

Intestinal growth factors

An information sheet for patients with intestinal failure on intravenous nutrition support

This information sheet is to help you understand about a treatment that is developing for patients who have a short bowel. In recent years, a new group of medications are becoming available, and it can be helpful to understand how these work as well as if they are relevant for you.

Authors:

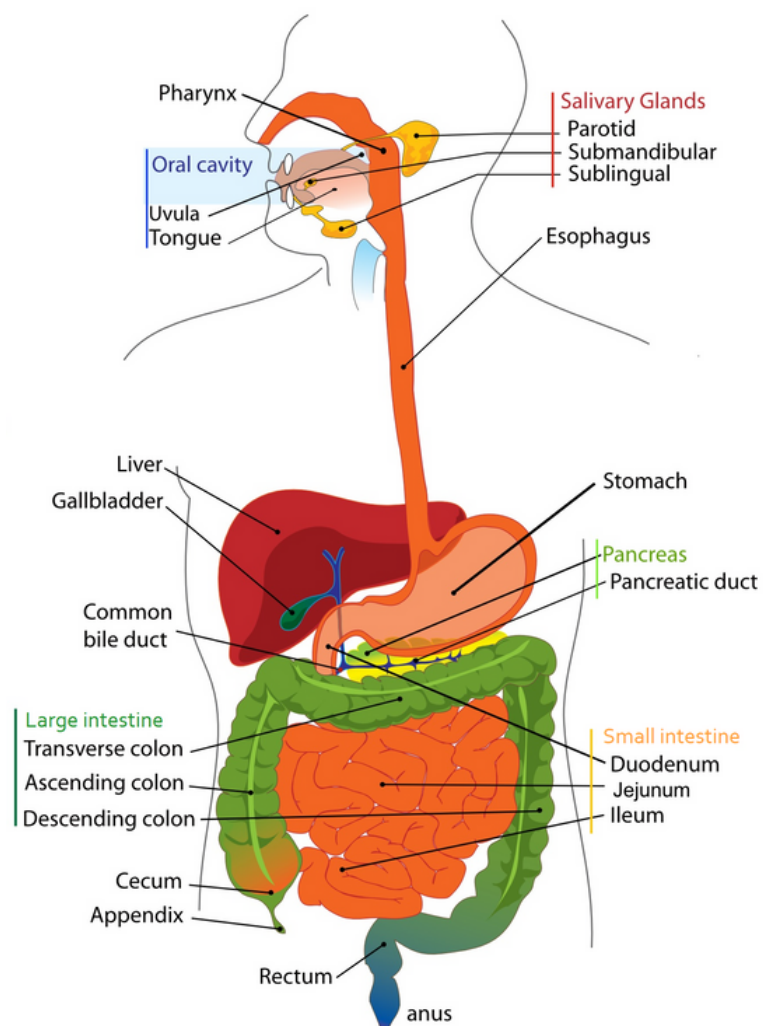
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The bowel

The normal human bowel extends from the mouth to the anus (back passage). There is the oesophagus (gullet) leading into the stomach. From the stomach, food and fluid passes into the small bowel. This leads onto the large bowel (colon) which goes down to the rectum and then to the anus.

The normal small bowel

Our small bowel is quite a remarkable organ. It is called small bowel as it is small in diameter compared to other parts of the bowel, however it is far from small in length. In adults the length of the small bowel varies between 3.5-8 metres. Although it is one long tube, the first part of the small bowel is called the duodenum, the second part is called the jejunum and the last part is called the ileum. That is because they have slightly different structural appearances when looked at in detail.

