A pilot study to explore the role of a low-carbohydrate intervention to improve GGT levels and HbA_{1c}

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Article points

1. The authors implemented a low-carbohydrate (CHO) intervention in a primary healthcare setting and assessed its effect on weight, HbA_{1c}, serum gamma-glutamyl transferase (GGT) and cholesterol.
2. This study suggests that a low-CHO diet intervention (including associated support from healthcare professionals) that has been initiated and managed in a primary healthcare setting can reduce GGT, weight and HbA_{1c}.

Key words

- Liver function
- Low-carbohydrate diet
- Non-alcoholic fatty liver disease
- Weight loss

Authors

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Excess dietary glucose is believed to lead to insulin resistance, type 2 diabetes and also progressive hepatocyte triglyceride accumulation (non-alcoholic fatty liver disease [NAFLD]). Considering the increased cardiovascular risks associated with NAFLD and type 2 diabetes, effective risk factor management of individuals with these conditions is critical. Weight loss can improve abnormal liver biochemistry, the histological progression of NAFLD and diabetes control. However, the most effective diet remains controversial. The authors implemented a low-carbohydrate (CHO) diet in a primary healthcare setting and assessed its effect on weight, HbA_{1c}, serum gamma-glutamyl transferase (GGT) and cholesterol. In this article, the authors present their findings and question the role of dietary CHO in the aetiology of abnormal liver biochemistry and diabetes.

We are all familiar with the two great health epidemics of our time: obesity and type 2 diabetes. A third creeping upon us, almost unnoticed, is non-alcoholic fatty liver disease (NAFLD). NAFLD is a spectrum of conditions that is caused by hepatocyte triglyceride accumulation (a build up of fat within the liver cells [Lam and Babu, 2015]). NAFLD now affects 20–30% of adults in the developed world, which is of clinical importance as it can progress to non-alcoholic steatohepatitis, cirrhosis and hepatocellular carcinoma (Anstee et al, 2011). NAFLD has also been found to increase overall cardiovascular mortality (Adams et al, 2005; Marchesini et al, 2005; Chalasani et al, 2012).

Biochemical testing is one of the main tools for NAFLD diagnosis. Abnormal liver transaminases are observed, and elevated gamma-glutamyl transferase (GGT) is one of the markers indicating fatty liver. In primary care, elevated GGT levels are commonly detected as a result of routine biochemistry and attributed to alcohol consumption or drugs (e.g. statins) without further investigation. However, the Framingham Heart Study has provided evidence that individuals with high GGT levels in the highest GGT quartile experienced a 67% increase in cardiovascular disease incidence (Lee et al, 2007). Therefore, it is important to investigate a raised GGT result, which could be due to diet, excess alcohol consumption or medication.

Elevated GGT levels have also been identified as an independent risk factor for type 2 diabetes (Perry et al, 1998). A systematic review and meta-analysis of 18 prospective, population-based studies, comprising over 280 000 patient-years of follow-up, suggested that mildly raised serum liver enzyme results were independent, long-term predictors of incident type 2 diabetes (Fraser et al, 2009). Such studies provide evidence that suggests there is a link between raised GGT and type 2 diabetes. We postulate that excess dietary carbohydrate (CHO) is that link and, as such, following a low-CHO diet could be an effective way to improve liver biochemistry and glycaemic control.

The low-CHO diet

The low-CHO diet and its association with diabetes can be traced back to 1797 when Dr John Rollo was said to have "cured" an army officer named Captain Meredith of his diabetes by directing "…an entire abstinence of every kind of vegetable matter in the diet"

(Rollo, 1797), which by default became a diet of nearly all meat. Then in 1863, William Banting's *Letter on Corpulence, Addressed to the Public* (Banting, 1863) was published, in which he advocated removing all "starch and saccharine matter", which he felt "created fat", from the diet. Beyond fasting, the low-CHO diet was the only treatment option for diabetes in the pre-insulin era (Westman et al, 2006), and it is now in vogue, particularly as a treatment for the metabolic syndrome and type 2 diabetes (Volek and Feinman, 2005; Unwin and Unwin, 2014; Feinman et al, 2015).

