ALINEA

NUTRITION

AUGUST 2020

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Taylor R, Al-Mrabeh A, Zhyzhneuskaya S, Peters C, Barnes AC, Aribisala BS, et al. Remission of Human Type 2 Diabetes Requires Decrease in Liver and Pancreas Fat Content but Is Dependent upon Capacity for β Cell Recovery. Cell Metab [Internet]. 2018;28(4):547-556.e3.

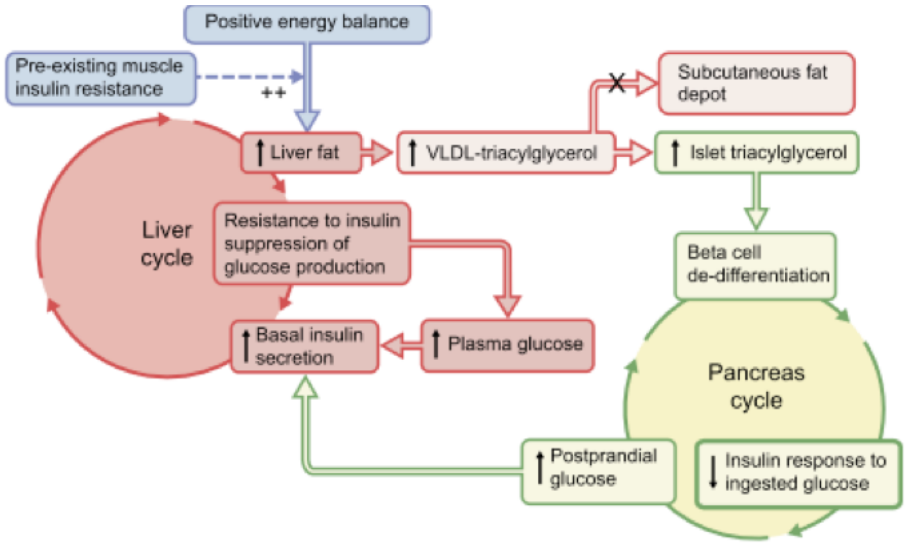
What We Know, Think We Know, or Are Starting to Know

We certainly know this: Type-2 Diabetes [T2DM] is the seventh leading cause of mortality globally, and affects nearly 1 in 11 worldwide [(1)]. We also know that perhaps the greatest burden of T2DM is not only the condition itself, but the high prevalence of comorbidities, in particular increased risk for cardiovascular disease associated with elevated blood cholesterol and hypertension [(2)].

Historically, T2DM has been viewed through two predominant lens: obesity and glucose. However, we know that the former [obesity] is not clear cut: adiposity as defined by BMI varies greatly in T2DM at time of diagnosis, indicating that the risk is associated with the underlying metabolic complications which accompany adiposity.

Which leads us to the former [glucose], which has often been the main focus for a condition characterised by elevations in blood glucose and insulin resistance. Insulin resistance in peripheral tissues in which glucose is disposed is known to develop first [(3)]. Therefore, what characterises T2DM progression is not insulin resistance alone, but the progressive decline in the capacity of pancreatic beta-cells to produce and secrete insulin [(4)]. The UK Prospective Diabetes Study Group highlighted that beta-cell decline occurs linearly over time irrespective of whether T2DM is controlled with diet, insulin or sulfonylurea therapy [(4)].

Thus, the fundamental question: can interventions restore beta-cell function? Roy Taylor' s research group at Newcastle University developed the "Twin Cycle Hypothesis" that visceral fat in the liver spilling over to the pancreas resulted in impaired beta-cell function, and that dramatically reducing this visceral fat could rejuvenate beta-cell function.



Graphical illustration of the "Twin Cycle Hypothesis". From Taylor R, Barnes AC. Translating aetiological insight into sustainable management of type 2 diabetes. Diabetologia. 2018;61(2):273–83.

