HOW TO GET THE RIGHT MEAL TIME INSULIN DOSE WITH TYPE 1 DIABETES

Diabetic™

MUSCLE & FITNESS

PROTEIN ONLY

JOHN PEMBERTON | TYPE 1 DIABETES | REGISTERED DIETITIAN

WWW.DIABETICMUSCLEANDFITNESS.COM

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

WHAT DOES THE PANCREAS DO WHEN PROTEIN ONLY IS CONSUMED?

INSULIN

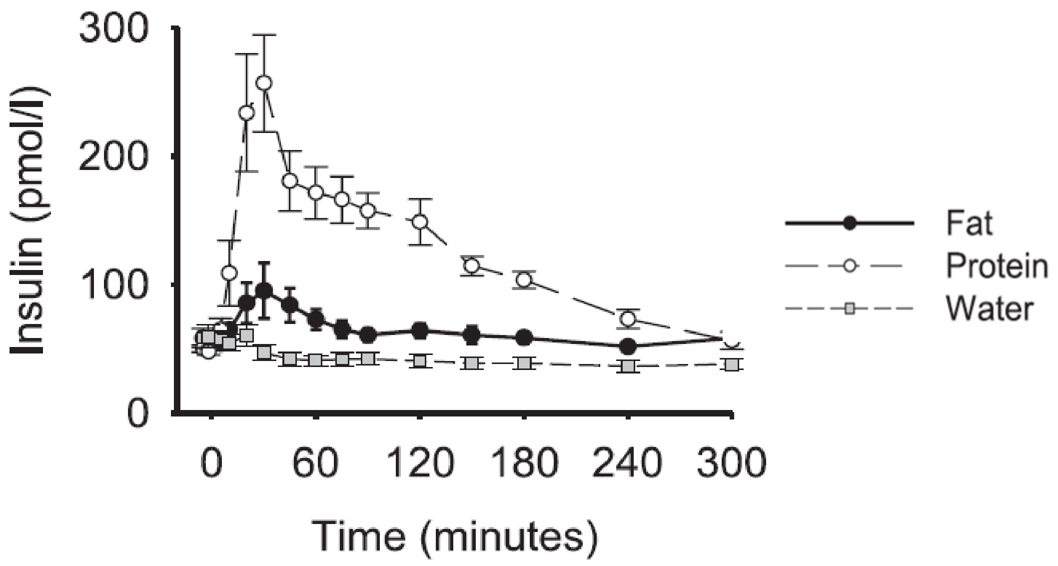
Put simply, the B-Cells secrete extra insulin into the blood to move the AA from digested protein from into the body's cells for anabolism. This has been proven by an increase in non-oxidative Leucine flux (7). The increase insulin also moves glucose from the blood into the cells for usage and storage as glycogen.

The main signals that control insulin secretion are:

A. Intestinal Y cells release GLP-1 which is a strong positive regulator of B-Cell insulin secretion (10). The level of GLP-1 response to AA is much lower than that exerted by glucose (65).

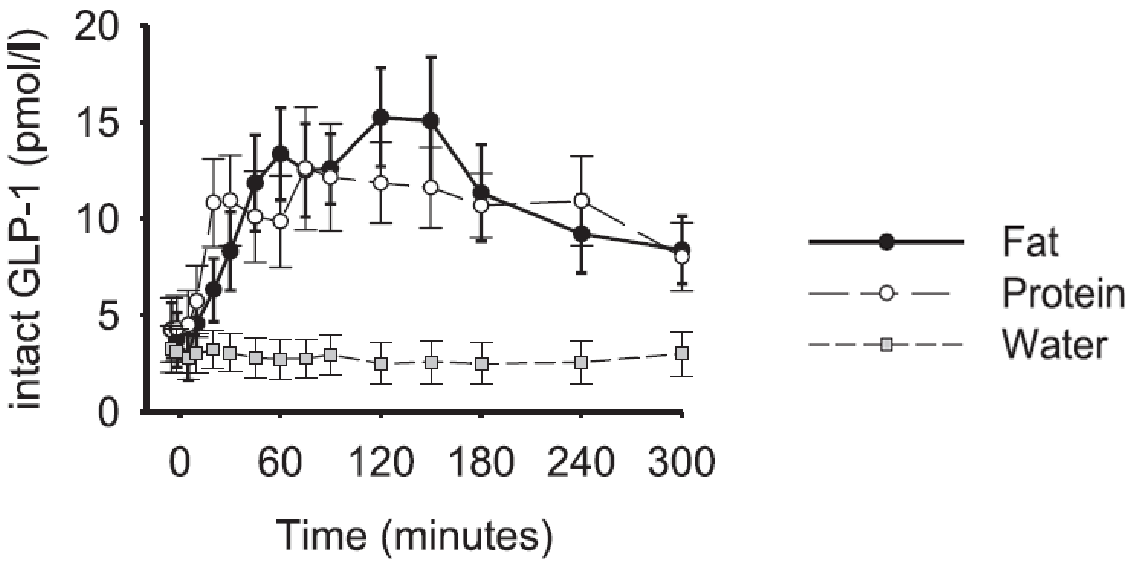
B. Increased AA uptake by the B-Cells increases the energy state leading to insulin secretion. The AA increase the energy state by providing substrates for glycolysis, but not direct fuel like when glucose is consumed. Therefore, the insulin response is much lower for AA compared to glucose.