The basis of the low-CHO diet is that CHO, as a source of glucose, should be restricted and that the starch found in bread, pasta, rice and potatoes supplies more dietary glucose than is commonly appreciated. For example, wholemeal bread (glycaemic index [GI] 71) and a baked potato (GI 85) both have a higher glycaemic index than table sugar (GI 68 [Foster-Powell et al, 2002]).

Theoretically, following a low-CHO diet could be an effective way to delay the histological progression of NAFLD for people with abnormal liver biochemistry. The liver has the highest density of glycogen storage in the body, but once these stores are full, further excess dietary glucose leads to progressive hepatocyte triglyceride accumulation (fatty liver) via "*de novo* lipogenesis" (Taylor, 2013). This then predisposes insulin resistance and type 2 diabetes (Anstee et al, 2013).

There is general agreement within the literature that an effective intervention for NAFLD, type 2 diabetes and metabolic syndrome is weight loss through dietary intervention (Preiss and Sattar, 2008; Chalasani et al, 2012). Furthermore, the evidence indicates that a reduction in GGT, which accompanies weight loss, is associated with histological improvements in NAFLD (Dixon et al, 2006). The most effective diet remains controversial (Musso et al, 2012), and although dietary intervention studies in NAFLD have been documented (Browning et al, 2011; Haufe et al, 2011; Musso et al, 2012), investigation of a low-CHO diet to treat both abnormal liver biochemistry and type 2 diabetes in a primary healthcare setting (as opposed to as part of a clinical research study) is yet to be seen. We hypothesised that a low-CHO diet would result in improvements in three parameters – GGT level, weight and HbA_{1c}. Funding for a pilot study was obtained from Southport and Formby Clinical Commissioning Group (CCG), and the aims were to examine the following:

(i) The adherence to a low-CHO diet plan in a primary healthcare setting.
(ii) The effect of a low-CHO diet on GGT level (as a surrogate marker for abnormal liver biochemistry and NAFLD), weight and HbA_{1c} levels (as a surrogate marker for type 2 diabetes).

Method

Participant selection

Over a period of 18 months, a low-CHO diet was recommended opportunistically to patients in a primary healthcare setting who demonstrated two or more features associated with metabolic syndrome: obesity (BMI >30 kg/m^2), raised GGT, hypertension, glucose intolerance or type 2 diabetes. Individuals who agreed to participate were allocated a second appointment with a GP (DU) or practice nurse (HC) within a few days. At this appointment, weight, blood pressure, HbA_{1c}, liver, renal and thyroid function, cholesterol and cholesterol:HDL-cholesterol ratio were measured. All measurements were collected and analysed using standard NHS equipment and laboratory analysis.

The low-CHO diet

Participants were counselled by the GP and practice nurse about the clinical benefits of weight loss, making an effort to link this with patients' own best hopes for health improvement. A diet sheet was provided (see *Box 1* in Unwin, 2014) containing a brief explanation of the low-CHO diet as a possible weight loss strategy by reducing dietary sources of sugar; in particular, high-starch foods, such as bread, pasta and rice. Weighing of food or calorie counting was not advised as this was thought to be less sustainable (Ogden and Wardle, 1990). In place of carbohydrate-rich foods, an increased intake of green vegetables, whole-fruits, such as blueberries, strawberries, raspberries and the "healthy fats" found in olive oil, butter, eggs, nuts and full-fat plain yoghurt were advocated.

The minimum follow-up period was 3 months and participants were required to self-report what they ate in sessions and appointments with the GP and practice nurse.

Further support

Individuals who opted to follow the low-CHO diet were followed up by the GP or practice nurse on a monthly basis and encouraged to bring any interested or supportive family members along in order to create

Page points

1. The low-carbohydrate (CHO) diet was first associated as a potential treatment for diabetes in the 18th century by Dr John Rollo.
2. The basis of the low-CHO diet is that CHO, as a source of glucose, should be restricted and that the starch found in bread, pasta, rice and potatoes supplies more dietary glucose than is commonly appreciated.
3. In a primary care setting over a period of 18 months, a low-CHO diet was recommended opportunistically to patients who demonstrated two or more features associated with metabolic syndrome: obesity (BMI >30 kg/m^2), raised gamma-glutamyl transferase, hypertension, glucose intolerance or type 2 diabetes.

