

Study protocol

**Hypoglycemia requiring emergency services
intervention: patient characteristics,
outcome and cardiovascular risk profile**

PI: R Ajjan

Co-Investigators: S Heller, L Clapham

Statistical analysis: P Baxter

Background

Hypoglycemia is a common complication of diabetes treatment, particularly when glucose control is intensified (1-3). Until recently, hypoglycemia was regarded as an acceptable “side effect” of glucose lowering therapy, given the benefits of tight glycemic control at reducing microvascular, and to some extent macrovascular, complications of diabetes (2-7). However, studies in the past few years have demonstrated that hypoglycemia is probably a more serious side effect than initially thought (8-11). A major warning as to the potential dangers of hypoglycemia was delivered in the ACCORD study (12), when excess mortality was demonstrated in the intensive glucose arm of the trial, necessitating study termination and fuelling speculation about the role of intensive glucose control in the management of diabetes. The fear of hypoglycemia-induced death in diabetes is not unfounded as there are clear mechanistic pathways to explain this link. Hypoglycemia is associated with repolarisation abnormalities in the heart and increased thrombosis potential as we and others have shown (13-15). Indeed, large scale studies and anecdotal reports have shown associations between acute cardiac events/mortality and hypoglycemic events (11,16-18). Moreover, our preliminary data in Leeds have revealed that severe hypoglycemia, requiring emergency services intervention in 856 patients, is associated with 17.1% mortality within 12 months of the event (unpublished data). This death rate is comparable to diabetes patients sustaining acute cardiac ischemic event in Leeds, which currently stands at 15.8% (19). Also, the mean age of the diabetes cohort was only 61 years, and therefore the high death rate following hypoglycemia is certainly a major cause for concern (for gender and diabetes type distribution, see Figure 1). Moreover, our data showed that in excess of 200 individuals had recurrent severe hypoglycemic events, despite local pathways designed to ensure higher levels of clinical support. Interestingly, of the type 2 diabetes subjects, 28% were not on insulin, being managed with oral hypoglycemic agents (95% treated with sulphonylureas). The degree of documented hypoglycemia in this group was comparable to individuals on insulin therapy with glucose levels at the arrival of ambulance crew of 1.8 ± 1.1 and 1.9 ± 0.7 mmol/l, respectively ($p > 0.1$, unpublished data).

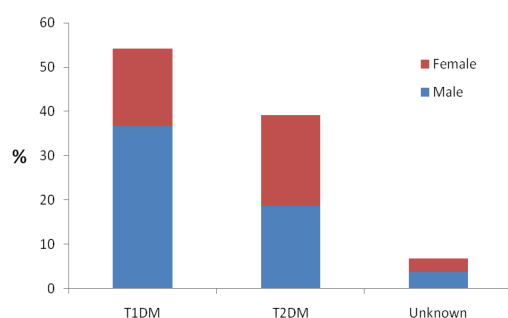


Figure 1. Type of diabetes and gender distribution of individuals with severe hypoglycemia requiring emergency services intervention in Leeds (1307 events).

It is unclear at this stage whether the observed increased mortality following severe hypoglycemia is directly related to low plasma glucose or whether severe hypoglycemia is more likely to occur in individuals with terminal clinical conditions (20), which may be due, for example, to weight loss and/or decreased appetite. Naturally, this needs to be clarified as it has important clinical implications for the treatment of these individuals.

Studies on the occurrence of severe hypoglycaemia in the community have been both limited and incomplete. In particular, the predictors of severe hypoglycemia

in the community have not been fully evaluated, which is partly due to the inadequate methodologies used or the inappropriate statistical methods employed (21-23). A recent retrospective observational study, conducted in Australia, has shown that duration of insulin treatment, renal factors and diabetic neuropathy are some of the predictors of severe hypoglycemia (24). Furthermore, this study has demonstrated that high HbA1c levels are not necessarily associated with lower risk of severe hypoglycaemia. It remains unclear, however, whether infrequent blood glucose testing and inadequate clinical support has a role in increasing the risk of severe hypoglycemia, whereas the effect of co-morbidities requires further clarification. For example, any clinical condition that is associated with weight loss or reduced appetite may be contributing to hypoglycemia. Another example is excess alcohol intake, which may also result in frequent and severe hypoglycemia (more details are provided below).