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 (9). 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.



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. 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:

C. 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.

D. The drop in glucose level from the increase insulin secretion is detected in the hypothalamus. This stimulates adrenaline release that positively regulates Glucagon secretion (15).

E. 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 (7).

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.

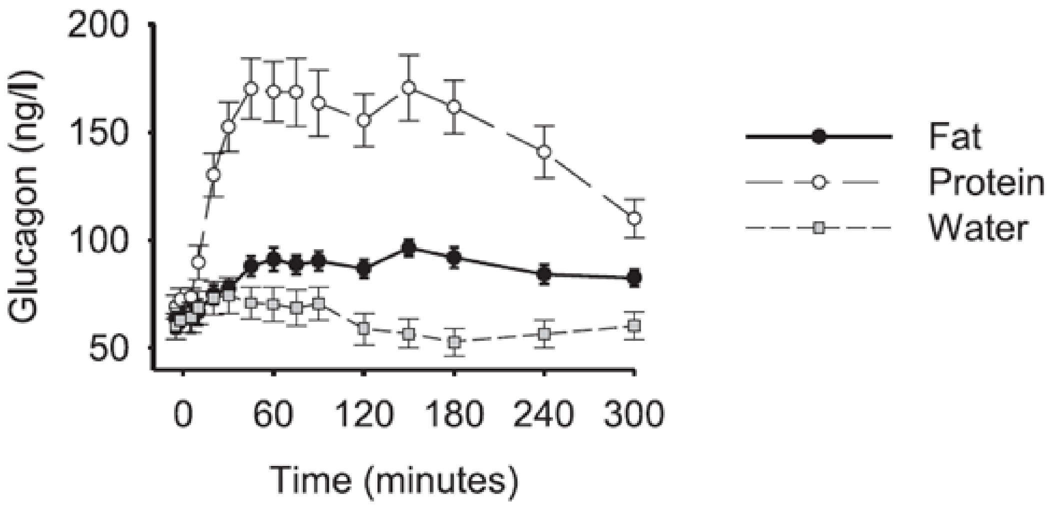
Consider this situation:

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

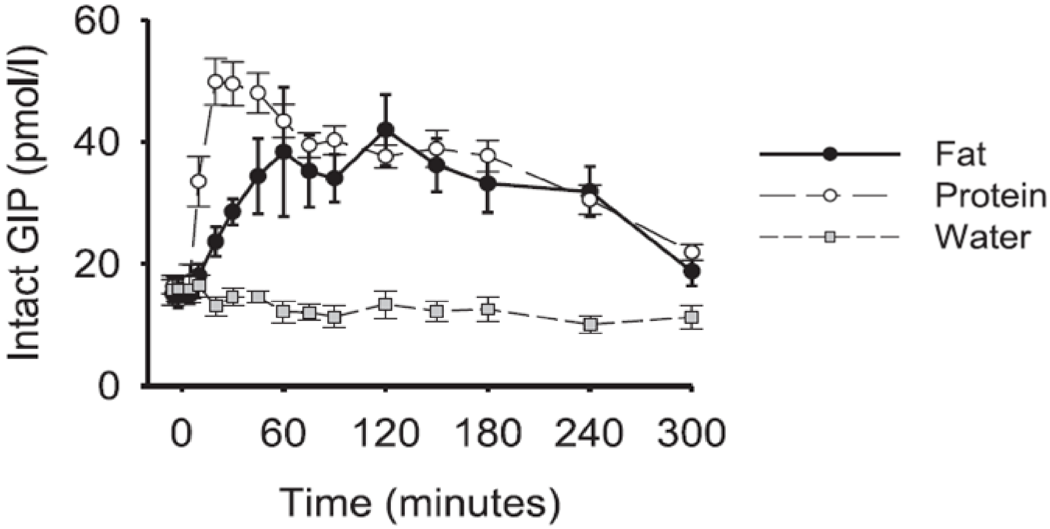
- Not enough insulin to move AA into the cells for anabolism. You miss out on growth and repair.