Page points

1. Individuals who opted to follow the low-carbohydrate (CHO) diet were followed up by the GP or practice nurse on a monthly basis and encouraged to bring any interested or supportive family members along to appointments and sessions in order to create a holistic support network.
2. Sixty-seven out of 69 people who agreed to follow the diet adhered to the plan fully for at least 3 months.
3. The improvements in both cholesterol levels and cholesterol:HDL-cholesterol ratio were reassuring in a diet that is higher in fat than the norm.

a holistic support network. The primary objective of these monthly reviews was personal goal setting and motivation to improve adherence. Evening nurse-led clinics were held for those in full-time employment. Participants were weighed and provided with computer-generated graphs to demonstrate their progress. Blood tests were repeated every 2 months and HbA_{1c} testing was only repeated if the baseline result was >41 mmol/mol (5.9%). Furthermore, every 2 months, an educational "low-carb evening" was held to provide participants and their families with the opportunity to swap success stories and help each other with problems.

Statistics

Analyses were performed using the Statistics Package for Social Sciences for Windows, version 20.0 (SPSS Inc. Chicago, IL, USA). The difference in characteristics from pre-intervention to post-intervention were examined using paired *t*-tests. Data are presented in the text as mean (95% confidence interval [CI]), unless otherwise stated. Statistical significance was delimited at $P<0.05$ and exact P values are cited (P values of "0.000" provided by the statistics package are reported as "<0.001").

Results

The total process of recruitment and follow-up took almost 2 years and, during this time, 69 people agreed to participate in the low-CHO diet. A small number of people (fewer than five) when asked whether they would like to follow the low-CHO diet declined immediately. The average age of participants who agreed to follow the low-carb diet was 58 years, and there were 36 women and 33 men.

Compliance

Compliance was defined as individuals following the diet for a minimum of 3 months and attending their clinic appointments. Sixty-seven out of 69 people who agreed to follow the low-CHO intervention adhered fully to the plan for a minimum of 3 months. Thus, a 97% compliance rate was achieved. Of the two participants who did not adhere to the low-CHO diet, one female participant terminated the diet after 2 weeks due to lethargy. The second female participant could not tolerate the diet so adapted the plan to eliminate sucrose and continued to consume small quantities of bread. She attended the low-carb evenings and clinic appointments and later lost 17 kg over 23 months.

The average follow-up was 13 months, and pre- and post-intervention readings were obtained for the 67 participants who continued to follow the low-CHO intervention and the female participant who adapted the diet to remove sucrose (*Table 1*). The educational low-carb evenings were attended by approximately 20 individuals to each session.

A common patient concern in the early stage of the diet was the possibility of constipation because of presumed lack of fibre due to removing cereals and whole-grains from the diet. In fact, participants largely consumed greater quantities of vegetables and this did not present a significant problem. Many participants verbally reported improvements

Table 1. Clinical characteristics prior to and following a low-carbohydrate intervention for an average of 13 months.

	n	Pre-intervention (95% CI)	Post-intervention (95% CI)	Change between pre- and post-intervention (95% CI)	*P* value
Sex (male/female)	68	33/35	–	–	–
Age (years)	68	58.3	–	–	–
Weight (kg)	64	97.8 (93.6, 101.9)	89.0 (84.9, 93.1)	−8.8 (−10.0, −7.5)	<0.001
SBP (mmHg)	27	144 (136, 152)	135 (130, 140)	-9 (4, 15)	0.002
DBP (mmHg)	27	85 (80, 89)	79 (75, 83)	-6 (2, 10)	0.005
GGT (iu/L)	65	76.9 (58.3, 95.6)	41.8 (33.0, 50.3)	−29.9 (−43.7, −16.2)	<0.001
HbA_{1c}* (mmol/mol)	38	52.4 (48.0, 56.9)	42.4 (39.7, 45.0)	−10.0 (−13.9, −6.2)	<0.001
Total cholesterol (mmol/L)	58	5.7 (5.4, 6.0)	5.3 (5.0, 5.7)	−0.3 (−0.5, −0.1)	<0.001
Cholesterol:HDL-cholesterol ratio	57	4.3 (3.9, 4.6)	3.8 (3.5, 4.1)	−0.4 (−0.8, −0.1)	<0.001