Hypothesis

Inadequate education, infrequent glucose testing and clinical co-morbidities in subjects with diabetes are associated with severe hypoglycemic episodes. Therefore, structured diabetes specialist input with regular glucose testing is important to reduce the risk of severe hypoglycemia.

Aims

The proposed work is divided into two parts through an observational and an interventional study.

1. Observational study: characterise individuals with severe hypoglycemia.
2. Interventional preliminary study: investigate the effect of regular glucose monitoring and specialist nurse input into a) future hypoglycemic events, b) confidence with diabetes management/quality of life and c) clinical outcome.

Plan of investigation

We have already developed a pathway for ambulance services to report cases of severe hypoglycemia in Leeds requiring their intervention (Figure 2).

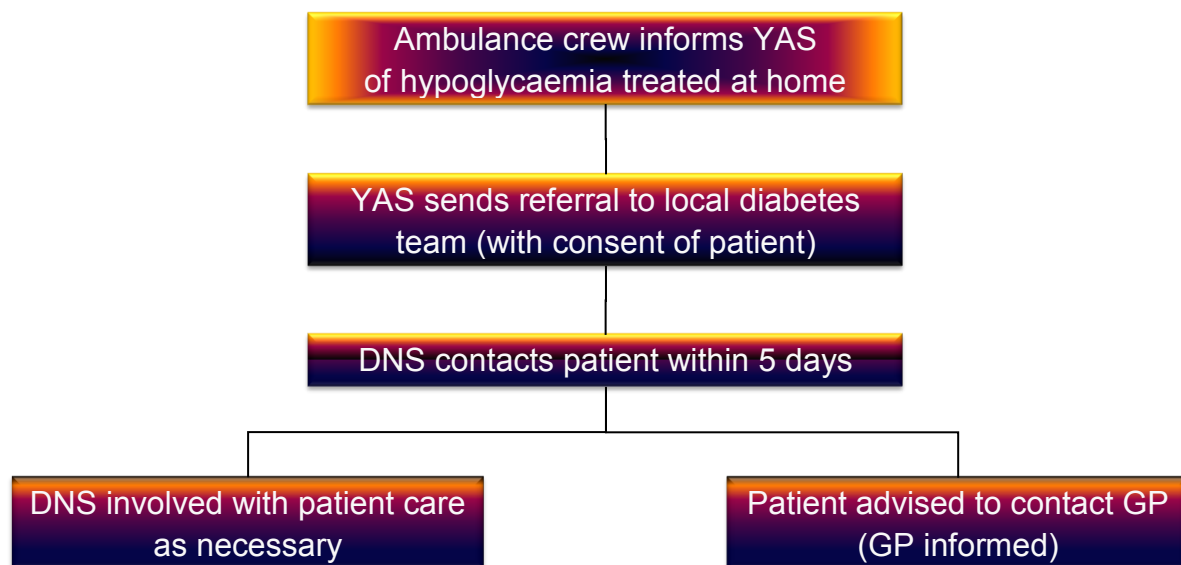


Figure 2. A summary of the current severe hypoglycemia pathway in Leeds. YAS: Yorkshire Ambulance Services, DNS: Diabetes Nurse Specialist, GP: General Practitioner.

We will continue to follow this pathway but will have a dedicated nurse to deal with the patients and will extend the study to include Sheffield. Inclusion of Sheffield will help to boost the number of patients enrolled and will clarify any potential regional variability. The research nurse will be experienced in managing individuals with diabetes and will be conducting both parts of the study, under the supervision of the principal investigator. The proposed study is summarised in Figure 3 and further detailed below.

