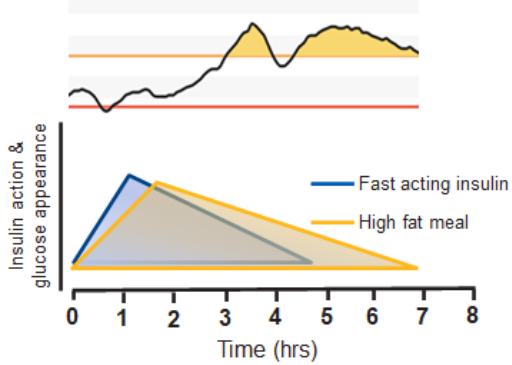
Breakfasts: Porridge with semi or full milk, egg on toast
Meals: Meat & potatoes & veg, jacket potato & cheese & salad
Snacks: Whole fruit with nuts, nut butter on toast, whole yoghurt

How to better match insulin to a balanced meal?

1. Count carbs (g) within 10g accuracy & use ICR
2. Normal bolus 20 minutes before eating

Want simple changes for balanced meals?

High fat meals



Glucose appearance peaks at 120-180 mins, lasts 6-9 hours

Fat more than 40g with at least 30g carbs

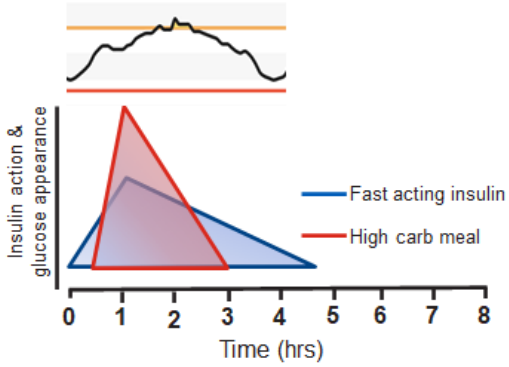
Pizza, takeaways, creamy curry, Sunday roast, English fry-up

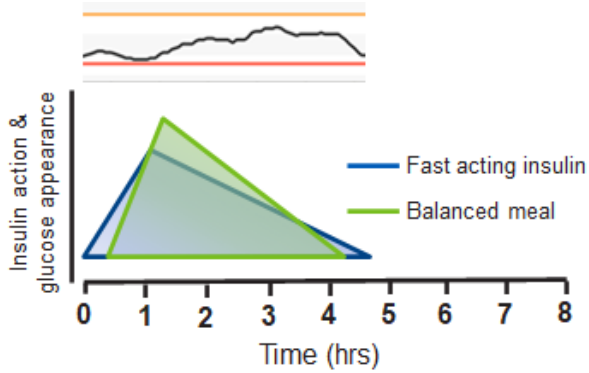
How to better match insulin to a high fat meal?

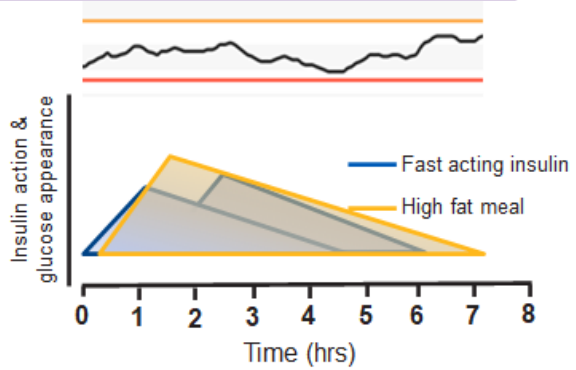
1. Count carbs (g) within 10g accuracy & use ICR
2. Increase insulin by 25% (may need 17-124%)
3. Pump: 50% 20 minutes before, 50% over 120 mins

MDI: 50% 20 minutes before, 50% in 60 mins

4. KISS method to adjust extra insulin and how to split







Stopping after meal glucose spikes

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Nutrition tactics

Three balanced whole food meals with minimal snacks

Do not follow:
"Eat what you like, when you like, just give insulin"