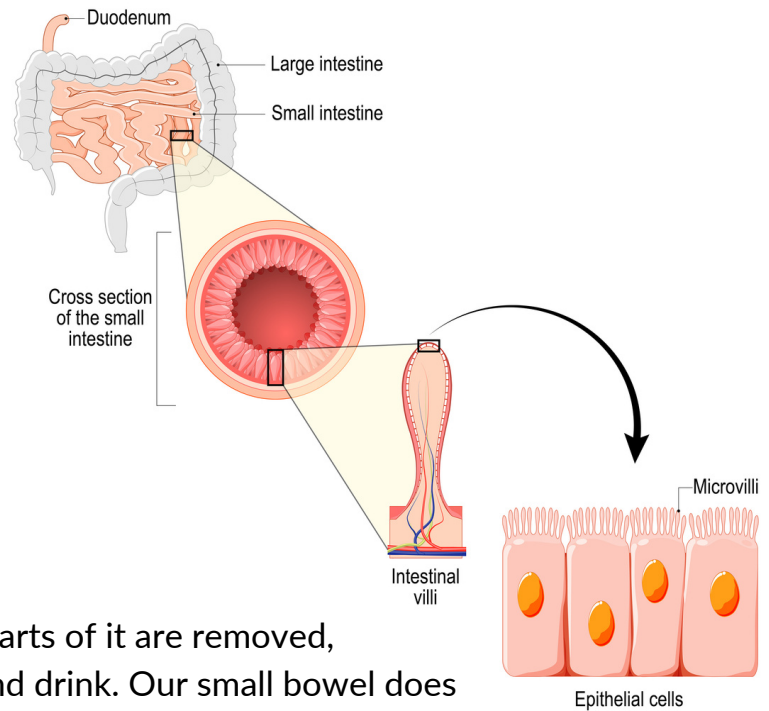


What is so special about the small bowel?

The small bowel is a long thin tube, but it has a massive surface area. The surface area is the equivalent of a tennis court! The reason why this is important is that to absorb all that we eat and drink, we need to have a large surface area inside us for everything to be absorbed into the body.

The way that this happens in the small bowel is that it has millions of tiny projections inside the bowel, called villi and microvilli. These tiny bumps increase the surface area enormously.

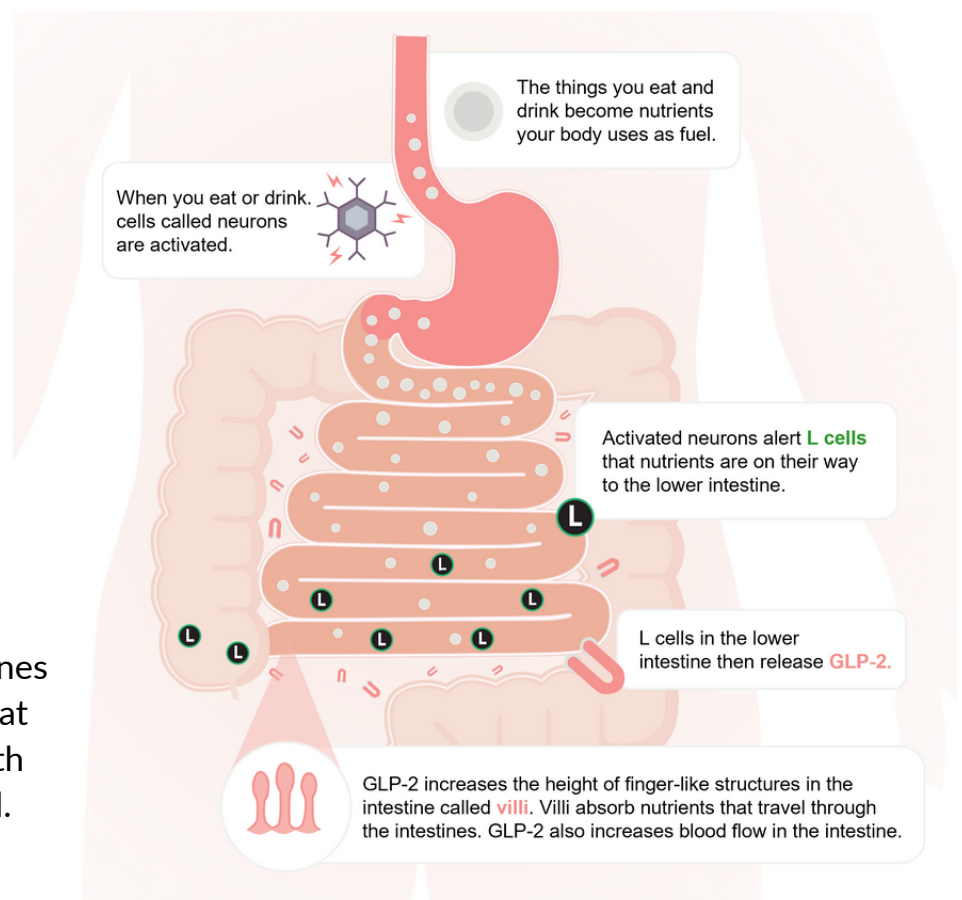
If something happens to our small bowel and parts of it are removed, then we can't absorb everything that we eat and drink. Our small bowel does adapt but there is a point when the surface area becomes too small for us to be able to absorb all the fluid and nutrition that we need to be able to survive. This is termed intestinal failure due to short bowel syndrome.