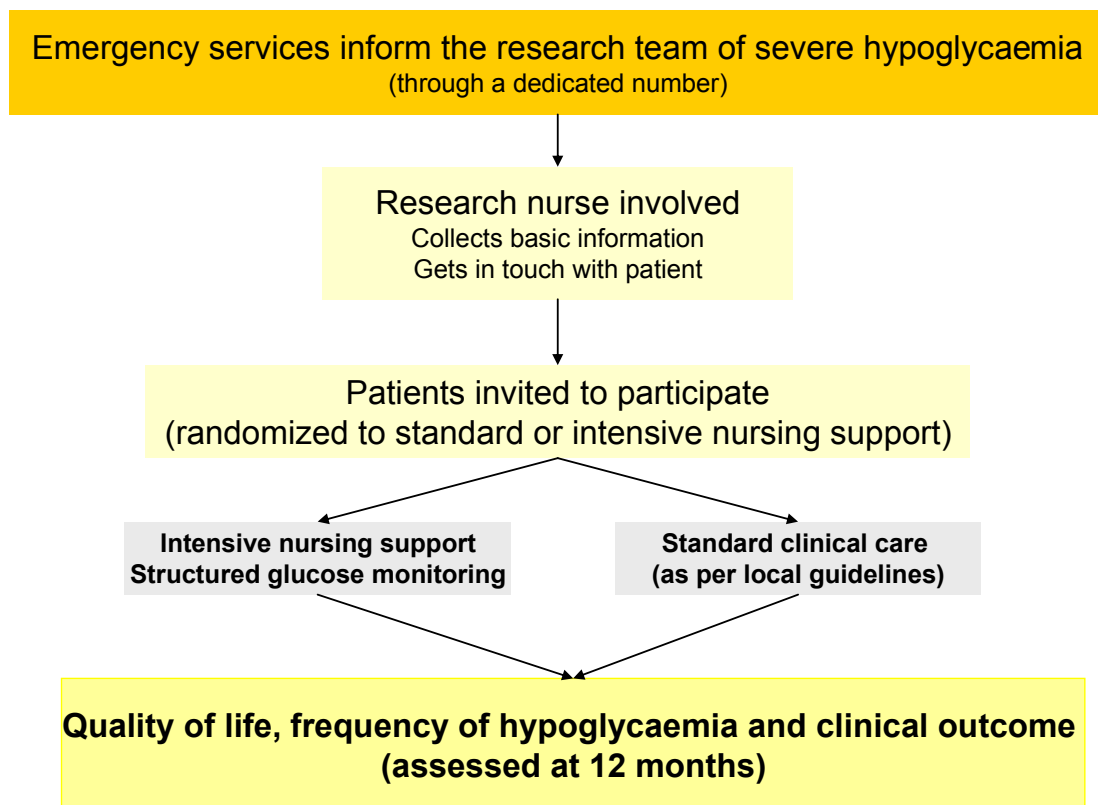


Figure 3. Summary of study design, including both observational and interventional parts. Intensive nursing support and standard clinical care are explained in more detail below.

Observational study

Various details will be collected to elucidate the characteristics of patients undergoing severe hypoglycemia requiring emergency services intervention.

Demographic and general data. Address, age, sex, type of diabetes and duration, weight, body mass index, blood pressure, presence of macrovascular and microvascular complications, current treatment, status at home (living alone), driving status, alcohol consumption, smoking history, mobility, non-diabetes related co-morbidities. We will also clarify who made the ambulance call (patient/carer/other).

Patient questionnaire (see appendix 1). This will address whether a patient feels confident regarding managing his/her diabetes, how often glucose is monitored, can the patient adjust insulin, does the patient understand the dangers of hypoglycemia, presence of hypoglycemia awareness, frequency of low glucose levels, treatment options of hypoglycemia.

Examination. Check injection sites for lipoatrophy or lipohypertrophy and examine for signs of peripheral neuropathy (monofilament test).

Blood and urine tests. These will be arranged as part of routine clinical care in both groups, unless recent blood tests have been done. The following tests will be included: HbA1c, urea and electrolytes, liver function tests, full lipid profile, thyroid function tests (where appropriate), urinary albumin/creatinine ratio (ACR). HbA1c will be measured every 3 months, U&Es, LFTS and lipid profile 6 monthly. ACR will be checked at enrolment and at 12 months. All above tests will be requested more frequently if clinically indicated.