The Study

The Diabetes Remission Clinical Trial (DiRECT) study was a cluster-randomised trial* including 306 participants [149 in each of the intervention and control group, respectively] with T2DM diagnosis within 6-years duration, from primary care practices in the greater Tyneside area and Scotland.

Participants were assigned to receive either a very-low-calorie liquid diet designed to achieve ~15kg weight loss, or continue with their conventional medication and management. The intervention period lasted an average of 4-months, which was followed by an 8-week step-wise food reintroduction period, then maintenance up to 12-months.

A specified subgroup of the study - 64 participants from the intervention and 26 from the controls - were selected to undergo metabolic studies to measure liver fat, pancreatic fat, beta-cell function, and very-low-density lipoprotein triglyceride [VLDL-TG] content.

This sub-study examined differences between participants who responded to the intervention and returned to normal glucose control and participants who completed the intervention but did not return to non-diabetic glucose control. These participants from the intervention group will be referred to as 'Responders' and ' Non-responders' , respectively.

*Geek Box: Cluster Randomisation

When you read about 'randomisation' in a study, more often than not this is referring to randomising of individuals - often in a computer-generated 1:1 fashion - to an intervention or control group. However, there are circumstances where the nature of the intended intervention mean that randomisation of groups, or clusters, may be more attractive. For example, in the present study it was the General Practices that were randomised, and therefore all participants enrolled in the study at a GP randomised to the intervention would be in the intervention group, while all participants enrolling at a GP randomised to the control group would be control participants. Some biomedical purists do not look favourably on cluster randomisation, as they are deemed to compromise on precision. However, 'compromise' is the key word here: what is being gained is pragmatism, as generally the cluster is within the community, and the trial is therefore being conducted under more "real world" conditions. Cluster-randomisation also helps avoid what is known as 'contamination', which is where there is potential for an intervention group and placebo group to overlap and have contact. For example, in this study, if individuals were randomised from the same GP practice, there could be contact between participants in the intervention group and control group in the practice. Cluster-randomisation also captures a more whole-population approach, when often many RCTs may lack applicability to the wider population. By conducting a cluster RCT, it is therefore possible to know that an intervention could be scaled. So, it depends on the research question, the type of intervention, and the context, and there may be times when randomising larger level units is appropriate.

Results: Responders were defined as achieving HbA1c levels <6.5%, blood glucose of <126mg/dL, and no medications for a minimum of 2-months. In baseline characteristics, there was no significant difference in bodyweight, VLDL-TG production, liver fat [which was 16% in the entire intervention group], pancreatic fat [7.8-8.9%].

- ***Weight Loss:*** Weight decreased similarly by 16.2kg and 13.4kg in Responders and Non-responders, respectively. While weight regain was similar during the maintenance phase - 3.3kg and 4.9kg in Responders and Non-responders, respectively - none of the Non-responders achieved remission from the intervention or during maintenance. At 12-months, overall average weight change was 14.1kg and 9.4kg in Responders and Non-responders, respectively.
- ***Liver Fat:*** Liver fat decreased to 3.0% [-13.4%] and to 2.6% [-11.9%] in Responders and Non-responders, respectively, during the weight loss intervention. At 12-months, liver fat was 3.3% in Responders and 6.1% in Non-responders: increases in liver fat correlated to weight regain in the maintenance phase, with weight gain above the Responders mean regain of 3.3kg resulting in an increase of 1.5% in liver fat.