- 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 (9). 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 (9). 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.



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 (9).



A recent review paper has highlighted there are different forms of GIP. Some that stimulate insulin secretion and other forms that stimulate Glucagon secretion (15). 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 (1,13,15).

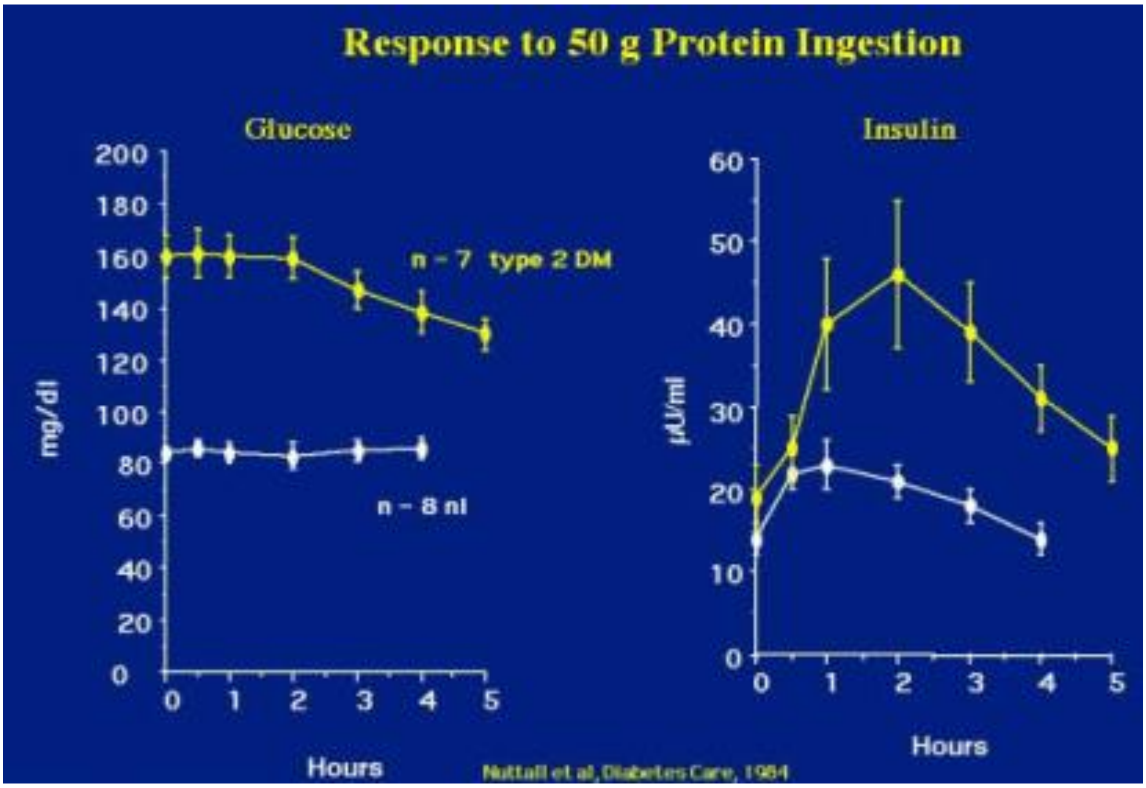
RESEARCH

In healthy subjects, ingestion of 50 g of protein as lean beef elicited a significant increase in insulin over four hours (55). The amount required was 28% of that required for 50g of pure glucose (55).Similarly Berger found that ingestion of 50-100g protein elicited 21% of the insulin response of 100g glucose (57). 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 (9).

