UNIVERSITY OF Hull

Factors governing gastrointestinal motility

Submitted for Degree of Doctor of Medicine 2012

By

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Abstract

Introduction: The reasons for the rapid resolution of diabetes (DM) following bariatric surgery in a significant proportion of patients with morbid obesity remain unclear. This thesis investigates the putative role of changes in gastrointestinal (GI) motility and GI hormones as well as the possible significance of alterations in energy expenditure that occur as a consequence of weight loss.

Methodology: My preliminary studies involved a systematic review of GI motility in obesity, and retrospective studies measuring GI motility with alternative methods including capsule endoscopy and hydrogen breath test. Subsequent to this I measured changes in GI motility in two very different patient cohorts; one following bariatric surgery for morbid obesity and the other a group of patients with proven gastroparesis treated with gastric neuromodulation (GNM). Parallel to the above I conducted studies of indirect calorimetry in these patients in an attempt to determine if changes in energy expenditure which occur as a consequence of weight loss were significant.

Results: In our prospective study temporary GNM significantly improved gastric emptying and nutritional intake.

There was conclusive evidence to causally relate alterations in GI motility and Glucagon like peptide -1 (GLP-1) with weight loss and resolution of DM following bariatric surgery.

An interesting "spin off" result of my studies was validation of capsule endoscopy (CE) as a means of assessing GI motility.

My results obtained from measure if indirect calorimetrty clearly show that standard equations tend to over estimate the energy requirements of this group. The implications of this are discussed.

Conclusions:

1. Fast pouch emptying; an early and exaggerated GLP-1 response contributes in resolution of type 2 diabetes following RYGB.

2. GNM is an effective treatment for gastroparesis.

3. Capsule endoscopy may be used to assess GI motility.

4. Prediction equations over estimate energy requirements in morbidly obese patients.

This thesis is submitted in accordance with the requirements of the Degree of Doctor of Medicine (MD), University of Hull.

The candidate confirms that the work submitted is his own and appropriate credit has been given where references have been made for the work of others.

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Statement of originality

This thesis has been prepared by the candidate. Work comprises of a review of the relevant literature and original studies (4 clinical trials and 3 retrospective studies). The investigative work described in this thesis was performed solely by the candidate, except where clearly described. Appropriate credit has been given where references have been made to the work of others. This thesis has not been submitted for any other academic/professional degree. Publications and academic recognition as a result of work in this thesis are described in the appendices.

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Abbreviations

AOI	Area of interest
ARSAC	Administration of Radioactive Substances Advisory Committee
BMI	Body mass index
BPD	Biliopancreatic diversion
BPD-DS	Biliopancreatic diversion + duodenal switch
BSG	British Society of Gastroenterology
CCK	Cholecystokinin
CE	Capsule endoscopy
CHO	Carbohydrate
CT	Computed tomography
DDP-IV	Dipeptidyl peptidase IV
DM	Diabetes mellitus
EGG	Electrogastrography
GE	Gastric emptying
GES	Gastric electric stimulation
GI	Gastrointestinal
GIP	Gastric inhibitory peptide
GLP, GLP-1	Glucagon-like peptide, Glucagon-like peptide-1
GNM	Gastric neuromodulation
GS	Gastric scintigraphy
H2	Hydrogen
HB	Harris-Benedict
HCL	Hydrochloric acid
IC	Indirect calorimetry
IPG	Implantable pulse generator
IR	Insulin resistance
IT	Intestinal transit
JIB	Jejunoileal bypass
LAGB	Laparoscopic adjustable gastric band
MMC	Migratory motor complex
MRI	Magnetic resonance imaging

NHS	National Health Service
NICE	National Institute of Clinical Excellence
OCTT	Orocaecal transit time
PCT	Primary Care Trust
PN	Parenteral nutrition
Ppm	Parts per million
PYY	Polypeptide Y
QOL	Quality of life
REE	Resting energy expenditure
RYGB	Roux-en-Y gastric bypass
SC	Schofield
T50	Gastric half-emptying time
TPN	Total parenteral nutrition
TSS	Total gastroparesis symptom score
USG	Ultrasonography
VFS	Vomiting frequency score/week
VIP	Vasoactive peptide

1 <u>Introduction and literature review</u>

"That Quantity that is sufficient, the Stomach can perfectly concoct and digest, and it sufficeth the due Nourishment of the Body."

Benjamin Franklin 1706–1790

1.1 Introduction to GI motility

1.1.1 Gastric emptying (GE)

Definition: The fraction of food delivered into the intestine in unit time is called *the gastric emptying time* (GE time).

Basic physiology of the GI tract: The basic structure of the alimentary canal shows that its wall follows a constant pattern from the oesophagus onwards. The wall of the alimentary canal consists of the following layers (Figure 1-1):

1. Adventitia or serosa (outer layer)
2. Muscle layer
3. Submucosa
4. Mucosa (inner layer)

Adventitia is a loose fibrous tissue and in the abdomen it is covered by a serous membrane called the *peritoneum*. The muscle layer consists of two layers of involuntary muscle including an outer longitudinal layer and an inner circular layer. Blood vessels, lymphatics and nerves (including the plexus) run between these two layers. This plexus (network) consists of nerve fibres from sympathetic and parasympathetic tracts and is called the *myenteric/Auerbach's plexus*. Contraction and relaxation of these muscles cause peristalsis. Peristalsis of the oesophagus delivers the food into the stomach. This involves symmetrical contraction and relaxation of the muscles which propagates in a wave down the muscular tube. Intestinal and gastric hormones also play a vital role in this process. Some of them are briefly described in Table 1-1. Muscle contraction is also used to mix food with the digestive juices. At various points the sphincters control this movement. These sphincters consist of a thick layer of circular muscle and are innervated by the parasympathetic and sympathetic nervous systems. Contraction of sphincters regulates food movement. They also act as a one-way valve and prevent the backward flow of GI contents. This control helps the food to be digested and absorbed in various parts of the GI tract.

The submucosal layer consists of loose connective tissue (containing collagen and elastic fibres) which binds the muscle layer with mucosa. Another plexus of blood vessels, lymphatics, and nerves lie within this layer. The nerve plexus in this layer is called *Meissner's plexus* and also consists of parasympathetic and sympathetic connections. Meissner's plexus and the myenteric plexus are explained in detail below.

Mucosa (the inner most layer) consists of 3 layers:

A. Mucosal membrane: This is formed by stratified squamous epithelium in the oesophagus and columnar epithelium in the stomach, and the small and large intestine. Its main functions include secretion and absorption. Below the surface of the mucous membrane in specific areas, collections of specialised cells (glands) are present which release their secretions in various parts of the GI tract. This includes gastric, intestinal, pancreatic, and bile secretions.

B. Lamina propria: Loose connective tissue containing blood vessels and lymphatics.

C. Muscular mucosa: A thin layer of smooth muscles.
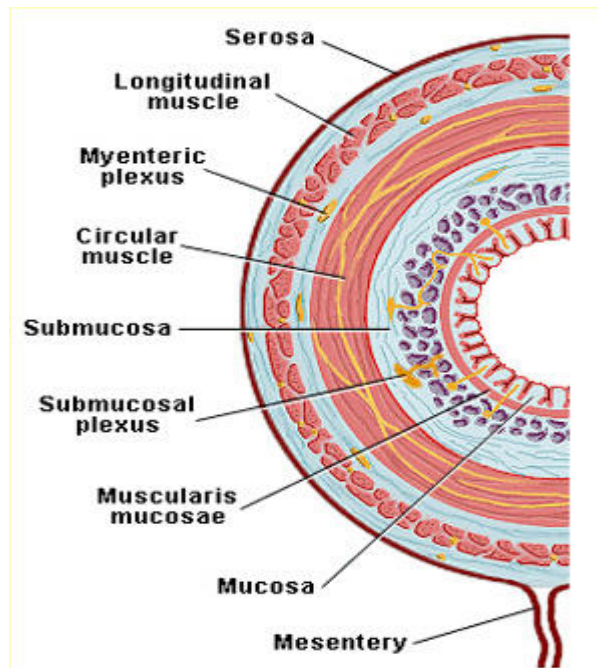
Figure 1-1: Layers of the GI tract

Serosa (outer layer), longitudinal muscle, Myenteric plexus, circular muscle, submucosal plexus, muscular mucosae, mucosa (inner most).

Anatomy and physiology of stomach:

The average capacity of an adult stomach is 1.5 litres. The basic anatomy includes a J-shaped dilated abdominal part of the GI tract. Different parts of the stomach are briefly described below in Figure 1-2:

1. Cardia: the upper part is connected to oesophagus.

2. Fundus: under the diaphragm and which is usually filled with gas.

3. The body extends from the cardia and fundus to continue to the antrum. The body of the stomach contains 2 surfaces and 2 curvatures (lesser and greater curvature).

4. Antrum: starts at the level of the lower part/notch of the lesser curvature (incisura) and continues down as the pylorus.

5. Pylorus/pyloric canal: the last part of the stomach, it is controlled by the pyloric sphincter. This continues as the first part of the duodenum.
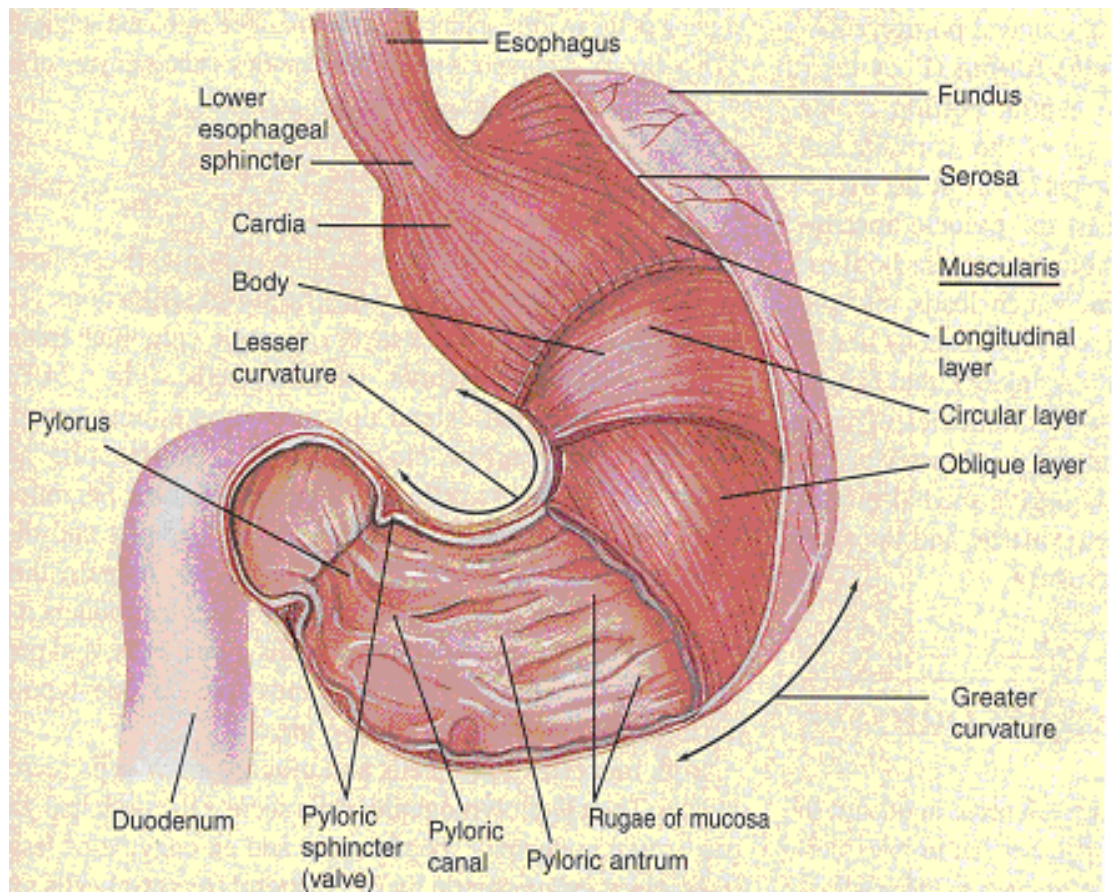
Figure 1-2: Anatomy of the stomach

Anatomical location, parts of the stomach, musccle layers of the stomach.

The stomach serves three main <u>functions</u> which are:

1. Food storage: an adult stomach can accommodate 1.5 litres of food. However, this may vary depens ding on eating habits and increases in obesity.

2. Mixing the food with gastric secretion and formation of chyme. There are 2 types of waves in the stomach which serve this function: the peristalsis waves and mixing waves. Mixing waves originate mid-stomach (body) at a rate of 8–10 per minute. In the stomach these waves are strong and they rise above the threshold even without action potential. Rhythmic gastric peristalsis without food in the stomach is called hunger pangs/hunger contractions. They usually begin 12–24 hours after the last meal. The constrictive peristalsis and mixing waves together convert the food particles into chyme in the presence of gastric juice.

3. Controlled delivery of food into the intestine (GE).

Electrical activity in the GI's smooth muscles

Smooth muscles in the GI tract contain a continuous electrical activity. This consists of two types of waves:

1. Slow waves
2. Spikes

Slow waves: slow waves are the main determinants of rhythmic contraction throughout the GI tract. Their occurrence is secondary to change in the underlying resting membrane potential in the smooth muscles of the GI tract. Their typical intensity varies between 5–15 millivolts. The frequency of slow waves varies in different parts of the GI tract. In the stomach the typical frequency is 3 per minute, in the duodenum it is 12 per minute and in the rest of the small intestine it is 8–9 per minute. The exact mechanisms of slow-wave production are not known; however, it is believed that they may result from the activity of a sodium-potassium pump in the GI's smooth muscle. The gastric slow waves result in muscle contractions in the stomach; however, they control the spike waves in other parts of the GI tract which potentiates the muscle contraction.

Spike waves: spike waves are true action potential. They are generated in the *interstitial cells of Cajal*.[1, 2] These cells are satellite pacemaker cells with multiple branches that send to the GI smooth muscles. In the stomach and small intestine they are located in the outer circular layer of smooth muscles. Upon activation of these pacemaker cells, the resting membrane potential in the GI's smooth muscles becomes more +ve. The usual resting membrane potential in GI smooth muscles is between 50 and -60. A large influx of calcium ion (Ca) along with a small amount of sodium (Na) results in an increased +ve charge inside the muscle fibre. This process is conducted through Ca-Na channels. This results in decreased -ve charge (influx of +ve ions) and the membrane potential drops from -60 to -40. The typical frequency of these waves ranges between 1 to 10 spikes per second. The action potential generated by the GI smooth muscles is different compared to the nerve fibre, as in nerve fibres the action potential is generated by Na-K (potassium) channels and the entry of ions in smooth muscles is significantly slow compared to nerve fibres. The influx of Ca ions in gastric smooth muscle is the key factor in the generation of contraction of the intestinal smooth muscle.

In a fasting state, the electrical and motor activity of the GI tract is slightly modified, and the cycles of this activity propagate from the stomach to the ileum and this is known as the *Migratory Motor Complex*.[1] The pattern runs in three phases. Phase 1: no spike potentials/contractions; Phase 2: irregular spike potentials resulting in irregular contractions; Phase 3: regular spike potentials and contractions. This pattern is inhibited by the meal and reoccurs after 90–120 minutes following a meal.