Interventional study

We will conduct a preliminary interventional study, where patients will be randomised to either intensive monitoring/treatment modification, where patients are closely followed up by the research nurse, or conventional therapy following local protocols. Individuals in the interventional part of the study will be:

- i) Regularly contacted by the research nurse as detailed below.
- ii) Encouraged to check their glucose levels as appropriate, at least twice a day or more frequently as necessary.
- iii) Special leaflets regarding different aspects of diabetes will be given to patients and will be discussed. These will include leaflets for alcohol, exercise, Carbohydrate counting and awareness as appropriate (please see below).
- iv) Patients will have a dedicated phone number that they can ring for urgent advice.
- v) There will be a dedicated email line set up to answer less urgent queries and help with patient support. An email system is already set up in Leeds by the PI, and patients using this service experienced significant improvement in diabetes control (data not shown).

The research nurse will make every attempt to establish the cause of severe hypoglycemia by taking a detailed medical history in order to clarify clinical co-morbidities and assess social circumstances including alcohol intake, patient independence and help provided by carers. The nurse will also document current medications with special attention to dose and frequency of hypoglycemic agents, including insulin. Routine blood tests to assess overall glycemic control, renal and liver function will be performed, which may further help to shed light on the cause of low blood glucose. Hypoglycemic treatment may be changed in cases of concern but only after review by the PI, and the medical team in charge of the patient will be informed. For example, a sulphonylurea may be stopped or replaced if deemed inappropriate for the patient and insulin regimens/doses may also be altered. Follow up of patients after changes to medical therapy are detailed below but some may have more frequent contact with the nurse as per clinical need. The nurse employed will have extensive experience in the management of diabetes and will have the necessary knowledge to adjust doses/mixtures/intervals of insulin as appropriate, with adequate support provided by the PI in difficult clinical scenarios. Other diabetes disciplines, such

as dietician support may be sought if the research nurse and/or PI find this to be necessary. In cases of newly diagnosed (or suspected) clinical conditions, referrals to an appropriate specialty will be made after review by the PI. If social circumstances are found to be inappropriate, for example in the case of older individuals not managing on their own, the physician in charge of the patient will be informed and steps will be taken to provide support according the need of each individual.

In summary, the research nurse will concentrate on establishing the cause of the severe hypoglycemic episode and together with the PI will alter treatment, involve other diabetes/non-diabetes disciplines as appropriate and introduce changes to social support as required.

The research nurse will contact the patient weekly for the first month, every two weeks for the following month followed by contact at months 3, 6 and 12. Face to face contact with the patient will be arranged at enrolment, 1, 3 and 12 months. Patient will be asked to fill in the questionnaire at enrolment and end of 3rd month, with selected patients asked to complete the form again at 12 months (explained in Figure 4). Blood tests will be arranged as detailed above. In the standard arm, patient will be contacted only once as per current arrangement and subsequent treatment left to the discretion of the attending physician (summarised in Figure 4).