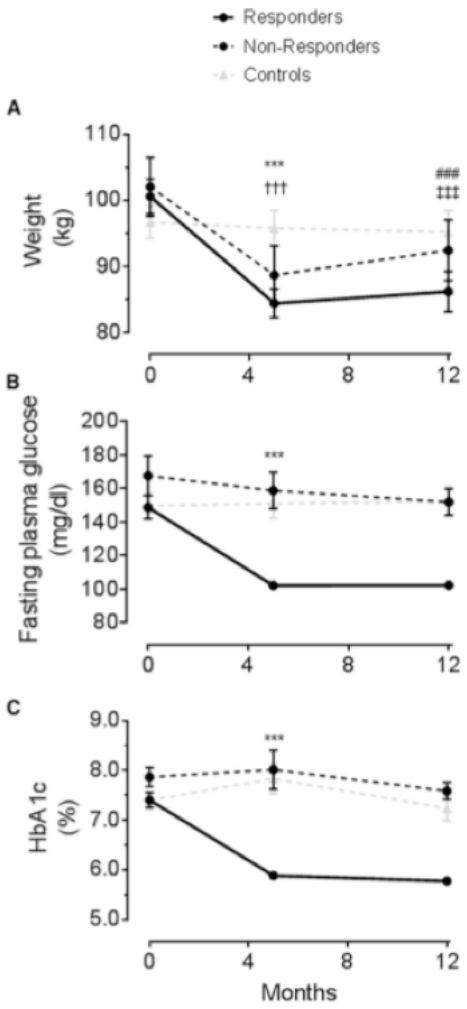


Figure *from paper illustrating changes in bodyweight* ***(A)****, fasting glucose* ***(B)****, and HbA1c* ***(C)*** *in Responders (full black line), Non-responders (broken black line), and controls (broken grey line).*

- ***Pancreatic Fat:*** Pancreatic fat decreased to 7.8% [-0.9%] and to 7.1% [-0.7%] in the Responders and Non-responders, respectively. Pancreatic fat remained stable in both groups during maintenance: 7.9% in Responders and 6.8% in Non-responders.
- ***VLDL1-TG:*** Production of VLDL1-TG* decreased significantly by 147mg after weight loss in Responders, but decreased by 59mg in Non-responders which was not significant. During maintenance, VLDL1-TG production increased by 43mg in Responders and 155mg in Non-responders. Thus, after 12-months the Responders maintained a mean decrease of 119mg, while the Non-responders increased production by 72mg. Plasma concentrations decreased significantly by 10mg in Responders during weight loss, and maintained at 8.1mg at 12-months; conversely there was no significant change in Non-responders during weight loss or maintenance.
- ***Glucose:*** In Responders, fasting blood glucose decreased from 148.8mg/dL to 102.2mg/dL following weight loss - this was maintained at 12-months. In Non-responders, there was no significant change in blood glucose - 167.8mg/dL to 158.9mg/dL - during weight loss, or further significant change during maintenance. HbA1c decreased significantly from 7.4% to 5.9% in the Responders, and was maintained at 5.8% at 12-months. In Non-responders, there was no significant difference in HbA1c during weight loss or maintenance, which levels remained at 7.6% at 12-months.

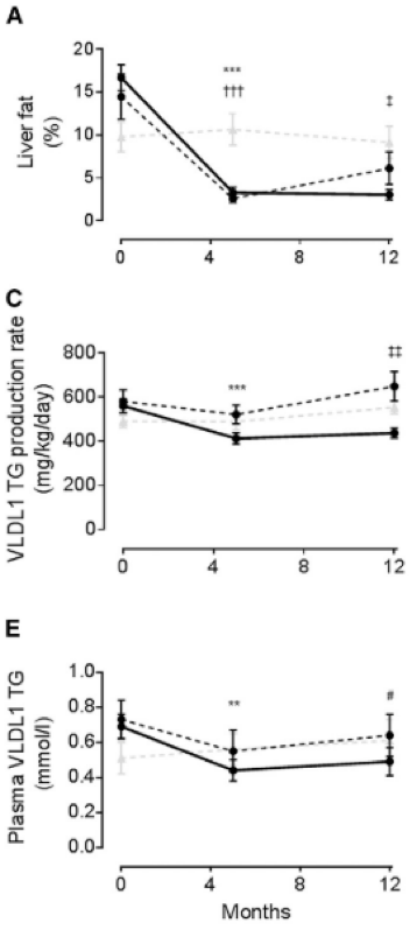


Figure *from paper illustrating changes in liver fat* ***(A),*** *production of VLDL1-TG* ***(C)****, and circulating VLDL1-TG levels* ***(E)*** *in Responders (full black line), Non-responders (broken black line), and*