Tonic contraction: Some smooth muscles of the GI tract display tonic contraction. This may be in conjunction with GI contraction waves or isolated and not combined with these contractions. Tonic contractions usually last for several minutes or even hours. The intensity may increase or decrease; however, sometimes they may be caused by continuous spike potentials. The other possible causes of tonic contractions include depolarisation of smooth muscles caused by hormones and Ca influx in the GI smooth muscles[3, 4]

Nerve supply of GI tract

The nervous system in the GI tract and associated organs are supplied by both divisions of the autonomic nervous system, i.e. sympathetic and parasympathetic nervous system. In addition, the network of two plexus (myenteric and Meissner's) in the GI tracts remains the mainstay of GI control. They have briefly been described above. Collectively this system is called the *enteric nervous system*. It extends from the oesophagus to the anus. The main function of the enteric nervous system is to control GI motility and secretions.

1. Enteric nervous system

The myenteric plexus (between the longitudinal and circular muscle layer) and Meissner's (submucosal) plexus are shown in Figure 1-3. The main function of Myenteric plexus is to control GI motility and the main control of Meissner's plexus is to control GI secretions and blood flow. Although the enteric nervous system may work on its own, its function is potentiated and controlled (increased or decreased) by the autonomic nervous system. Sensory control of GI epithelium is conducted to the enteric nervous system as well, and afferent fibres to prevertebral ganglia of the sympathetic

chain. Therefore, some of these signals travel to the spinal cord (through paravertebral ganglia) and the rest of them travel to the brain through the vagus nerve.

There is a structural difference between the two plexus. The myenteric plexus tends to run in a linear and chained pattern. These chains are located a few millimetres from each other. This pattern helps to control GI motility. The myenteric nervous system on activation results in increased intensity of rhythmic contraction by increased intensity, increased frequency and basal tone of the gut wall. It is, however, important to note that not all the fibres in the mesenteric plexus are excitatory. Some of these fibres secrete inhibitory peptides and signals to inhibit the food movement at sphincter levels. Amongst them, two sphincters are of great importance:

     a. Pyloric sphincter (to control GE)

     b. Iliocaecal sphincter (to control intestinal transit)

In contrast, the Meissner's plexus is mainly associated with GI secretions and absorption of food. It acts in response to the signals originating from the epithelium and produces secretions and/or absorb the food and other particles.

The important neurotransmitters at the nerve endings of the enteric nervous system include (1) acetylcholine and (2) noradrenaline. There are certain other neurotransmitters being discovered; however, their function and existence is still in the experimental stages. The main function of acetylcholine release at these nerve endings of the enteric nervous system is excitatory (i.e. it increases GI activity), and noradrenaline is inhibitory (i.e. decreases GI activity).

The Brain in Your Gut

The gut's brain, known as the enteric nervous system, is located in sheaths of tissue lining the esophagus, stomach, small intestine and colon.

SMALL INTESTINE CROSS SECTION

Submucosal plexus ·················
Layer contains sensory cells that communicate with the myenteric plexus and motor fibers that stimulate the secretion of fluids into the lumen.

Myenteric plexus ·················
Layer contains the neurons responsible for regulating the enzyme output of adjacent organs.

Lumen No nerves ·················
actually enter this area, where digestion occurs. The brains in the head and gut have to monitor conditions in the lumen across the lining of the bowel.

Mesentery
Attaches the bowel to the body wall and contains major arteries, veins, lymphatics and external nerves.

Source: Dr. Michael D. Gershon, Columbia University

Figure 1-3: Description of the enteric nervous system

Mesentry of GI tract elaborating enteric submucosal plexus, myenteric plexus.

2. Autonomic Nervous system

a. Sympathetic nervous system (Figure 1-3)

The sympathetic fibres innervating the GI tract originate from segment T5 (thoracic 5) to segment L2 (lumbar 2) of the spinal cord. Preganglionic fibres enter the sympathetic chains after leaving the spinal cords and end at their corresponding ganglia including the celiac and mesenteric ganglia. Postganglionic fibres originate from the ganglion and end at the neurons of the enteric nervous system. The sympathetic innervations comprise all parts of the GI tract, and the nerve endings of the sympathetic neurons secrete noradrenaline. The sympathetic stimulation of the GI tract results in the inhibition of GI activity. A strong stimulation of the sympathetic nervous system may

result in the blockage of food and motility through the GI tract. This is caused mainly by the direct effect of noradrenaline (secreted at the sympathetic nerve endings) on the gastric smooth muscles.

b. Parasympathetic nervous system (Figure 1-3, Figure 1-4).

The parasympathetic nerve supply to the GI tract is derived from cranial and sacral parts. Cranial parasympathetic nerve fibres are transmitted through the vagus nerve. These fibres innervate oesophagus, stomach, intestine, pancreas, gall bladder, proximal part of large intestine.

The sacral parasympathetic nerve fibres originate from segments 2, 3 and 4 of the sacral part of the spinal cord. These fibres run through the pelvic nerves and innervate the large intestine, sigmoid colon, rectum and anal canal. These fibres also control defecation reflux as internal anal sphincter is relaxed and a forceful pelvic muscle contraction and peristalsis of colon push the faeces when there is an urge. External anal sphincter is under voluntary control. Parasympathetic ganglia lie in the effector organs as a part of the enteric nervous system (enteric plexus) and the postganglionic fibres innervate the oesophagus, stomach, intestine, pancreas, gall bladder, liver, colon, rectum and anal canal. The main function of parasympathetic activity is excitatory (increased activity).

The vagus nerve (Xth cranial nerve)

This nerve originates from the medulla oblongata and leaves the skull through jugular foramen. These nerve comprise sensory and secreto-motor fibres. It passes through the carotid sheath and supplies meninges, auricle, pharynx, larynx and then enters the thorax. The left vagus nerve supplies the heart, lungs, great vessels, trachea, bronchi and oesophageal plexus before entering the abdomen anterior to the oesophagus. The right vagus passes behind the right lung and supplies the pulmonary plexus, oesophageal plexus (posteriorly) and reaches the anterior part of the stomach with the left vagus nerve. The oesophageal sphincter is also innervated by the fibres of both vagus nerves. In the abdomen, vagus nerves innervate most of the abdominal viscera including the GI tract, liver, gall bladder and pancreas. 80% of the vagus nerve fibres are afferent

(sensory) whereas the remainder act as efferent (secreto-motor) to all the organs below the neck (the organs in the thorax and abdomen). There is an exception, however, as the suprarenal gland and part of the large intestine is not innervated by vagus (as explained above).
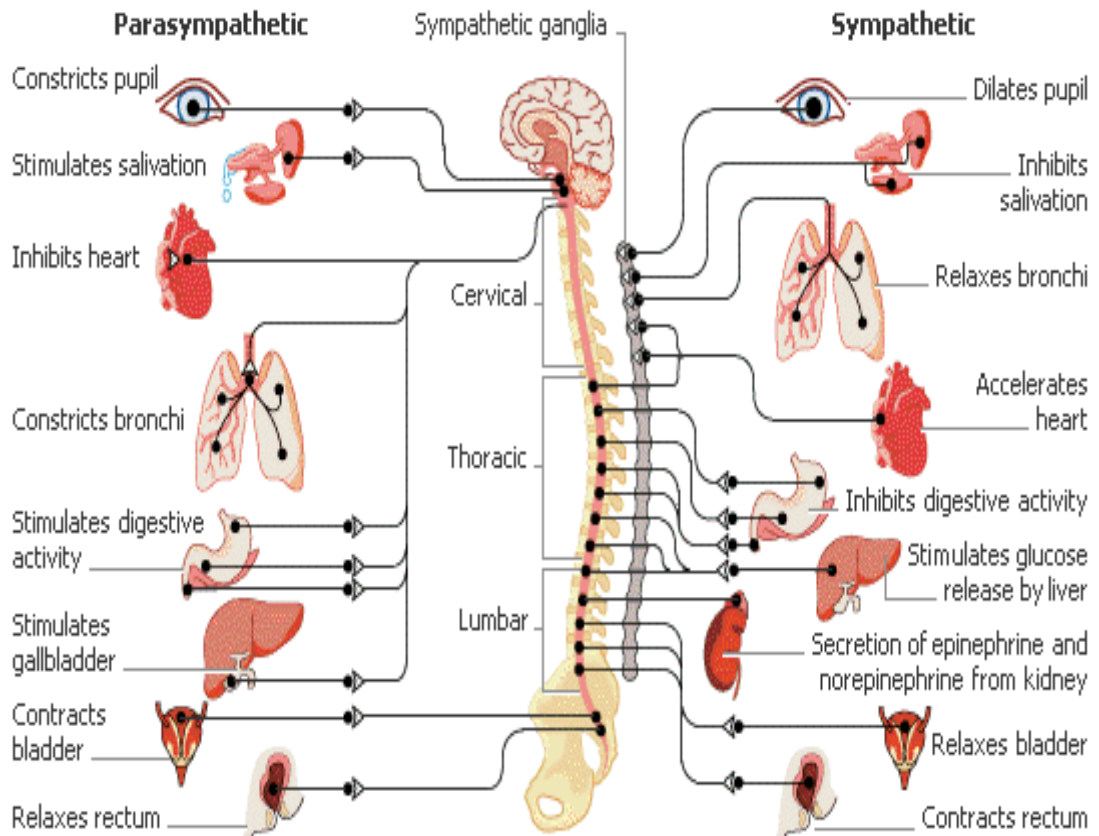
Figure 1-4: The sympathetic and parasympathetic nervous system
Cranio-sacral part of parasympathetic (left side) and thoraco-lumber (right side) part of autonomic nervous system.

c. GI reflexes

The enteric and autonomic nervous systems support three types of GI reflexes which are important for GI function.

1. Reflexes within the enteric nervous system. They facilitate GI secretions, contractions and maxing of food.

2. Reflexes between the GI tract and the sympathetic chain. They include *gastrocolic reflex* (to cause evacuation/defecation of faeces after intake of a meal), *enterogastric* (from intestine to stomach – to reduce/inhibit gastric motility and GE) and *colonoileal reflex* (to reduce GI transit of contents from small intestine to colon).

3. Reflexes between the GI tract and the spinal cord and/or brain. These include:

GE reflex (via the vagus nerve) to control gastric secretary and motor activity.

Pain reflex resulting in inhibition of GI motility and decreased GI function.

Defecation reflex involving the spinal cord. This involves the colon, rectum, anal sphincters and abdominal muscles for defecation.

Physiological GI motility

There are two types of movements in the GI tract to facilitate its function.

1. Propulsive/peristalsis

This is the basic and most important GI movement. A contractile ring appears at a particular part of the GI tract which propagates and is followed by a similar contraction ring. This is a result of synchronised smooth muscle activity of the GI wall. The same principle applies to the GI ducts, and hormone ducts. The food in the GI tract is detected by the stretch on its wall, which stimulates the enteric nervous system which, in turn, results in the formation of a ring above the bolus/food to propel it to the next part of the GI tract. In addition to food and dissention, they can also be activated by stimulation of parasympathetic activity by the vagus nerve. Therefore, peristalsis can be reduced or stopped if the cholinergic nerve endings of the myenteric plexus are paralysed or treated with atropine. Each peristalsis is considered to push the bolus or food for 5–10 cm before they finish and are preceded by another wave/movement. The peristaltic waves start in the pharynx and continue in the oesophagus after the pharyngeal stage of swallowing. A wave takes about 8–10 seconds to reach the stomach and if the subject is sitting upright the food may reach the stomach quicker than the peristalsis. Distension of the oesophagus results in a secondary peristalsis wave due to the presence of food. As the upper third of oesophageal muscles are stratified, this part of peristalsis is controlled by skeletal nerve impulse generated by the glossophareangeal nerve and the vagus nerve. However, from the second part of the oesophagus onwards the vagus nerve takes over the control. As the food passes through the oesophagus, the

inhibitory neurons in the enteric nervous system of the stomach and duodenum are activated, resulting in relaxation of the gastric and duodenal smooth muscles for the accommodation of food. In addition, the distal oesophagus acts as a one-way valve and prevents reflux of proteolytic gastric contents. Peristalsis in the oesophagus is elaborated in Figure 1-4 and Figure 1-5.
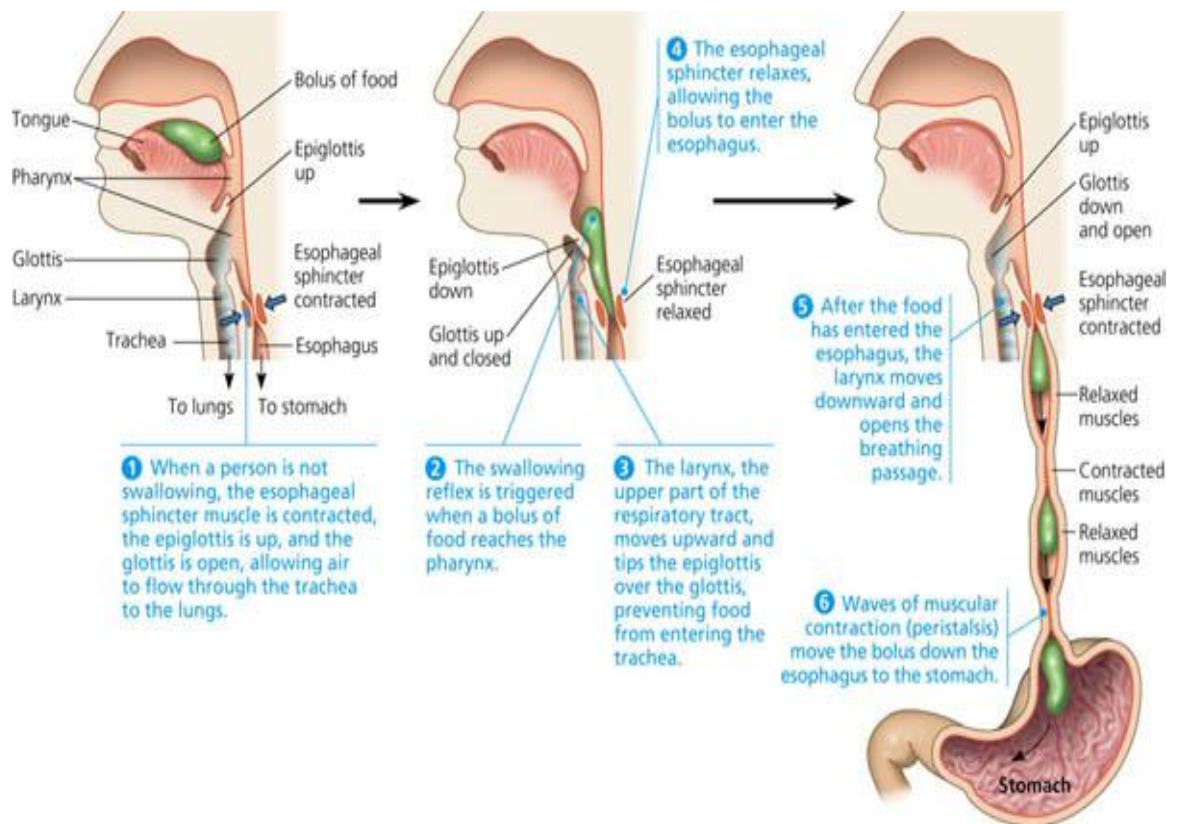
Figure 1-5: Mechanism of peristalsis

Upper oesophageal sphincter, swallowing reflex, mechanism of peristalsis elaborated in the figure above.

2. Mixing

Peristalsis acts as a mixing wave at certain parts in the GI tract. However, there are different forms of movements acting as mixing waves/movements in other parts of the

GI tract, especially in the stomach. A strong peristaltic wave throughout the stomach along with the mixing wave pushes the food down into the pylorus. However, the pylorus remains closed or opens only a few millimetres, permitting only a small amount of food into the duodenum. The remainder is pushed back into the body of the stomach for further mixing.