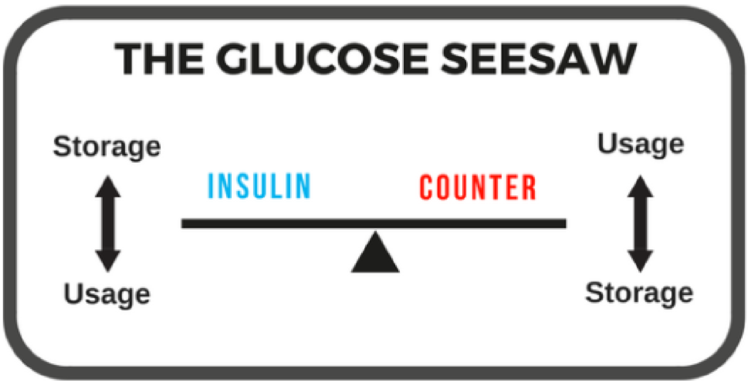
Interestingly Berger (57) investigated people with Type 2 Diabetes alongside the healthy cohort discussed above, and found a very different insulin responses. The insulin response for the people with Type 2 Diabetes to 50g protein was 80% of that of 50g pure glucose, a four-fold increase compared to healthy volunteers.

Gannon and Nutall (11) in the below graph reported similar studies comparing the insulin response to 50g pure protein in healthy men (white line) to those with type 2 Diabetes (yellow line). 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 (71). Cortisol is another counter-regulatory hormone that increases liver Glycogenolysis early after eating, and gluconeogenisis later after eating (71). Thinking back to our Seesaw you can see the increase in Cortisol will push the body into energy usage mode.

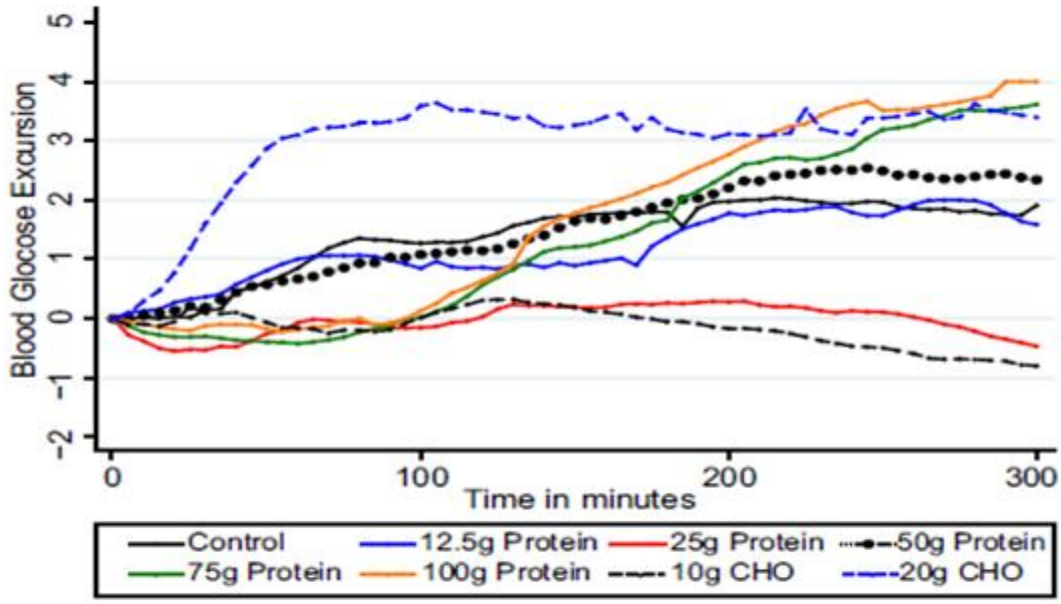


What about high protein meal research for people with Type 1 Diabetes?

Patterson (30) 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. 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.



Copied from Patterson (30)

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. 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).

- If insulin is delivered in small but adequate quantities to transport the AA for growth and repair, 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 (1,13,15). Therefore hypoglycaemia will be prevented, but only if the insulin delivered is not too much!

- Critique of this Patterson's Whey protein study (30) suggests the studies 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.

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.