*HbA_{1c} levels were only followed up in those cases where the baseline was >41 mmol/mol (5.9%).
DBP=diastolic blood pressure; GGT=gamma-glutamyl transpeptidase; SBP=systolic blood pressure; *n*=number of people; 95% CI=95% confidence interval.

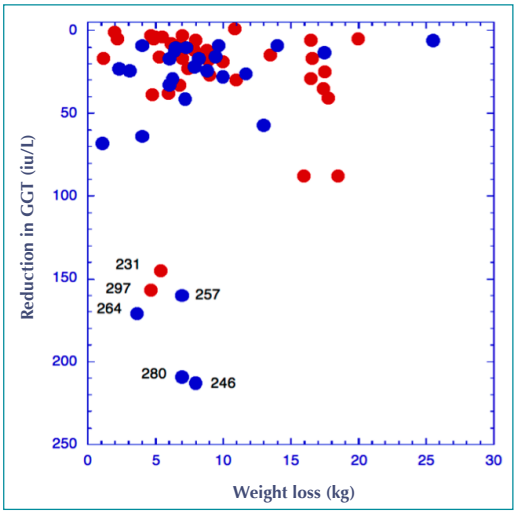

Figure 1. A scatter-plot indicating the lack of correlation between weight loss (kg) and gamma-glutamyl transpeptidase (GGT) reduction (iu/L) in 64 participants of the low-carbohydrate intervention. Red dots=initial HbA_{1c} >42 mmol/mol (6%); blue dots=initial HbA_{1c} <41 mmol/mol (5.9%). N.B. Numbers shown are stating GGT values in iu/L for individuals who had the greatest reduction in GGT.

in general wellbeing including a greater feeling of "health", more energy, better memory, improved skin condition and less abdominal bloating in the time they followed the low-CHO diet. Participants also reported a positive of the diet was that it involved "no food weighing or calorie counting".

Physiological assessments

After a mean period of 13 months on a low-CHO diet, there was a significant average reduction in weight of −8.8 kg (95% confidence interval [CI]=−10.0, −7.5 [*P*<0.001]). Significant improvements in blood biochemical profiles were also observed including a reduction in GGT of −29.9 iu/L (95% CI=−43.7, −16.2 [*P*<0.001]), a reduction in HbA_{1c} of −10.0 mmol/mol (95% CI=−13.9, −6.2 [*P*<0.001]), a reduction in cholesterol of −0.3 mmol/L (95% CI=−0.5, −0.1 [*P*<0.001]) and a reduction in cholesterol:HDL-cholesterol ratio of −0.4 (95% CI=−0.8, −0.1 [*P*<0.001]). *Figure 1* shows that all but two of the 64 individuals lost more than 2 kg in weight, but on inspection there was no correlation between weight loss and improvement in GGT.

Medication

Nine individuals were able to come off some or all of their medication. Drugs were stopped because blood pressure or glycaemic control improved and reducing medication fitted in with participants' personal health objectives. Three people stopped taking metformin (one because of severe gastrointestinal side effects), and all three still had a HbA_{1c} of 43 mmol/mol (6.2%) or less a year after stopping the drug. Two people stopped taking perindopril, and other drugs that individuals were able to stop taking were liraglutide, ramipril, fenofibrate, aspirin, amlodipine and simvastatin. In one individual who stopped simvastatin, the cholesterol:HDL-cholesterol ratio improved slightly from 2.8 to 2.7.

Case study

Box 1 reports on a case study of one of the individuals, a 55-year-old woman. This case study is of interest because, after following the low-CHO diet for a 3-month period, blood tests showed that GGT improved and ultrasound scans showed that there was a clearance of fat from the liver. It is a good example of how the low-CHO diet can benefit an individual and it suggests weight loss as an effective alternative to metformin to lower HbA_{1c}.