Gastric motility and emptying

GE is mediated by strong peristaltic contractions in the antrum of the stomach. When the food enters the stomach, the fundus and body of the stomach relax to accommodate the food with minimal increase in pressure. This phenomenon is called *receptive relaxation.* Most of the gastric contractions (80%) do not exceed the threshold; however, 20% become very powerful and do not act as mixing waves/contraction, but rather act as strong emptying waves. They become more intense in the lower body of the stomach and move further up and up in the stomach as the stomach empties. These strong antral contractions at this stage are called *antral systole.*[1] The pressure generated by these contractions is quite high and often reaches 50–70 cm of water pressure. Each peristalsis forces several millilitres of chyme into the duodenum through the pyloric pump. Normally the intestinal contents do not regurgitate as pylorus acts as a pump; however, it may be overridden by certain factors like atony of the distal part of the GI tract or mechanical obstruction.

The role of the pylorus in GE

The distal part of the stomach is called the *pylorus*, as shown in Figure 1-2. The circular smooth muscle increases up to 100% at this level and remains in a state of tonic contraction. Therefore, these muscles are called *pyloric sphincter*. The pylorus regulates food delivery by enterogastric reflux, as explained above. This is mediated by hormones, local signals by the enteric nervous system and the vagus nerve.

The suggested factors to contribute in GE are described as follows:

1. Gastric influence

A. Food volume: Increased food volume in the stomach is thought to promote GE. It is, however, considered that it is not the pressure of the food itself which generates the GE, but rather the stretch on the gastric mucosa resulting in myenteric reflexes promoting the activities like gastric contractility and increased pyloric pump activity.

B. Gastric hormones: Food in the stomach stretches the walls resulting in the release of gastrin hormone. Gastrin has a strong effect on the stimulation of gastric acid secretion; however, it is also considered to enhance the motor function of the stomach by the pylorus pump. It is, however, important to note that a new hormone, ghrelin, is also considered to enhance GE and its peak is considered to be much earlier than the food actually reaching the stomach. There is, however, very little objective evidence in terms of the release of this hormone in response to food and its impact on gastric empting in humans.

2. Duodenal/small intestine influence

A. Enterogastric reflex: the presence of food in the duodenum causes the reflex inhibition of gastric acid production and reduces GE by the activation of the enteric nervous system, and is also helped by certain hormones including cholecystokinin (CCK), gastric inhibitory peptide (GIP) and polypeptide Y (PYY). This also results in the inhibition of the gastric G cells to produce gastrin. Duodenal hypertonicity, duodenal acidic pH, and sympathetic stimulation also result in the inhibition of GE.

B. Hormonal control: Hormones such as CCK, GIP, PYY, motilin and secretin have extensively been studied in the past in relation to their role on GI motility. In addition, glucocorticoids and catecholamines (adrenaline and noradrenaline) also have an effect on GI motility. Some of them are released in the circulation and effect remote target organs/cells, and are called *endocrine hormones*. This includes gastrin and secretin. The peptides/hormones which act on nearby target organs/cells by diffusion through

interstitial apace are called *paracrine peptides/hormones*. This includes histamine and 5HT. Neurocrines release from the nerve endings and act through nerves and neurotransmitters. This difference of enteroendocrine cells is described in Figure 1-6.
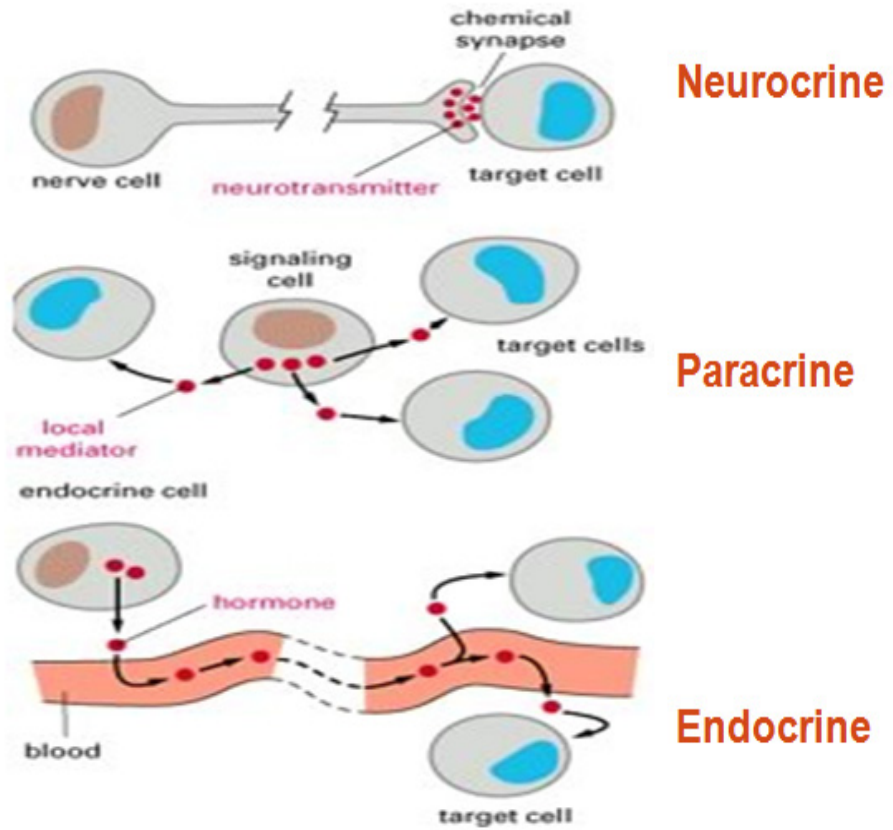
Figure 1-6: Enteroendocrine cells

Overview of signalling mechanism of neurocrine, paracrine, endocrine hormones in GI tract.

A brief description of these hormones along with their gastric metabolic role and their role in GI motility are described in table below (Table 1-1).[1, 3, 4]

Table 1-1: Hormones influencing GE and intestinal transit (IT)

Name	Organ	Physiology and mechanism of action
Gastrin	Secreted mainly from the stomach. Fractions secreted by the hypothalamus, vagus nerve.	Polypeptide with multiple forms. Types: There are different forms of gastrin, however, G17 is the commonest form secreted from the stomach. Secreted by: G-cells in the stomach in response to distension of the stomach. Also released in response to vagal stimulation, hypercalcaemia. ↑ Gastrin secretion by: gastric distension, vagal stimulation, Ca and epinephrine. ↓ Gastrin secretion by: acidic contents in bowel lumon, somatostatin, other hormones secretin, GIP, VIP (vasoactive peptide), glucagon and calcitonin these are considered to reduce the secretion of gastrin. Functions include: 1. Stimulating parietal cell maturation and fundal growth. 2. Causing chief cells to secrete pepsinogen. 3. Secretion of HCL from parietal cells. 4. Release of insulin after carbohydrate (CHO) meal. 5. Increasing antral muscle motility and promoting stomach contractions.[5] A small amount of this hormone is released from

		the duodenum and the pancreas as well. It also causes increased motility in the stomach. The role of gastrin is established in diseases like Zollinger-Ellison Syndrome and autoimmune gastritis.[5] Inhibition of gastrin: is caused by direct negative feedback to G cells. Other mechanisms include the release of somatostatin. Gastrin levels are high in conditions with pernicious anaemia because of damaged parietal cells.
Ghrelin	Stomach	28-amino acid peptide/hormone. Ssecreted by P cells in the stomach. It is also secreted from the intestines, kidneys, pituitary, hypothalamus and placenta.[6] Based upon previous studies, it is considered to be an appetite stimulatory hormone as levels were recorded high before meal intake.[6,7] It also: - Is considered to alter GE.[7] - Stimulates growth hormone from the pituitary gland. Ghrelin is described in detail below.
GIP	Small intestine	Secreted by the K cells in small intestine. Mainly from the duodenum and jejunum. It is also called *incretin* hormone (a hormone that enhances insulin secretion and/or sensitivity) along with GLP (a glucagon-like peptide). Functions:

		1. Inhibits gastric acid production by the direct inhibition of parietal cells or indirectly by G cell inhibition via somatostain.
		2. Insulinotropic (insulin release) from pancreas in response to glucose and fat in duodenum and jejunum.
		3. No strong evidence that it affects GI motility.
		GIP is inactivated by dipeptidyl-peptidase IV (DPP-IV).
GLP	Mainly by the small intestine. A small fraction is secreted by the pancreas and neurons in hypothalamus and pituitary gland.	Secreted: mainly by distal ilium (L cells). Functions: 1. It is also called *incretin hormone*, i.e. it is secreted in response to glucose in the GI tract and it potentiates the release of insulin from the pancreatic beta cells along with GIP. 2. It is considered to reduce food intake by decreasing GE.[8] 3. Reduces the release of Glucagon from alpha cells of pancreas. GLP is discussed in detail below.
Secretin	Small intestine	A polypeptide secreted from S cells of the duodenum and jejunum. Its target cells are located mainly in the pancreas. Function: 1. ↑ pancreatic enzyme secretion. 2. ↓ gastric acid secretion. 3. Pyloric sphincter contraction. 4. Produces watery bile rich in HCO_3.

Cholecystokinin (CCK)	Mainly from the small intestine. Also secreted from the distal ileum, colon and fractions in the hypothalamus.	Secreted by: mainly from the duodenum and jejunum I cells. Forms: there are multiple forms of CCK in circulation secreted in response to fatty and/or protein rich meals. The common forms of CCK include CCK8, CCK22 and CCK33. However, in the brain CCK8 and CCK58 are found, whereas the pancreatic cells secrete small amounts of CCK 4. Functions: CCK is considered to initiate gall bladder contraction and relaxation of the sphincter of Oddi to facilitate fat digestion and absorption. Increases pancreatic secretions. Enhances the effect of secretin in the release of pancreatic secretions. Adds to the contraction of the pyloric sphincter. Has a possible role in satiety induction through its effect on the hypothalamus. Reduces the meal intake, delaying GE.[9] Control of CCK: Most potent lapids. Proteins and amino acids also increase its release.

Amongst these hormones, ghrelin and GLP were considered to be most important in terms of their effect on GE and intestinal transit (IT). These hormones were also deemed important because of their proposed role in glucose homeostasis. Here follows a detailed description of these hormones along with their proposed role in GI motility and glucose metabolism:

Ghrelin: Its name is based on *ghre*, a Proto-Indo-European word meaning *grow*, in reference to its ability to stimulate growth hormone (GH) release.[6] It is a 28-amino acid peptide, as shown below. In the stomach the ghrelin-producing cells are present in the fundus and pylorus. The G cells (producing ghrelin) are present in the mucosal layer.
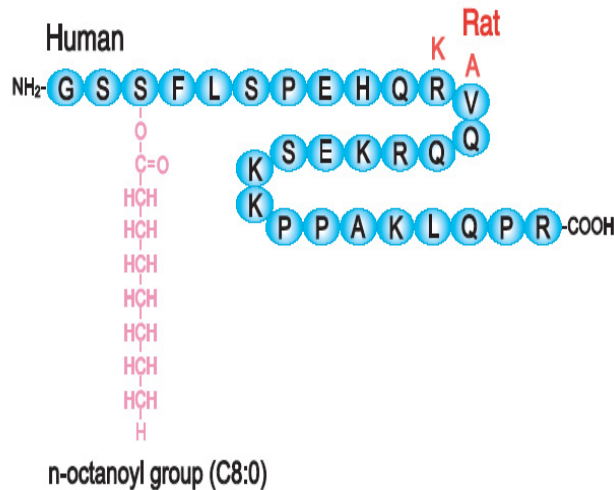
FIG. 3. Structures of human and rat ghrelins. Both human and rat ghrelins are 28-amino acid peptides, in which Ser3 is modified by a fatty acid, primarily *n*-octanoic acid. This modification is essential for ghrelin's activity.

Figure 1-7: Structure of ghrelin

Many forms of ghrelin have been described in literature; however, two common forms include active (acylated) and inactive (non-acylated) ghrelin.[6] Inactive ghrelin is found in larger quantities in the blood as its clearance rate is low and therefore its half-life is higher compared to active ghrelin. Inactive ghrelin is considered not to possess endocrine activities. The normal plasma levels in humans is 10–20 fmol/ml for active (acylated) ghrelin and 100–150 fmol/ml for total ghrelin, including both active and non-active ghrelin.

Ghrelin receptors are mainly present in the hypothalamus and pituitary gland. Ghrelin has mainly been found in the arcuate nucleus of the hypothalamus, which is an important region to control appetite.[6, 10] In addition, ghrelin is also found in the third ventricle and the paraventricular areas of the brain adjacent to the hypothalamus. These areas are related to food and appetite control. It is considered that by the activation of neuropeptite Y (NYP) and agouti-related protein (ARP), ghrelin helps to control appetite in the hypothalamus. Similarly, in the pituitary gland GH-releasing somatotrophs are the target cells for ghrelin. In addition, ghrelin is found in the pituitary gland and acts as an autocrine and paracrine hormone.

it is well accepted that feeding is mainly controlled by the hypothalamus. Feeding is controlled by a balance between excitatory and inhibitory signals in the hypothalamus. Previous studies have suggested that intravenous and subcutaneous injections of ghrelin increase food intake.[11] The same response has also been observed when ghrelin was injected into the third ventricles of the rat brain.[12] These studies along with some other studies elaborate the role of this hormone as an appetite stimulant.

The proposed mechanism of appetite stimulation by ghrelin is mediated by the release of NYP and ARP in the hypothalamus. This is mediated by ghrelin secreted by the stomach and signals conducted by the vagus nerve and through blood circulation.[6]

Ghrelin is considered as a satiety hormone as levels are considered to be higher in the fasting state and decrease after food intake.[13] The findings of this paper support the theory that ghrelin is a satiety hormone which does influence food intake. The findings of this paper are elaborated in Figure 1-8 below.
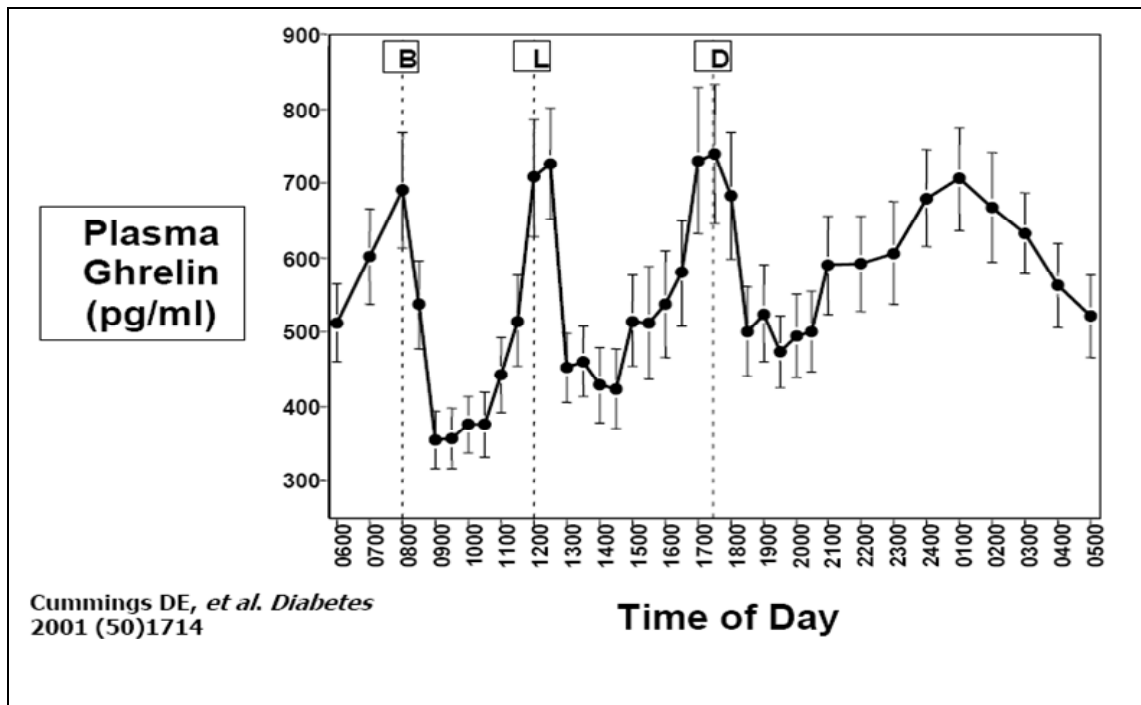
Figure 1-8: Change in ghrelin levels over 24 hours.