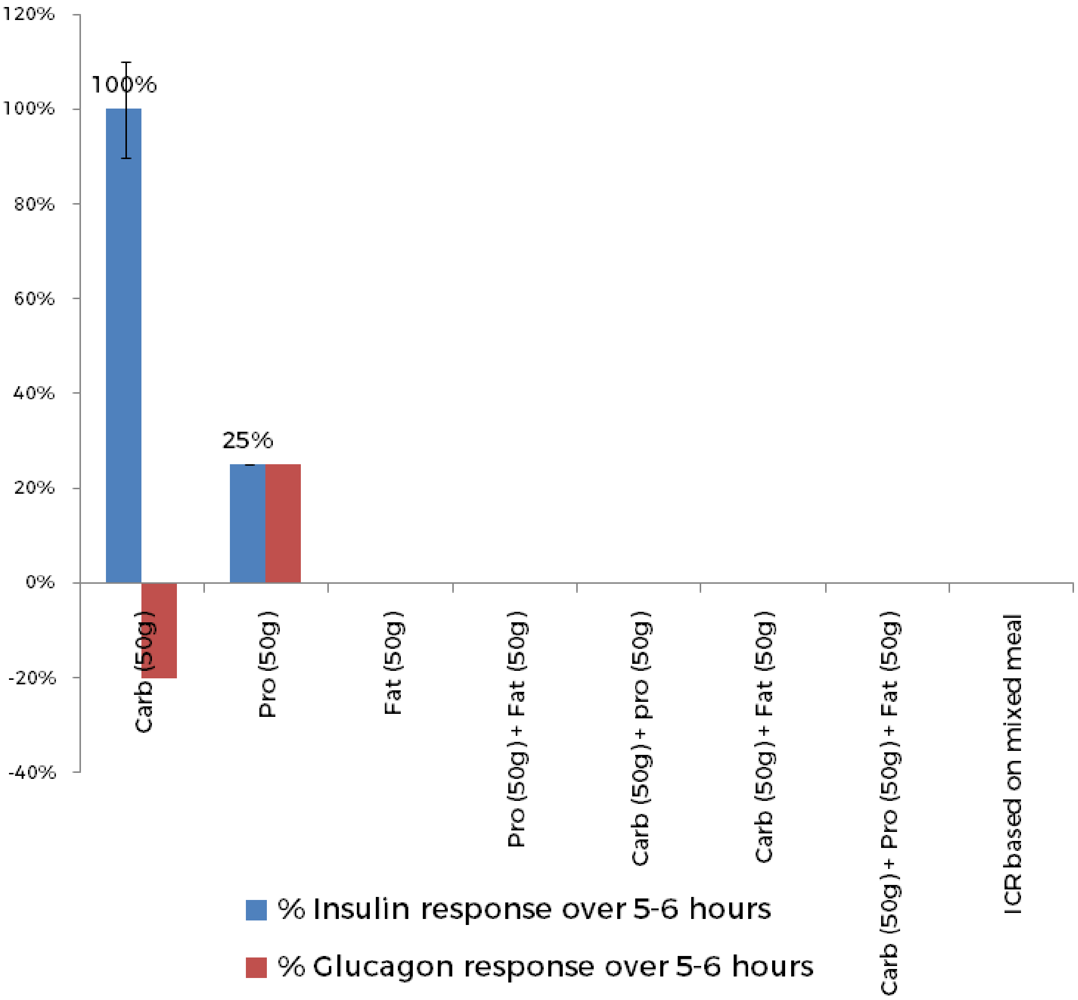
SUMMARY

Very simply, 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 stimulated 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, 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.

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 (26) 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.

AMINO ACID INGESTION AND GLUCOSE METABOLISM 663

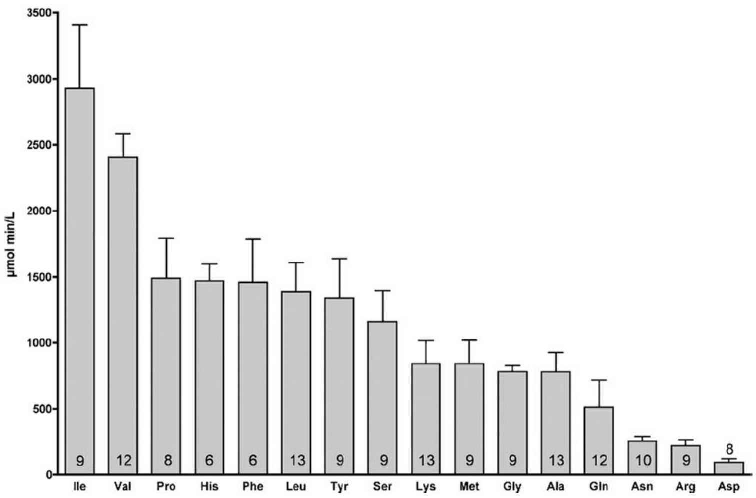


Figure 1. Amino acid area response following ingestion of individual amino acids. Bars indicate mean + SEM. Numbers within the bars indicate the number of subjects studied.