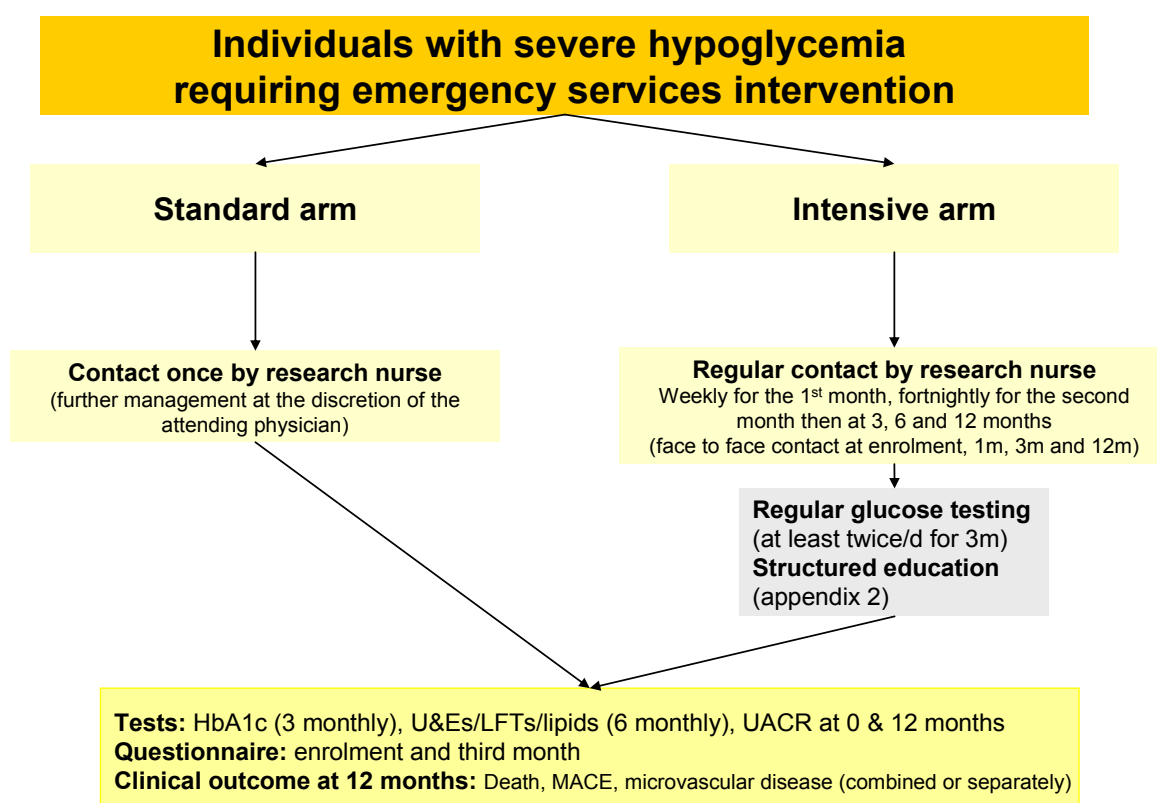


Figure 4. Summary of the preliminary interventional part of the study. U&Es: urea and electrolytes, LFTs: liver function tests, UACR: urinary albumin/creatinine ratio, MACE: major adverse cardiovascular events, m:

month, d: day. Questionnaire will be done at enrolment and 3 months in both groups. If a significant difference exists between the two time points in the same patient, the questionnaire will be repeated at 12 months. Clinical outcome at 12 months will also include frequency of hypoglycemia, analysed separately.

Pilot study to investigate hypoglycemia-induced thrombotic potential

Funding for this part is not sought and therefore no details are given (can be provided if requested).

Statistical analysis

The observational part of the study will collect various data and will be the basis for future studies. Power calculations were based on the interventional study. Given our current data showing a death rate in excess of 17% within one year of hypoglycemia, we calculated that 200 individuals are needed in each of the study arms to detect a drop in mortality to 10% in intensively monitored patients (at $p=0.05$). Between group analysis will be done using unpaired *t*-test for normally distributed data and the non-parametric Mann-Whitney test will be used for data that are not normally distributed. For categorical data, 2X2 contingency tables will be used and multiple regression analysis will be performed to determine potential causes of hypoglycemia.

Appendix 1 (patient questionnaire-will not be seen by the research nurse)

How much do you feel you understand about diabetes?

1. More than enough
2. Just enough
3. Could do with more knowledge
4. I know very little
5. I do not understand diabetes at all

Do you think diabetes education in your area is adequate at present?

1. Perfect
2. Acceptable
3. Could be better
4. Poor
5. Non-existent

How often do you test your blood glucose (sugar) levels?

1. At least twice a day with additional testing as needed.
2. At least once a day.
3. Less than once a day but at least twice a week.
4. Less than once a week.
5. Never.

Do you get concerned about testing your blood glucose and what it may show?

1. Never as I know what to do.
2. I do get concerned sometimes but this is rare.
3. I often get concerned.
4. I am always concerned.
5. I am terrified of checking my glucose levels as I have no idea how to manage the various numbers.

Do you check your blood glucose when you feel hypoglycemic?