Low glycaemic index carb choices

Insulin tactics

Insulin 20 mins before meal

Meal insulin into abdomen or upper arm not leg or buttocks

Avoid lumpy injection sites and rotate injection/cannula sites

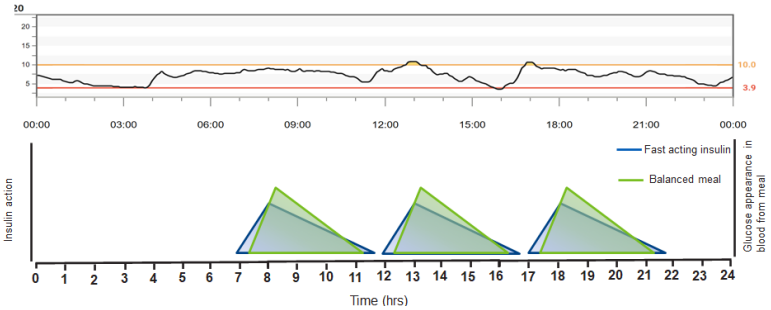
Activity tactics

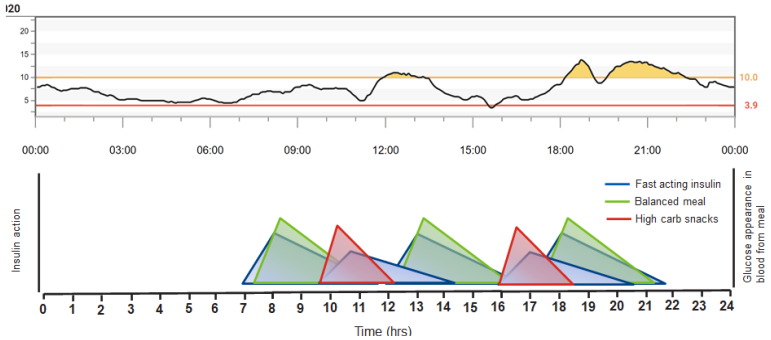
60 mins moderate activity a day, try three 20 minutes:

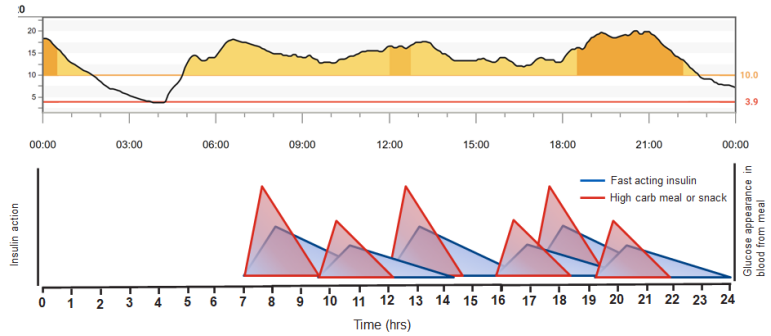
"Opens a side door to muscle cells to let more glucose in"

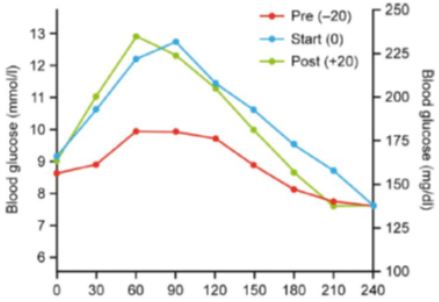
10 mins of moderate activity after meals:

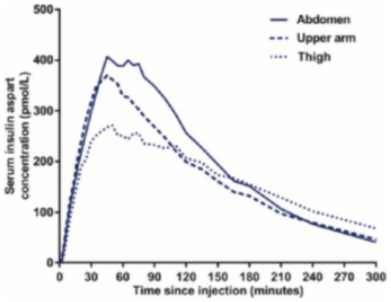
"Gets insulin to the muscles faster to speed up its action"

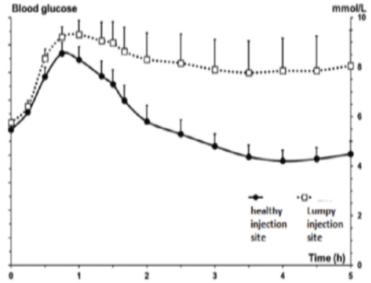


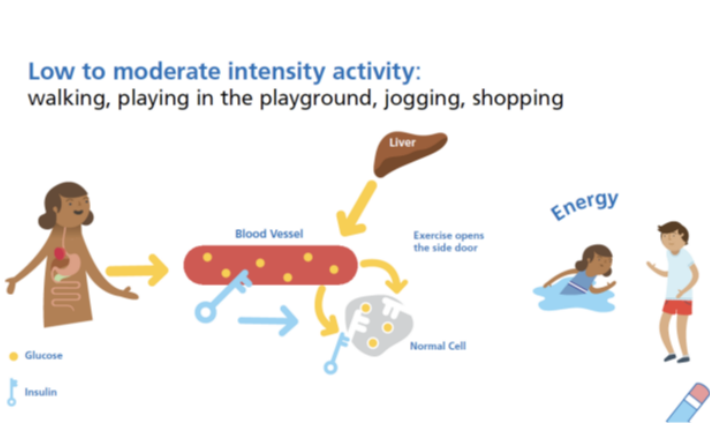


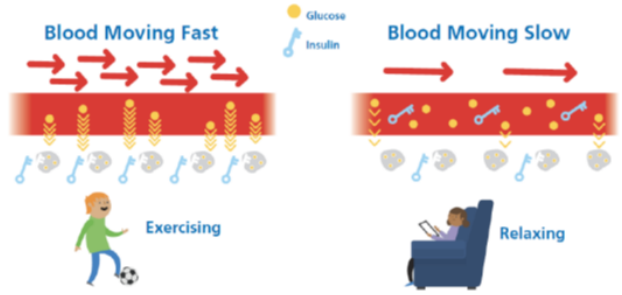












Keep it simple, do 10 minutes of moderate activity after each meal to stop glucose spikes!