Copied from Nutall& Gannon (26)

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 of Floyd et al (58), showing , Glycine and phenylalanine are the most potent insulin secretagogues when had in the absence of carbohydrate. The practical significance

of the difference elicited by AA on their own is very little, because they are rarely consumed singularly in the diet. The main point is that AA show a robust and repeatable insulin response.

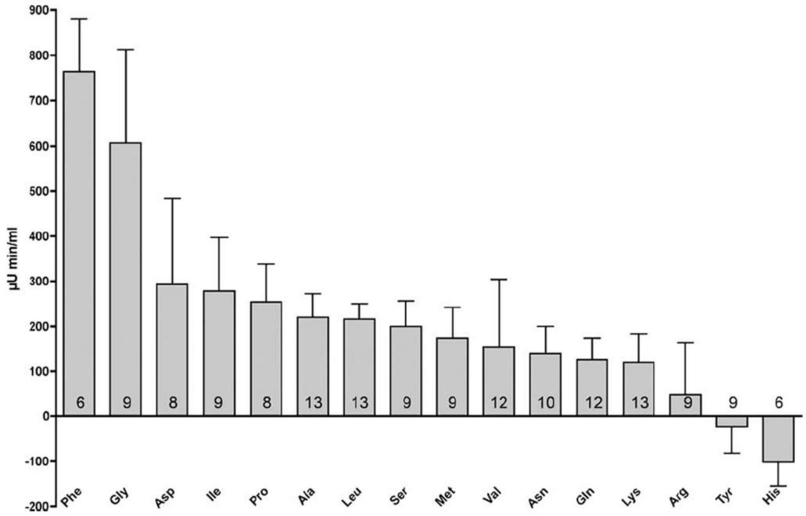


Figure 2. Insulin area response following ingestion of individual amino acids. The insulin area response to water only (control) was subtracted from the area response to the amino acid to give a net area. Bars indicate mean + SEM. Numbers indicate the number of subjects studied.

Copied from Nutall& Gannon (26)

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 very little, the main point is that AA show a robust and repeatable Glucagon response.

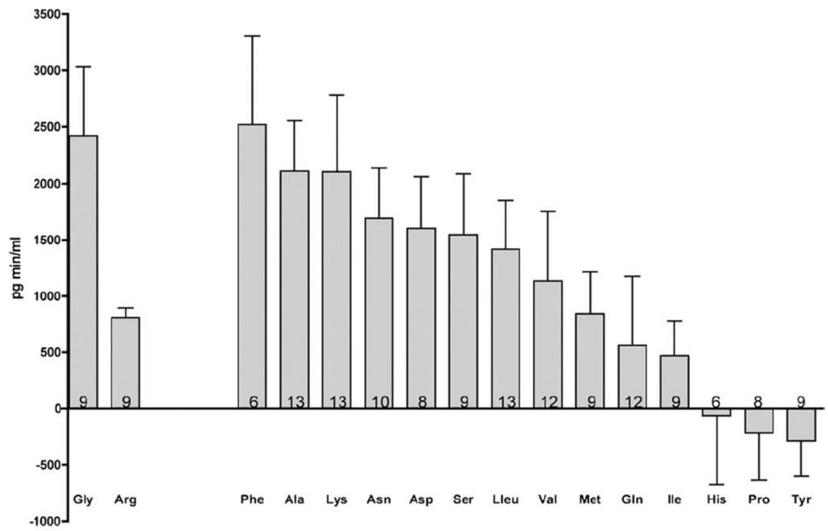


Figure 3. Glucagon area response following ingestion of individual amino acids. The data for glycine and arginine were obtained using a different assay, so the data are not directly comparable. The numbers on this graph for Gly and Arg should be multiplied by 10 to obtain the correct area response obtained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

Copied from Nutall& Gannon (26)

Diabetic™

MUSCLE & FITNESS