Higher Ghrelin levels observed before the meal intake.

Higher levels of ghrelin observed before meal intake (before breakfast, lunch, dinner).

The role of ghrelin in GI motility has been studied in very few studies. In a similar study, intravenous ghrelin resulted in an increase in gastric acid production and increased GE in rats.[14] There is, however, a lack of data in terms of the effects of ghrelin on GI motility in humans.

Ghrelin is also considered to be closely related to glucose homeostasis by its effects on insulin secretion. It is, however, yet to be proven whether a small amount of ghrelin may be released from the pancreas. A study by Date et al[15] reported that ghrelin increased insulin from the pancreatic cells in rats, suggesting its role in insulin and glucose homeostasis.

High plasma ghrelin levels have been reported in lean subjects and low levels observed in obesity.[7, 16, 17] Gastric bypass reduces the weight and ghrelin-producing cells are also bypassed. It is therefore believed that ghrelin levels may remain low after gastric bypass surgery.

Because of its impact on GH secretion, it is proposed that this hormone may be used in conditions associated with GH deficiency. In obesity, the blockage of appetite and an induced satiety may result in low food intake and treatment of obesity. However, further research is required on this hypothesis. In addition, there is limited data on its role to increase GI motility and GE.[14, 18] If proved, this may have a role in the treatment of paralytic ilius.

On the basis of these facts and hypothesis, ghrelin was considered to be an important hormone to be studied.

Glucagon-like peptide 1 (GLP-1):

Glucagon was discovered in 1923 as a hyperglycaemic agent in pancreatic juice.[19] The cells resembling pancreatic alpha (A) cells in gastrointestinal mucosa were subsequently discovered. These cells were further studied and found to be different in morphology compared to pancreatic A cells and were called *L cells*.[19] It was later established that the secretion/hormone secreted by these cells differs from glucagon in terms of morphology, physiology and biology.

GLP is derived from the proglucagon gene. In mammals, two different sequences of this gene result in two forms of GLP: GLP-1 and GLP-2. GLP-1 sequence remains preserved whereas GLP-2 changes into four different forms. L cells are mainly located in the distal small intestine and only a few cells are present proximal to ligament of Treitz.[20] The highest level of GLP-1 therefore is observed in iliel secretions.[21]

GLP-1 is very susceptible to degradation and catalytic activity of enzyme dipeptidyl peptidase IV (DDP-IV) results in a large amount of it becoming inactive immediately after release from the GI tract. It is estimated that 20–25% of newly secreted GLP-1 is inactive form, with further degradation of 50–60% in the liver, and therefore only 10–15% of active GLP-1 reaches systemic circulation.[19] The half-time of GLP-1 is very short (1–2 minutes). Release of the incretins (GLP-1 and GIP) along with insulin is described in the figure below (adopted from Wren et al).
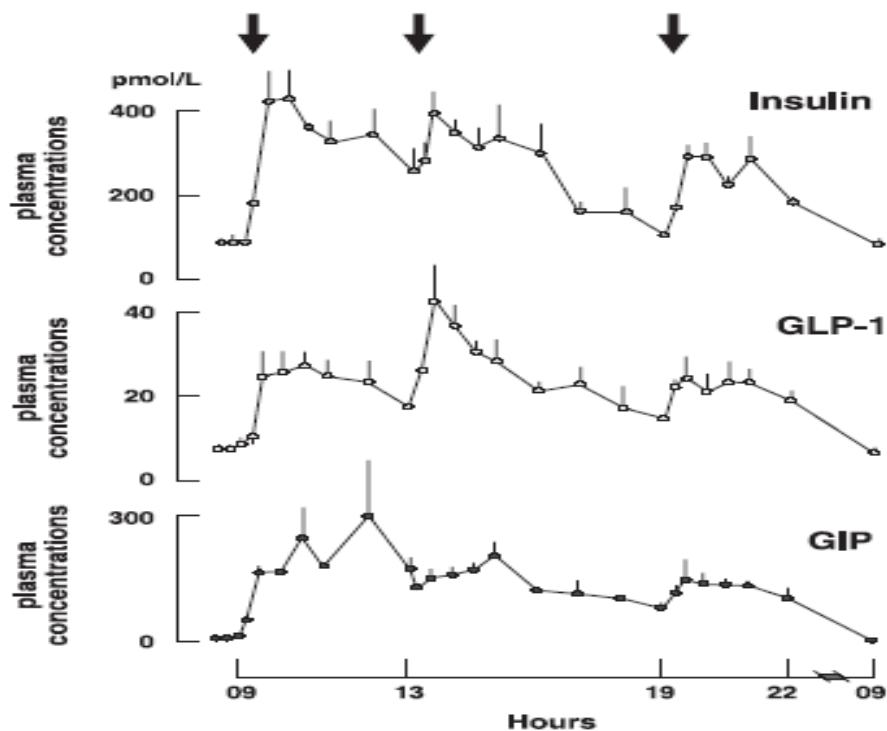
Figure 1-9: Release of incretins and insulin in healthy subjects
This figure suggests that a higher concentration of GIP is released; however, GLP was more related to the release of insulin.

GLP is a meal-related peptide. This has been demonstrated in previous studies.[19, 22] There is, however, a basal level of GLP secretion; therefore, in fasting state it is considered to be low but not zero. Furthermore, it is believed that the presence of food

in intestinal lumen results in the activation of L cells of the intestinal villi, causing GLP release.[23] Rapid release of GLP was seen when food was introduced into the ileum in normal subjects in an experimental setting.[24] In animal studies, GIP release may enhance GLP secretion; however, there was no evidence of this finding in human studies.[19] It was also observed that in a glucose meal response, atropine resulted in decreased GI motility and reduced GLP secretion.[19] The effect of vagal and sympathetic stimulation was observed in a recent study. This study demonstrated that sympathetic stimulation had an inhibitory effect on GLP secretion; however, it was concluded that vagal stimulation did not result in increased GLP secretion.[25]

GLP receptors are located in the pancreas, brain, kidney, heart and GI tract, including the stomach.[19] Their presence and the mechanism of action of GLP on these organs are not fully understood; however, the effects set out below have been studied in the past.

Incretin effect: This implies enhancement of the secretion of insulin after GLP is secreted from the GI tract. In previous studies it has been demonstrated that post-meal enhanced insulin release may be secondary to GLP-induced insulin release along with GIP.[19, 26, 27] Both of these hormones powerfully enhance the release of insulin and therefore collectively are called incretins. It is important to note that GIP secretions (including basal levels) are much higher (10-fold) compared to GLP. GLP predominates in meal-related response in terms of its incretin effect compared to GIP. In addition, GLP results in the inhibition of glucagon and this effect is not seen with GIP.[27-29] A detailed description of difference between GLP and GIP is described in the table below (Table 1-2).

Table 1-2: A detailed description of GlP-1 and GIP

	GIP	GLP-1
Peptide	42-amino acid	30/31-amino acid
Secreted by	K cells, primarily in the duodenum and proximal jejunum	L cells, primarily in the ileum and colon
Stimulated by	Oral ingestion of nutrients	Oral ingestion of nutrients
Effects on insulin secretion	Stimulates	Stimulates
Effects on GE	Slows?	Slows
Effects on beta-cell proliferation	Stimulates*	Stimulates*
Effects on glucagon secretion	None significant	Suppresses
Effects on food intake		
Effects on insulin sensitivity	?	Improves?
Secretion in type 2 diabetes	Preserved	Impaired
Adipose tissue		
Receptors	G-protein coupled receptors	G-protein coupled receptors

Effects on GI tract (gastric secretion and GI motility): GLP-1 is considered to decrease gastric secretions and GI motility.[30, 31] It was noted that GLP not only reduces gastric acid secretion but also results in the inhibition of GE and decreased pancreatic secretions.[31] This has further been demonstrated by a recent study by Schirra et al,[32] which demonstrated that GLP analogue Exenatide can enhance antroduodenal motility and pancreatic insulin secretion (Figure 1-10). This figure demonstrates that in healthy individuals GLP infusion along with glucose resulted in enhanced motor response. The

ileal brake activity of GLP has been demonstrated as the presence of unabsorbed food in ileum which results in decreased GE.[19, 24]
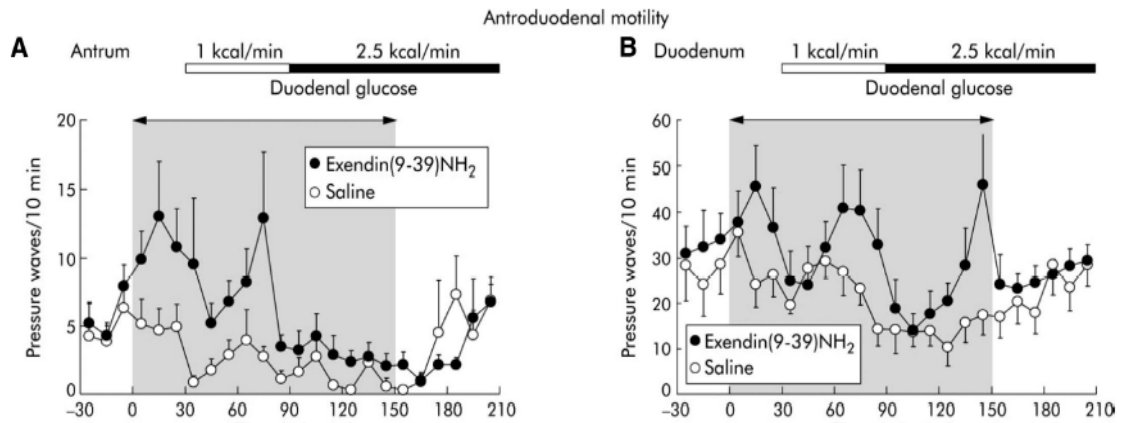
Figure 1-10: Enteroduodenal activity after GLP-1 infusion.

Schirra et al[32] demonstrated the enhanced enteroduodenal motility after GLP analogue infusion in healthy volunteers.

The proposed role of GLP-1 in obesity and type 2 diabetes: The role of GLP on the induction of obesity and type 2 diabetes mellitus (DM) was proposed because of its relation with food intake and satiety.[33] It was also noted that there was no measurable increase in GLP-1 secretion in obese subjects after meal intake[34] and it improved significantly after gastrojejunal bypass.[35, 36] Meal-related low GLP-1 secretion in obesity was also noted by others and it was reported that glucose levels significantly decrease after GLP-1 infusion; however, they may not reach a level of normoglycaemia.[37, 38] This review of literature suggests a very important role of GLP-1 in insulin secretion (incretin), obesity, GE and ileal brake activity. It is interesting to note that bariatric operations (particularly Roux-en-Y gastric bypass (RYGB)) result in weight loss; however, the normoglycaemia and improved insulin resistance is noted much earlier than a significant weight loss. Could this be related to a change in GI motility and a change in these GI hormones (ghrelin and GLP-1)? We conducted a prospective observational study (see Chapters 2 and 4).

Measurement of GE: Here follows brief descriptions of methods of GE measurement. They are covered in detail in Chapter 2 (section 2.2) and Chapter 4. These methods assess different aspects of gastric motility including:

1. GE

2. Gastric motor function

3. Gastric myoelectric activity

Gastric scintigraphy (GS): Solid phase GS is considered as a gold standard for assessment of GE. This is based upon the fact that a physiological meal is used; it quantifies the GE, and the rate of GE at any given point during the test can be calculated. Some clinicians have proposed to perform solid and liquid phase scintigraphy. In most of the centres 99m Tc (radioactive material) mixed in egg sandwich is used as a test meal.[39] In the past, different meals have been used for assessment of GE, including beef liver (radioactive labelled), chicken liver (radioactive labelled) and low-fat meal (radioactive labelled).[40-42] However, egg sandwich is readily available, easy to cook and more physiological compared to other meals. 100–120-minute GS should be for the evaluation of GE and the test can be extended for 4–6 hours for the assessment of IT. It is considered that solid GE shows a lag phase (no/little GE) followed by GE. Certain drugs may affect GE including opiates (to slow GE) and prokinetic and macrolides (to enhance GE). In addition, Ca channel blockers, K channel blockers, laxatives and other medication may affect GI motility. It is therefore recommended that such medicines should ideally be stopped 2–3 days before the test.

The table below sets out a list of medications affecting GI motility.

Table 1-3: Medicines affecting GI motility

```
        Delay gastric emptying
            Opioid analgesics
            Anticholinergic agents
            Tricyclic antidepressants
            Calcium channel blockers
            Progesterone
            Octreotide
            Proton pump inhibitors
            H₂-receptor antagonists
            Interferon alfa
            L-dopa
            Fiber
            Sucralfate
            Aluminum hydroxide antacids
            β-adrenergic receptor agonists
            Glucagon
            Calcitonin
            Dexfenfluramine
            Diphenhydramine
            Alcohol
            Tobacco/nicotine
            Tetrahydrocannabinol
        Accelerate gastric emptying
            Prokinetic agents
                Metoclopramide
                Erythromycin/clarithromycin
                Cisapride
                Domperidone
                Tegaserod
            β-adrenergic receptor antagonists
```

Adapted from Parkman et al[43]

GS results vary in each patient and they may differ in one patient if GS is performed at a different time. It is therefore recommended that centres should conduct their own studies and conclude the reference value. In addition, other factors such as gender, smoking and phase of menstrual cycle may also influence the GS results.[40, 44, 45] The basic equipment required to assess GS is a gamma camera (Figure 1-11).

Figure 1-11: Gamma camera

This is the picture of the camera used in our studies at the Department of Radiology and Nuclear Medicine, Castle Hill Hospital, Cottingham.