1. Always.
2. Almost always.
3. Sometimes
4. Rarely.
5. Never.

How often do you get hypoglycemic attacks (blood glucose less than 3.6 mmol/l)?

1. Less than once every 3 months.
2. Monthly.
3. Weekly
4. Twice to 3 times per week.
5. Daily.

In the past 12 months, how many times have you had hypoglycemic attacks requiring the assistance of another person?

1. None.
2. Once.
3. On 2-3 occasions.
4. On 4-5 occasions

5. More than 5 times.

Do you get hypoglycemic warning with low glucose levels?

1. Always.
2. Yes but they are getting less prominent.
3. Sometimes I do not.
4. Rarely and very little.
5. Not at all.

Do you know why diabetes control is important?

1. Yes, I fully understand.
2. I think I know.
3. I have a rough idea.
4. I may but not that sure.
5. I have no idea.

Do your hypoglycemic episodes have a major impact on your quality of life?

1. Never.
2. Rarely.
3. Sometimes.
4. They have a major impact on quality of life.
5. Hypoglycemia is making me miserable.

Is close support from a diabetes nurse helpful to control your blood glucose?

1. Definitely, no question about it.
2. Yes, but it depends on the person.
3. To some extent.
4. Only marginal benefit.
5. Useless.

For insulin users: Do you know how to adjust/modify your insulin doses according to your glucose readings?

1. I am in full control.
2. Yes, but I may need occasional advice.
3. Yes, but prefer to have advice for reassurance.
4. I have little knowledge.
5. I have no idea.

Do you know what to do when you get severe hypoglycemia?

1. Yes.
2. I have a good idea.
3. I know some but not all aspects.
4. My knowledge is weak.
5. I have no idea.

Does close diabetes nurse support make you more confident at managing your diabetes?

1. Definitely.
2. Certainly has an effect to some extent.
3. Has a marginal effect.
4. Very little effect.

5. No effect at all.

Are you aware of the guidance regarding hypoglycemia and driving?

1. Yes, I am fully aware of the guidelines.
2. I probably know all the details
3. I know some of the details but not all
4. I know very little.
5. I have no idea.

Appendix 2. Structured education (intensive arm of the study)

In all patients, diabetes and complications will be discussed with special emphasis on hypoglycemia. Attention will also be given to hypoglycemia and driving and appropriate leaflets will be distributed (please see below).

1. Insulin users

In all insulin users, hypoglycemia with insulin use will be discussed together with the effects of exercise and alcohol on blood glucose (see appendix 3a). Also, hypoglycaemia unawareness will be discussed in detail. More specific education will be given according to type of insulin regime

- a. Basal bolus and complex insulin regimes

Teach CHO counting (structured education with dietitian already in place)

- b. BD or od insulin

Discuss CHO awareness (see appendix 3a)

2. Non-insulin users

- a. Discuss various hypoglycaemic agents and explain dangers of hypoglycaemia with each (see appendix 3c)
- b. Discuss carbohydrate awareness (see appendix 3b)
- c. Effects of exercise and alcohol on blood glucose

Appendix 3. Educational leaflets

The following leaflets will be distributed and discussed (as appropriate):

- Alcohol and hypoglycemia
- Exercise and hypoglycemia
- Carbohydrate counting
- Carbohydrate awareness
- Oral diabetes tablets and the risk of hypoglycemia

Examples are given in appendix 3a, 3b and 3c

Appendix 3a

ALCOHOL and DIABETES

Try to keep to the safe limits

- Women: less than 2 units/day (max 14u / week)
- Men: less than 3 units/day (max 21u/week)
- 1 Unit= $\frac{1}{2}$ pint ordinary strength beer, lager or cider
1 small glass wine or sherry
1 pub single spirits



REMEMBER

not to drink on an empty stomach
not to drink and drive
alcohol is high in calories
carbohydrate (CHO) in alcohol is not counted!