- ***Beta-cell Function:*** First-phase insulin section [i.e., the initial response to increasing blood glucose levels] increased significantly after weight loss in the Responders from 0.04nmol/min to 0.11nmol/min: this was maintained at 12-month. Maximal insulin secretion increased after weight loss, and was most significant at 12-months where maximal secretion had increased from 0.62nmol/min to 0.94nmol/min. There was no change in first-phase insulin response or maximal insulin secretion in Non-responders at any point in the intervention.

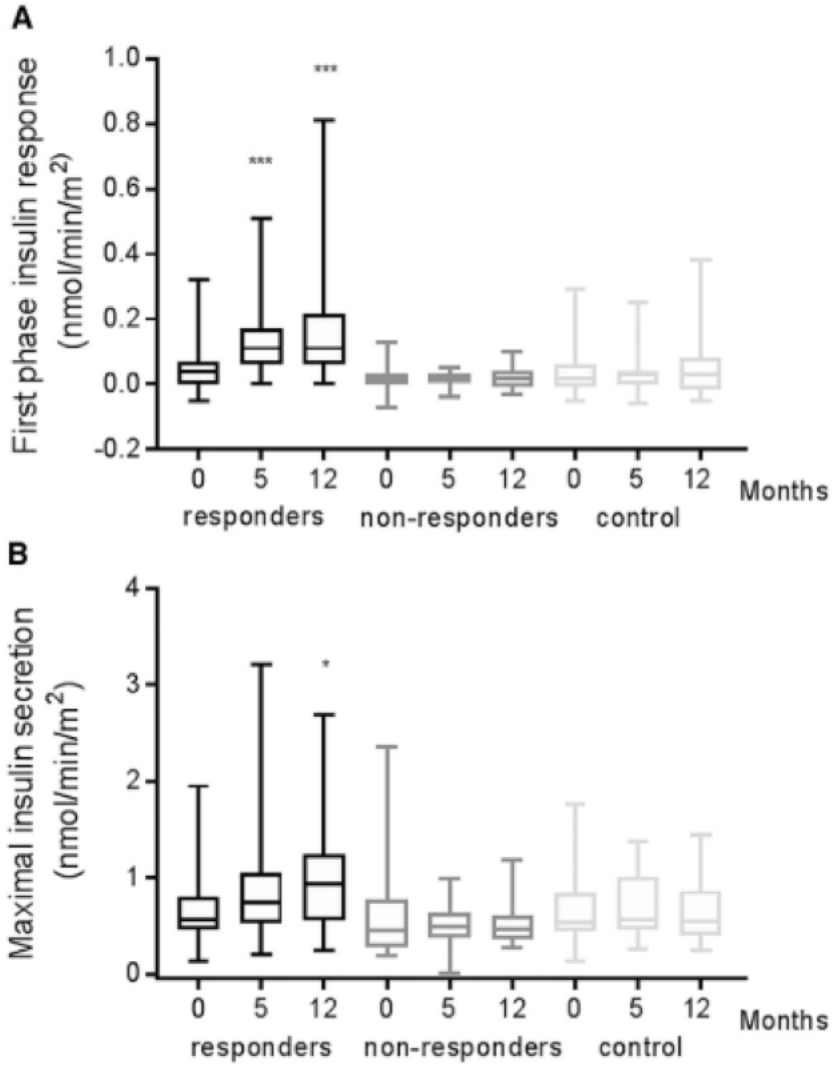
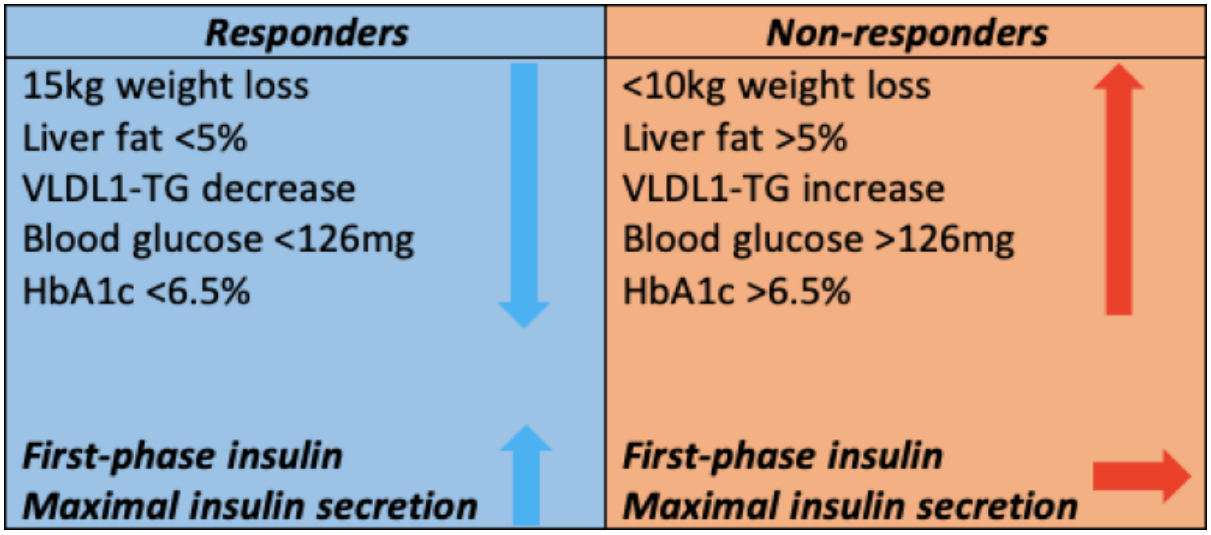