Assessment of GE by GS: After a meal intake, an area of interest is drawn around the stomach. Data points are corrected for decay, movements and skin marker (if used). Anterior and posterior acquisitions are calculated within the area of interest and a geometric mean is calculated for each data point. It is, however, one disadvantage of GS that there is radiation exposure even though the dose used in GS is very small. GE time can be described in terms of gastric half-emptying time ($T50$) and total emptying can also be calculated (Figure 1-12, Figure 1-13).
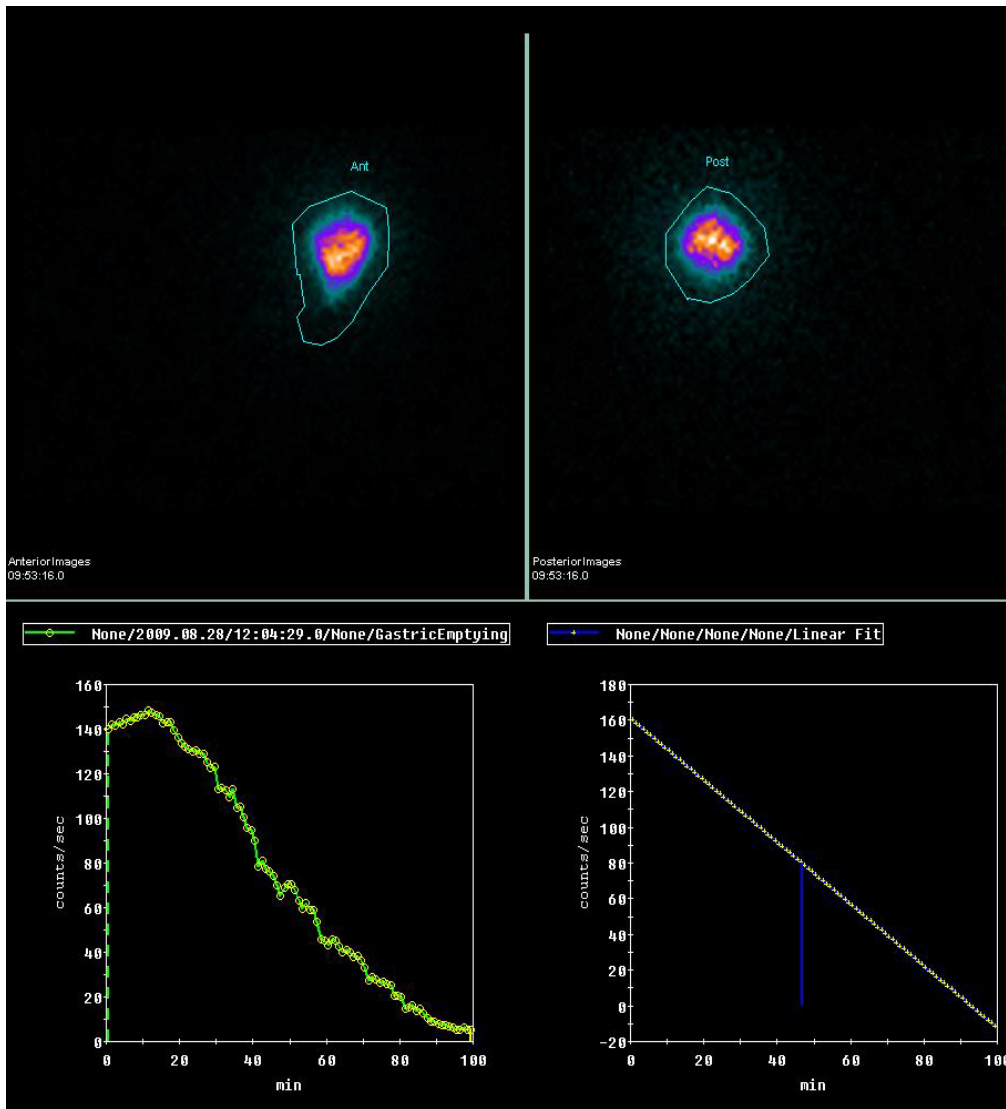
Figure 1-12: Assessment of GE by GS

An area of interest around the stomach is drawn in both anterior and posterior pictures (top two pictures). The geometric mean at each data point is shown in the lower left graph. T50 is then calculated as shown in the lower right graph.
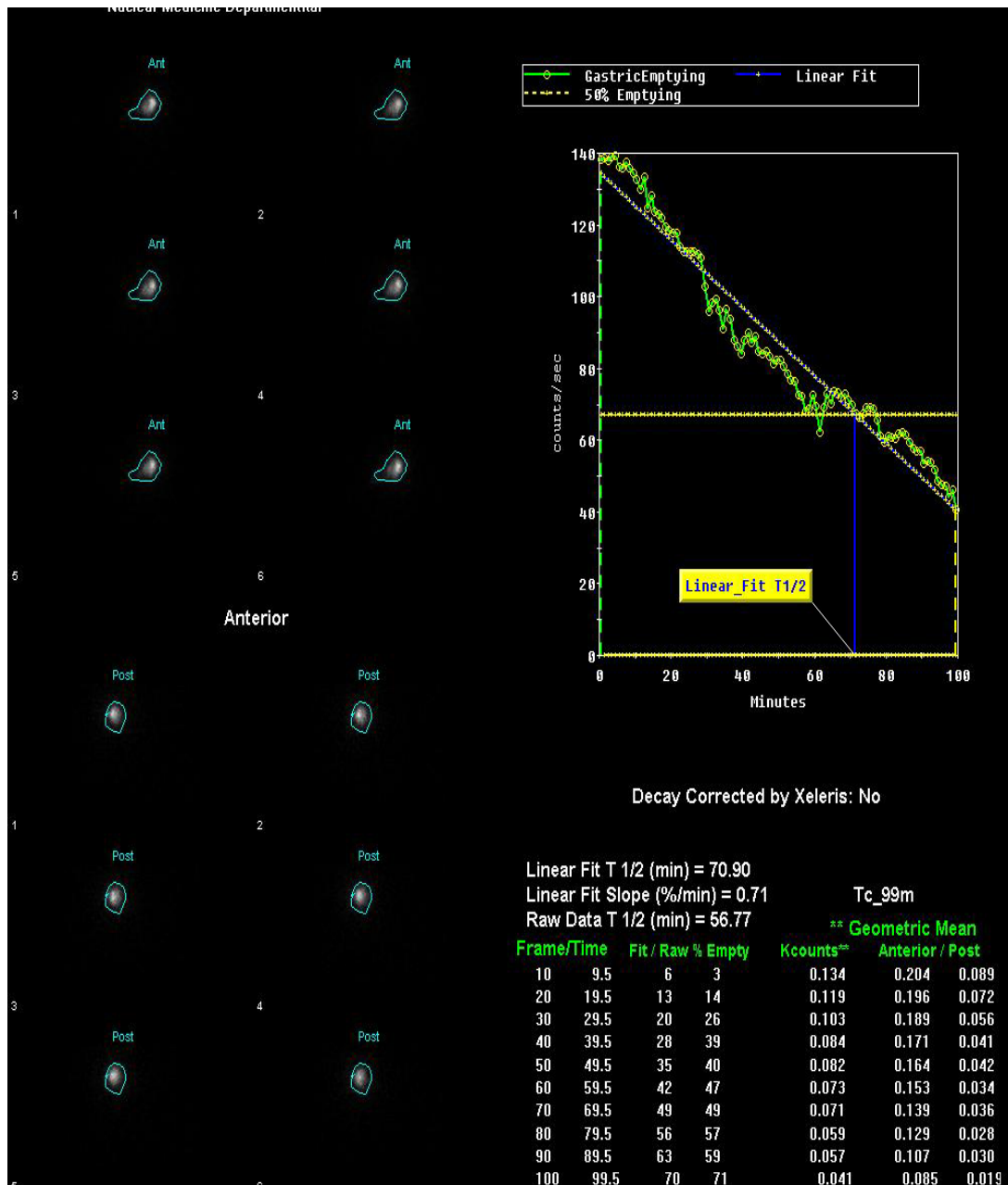
Figure 1-13: Calculation of T50 by GS

Showing radioactivity and time relation (data in the lower right corner).

% GE is calculated as shown.

T50 on a linear fit in this patient marked at 70 minutes (graph + reading).

Radiographic contrast studies: This is not a recommended method of assessment of GE; however, in certain cases poor emptying of barium from the stomach or gastric dilatation may be suggestive of gastroparesis. No emptying of contrast after half an hour

and retention even after six hours is suggestive of gastroparesis.[46] This is, however, non-physiological and not comparable to a test meal.

Lactulose breath test/hydrogen breath test (described in detail in Chapter 3): Non-radioactive isotope of C bound with substrate (usually a polysaccharide). The technique requires substrate to reach the caecum and get fermented, releasing H2. H2 is then detected in expired air. This, however, requires normal absorption, metabolism and pulmonary function to provide the appropriate results. Its utility in clinical services is still under review; however, it is used in experimental services.

EGG (electrogastrography): EGG measures the myoelectric activity of the stomach. Gastric slow waves are detected by skin electrodes on the abdominal wall and the frequency, pattern and intensity of myoelectric activity is recorded[47](see Figure 1-14).
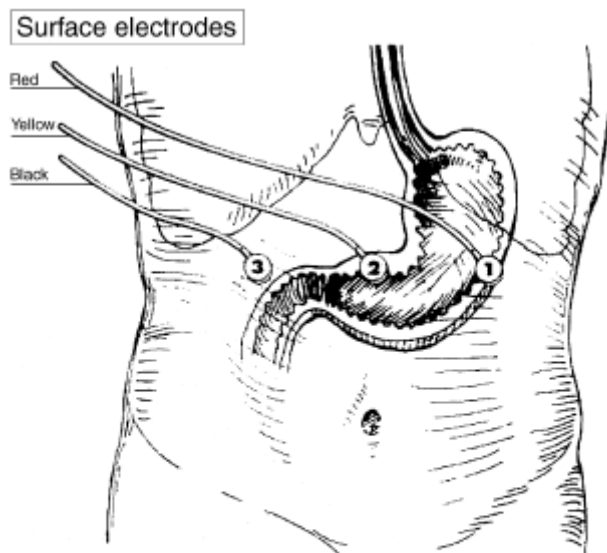
Figure 1 One commonly used electrode placement for electrogastrography recording is shown. Active electrodes are positioned below the left costal margin and, between the xyphoid process and umbilicus. The electrode positioned in the right upper quadrant is a reference or common electrode.

Figure 1-14: Electrogastrography (EEG)
Adapted from Parkman et al[47]

The EGG results are described in terms of bradygastria, tachygastria or normal. Normally, gastric myoelectric activity is recorded as 2–4 cycles/min. An increase

>4/min is called *tachygastria* and a decrease <2/min is classified as *bradygastria* (Figure 1-15).
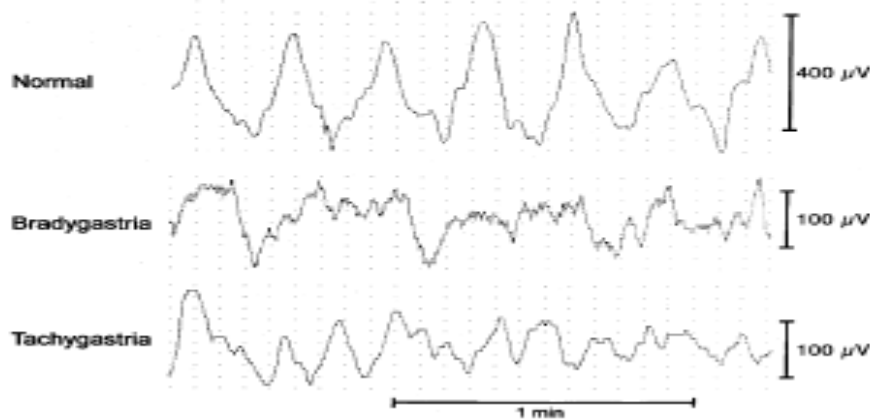
Figure 1-15: Gastric electrical activity on EEG

Adapted from Parkman et al[47]. Tachegastria > 4/minute, bradygastria < than 2 / minute.

This procedure is also not a part of routine clinical care and more research and movement may result in artefact and invalidate the results.

Antroduodenal monometry: This procedure is used to assess the duodenal and lower gastric motor function and is described in terms of the origin and propagation of migratory motor complex (MMC). These complexes occur in three phases: Phase 1 (no or little activity); Phase 2 (MMC irregular activity/spike potentials); and Phase 3 (MMC strong expulsive movement produced to push the food from the distal stomach to the ileum). This is a useful test to assess small IT problems and to evaluate the problems relating to the small intestine secondary to amyliodosis and myopathies. An abnormal Phase 3 MMC is considered an important finding to conclude motility-related problems. The test should ideally be performed in fasting and postprandial states. This test has not been validated and needs more research for routine clinical use. In addition, the intolerance of electrodes in the GI tract and wire migration/displacement may also invalidate the results.[43, 48]

Ultrasonography (USG): GE can be assessed by transabdominal USG. This is done by serial changes noted by USG in the antral part of the stomach. It can also assess the gastric and anteral wall movement. The antral blood flow can also be assessed by duplex. This is not a widely accepted method as it is highly operative dependent, difficult to perform in obese subjects and examination may be difficult due to the presence of air in the stomach and transverse colon. This is not a validated method for this purpose.[48]

Single photon emission computed tomography (CT): CT scan after radioisotope 99m Tc may be used for the assessment of gastric accommodation and GE. There is, however, a large amount of radiation exposure in this technique, and therefore it is not often used for this purpose.[43, 48]

Magnetic resonance imaging (MRI): Transaxial scans after every 15 minutes using MRI can be used to detect gastric accommodation and GE. The advantages of this method include no exposure to radiation; however, it requires special equipment and is still quite expensive, and therefore not widely used except in experimental studies.[43, 48]

Water/nutrient test for gastric accommodation: In this simple test, subjects are asked to drink mineral water at a specific rate (such as 15 ml/hr). 30 minutes later a visual analogue score is used to assess the gastric distension, and the amount of fluid intake is also recorded. This is not a standardised method and therefore is not valid and accepted across most of the centres.[48]

Paracetamol absorption test: This method has been used extensively in the past. Paracetamol is completely absorbed in the small intestine and levels can be calculated by serial plasma/serum levels. This is an easy test and most of the labs perform paracetamol levels; therefore, the measurement of the samples is not difficult. The test is valid for liquid GE only and is not valid for solid emptying. In addition, a normal intestinal absorption/function, metabolism and liver function are required. Certain drugs also interact with paracetamol, invalidating the results.[48]

A brief description of the above methods is provided in Table 1-4 below.

Table 1-4: Methods of assessment of GE

	Advantages	Disadvantages
Tests assessing gastric emptying		
Upper gastrointestinal barium radiographic study	Assess for mucosal lesions	Nonphysiologic Radiation exposure (moderate)
Scintigraphy	Gold standard Noninvasive Able to assess solid and liquid emptying	Radiation exposure (minimal)
Breath tests using ^{13}C	Noninvasive	Need normal small intestinal absorption, liver metabolism, pulmonary excretion
Ultrasonography for serial changes in antral area	Noninvasive Physiologic	Requires expertise for imaging and interpretation Primarily measures liquid emptying
Magnetic resonance imaging	Noninvasive	Expensive, time consuming Need specialized centers and software
Tests assessing gastric contractile activity		
Antroduodenal manometry	Assesses contractility in fasting and postprandial periods	Invasive Need expertise to perform and interpret
Gastric barostat	Measures proximal stomach relaxation and contraction	Invasive Research technique
Tests assessing gastric myoelectrical activity		
EGG	Noninvasive	Movement artifact may make recording difficult to interpret
Tests assessing gastric accommodation		
Gastric barostat	Measures proximal stomach accommodation response	Invasive Research technique Balloon may interfere with accommodation
Satiety test	Measures combination of accommodation and sensitivity	Simple Not well standardized or accepted

Adapted from Quigley et al[24] and Hasler WL, Koch KL. Diabetic gastroparesis. AGA Postgraduate Course, May 19–20, 2001.

1.1.2 Intestinal transit (IT)

<u>Definition:</u> The transit of food through the small bowel (duodenum to caecum) is called *small intestinal transit*. The time taken by food to transit through the intestine is called *intestinal transit time*.

<u>Mechanism of intestinal motility</u>: The mechanism of GI motility has been explained in detail in section 1.1.1 above. Small IT is an important factor that determines the absorption of food. Variation in intestinal motility and transit is also mediated by a feedback mechanism though the enteric nervous system and GI tract hormones.[49] Following a meal intake, the following types of intestinal motility are observed:

1. Segmental contraction to roll and mix the chyme.

2. Peristalsis to propagate the food to the large intestine.

Segmental contraction: When the chyme enters the small intestine, this exerts pressure/stretch on the wall of the small intestine which triggers the slow-wave action potentials at that area. These slow waves are a continuation of gastric slow waves; however, their rate is different in the small intestine. This varies from the duodenum (12/min) to the terminal ileum (9/min).[3] These slow waves cause localised segmental

contraction (a few cm) followed by relaxation which propagates in the entire small intestine. They are controlled locally by the enteric nervous system (excitatory effect); however, application of an external stimuli like atropine may cause blockade of these contractions.[3] During inter-digestive periods, the housekeeping of the intestine is observed by contractions of the stomach which propagate through the small intestine to clear the debris and digested food. This may cause growling. These contractions are called migratory motor complex (MMC).[1, 3]

Peristalsis/propulsive movements: Peristaltic contractions are weak intestinal contractions which propagate the food into the next part of the GI tract. They usually die after 5–10 cm and push a small amount of food after every 1–2 minutes. Therefore, it requires 3–5 hrs for them to take the chyme from the pylorus to the ileocecal valve.[3] The control of these movements by the enteric nervous system, the effect of the vagus nerve and the hormonal influence has been discussed in detail in section 1.1.1.