Discussion

Summary of findings

This study suggests that a low-CHO dietary intervention (including associated support from healthcare professionals), initiated and managed in a primary healthcare setting, can reduce GGT, weight and HbA_{1c}. The data presented also suggest that a low-CHO diet can be tolerated by individuals in primary care and may serve as an effective and economical non-pharmacological management strategy for people with non-alcohol-induced raised GGT or type 2 diabetes. Given the epidemic of type 2 diabetes, and that approximately 20% of the adult population in the UK has elevated GGT (and possibly NAFLD [Anstee et al, 2011]), investigating dietary interventions for weight loss in these individuals would seem to be of national priority, especially as there is currently an absence of effective drug therapy for NAFLD.

The observed improvements in cholesterol and cholesterol:HDL-cholesterol ratios following the low-CHO intervention were reassuring in a diet that is higher in fat that the norm.

Strengths and limitations of the study

Prior to this work the GP and practice nurse had struggled to help obese people achieve significant weight

Page points

1. After a mean period of 13 months on a low-CHO diet, there was a significant average reduction in weight of −8.8 kg (95% confidence interval, −10.0, −7.5 [*P*<0.001]).
2. This study suggests that a low-CHO dietary intervention (including associated support from healthcare professionals), initiated and managed in a primary healthcare setting, can reduce gamma-glutamyl transferase, weight and HbA_{1c}.

Page points

1. This report demonstrates how an effective weight loss regimen can be implemented into an ordinary GP practice.
2. Compliance to the intervention was high, which may have been due to good case selection, participants freely choosing the diet and the low-carbohydrate (CHO) diet itself, which generally has a greater feeling of satiety that results from eating fats and proteins compared with CHOs, which cause insulin spikes
3. Although many participants noticed improvements in general wellbeing, we did not formally measure these parameters.

Box 1. Case study of a 55-year-old woman participating in the low-carbohydrate diet.

A 55-year-old female individual presented with tiredness, polydipsia and an HbA_{1c} of 84 mmol/mol (9.8%) during a hospital admission. There was marked hepatomegaly, and a fatty liver was confirmed on ultrasound scan associated with deranged liver function tests (gamma-glutamyl transpeptidase [GGT], 103 iu/L). The hospital correctly started metformin, but the individual was keen to explore possible lifestyle alternatives to long-term medication, which she found "depressing". She attended a GP appointment and agreed to follow the low-carbohydrate diet. It was decided we would monitor her liver function and HbA_{1c} on a monthly basis in clinic while she lost weight. After the first 3 months on a low-carbohydrate diet, the individual lost 7.9 kg, the liver was reported as normal on repeat ultrasound and her GGT was down to 12 iu/L. Six months on, there was a total weight loss of 9.9 kg and HbA_{1c} had reduced to 41 mmol/mol (5.9%) despite a phased cessation of metformin. The patient also lost 17 cm from her waist circumference and reported feeling "great, 10 years younger". After 19 months following the diet she continues to attend "low-carb" evening events in the practice. Her GGT is still low and within normal range at 19 iu/L, and she remains off the metformin with an HbA_{1c} of 45 mmol/mol (6.3%).

loss. This report demonstrates how an effective weight loss regimen can be implemented into an ordinary GP practice. By working collaboratively with patients and creating a holistic support network including spouses and holding support evenings with regular weight checks for motivation, significant positive results in health and well-being can be achieved. It is worth noting that the GP and nurse both took part in the low-CHO diet, so the experience was shared, which stimulated a more collaborative, co-operative approach.

Compliance to the intervention was high, which may have been due to good case selection and participants freely choosing the diet. However, biased participant recruitment most likely occurred. Due to the nature of general practice, the GP and practice nurse already knew their patients in some capacity and so may have invited those that they thought would benefit most from the diet. Furthermore, the individuals chose to follow the diet because they had hoped it would suit them – hope is an integral part of patient choice. This variable is difficult to eliminate and would make designing a trial with a comparator group problematic.