The bowel has hormones

Our bowels have a big job to do and this requires that all the different parts of the bowel work together. To do this we have a number of signalling systems within our bowels that help control the flow and movement of the food and drink that we eat, so that we can digest it. These signalling systems include the nerves as well as some specific hormones.

We also have a number of hormones that are produced in the bowel that help to stimulate repair and growth in the normal and damaged bowel. We have only recently started to understand the importance and function of some of these hormones.



What are intestinal growth factors?

The intestinal growth factors are a group of hormones that stimulate some form of growth within the bowel. This does not mean that the bowel gets longer in length. It means that the villi (tiny projections on the inside of the bowel) become longer and therefore the surface area increases. If surface area increases, then more fluid and nutrition can be absorbed.

There is quite a long list of intestinal growth factors (see below) which means that there is a lot of potential to find medicines that will work in the same way. So far, clinical trials have studied the more promising ones.

| Known growth factors |
|---|
| Growth hormone (GH) |
| Glucagon-like peptide 2 (GLP-2) |
| Glucagon-like peptide 1 (GLP-1) |
| Epidermal growth factor (EGF) |
| Insulin-like growth factor 1 (IGF-1) |
| Hepatocyte growth factor (HGF) |
| Keratinocyte growth factor (KGF) |
| Transforming growth factor alpha (TGF- α) |
| Neurotensin |
| Leptin |
| R-spondin |

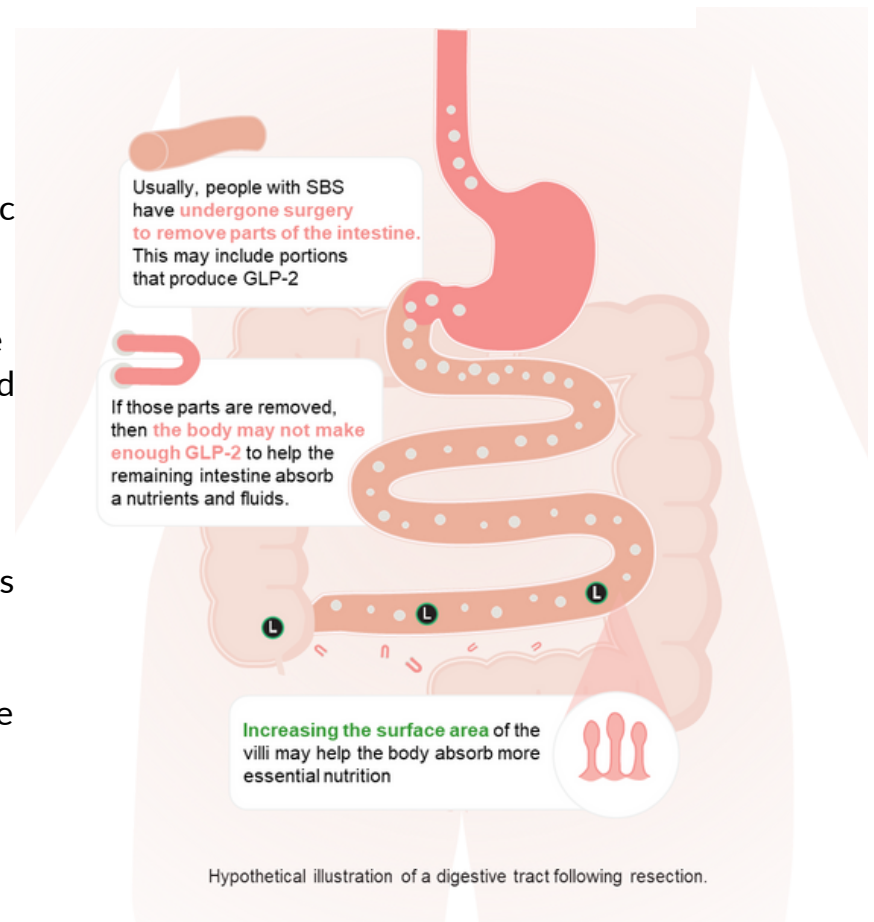
| Clinical trials using growth factors |
|--------------------------------------|
| Growth hormone |
| Glucagon-like peptide 2 |
| Glucagon-like peptide 1 |