Iliocecal Valve: The main functions of the ileocecal valve are to prevent the backflow of colonic contents to reach the small intestine. In addition, the periodic opening of this valve allows the maximum time for chyme to stay in the small intestine to get absorbed and approximately 1500 ml/day to reach into the caecum. This valve is supported by the thick muscles of the small intestine which act as ileocecal sphincter. Peristalsis in the terminal ileum and the frequency of the ileocecal valve opening and closure is determined by local reflexes (colonoileal reflex). If the caecum is full/distended, this local myenteric reflux inhibits the peristalsis in the terminal ileum and intensifies the ileocecal valve/sphincter not to permit chyme from the small intestine into the caecum.[1, 3]

Measurement of IT:

GI Scintigraphy: Small intestine scintigraphy is considered as a gold slandard for assessment of intestine transit (IT).[50] The methodology of IT remains the same; however, the interpretation of results differs in different centres. It can be measured as colonic filling (% filling at certain time points), or in mayo method <10% colonic filling after six hours is considered as slow IT and >70% filling at six hours is considered as rapid IT.[50] In the Tample method 70% radioactivity is reached in the ileocecal region after 205 minutes.[50] In another study on health volunteers, radioisotope tablets were used and the results revealed similar fasting and postprandial IT (204 minutes and 210

minutes respectively).[51] There are, however, difficulties related to the test as this requires multiple scans and radiation exposure and it is an expensive method.

Lactulose breath test: This is a minimally invasive test. Subjects are required to take a labelled lactulose. This is fermented in caecum and the exhaled gases are expired and measured reflecting the IT time. In previous studies, methane, CO2 and hydrogen have been used to measure the results in this test. The problem with the interpretation of these results is that this can only be representative of the transit of lactulose, which cannot serve as a substitute to a transit of a physiological meal. In addition, the timing of the food may affect the small IT time.[51] In literature, the normal orocaecal transit time (OCTT) varies between 192–234 minutes.[50]

Wireless capsule endoscopy: Capsule endoscopy is mainly used for the assessment of occult GI bleeding. However, its utility as a tool to assess GI motility is not widely explored. Figure 1-16 below briefly describes the procedure.
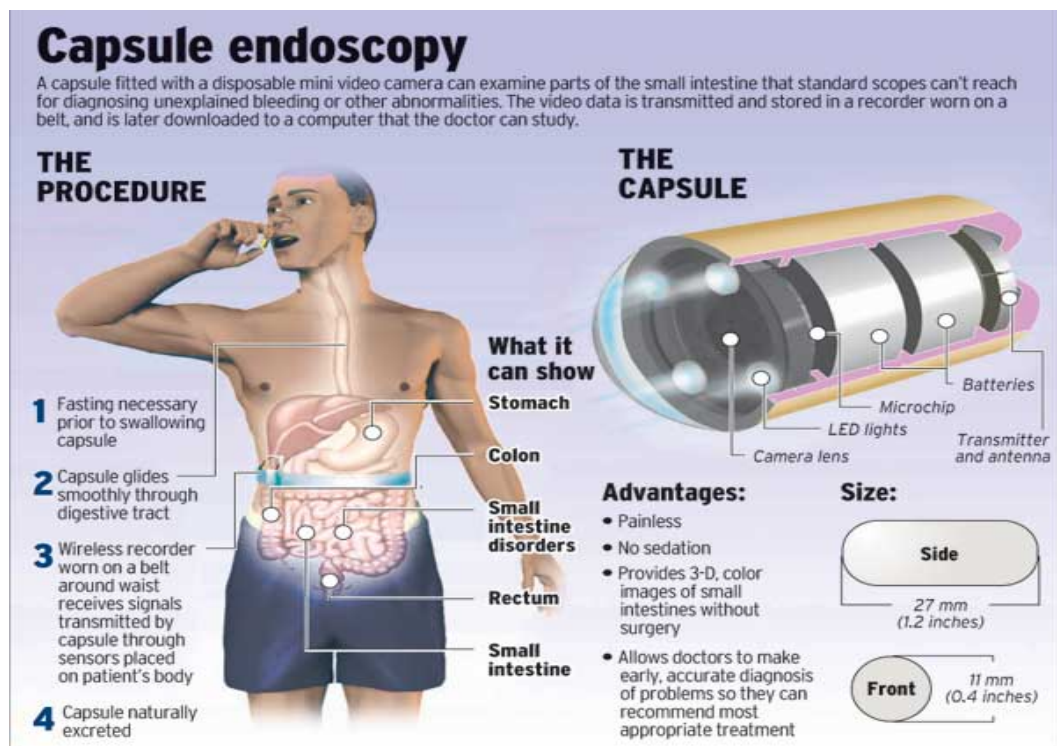
Figure 1-16: Capsule endoscopy (CE)

Copied from Birmingham GI association website

The utility of these methods (lactulose breath test and CE) as an alternative to small intestine scintigraphy is described in detail in Chapters 2 and 3.

1.2 Delayed GE/gastroparesis

Definition: Gastroparesis is a chronic motility disorder of the stomach, defined as delayed GE of the solid meal in the absence of mechanical obstruction. The most frequent symptoms of gastroparesis include nausea, vomiting, early satiety and postprandial fullness. Abdominal discomfort and pain are also reported. Weight loss, malnutrition and dehydration may be prominent in chronic cases.

Aetiology

The three most common aetiologies include:

1. Diabetes mellitus (DM)
2. Gastric surgery involving vagotomy
3. Idiopathic (no identifiable cause)

Other causes of gastroparesis have also been described in literature. They include intra-abdominal malignancy, eating disorders, chronic renal failure, muscular dystrophy and certain medications including atropine, opiates, tricyclic antidepressants, phenothiazines, calcium channel blockers and lithium.[8]

The true prevalence of gastroparesis is not known; however, it has been estimated that up to 4% of the population experiences symptomatic manifestations of this condition.[3]

Prevalence of gastroparesis is increased in diabetic patients and may occur in 30–50% of patients with DM.[4,5]

Gastroparesis in these patients interferes with oral drug absorption and impairs blood glucose levels, leading to further complications as a result of problems with ineffective blood sugar control.

Gastroparesis is a debilitating condition, which can reduce a functional individual into an existence tied to hospitals and emergency rooms. Gastroparetic patients have no good long-term solutions and death can result from interventions and life-threatening complications, such as electrolyte imbalances, dehydration and malnutrition. Soykan et al in their analysis of 146 patients seen over six years in two centers[2] indicate that 10% of patients died during the follow-up period. They describe gastroparesis as "far from being a benign disorder". A detailed description of this condition and treatment options are described in Chapter 5.

1.3 GI motility in obesity

Obesity is known to be attributed to an imbalance between food intake and energy expenditure. Food intake and its absorption is carried out by a complex mechanism of GI motility regulated by signals (hormones, neuropeptides and the autonomic nervous system), metabolic cues from hormones, peptides and absorbed nutrients, and hypothalamic brain centres. Rapid GE is thought to deliver more nutrients and also reduces negative feedback of satiety signals, resulting in more feelings of hunger and an increased demand for food.[52]

GE and accommodation plays an important role in the delivery of nutrients to the intestine. High-energy-density meals reduce GE, which levels the rate of energy delivery to the intestine.[53,54] There are also apposite reports suggesting that high-calorific food may lead to rapid GE in obese subjects.[55] It is suggested that GE is altered in obesity. Small intestinal motility and absorptive capacity also play an important role in the absorption of nutrients. It has been speculated that intestinal absorption of nutrients is rapid, more efficient and not related to IT rate but there is not much evidence to support this hypothesis.[52] On the other hand, it is stated that obesity is related to increased IT and contractile activity, resulting in excessive nutrient absorption.[52, 56] GI transit studies provide an assessment of overall GI motor activity. Slow GE may result in retention and early satiety, which may result in weight reduction[57]

GE is slow in 30–50% of long-standing diabetics. The relation of GE with symptoms is poor. GE is slow in hyperglycaemia, and fast in hypoglycaemia. A number of therapies are being developed to modulate the delivery of nutrients to the intestine.[8]

A trend for bariatric surgery has increased significantly and, according to the National Institute for Clinical Excellence (NICE) guidelines, subjects with a body mass index (BMI) of 40 or over without comorbidities and a BMI of 35 or more with comorbidities should be considered for bariatric surgery.

GE in obesity:

There is conflicting data regarding the GI transit (GE and IT) in obesity (see Table below).

Table 1-5: GE in obesity

A total of 16 studies; including 7 in favour of increased GE, 4 decreased GE and 5 demonstrated normal GE in obesity.

Evidence of increased GE in obesity			
Study ref	Type	Number of subjects	Outcome
Cardoso-Júnior A[58]	Controlled	14 obese + 24 control	Increased GE in obese
Valera Mora ME[59]	Controlled	20 obese + 16 control	Increased GE in obese
Bertin E[60]	Controlled	13 obese + 7 control	Increased GE in obese
Wright RA[53]	Controlled	46 obese + 31 control	Increased GE in obese
Tosetti C[61]	Controlled	20 obese + 20 control	Increased GE in obese
Grybäck P[54]	Controlled	9 obese + 21 control	Increased GE in obese
Verdich C[62]	Controlled	19 obese + 12 control	Increased GE in obese during initial 30 minutes
Evidence of decreased GE in obesity			

Glasbrenner B[63]	Controlled	24 obese + 8 control	Normal solid emptying Decreased liquid emptying in obese
Maddox A[64]	Controlled	31 obese + 31 control	Decreased GE In obese
Horowitz M[57]	Controlled	15 obese + 11 control	Decreased solid GE Normal liquid emptying
Jackson SJ[65]	Controlled	16 obese + 16 control	Delayed GE in obese
Normal GE in obesity			
Mathus-Vliegen EM[66]	Uncontrolled	45 obese	Increased liquid emptying Normal solid emptying
Verdich C[62]	Controlled	19 obese + 12 control	Normal solid emptying
Hutson WR[67]	Controlled	30 obese + 23 control	Normal GE
Zurakowski A[68]	Controlled	10 obese +10 control	Normal GE
Glasbrenner B[63]	Controlled	24 obese + 8 control	Normal solid emptying Decreased liquid emptying in obese

This systematic review of literature demonstrated that 7 studies showed an increase in GE in obesity, 4 in favour of decreased GE in obesity and 5 in favour of normal GE in obesity. It is, however, important to know that there was great diversity in their methodology, interpretation of GE results and meal composition. In addition, there was a wide range in BMI and gender differences in these studies. This may have an implication for their results.

Change in GI motility after bariatric procedures

A systematic literature review was conducted regarding the impact of bariactric procedures on GI motility.

Search criteria

Medline, Embase, PubMed databases and the Cochrane Library were searched independently by two authors. The search was limited from January 1980 to July 2009 and to the English literature.

The following keywords were searched: ("Gastric Emptying" OR "Gastric Motility") AND ("Bariatric Surgery" OR "surgery" OR "Gastric bypass" OR "gastric banding") AND ("obesity").

Further searches were made from the references of the original articles. A separate search was performed in non-indexed citations and relevant scientific meeting abstracts. The search result of each author was combined with removal of duplicate references.

Inclusion criteria

All human studies looking into any aspect of GE or motility before and after any form of bariatric surgery were included in the review. All forms of study designs, including case-control studies, case series and case reports, were included. Animal studies were excluded.

Results

Gastroplasty:

Gastroplasty is a restrictive operation for weight control and it has been in practice since 1970. The original horizontal gastroplasty operation (stapling the stomach horizontally and leaving a small stoma) has been replaced by vertical band gastroplasty, which involves creating a small (15–25 ml) pouch by stapling line and the outlet is controlled by a silicon band. The size of the created stoma is approximately 1 cm.[69] The lap adjustable gastric band was introduced in 1990. It is the least invasive procedure and it involves creating a small pouch on the upper part of the stomach. Patients require outpatient follow-ups for adjustment of the band through the access port.[69] Previous studies have demonstrated that the weight loss in such procedures is caused by food restriction, change in pouch and GE following the procedure.[57, 70-82]

A total of 13 case series, including 3 case control studies were identified in the literature. Studies only using scintigraphy as a method of GE were considered appropriate for inclusion (see Table 1-6). The time of gastric and pouch emptying assessment varied between two weeks to over two and half years after surgery in these studies. Five studies[72, 73, 76, 78, 82] noticed slow GE, two noticed rapid GE[73, 74] and two[79, 80] reported normal GE after gastroplasty. Pouch emptying is considered as an important determinant for food delivery and inducing early satiety following bariatric surgery. Most of the studies reported rapid pouch emptying[70, 73-75, 77, 81, 82]; however, only one study[71] reported slow pouch emptying. Most of the papers also concluded that there is no correlation between GE and weight loss.[70, 73, 74, 76, 78, 80, 81] The total number of patients studied in each study were low (11–50) and only four studies compared the GE results with a control group. Similarly, there is large heterogeneity in method to conduct scintigraphy, meal composition and duration of scintigraphy. Different types of gastroplasty procedures were conducted including vertical, horizontal, Gomez, Mason, Magenstrasse and Mill gastroplasty. Despite the fact that there were different procedures, the principle of the procedure was the same – to create a small pouch (approximated size 5 ml) and a stoma (1–1.5 cm) in the proximal stomach. The mechanism of pouch function is mainly restrictive and all studies reported weight loss following the procedures. ***This published data regarding gastroplasty suggests that post-operatively a slow total GE and rapid pouch emptying was observed; however, the changes may not be fully accountable for the weight loss in these patients (Table 1-6).***

Gastroplasty was common from 1970 to the 1990s. However, because of poor long-term weight loss[83, 84] and a high rate of late complications, it has been replaced by alternative procedures.[85]

Table 1-6: Pouch emptying and change in GE following gastroplasty

Study	Design	Intervention	Method of GE	Time of measurement	N	Control	Conclusion
Horowitz M[82] 1982	Case control	Gastroplasty (vertical)	Scintigraphy	Post-op at 6–8 months.	11	22	Slow GE after surgery. Rapid pouch emptying.
Drane W E[71] 1983	Case series	Gastroplasty (horizontal)	Scintigraphy	Post-op.	14		Slow pouch emptying results in weight loss.
Andersen T[81] 1985	Case series	Gastroplasty	Scintigraphy	Post-op pouch emptying at 0, 6, 12, 18, 24 months.	27		Rapid pouch emptying. No correlation with weight loss.
Gannon MX[72] 1985	Case series	Gastroplasty	Scintigraphy	Pre-op, 7 months post-op.	13		Slow GE after surgery. This may result in early satiety and weight loss.
Miskowiak J[73] 1985	Case series	Gastroplasty	Scintigraphy (liquid)	Pre-op, 3, 12 months post-op.	16		Slow GE at 3 months. Rapid GE at 12 months. Rapid pouch emptying. No correlation with weight loss.
Arnstein N B[74] 1985	Case series	Gastroplasty (Gomez n=30,Mason n= 20)	Scintigraphy	Pre-op,1–4 weeks, 2–24 months post-op.	50		Rapid pouch emptying after surgery Rapid GE after surgery No correlation with weight loss.
Christian P E[75] 1986	Case control	Gastroplasty	Scintigraphy	Pre-op in obese, normal weight subjects. Post-op 3 ,12 months.	16	17	Normal GE in obesity. Rapid pouch emptying. Efficacy of surgery lies in food limitation, not GE.
Vezina W C[76] 1986	Case series	Gastroplasty	Scintigraphy	Pre-op,3,12 months post-op.	23		Slow GE at early post-op period. Normal GE after 1 year. No correlation with weight loss.