Figure *from paper illustrating changes in first-phase insulin response* ***(A)*** *and maximal insulin secretion* ***(B)*** *controls (broken grey line).*

Let's wrap up the key differences between Responders and Non-responders, with an emphasis on the findings in the Responders:

- Greater total weight loss and less weight regain
- Greater reduction in liver fat and maintenance of liver fat <5%
- Greater reduction in VLDL1-TG production and circulating levels
- Greater reduction in fasting glucose and HbA1c and maintenance of non-diabetic ranges;
- Restoration of first-phase insulin secretion and increased maximal insulin secretion over 12-months



*Geek Box: Very-Low Density Lipoprotein

Most people are very familiar with low-density lipoprotein - LDL, the "bad cholesterol" - but not as familiar with its very-low cousin, VLDL. But we should be, because VLDL is hugely important in the overall picture of both metabolic health, particularly as it relates to liver fat, and cardiovascular health, as it relates to circulating cholesterol and cholesterol transport. We have two main pathways of fat metabolism, one is exogenous and the other endogenous. The exogenous pathway takes in the fat - triglycerides - we consume through diet, which are transported from intestinal cells by chylomicrons. The endogenous pathway takes triglycerides that are synthesised in the liver from circulating free fatty acids, a majority of which are broken down from storage, i.e., adipose tissue lipolysis. These triglycerides also need a vehicle to carry them out of the liver to tissues which can use or store them, and this vehicle is VLDL, which is secreted by the liver. There are broadly two types, which are differentiated by their content of triglycerides. VLDL1 is very large and rich in triglycerides; VLDL2 is depleted of triglycerides and is a smaller and more dense VLDL particle. Thus, the primary relevance of the '1' after VLDL is that it denotes the larger VLDL particles, which carry more triglycerides.

The Critical Breakdown

Pros: The metabolic study was conducted using state-of-the-art measures of visceral fat, lipids, glucose and insulin. The study compared not only intervention to control, but Responders vs. Non-responders within the intervention group [see ***Key Characteristic***, below]. 39% of the participants were from the lowest quintiles of socio-economic deprivation.