How do they work?

These growth factors stimulate specific cells in the bowel. Apart from growth hormone, the growth factors are specific proteins produced in one part of the bowel but act on a different part of the bowel. The growth factor which has the most effect on intestinal growth is called glucagon-like peptide 2 (GLP 2).

GLP 2 is produced in the lower part of the small bowel (ileum) by enteroendocrine L cells. When food gets to that part of the bowel then GLP 2 released into the bloodstream. GLP 2 then acts on the small bowel causing the villi to become longer and that way the surface area of the small bowel increases, allowing more fluid and nutrition to be absorbed.

Also, GLP 2 does not just act on the small intestine. It also increases the blood flow to the bowel and to the liver, can improve liver function, and can help bone strength to improve.



Intestinal adaptation

Our bowels continually adapt to the environment that we live in. If we move from one part of the world to another, then our bowels will adapt to them. The same is true if diets change. Intestinal growth factors are likely to play a significant role in this process.

Is GLP 2 available?

GLP 2 is a fragile protein, which degrades in the body in minutes. As a result, it is not very useful in its natural form as it would have to be given as very frequent injections or as a continuous infusion.

However, by making small changes can be made to the GLP 2 protein, it is not broken down so quickly and therefore can be given as a once-a-day injection, or less. These are called GLP 2 analogues. Different pharmaceutical companies are working on different types of molecules. At the moment there is only one licensed medication called teduglutide (Gattex®, Revestive®). Other products will be available in time.

What do the studies show for the GLP 2 analogues?

The clinical studies that have been published so far using teduglutide show that patients who receive this treatment manage to decrease their dependence on parenteral nutrition or parenteral fluids. For some people this means that they have fewer bags infused overnight every week. There are some people also who have been able to come off their parenteral nutrition or parenteral fluids completely. Other benefits have been noted including improvement in liver function for these patients.

Who could this be helpful for?

Patients who have had surgery and have had large parts of their small bowel removed could benefit from this sort of treatment. This treatment can be considered in patients who have “short bowel syndrome” and are dependent on parenteral nutrition or parenteral fluid support.

Patients who have had a large amount of their small bowel removed have generally had the lower part of their small bowel removed. This is important as GLP 2 is produced in the lower part of the small bowel and therefore these patients will not be able to produce the GLP 2 hormone. As a result, the remaining small bowel does not have the stimulus from this hormone to grow in the same way as before. Therefore, giving medication that reproduces the GLP 2 hormone can be very effective.

Patients who do have their colon joined to their remaining small bowel do also respond to this treatment, but it can take longer.