EXERCISE and DIABETES

If you are exercising you may need to:

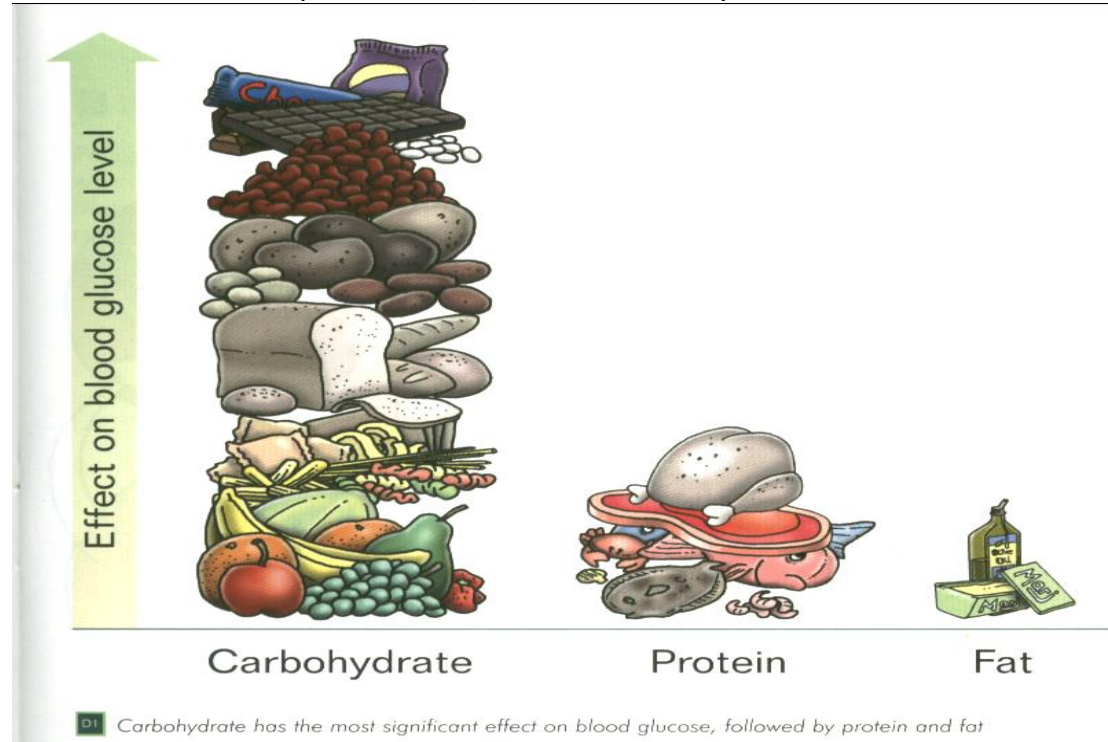
- Reduce your insulin dose pre exercise by up to 25%
- Reduce your insulin dose post exercise by up to 25%
- If it is high intensity then you will need to take extra CHO before or during and after exercise
- Check blood glucose levels regularly
- www.runsweet.com



Appendix 3B

Carbohydrate awareness

Your diet is made up of Protein, Fat and Carbohydrate



What are carbohydrate foods?