Andersen T[77] 1988	Case series	Gastroplasty	Scintigraphy	Post-op pouch emptying at 6, 12 months.	27		Rapid pouch emptying.
Anderson T[70] 1989	Case series (rando mised)	Gastroplasty (vertical, horizontal)	Scintigraphy	Post-op pouch emptying at 2 weeks and 6 months.	45		Rapid vertical pouch emptying. No relation of GE with weight loss.
Bendet N [78] 1996	Case series	Gastroplasty	Scintigraphy	Pre-op, 1, 3, 6 month post-op.	24		Slow GE after surgery. No relation with weight loss.
Mistiaen W[79] 2000	Case series	Gastroplasty	Scintigraphy	Pre-op, 2 week post-op pouch emptying.	13	11	Normal GE after surgery. Rapid pouch emptying.
Carmichael A R[80] 2001	Case control	Gastroplasty (Magenstrasse & Mill)	Scintigraphy	Post-op 2.8 year. Matched pre-op obese. Age matched non-obese.	13	10 (obese), 7 (normal weight)	Normal GE in obesity. No significant change after surgery.

Majority of the studies (5) noticed slow GE, 2 noticed rapid GE and 2 reported normal GE after gastroplasty

Jejunoileal bypass (JIB):

The jejunoileal bypass (JIB) was designed solely for weight loss and this procedure has been in practice since the late 1960s and 1970s. JIB induces malabsorption by bypassing most of the intestines while the stomach is kept intact. This procedure induces good weight loss, but many patients, post-operatively, have developed severe complications like liver diseases, night blindness secondary to vitamin A deficiency, vitamin D deficiency, bacterial overgrowth and kidney stones.[86] Consequently, many of these patients have required reversal of the procedure, resulting in further operations.[86, 87]

Only four studies (Table 1-7), including three by one author, were identified in literature looking into GE following JIB.[34-36, 88, 89] Short- and long-term GE did not change after JIB.[35, 88] However, other studies published by Naslund et al revealed slightly slower GE after JIB. All the studies were conducted on a small number of patients with possible duplication of data in papers by Naslund et al.[34, 36] They also looked into the hormonal changes following JIB and noticed elevated fasting PYY, elevated postprandial NT, PYY, and GLP-1 and delayed GE. ***These studies suggested a possible association***

between impaired postprandial GLP-1 response in obesity, and after JIB, PYY seems to regulate GI motility whereas GLP-1 may regulate GE.

Table 1-7: Change in GI transit following JIB

Study	Design	Intervention	Method of GE	Time of Measurement	N	Control	Conclusion
Moberg S[88] 1976	Case control	JIB	Scintigraphy	Post-op (months)	9	7	No change in GE after JIB (short term).
Naslund E[35] 1998	Case control	JIB	Scintigraphy	Post-op 20 years, pre-op obese (control group)	7	7	No change in GE after JIB (long term).
Naslund E[36] [34] 1997,1998	Case control	JIB	Scintigraphy	Pre-op, 9 months post-op. Pre-op non-obese (control group).	9	9	Rapid GE in obesity. Slow GE after surgery.

No change in GE following JIB in 2 papers, slow GE after JIB in 1 published study. Small number of patients included.

Laparoscopic adjustable gastric band (LAGB):

Laparoscopic adjustable gastric band has been in practice since 1993. The procedure involves placement of an inflatable balloon on the gastric cardia 1 cm below the gastroesophageal junction. It is connected with a tube to a subcutaneous port attached to the rectus sheet. The size of the balloon is adjusted by injecting normal saline, resulting in narrowing of the stomach. The advantage of LAGB over other procedures is that it does not require an anastomosis and stapling, therefore the morbidity and mortality of LAGB is lower than RYGB. Unlike other operations, LAGB needs band adjustments necessitating multiple appointments, delayed or unsatisfactory weight loss, band slippage, band erosion and port site complications.[90]

Five studies, including one case control study, were identified in published literature (Table 1-8). One of them was included in this review despite the fact that they used electrogastrography[60] for the assessment of gastric motility. Two to four myoelectric waves/min are considered normal, whereas >4 are classed as tachygastria and <2 as bradygastria, as described in the section on EEG above.[47] Two studies reported normal GE in obesity,[91, 92] two reported no change in GE after LAGB[91, 93] and one noticed slow pouch emptying.[92] One study compared different sizes of pouch and noticed that the

small pouch fills and empties quickly.[94] *However, none of the studies established any firm relation of change in gastric and pouch emptying with weight loss.*

Table 1-8: Change in gastric emptying following LAGB

Study	Design	Intervention	Method of GE	Time of Measurement	N	Control	Conclusion
Hladik P[95] 2008	Case series	LAGB	Scintigraphy	Pre- and post-op.	6		Slow GE after LAGB.
Gao F[94] 2008	Case series	LAGB	Scintigraphy	Post-op pouch emptying.	17		Small pouch fills and empties quickly.
Jong J R[93] 2009	Case series	LAGB	Scintigraphy	Pre-op, 6 months post-op.	16		Normal GE after LAGB. No correlation with weight loss.
Tiktinsky E[92] 2009	Case control	LAGB	Scintigraphy	Pre-op, 6–12 months post-op.	11 (pre-op), 16 (post-op).	10	Normal GE in obesity. Slow pouch emptying.
Van Dielen F M H[91] 2003	Case series	Lap band (N=21) Gastroplasty (N=19)	*EGG (before & after test meal)	Pre-op, 3 months post-op.	40		Normal GE in obesity. No change after LAGB.

Two studies reported normal GE in obesity, 2 reported no change in GE after LAGB and one noticed slow pouch emptying.

Change in GI motility following Roux-en-Y gastric bypass (RYGB):

Gastric bypass has been in practice since 1960, and it was developed to combine malabsorptive and restrictive components. In addition to weight loss, other changes like neuroendocrine and dumping may also seem to play a role in weight loss following this procedure. This procedure involves formation of a small lesser curvature pouch, transaction of the stomach and Roux-en-Y reconstruction. The jejunum is typically divided at the level of the ligament of Treitz and anastomosed with a gastric pouch, creating an alimentary limb. The biliopancreatic limb is typically connected at 75–150 cm distal to the gastrojajunostomy. Patients undergoing RYGB lose 60–70% of excessive body weight, with a 75% resolution of comorbidities. In general, the outcome is considered better than LAGB and less than biliopancreatic diversion and duodenal switch.[90, 96]

Five case series, including one case control study, were identified (Table 1-9). ***Rapid post-op GE was reported in two studies,[97, 98] whereas one study reported slow GE.[57] Only one study looked into IT (using the lactulose breath test) and they reported rapid IT following surgery.[98]*** Another study looked into the contrast held up as a representative of delayed GE. This was mainly performed to assess the anastomosis leak using gastrograffin in this study.[99] They reported 188 patients with normal GE, and 116 patients with very slow or no emptying of contrast from the gastric pouch. Patients with normal initial pouch emptying lost more weight.[99] Although this is not a preferred method of GE assessment, further data on gastrograffin pouch emptying may help to understand pouch dynamics in the future.

Table 1-9: Change in GI transit following RYGB

Study	Design	Intervention	Method of GE	Time of Measurement	N	Control	Conclusion
Villar H V[97] 1981	Case series	Gastric bypass (N=19) Partitioning (N=12)	Scintigraphy	Post-op 4 months	19, 12		Rapid GE after gastric bypass. Slow GE after gastric partitioning.
Naslund I[89] 1987	Case series (randomised)	Gastric bypass (N=29) Gastroplasty (N=28)	Scintigraphy	Pre-op, post-op 2,12 months.	29, 28		Equal pre- and post-op GE. Slow GE (pouch) after RYGB. No relation of GE with weight loss.
Morinigo R[98] 2006	Case series	Lap RYGB	Paracetamol (GE). Lactulose breath test (for orocaecal transit).	Pre-op,6 weeks post-op.	6		Rapid GE and IT following RYGB.
Akkary E[99] 2009	Case series	Lap RYGB	Gastrograffin (liquid)	Post-op day 1 (retrospective review)	304		More weight loss in patients with normal GE. Post-op oedema may decrease GE.
Horowitz M[57] 1982	Case control	Gastric bypass	Scintigraphy	Post-op 12 months	12	11	Slow GE after RYGB for solid meal. Fast GE after RYGB for liquid meal.

Rapid post-op GE was reported in two studies whereas one study reported slow GE. Intestinal Transit (IT) was studied in only one study (using the lactulose breath test) and they reported rapid IT following surgery.

GE following sleeve gastrectomy:

Sleeve gastrectomy is a fairly new procedure. The procedure involves removing 80% of the stomach, leaving behind only a sleeve of stomach along the lesser curvature. Sleeve gastrectomy was initially described as a first-line procedure to be followed by BPD-DS or RYGB in super-obese groups (BMI>60 kg/m2).[100] However, it is also used as a primary treatment in morbidly obese patients.[101] The gastric tube created by this method is considered to restrict the food intake. *It is believed that in addition to food restriction, slow GE and a possible role of a gastric satiety hormone (ghrelin) may play an important role in weight reduction following this procedure.[102]*

Only two studies on a small number of patients have looked into GE following sleeve gastrectomy (Table 1-10). The results remain inconclusive as one reported slow GE and other recorded no change in GE following sleeve gastrectomy.[101, 102] Bernstine et al emphasised the fact that this may be because of preservation of anteroduodenal control and the difference in their finding with Melissas et al may be because of different operative techniques.[102]

Table 1-10: Change in GE following sleeve gastrectomy

Study	Design	Intervention	Method of GE	Time of Measurement	N	Conclusion
Melissas J[101] 2008	Case series	Sleeve gastrectomy	Scintigraphy	Pre-op,6, 24 months post-op	14	Rapid GE after surgery.
Bernstine H[102] 2009	Case series	Sleeve gastrectomy	Scintigraphy	Pre-op, 3 months post-op	19	No significant change in GE following surgery. No relation of GE with weight loss.

One study demonstrated slow GE and other no change in GE after sleeve gastrectomy.

Role of gastric electric stimulation (GES) as bariatric procedures and change in GE following GES:

Electric stimulation of the GI tract has been in practice for the last two decades. GES is applied to control the muscle contractility, similar to the concepts in practice for cardiac stimulation. Two types of GES devices have been used in the past including MEDTRONIC and TANTALUS gastric electric stimulators. TANTALUS is considered as a non-excitatory mechanism of GES since the signals do not entrain the muscle, but maintain the basic rhythm by synchronising their delivery to gastric slow waves. This results in increased force of gastric contractions during stomach distension, contributed by increased vagal afferents resulting in satiety.[103, 104]

The treatment of heart failure stimulation parameters approved in clinical practice do not regulate gastric slow-wave activity and have an inconsistent effect on GE.[105] Improved glucose and weight reduction have been noticed in studies using TANTALUS.[106, 107]

It is, however, interesting to know that antergrade[103, 104, 107-109] as well as retrograde[110] GES was used in these studies. One study was conducted in a normal weight population.[110] In most of the TANTALUS-based studies, improved weight loss was reported.[103, 107, 108] MEDTRONIC antegrade[109] GES was used in one study after failed gastric bands, and there was no weight improvement seen. MEDTRONIC retrograde GES in one study was used on normal weight volunteers which showed decreased food intake[110] GE was recorded to be normal in obesity,[104] increased after antegrade GES using TANTALUS[104] and decreased after retrograde GES using MEDTRONIC device in normal weight subjects.[110]

This data of mixed results still remain inconclusive in terms of the results and mechanism how GES may work in obesity treatment.

This is based upon the facts that two out of three studies showing improvement in weight after TANTALUS were reported from one centre with possible duplication of results,[106, 108] whereas the only study with relatively long-term results (5 years) used antegrade GES (Medtronic device) and reported no weight reduction in obese patients.[109]

Table 1-11: Gastric motility following gastric neuromodulation (GNM)

Study	Design	Intervention	Method of GE	N	Results	Conclusion
Policker S[103] 2009	Review	Gastric electric stimulation (TANTALUS)	NA	132	24 weeks follow-up. 5.5 kg weight reduction, ↓(1.1) HbA1c, improved DM.	Weight improved, DM improved, GES is an effective treatment.
Bohdjalian A[107] 2009	Case series	Gastric electric stimulation (TANTALUS)	NA	24	1 year follow-up. 4.5 kg weight reduction in 21 ptatients No improvement in pts on insulin.	Weight improved, GES effective.
Bohdjalian A[108] 2006	Case series	Gastric electric stimulation (TANTALUS)	NA	12	52 weeks follow-up, improved weight in 8 pts. No improvement in 3 pts. Two quit the study.	Weight improved (possible replication of data).
Hoeller E[109] 2006	Case series	Antigrade Gastric Electric Stimulation (Using MEDTRONIC device)	NA	8	Post-failed gastric band patients. IGS device (Medtronic). No weight reduction 5 years following GES. Further surgical intervention required.	Weight not improved, GES ineffective.
Yao S[110] 2005	Case series	Retrograde Gastric Electric Stimulation (Using MEDTRONIC device).	NA	12	Normal weight subjects 13% fluid reduction, 16% food reduction. Sham pacing GE T50(177m), pacing GE T50(235).	↓ GE following retrograde GES. ↓ Food intake.
Sanmiguel C P[104] 2007	Case series	Gastric electric stimulation (TANTALUS)	Scintigraphy Without stimulation, 6 weeks after stimulation.	12	% GE at 2 hrs (slow if >60%, fast if <16% left in stomach). Normal GE before GES. ↑ GE after GES (gastric retention decreased from 31.9±16.4 to 18.7±12.2%) after 2 hours).	Normal GE in obesity. ↑ GE after GES.

Two types of GES systems have been used (Medtronic, TENTALUS). Decreased weight reported in most of TENTALUS based studies. Antegrade and retrograde GES has been experimented using Medtronic device.

Summery of literature review and aims of this thesis:

1. GI motility may closely be related to GLP, Ghrelin and these hormones may have a therapeutic role in obesity, weight reduction and resolution of DM. Rest of the hormones were not significally relavent and therefore excluded for further discussion and research in our studies.

2. Methods of assessment of GI motility were studied and concluded that GI Scintigraphy is gold standered method; however further research is required to improve the interpretation and alternative method should also be explored. We focused on Capsule endoscopy and lactulose breath test in addition to GS in our studies.

3. Data regarding GE in obesity and change in GE following bariatric procedures remain inconclusive because of hetrogeniety of the studies, methods implied; non standerdised interpretation of results. There is a change in practice as RYGB is now considered as an intervention of choice in morbid obesity. Diabetes resolved very quickly following this procedure and is considered to be a result of change in GI motility and change in GI hormones. We conducted a prospective study to lood into resolution of DM following RYGB with special focus on GI motility and hormones effecting GI motility, DM and insulin resistance (ie Ghrelin and GLP).

4. Slow GE (gastroparesis) is a major problem in a small number of patients and it is a clinical and nutritional challenge to manage these patients. There is limited data in support of the use of GES in such patients. We conducted a prospective study on such patient and treated them with GES and closely monitored their clinical, nutritional, QOL outcomes.