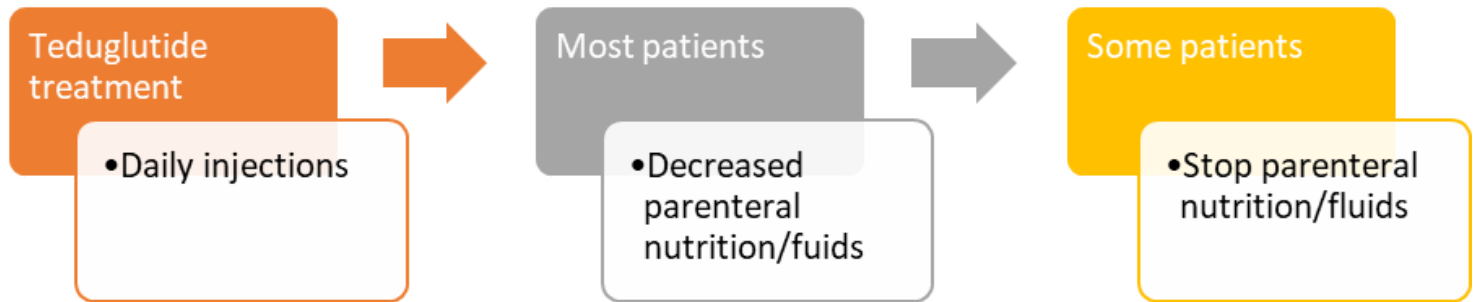
It also seems to be that patients who eat well are more likely to respond better to the treatment.

Who is this not helpful for?

This sort of treatment is not helpful for patients with intestinal failure, requiring intravenous nutrition or fluid support, but who do not have a short bowel. Also, patients who have obstructive symptoms (nausea and vomiting with abdominal pain) may get worse with this type of treatment.

What are the benefits?

From the trials that have been performed, it is clear that patients with a short bowel who receive teduglutide are more likely to be able to decrease their parenteral nutrition support, with a proportion of patients who were able to come off their parenteral nutrition support altogether. Another benefit seems to relate to liver function which can improve in patients on this type of treatment, however more research needs to be performed in this area. These benefits can be over the course of 1 or 2 years.



What are the side-effects?

This type of treatment is given as an injection. It is possible to have allergic type side-effects from the injection. Common side effects, occurring in over 10% patients include:

- Stomach pains
- Nausea
- Vomiting
- Swelling of the hands or feet
- Cold or flu symptoms
- Allergic reactions
- Skin reactions where the injection was given

In addition, patients who have had a cancer within the last 5 years should avoid taking anything considered to be a growth factor. So far, we are not sure if these growth factors accelerate the growth of cancers. Patients who have a residual large bowel (colon) do need to have regular surveillance to see if they form any polyps or early cancers.

Can I get this treatment?

In England & Wales, the National Institute of Clinical Excellence (NICE) approved teduglutide (Revestive®) in June 2022. It should start to be available for the treatment of patients aged 1 year and above with short bowel syndrome (SBS) from around October 2022. Patients should be stable following a period of intestinal adaptation after surgery.

In Scotland, the Scottish Medicines Consortium approved teduglutide in the context of an approved NHS Scotland Patient Access Scheme arrangement for children in April 2018 and in adults in February 2020.

Other GLP 2 analogues are currently being developed. Glepaglutide and Apraglutide are currently undergoing a worldwide clinical trial and there are centres in the UK who are part of this trial. Therefore, it is possible to get onto a trial and receive the medication while the trial is running. Ask your doctor or nutrition team for more information.

Glossary of terms

| | |
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| Duodenum | The first part of the small bowel |
| Jejunum | The second part of the small bowel |
| Ileum | The third (last) part of the small bowel |
| Villi | Small project or ions or bumps on the surface of the small bowel |
| Microvilli | Small projections or bumps on the surface of the villi |
| Glucagon-like peptide 2 (GLP-2) | A natural hormone produced by the ileum that stimulate the growth of the upper small bowel |
| Glucagon-like peptide 2 analogues | Artificially produced proteins that mimic GLP-2 and are used as treatments |
| Teduglutide | The first GLP-2 analogue that has become available for use in patients with short bowel syndrome |
| Glepaglutide | A GLP-2 analogue undergoing trials |
| Apraglutide | A GLP-2 analogue undergoing trials |

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