STARCHY FOODS

Bread
Potato
Rice
Pasta
Breakfast cereals
Biscuits and other
flour products

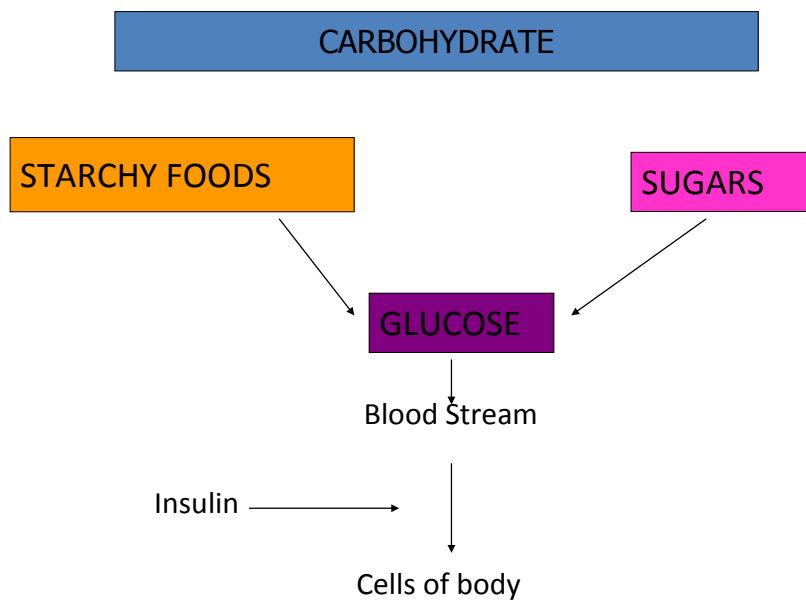
SUGARS

sugar
glucose
sweetened drinks
sweets, chocolate
sweet puddings
fruit
milk
yoghurt

How does CHO affect my blood glucose?

CHO will increase blood glucose depending on...

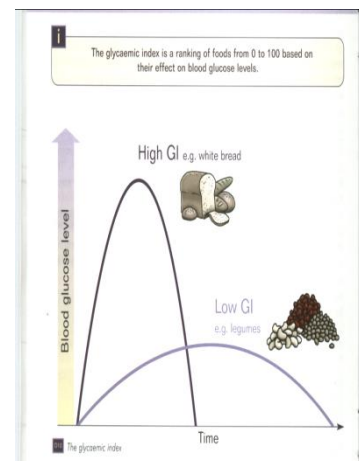
- Whether it is quick or slow acting
- The amount you eat
- Your sensitivity to insulin
- Your activity level



WHAT IS glycemic index (GI)?

The glycaemic index of foods is simply a 'ranking' of foods based on their immediate effect on blood glucose levels.

- Starch type
- Particle/grain size
- Processing methods
- Cooking methods
- Intact fibre
- Type of sugar present
- Ripeness of fruit
- Fat & protein content



SLOW ACTING CARBOHYDRATES

- Granary bread
- Boiled potatoes
- Pasta and noodles
- Pitta bread
- Porridge
- All Bran
- Small portion Fruit 'n Fibre
- Basmati rice
- Pulse vegetables
- Ryvita
- Oatcakes
- Fruit
- Milk
- Yoghurt

QUICK ACTING CARBOHYDRATES

- White bread, wholemeal bread
- Mashed potato, jacket potato, chips
- Cornflakes, rice krispies

Daily Carbohydrate Intake

Calorie intake (kcal)	CHO (grams)
• 1500	180 – 240 (Male / Female, inactive)
• 2000	240 – 320 (Male / Female moderate activity)
• 2500	300 - 400 (Male / Female active)

ARE SNACKS NECESSARY?

- For those on DIET ALONE, especially if overweight, snacks are not really necessary
- If having a snack, a portion of fruit, diet yogurt or slice of bread are good choices
- Those on certain oral hypoglycaemic agents or insulin may need between meal &/or bedtime snacks

FAQ'S

What about bananas?

- Like all fruit, bananas form part of a healthy diet
- Weight for weight they have a higher CHO content than many other fruit
- A medium banana contains approx. 30g CHO & 130 kcals
- A medium apple contains 10 – 15g CHO & 50 kcals
- Bananas are fine for those with diabetes but there is no reason to suggest that they are more beneficial than other fruits

And grapes?

- Again, a higher CHO fruit; 10–12 grapes are the same as an apple. Fine in moderation but eat the whole bunch & expect BG to rise!

Dried fruit?

- Concentrated source of CHO so modest portions

Fruit juice

- Contains sucrose & fructose so take as small portions (125ml)

Encourage

- 3-4 portions fruit spread out over the day

Appendix 3c

Diabetes medications and the risk of hypoglycemia

Low	High
Metformin	All agents in the sulphonylurea group (gliclazide and glimepiride are the most widely used in the UK) Nateglinide and repaglinide
Pioglitazone	
Sitagliptin	
Vildagliptin	
Saxagliptin	
Linagliptin	
Acarbose	
GLP-1 analogues (exenatide and liraglutide)	

Circle any medication the patient is taking and discuss potential side effects.

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