The low-CHO diet itself could have contributed to the high rate of compliance. There is generally a reduced feeling of hunger compared with very-low-fat diets because of the greater satiety that results from eating fats and proteins compared with CHOs, which cause insulin spikes (Erlanson-Albertsson and Mei, 2005).

Although many participants noticed improvements in general wellbeing, we did not formally measure these parameters. Future research involving patient questionnaires is warranted in order to be able to comment on the holistic effect of the intervention.

We also accept that, in our determination to help patients, more variables and interventions have been introduced than the low-CHO diet alone (i.e. support and education sessions). Similarly as there was no comparator group, it is not possible to say definitively whether the reductions in weight, HbA_{1c} and GGT observed were due to following the diet alone.

It is also important to note that using biochemical diagnosis of NAFLD is notoriously difficult; approximately 80% of people with NAFLD can have normal liver enzyme results (Mofrad et al, 2003). Therefore, relying on biochemical abnormalities alone is a poor marker (Lam and Babu, 2015) and not the most effective way to determine the presence of abnormal liver biochemistry and NAFLD.

Lastly, despite the improvements in GGT, weight and HbA_{1c} recorded, further research is needed to determine whether these results can be replicated on a larger scale and whether the intervention is cost effective. Thus far, we are only aware of one long-term evaluation of the low-CHO diet, which lasted 44 months (Nielsen and Joensson, 2008).

Debate: Does CHO restriction have a serial or parallel effect on weight loss and GGT reduction?

As previously stated, weight loss is most often suggested as a remedy for NAFLD and improved liver biochemistry. We were, therefore, surprised to observe the lack of correlation between weight loss and improvements in GGT (*Figure 1*). This made us

think whether or not the improvements in GGT were actually linked to the weight loss at all? Instead of the low-CHO intervention causing weight loss, which leads to improvements in GGT (serial effect), it is possible the diet leads separately to improvements in liver function and weight loss (parallel effect [*Figure 2*]).

The rationale for the low-CHO diet emphasises improvement in the glucose–insulin axis with weight loss as one of the downstream consequences of this metabolic change (Nielsen and Joensson, 2008). While changes in adipose physiology may also play a role, changes in body mass are primarily responses not stimuli. The work of Gannon and Nuttall (2006), who observed improvements in type 2 diabetes with diet but without weight loss, supports this parallel effect. Certainly in our study, most improvements in GGT were seen in the first month, well before the majority of weight loss was achieved, which would suggest a parallel effect.

Implications for practice

Our study suggests that this intervention can be successful in a primary healthcare setting and could have major implications for clinical practice in the UK. We propose that a raised GGT result in the absence of excessive alcohol consumption should be an opportunity to investigate for metabolic disturbance, and can be a useful motivator to begin a dietary (low-CHO) intervention. Furthermore, when a patient denies a high-alcohol intake, clinicians should bear in mind that they may well be telling the truth.

Perhaps the most important outcomes that seemed to be associated with the low-CHO intervention in this study were the improvements in blood pressure and HbA_{1c} resulting in a reduction in prescribed medications. The decrease in patient medication we observed hints at the potential cost savings that could be achieved when a low-CHO diet is implemented. Over the study period not a single patient opted to start anti-diabetes medication, instead choosing to follow a lifestyle intervention with the goal to lose weight. This may explain why our practice is the only one in the Southport and Formby CCG to have static diabetes drug costs for 3 years running, generating savings of approximately £20 000 per year.

Conclusion

We feel this work supports the notion that excess dietary glucose could be central to both fatty liver and type 2 diabetes. Furthermore, in his 2012 Banting lecture, Professor Roy Taylor effectively highlighted that abnormal liver function tests and NAFLD often predate the onset of diabetes by many years; "Before diagnosis of Type 2 diabetes, there is a long silent scream from the liver" (Taylor, 2013). The low-CHO intervention initiated in a primary healthcare setting was well received by the individuals who agreed to follow the diet. The improvements in GGT, HbA_{1c} and weight were encouraging and seem to support the idea of excess dietary CHO being implicated in fatty liver,