Cons: This subgroup analysis was based on the Tyneside participants, whom were 98% White/Caucasian, and T2DM has high prevalence in Black and Asian Minority Ethnic [BAME] communities. The statistical analysis was basic before-after comparisons [using what are known as paired t-tests], and given the range of variables measured, it would have been interesting to use a multi-variable statistical analysis to tease out the variable most associated with the restoration of beta-cell function.

Key Characteristic

The comparison between Responders and Non-responders provided substantially greater insight into the pathophysiology of T2DM and remission. Standard practice is, of course, to compare an intervention group to a control group. And in the DiRECT study, this has been done. For example, comparing the entire intervention group to the control group, 46% of participants in the intervention group achieved remission at 12-months compared to 4% of the control group [(5)]. But if participants in the intervention group were achieving, broadly, targets for weight loss but not achieving remission, what were the underlying metabolic differences - if any - between Responders and Non-responders? The present study answered that by directly comparing the underlying metabolic physiology of participants within the intervention group, differentiated by their response to the intervention and whether T2DM remission had been achieved.

Interesting Finding

The link between lower VLDL1-TG production and circulation, liver fat, and maintenance of remission, is consistent with the "Twin Cycle Hypothesis".

A fatty liver increases insulin resistance in the liver and adipose tissue; high circulating levels of fatty acids and fat within the liver lead to an increase in triglyceride synthesis, in turn causing an over-production of VLDL1 particles in the liver to carry excess triglycerides out of the liver, to other tissues [including the pancreas] [(6)]. This twin cycle is in fact a vicious cycle, of high levels of liver fat causing increased VLDL1 production, high levels of triglycerides in VLDL1, in turn causing insulin resistance and impaired glucose tolerance.

In the present study, the fall in VLDL1-TG production and circulating levels was significantly more pronounced in Responders, and Responders maintained a liver fat of 3.3% [down from 16.4% at baseline]. Given that the change in pancreatic fat was relatively modest even in Responders, but beta-cell insulin response and maximal secretion increased significantly, it is mechanistically plausible that the improvements in blood glucose and HbA1c were conditional upon reductions in liver fat and decreased VLDL1-TG production and circulation. In the Non-responders, as the authors suggest, it may be that they are at a more advanced and irreversible stage of beta-cell dysfunction. This could relate to duration of disease: Non-responders did have a slightly longer duration since diagnosis of 3.8yrs vs. 2.7yrs in Responders.

Relevance

In may respects, the whole research project has been a case study in good science. From starting with the "Twin-Cycle Hypothesis", in 2011 Taylor' s group published a pilot study in 11 participants with T2DM demonstrating that a very-low-calorie liquid diet resulting in restoration of beta-cell function and liver insulin sensitivity following significant reduction in liver fat content [(7)]. This was followed by the Diabetes Remission Clinical Trial (DiRECT), which has demonstrated the effectiveness of the intervention delivered through primary-care practices, in which 86% of participants achieving weight loss of ~15kg achieved remission [(6)].

However, only 57% of participants achieving 10-15kg weight loss achieved remission, and the present study examined further the the underlying metabolic physiology leading to remission of T2DM. A recent cost-effectiveness analysis indicated that the intervention resulted in a mean lifetime cost saving of £1,337 per participant [(8)]. While the mechanistic differences between participants who respond and do not respond can continue to be teased out, and further pathophysiological insights into T2DM will no doubt result, to date this intervention appears to be the most efficacious at achieving remission of T2DM. The caveat emerging from this research is that initiating interventions earlier, i.e., as soon as practicable following diagnosis, may be a crucial mediating factor in success.

Application to Practice

The DiRECT interventions were carried in General Practises with dietetic input and oversight. While this may not necessarily cover all nutrition professionals, it does demonstrate the such an intervention may be carried out safely and efficaciously in a primary-care context.

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