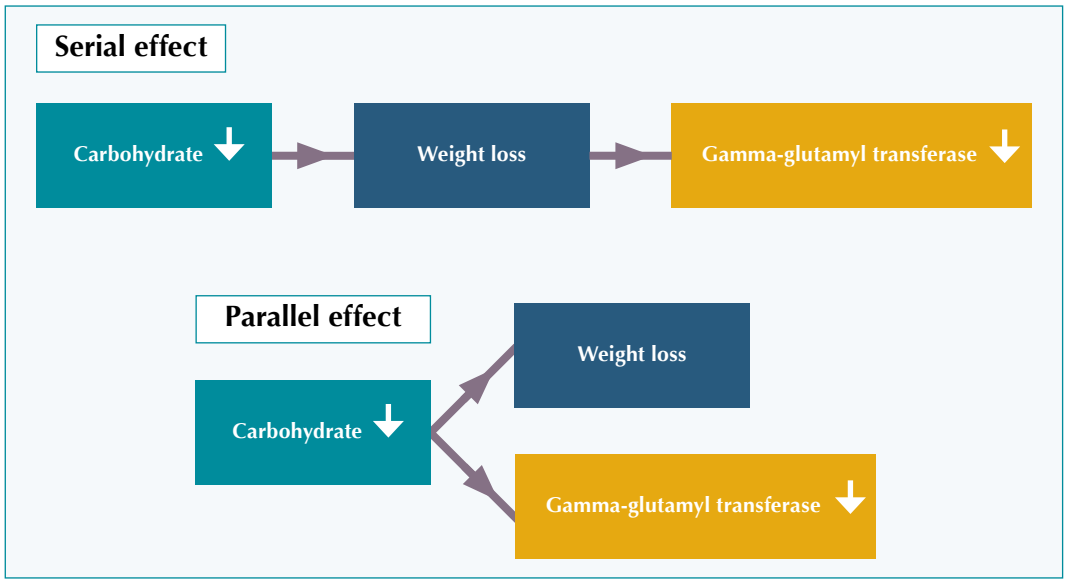

Figure 2. Does the effect of carbohydrate restriction have a serial or parallel effect on weight loss and gamma-glutamyl transferase reduction?

Page points

1. The authors hypothesise that diet leads separately to improvements in liver function and weight loss, rather than weight loss leading to improvements in liver function.
2. We propose that a raised gamma-glutamyl transferase result in the absence of excessive alcohol consumption should be an opportunity to investigate for metabolic disturbance, and can be a useful motivator to begin a dietary (low-carbohydrate) intervention.
3. The GP practice where the low-carbohydrate diet is taking place is the only one in the Southport and Formby Clinical Commissioning Group to have static diabetes drug costs for 3 years running, generating savings of approximately £20 000 per year.

"The improvements in gamma-glutamyl transferase, HbA_{1c} and weight were encouraging and seem to support the idea of excess dietary carbohydrate being implicated in fatty liver, as well as type 2 diabetes and obesity."

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as well as type 2 diabetes and obesity. Clearly larger and longer studies comparing dietary strategies are warranted over and above this pilot study. ■

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Ethics
The British Medical Association Ethics Department was consulted and their guidelines were adhered to. The patient described in the case study gave written informed consent for publication of the description.

Competing interests
The authors have nothing to declare.

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Comment from British Liver Trust

This pilot study offers a very useful insight in to how liver function can improve when healthier lifestyle choices are made, in this case a decrease in dietary carbohydrates.

Unfortunately, liver disease is now the third main cause of premature death in the UK (Williams, 2014), with metabolic and obesity-related issues being one of the main causes. This study suggests that one way to reduce this may be to lower carbohydrate intake. It is now vital to ensure further research is done to see what role dietary carbohydrate plays in the aetiology of diabetes and non-alcoholic fatty liver disease (NAFLD), as well as obesity. If the increasing epidemic of liver disease in the UK and the rising numbers of deaths due to preventable liver disease are to be decreased, then it is vital to know how to support and treat any of us who may be at risk of or are currently living with NAFLD or nonalcoholic steatohepatitis.

The British Liver Trust congratulates this research team in exploring an area of liver disease that requires far more patient-related research.

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