5. Accorate assessment of nutritional intake in obesity and in critically ill patients were also the focus of our research as they are closely related to GI motility, metabolism, GUT function, weight loss/weight gain.

2 Alternative methods of assessment of GI motility

Excerpts of this chapter were presented as a poster in the Association of Surgeons of Great Britain and Ireland (ASGBI).

Ullah S, Sadia M, Dakkak M, Babu S, MacFie J. Role of Capsule endoscopy in GI transit. ASGBI 2011.

Ullah S, Khan S, Tayyab M, Babu S, MacFie J. Measurement of gastrointestinal transit using capsule endoscopy. ASGBI April 2010.

2.1 Role of capsule endoscopy in GI motility

2.1.1 Introduction

The small intestine has been considered to be a difficult area to assess because of the distance from the mouth to the ileum. The mainstay of investigations for the small bowel has been radiological investigations (contrast studies and CT scan), nuclear scan (scintigraphy) and MRI. Although there are certain advantages of CT scan and MRI, such as diagnosing a relatively large lesion in the small intestine, small and flat lesions and small intestinal wall pathologies may be missed with these modalities.

Traditional endoscopy has its advantages but comes with discomfort and requires significant skills to perform. It is still not possible to completely visualise the small bowel, especially the distal jejunum and ileum. Capsule endoscopy (CE) emerged as an option to diagnose small intestinal problems in 2001.[111] Technology has improved since then and now high-resolution video of the small intestine is possible with capsule endoscopy without the need for sedation and/or radiation.

Indications of capsule endoscopy:
Obscure GI bleeding is the main indication for CE. 70–80% patients undergo CE for this indication,[112] and two recent meta-analyses have shown that CE is better in

diagnosing obscure GI bleeding compared to radiological investigations and that it is safer than push endoscopy.[113, 114] Furthermore, it eliminates the need for further tests and lengthy hospital stays.[115, 116] On the basis of a large amount of published data, it is now considered a valuable tool to diagnose obscure GI bleeding.

Incidence of small intestinal <u>Crohn's disease</u> is about 45% of the total number of patients with Crohn's and in 25% it is confined to the terminal ileum.[117] The diagnostic yield of CE in Crohn's disease is between 30–70%.[113, 114] There is a theoretical risk of capsule retention in patients with Crohn's disease; however, this risk was not more than in patients with obscure GI bleeding.[118] The risk of capsule retention in patients with diagnosed Crohn's stricture is high (5–13%).[112, 119] CE is therefore considered an important tool in diagnostic work-up in patients suspected of Crohn's disease.

<u>Other indications</u> for utility of CE include non steroidal anti inflammatory drugs (NSAID-induced small ulcerations, and erosions in the stomach and the intestine. Although traditional endoscopy and biopsy remains the gold standard for the diagnosis of celiac disease, some authors have noticed significant positive and negative predictive values of CE in these patients.[120, 121] Small intestinal tumours account for 1–2% of primary GI tumours. The rate of capsule retention in larger-size tumours will be relatively high; however, these patients will subsequently require surgical resection decreasing the risk of the capsule being left in the small intestine. CE is also used in a small number of patients with abdominal pain. Two studies used CE in such patients after extensive diagnostic work-ups and did not find any significant pathology in 85% of cases.[122, 123]

<u>Current British Society of Gastroenterology (BSG) guidelines on the role of CE:</u>[124]

1. Second look upper GI endoscopy before CE in patients with high suspicion of upper GI bleeding.
2. An upper and lower GI endoscopy should be performed for obscure GI bleed before CE.
3. Patients should be counselled and the risk of capsule retention should be explained.

4. The role of intra-operative CE should be kept for patients with undiagnosed obscure GI bleeding.

5. Patients with high suspicion of small bowel Crohn's should be considered for CE.

6. There is a role of CE in refractory celiac disease and its associated complications.

AIM: The review of the published literature and the BSG guidelines elaborate the role of CE in obscure GI bleeding, Crohn's disease and small intestinal tumours. This is, however, dependent upon its transit through the GI tract, and subsequently dependent upon GI motility. The role of CE in GI transit is not very well established and we therefore conducted a retrospective study to elaborate its role in the assessment of GI motility.

2.1.2   Methodology

A total of 113 patients underwent CE in two regional (East Yorkshire) centres from 2006 to 2010. The centres included:

1. Hull and East Yorkshire Hospital NHS Trust

2. Scarborough Hospital NHS Trust.

The number of capsule endoscopy/centres were:

Scarborough (Aug 2007–Dec 2009) = 43

Hull (June 2006–June 2010) = 70

Patient preparation and procedure:

Patients were instructed to continue a normal diet up to one day before CE. They were advised to continue tea, coffee, juice and clear fluids in the evening before CE and not to eat and drink anything after midnight. Bowel preparation was not used routinely in these patients. Patients were also suggested to continue their medications on the morning of the test. They were advised to wear loose clothes and attend the CE suite in these centres. They were seen by the CE specialist nurse and an informed consent was taken. Small adhesive pads were applied at the abdomen and data recorders were

attached (Figure 2-1). Patients were then advised to swallow a capsule with sips of water. They were advised not to eat and drink anything for two hours, with only clear fluid after two hours, and were allowed to have a light snack after four hours. They were free to walk around or stay in the CE unit and they were also allowed to go home and come back after eight hours. Waist belts and data recorders were retrieved and video data later was reviewed by clinicians.
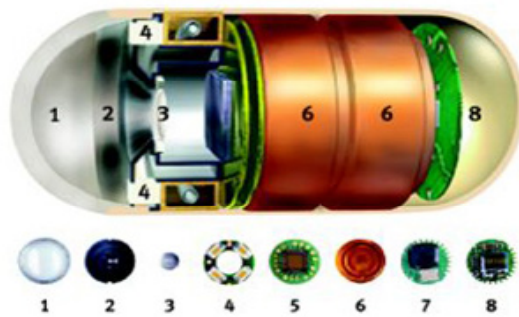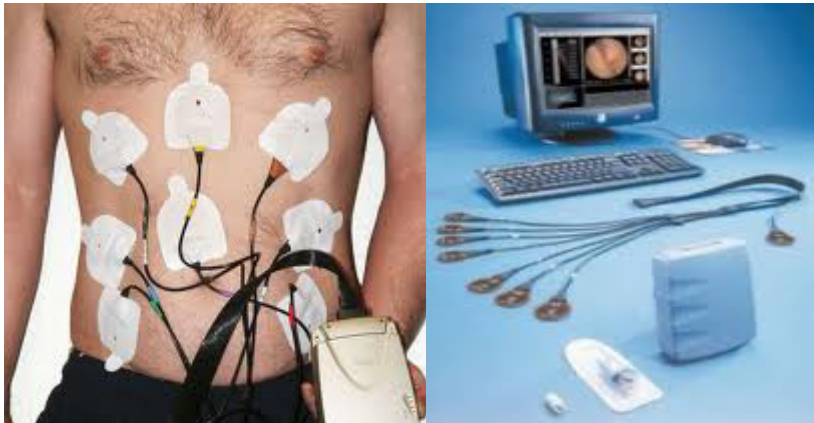
INSIDE THE M2A™ CAPSULE

1. Optical dome
2. Lens holder
3. Lens
4. Illuminating LEDs (Light Emitting Diode)
5. CMOS (Complementary Metal Oxide Semiconductor) imager
6. Battery
7. ASIC (Application Specific Integrated Circuit) transmitter
8. Antenna

Figure 2-1: Components and methodology of CE

Leads, data recorder, equipment and CE

Data collection:

Clinical reports of CE were generated by consultant physicians. Data (video, letters, notes) was revisited by the researcher for the assessment of GI motility. The following additional information along with the demographic data was recorded.

1. Time of capsule ingestion

2. First image of stomach and time of this image

3. First image of D1 (first part of the duodenum) and time of this image

4. Identification of caecum and time

GE time was calculated by the time taken from the first image of the stomach to the first image of the duodenum. This was also confirmed by the data of the capsule journey in the GI tract. (See Figure 2-2 – the capsule journey in the stomach is marked with a blue line.)
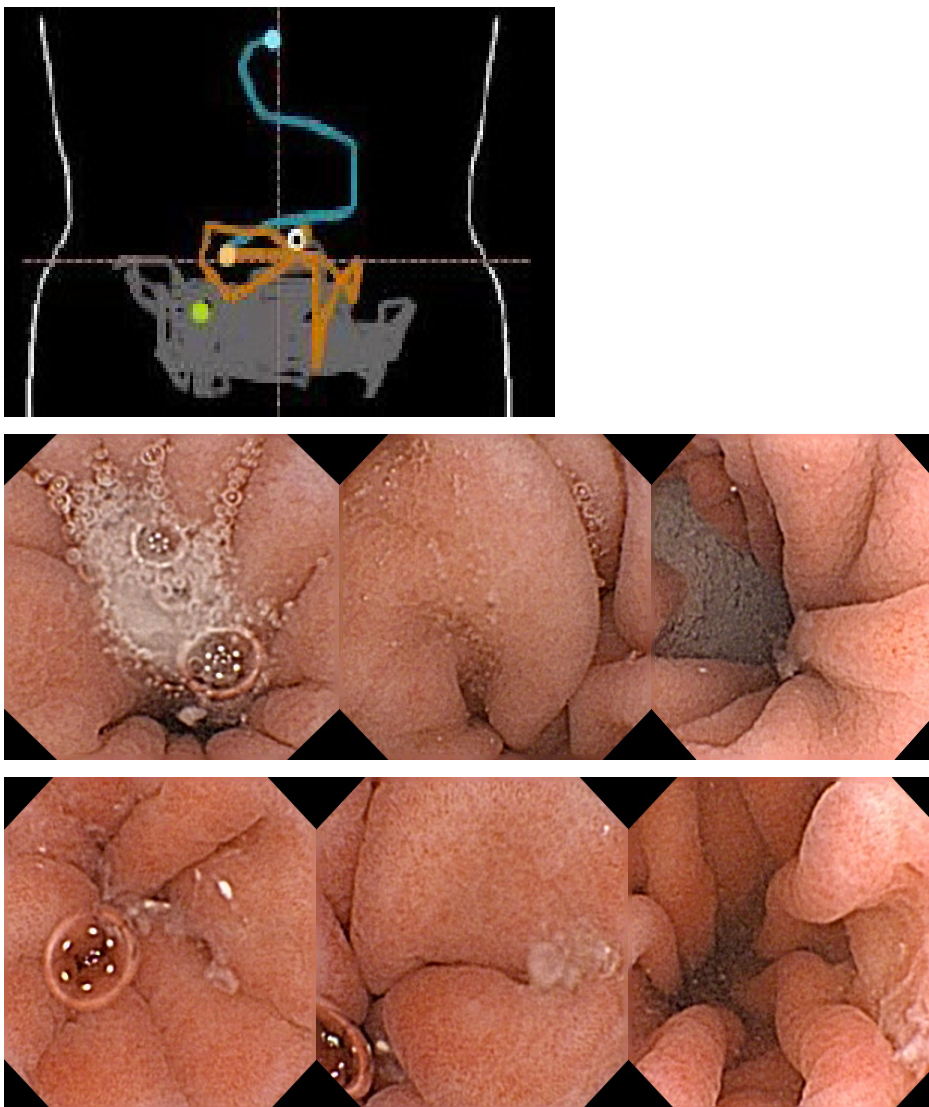
Figure 2-2: Capsule journey and GE

Blue line indicates the capsule journey in stomach, brown line indicates the capsule journey in the small intestine.

The journey of the capsule in the stomach marked in blue and pictures taken during its journey in the stomach.

Intestinal Transit Time: Calculated by the time taken by the capsule from D1 to the caecum (Figure 2-3, Figure 2-4, Figure 2-5, Figure 2-6).
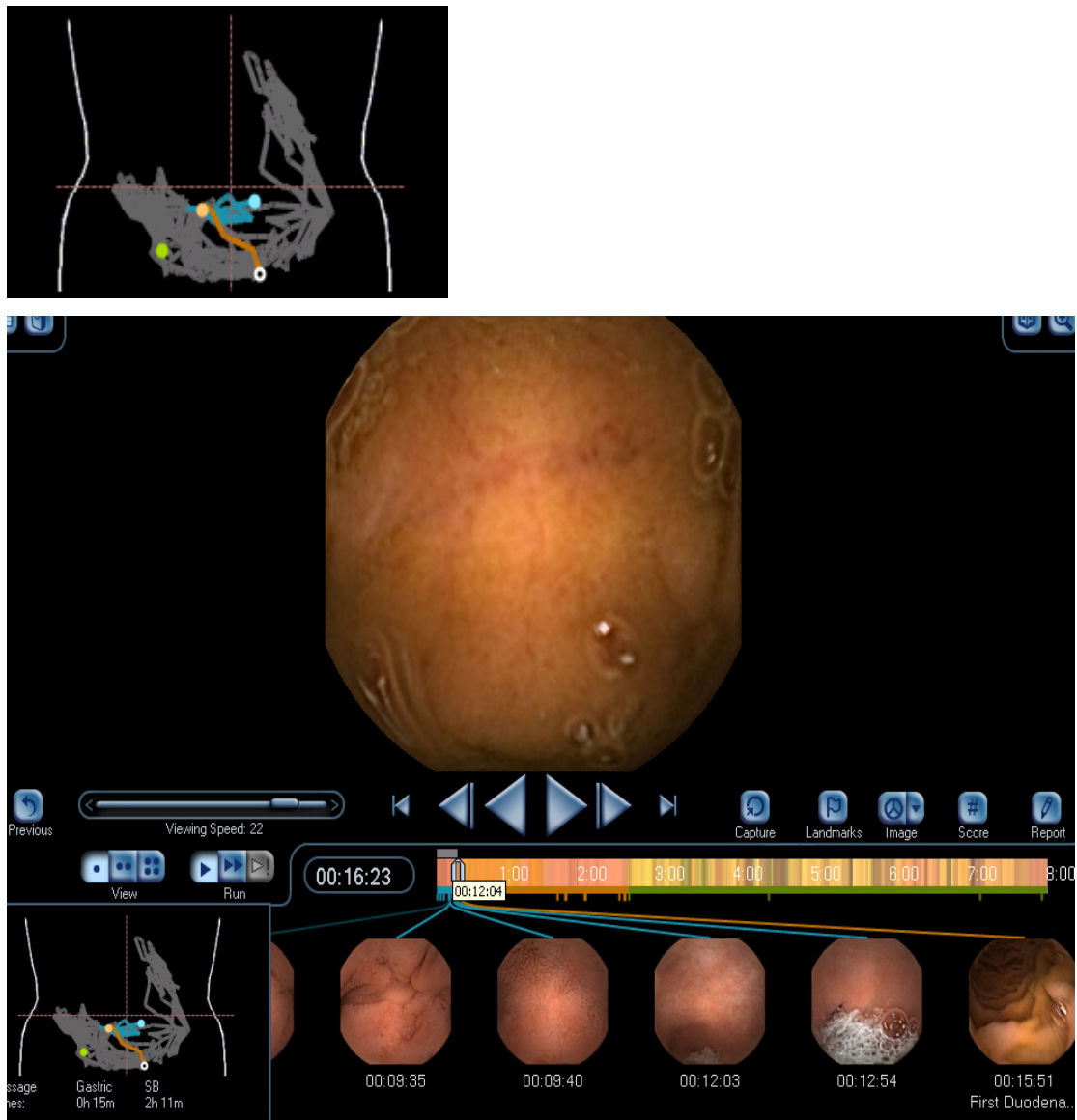
Figure 2-3: Capsule journey in the duodenum

Figure 2-3: Capsule journey marked with brown colour in the duodenum. And the figure below showing the images of the distal stomach and first duodenal image when the capsule enters the duodenum.
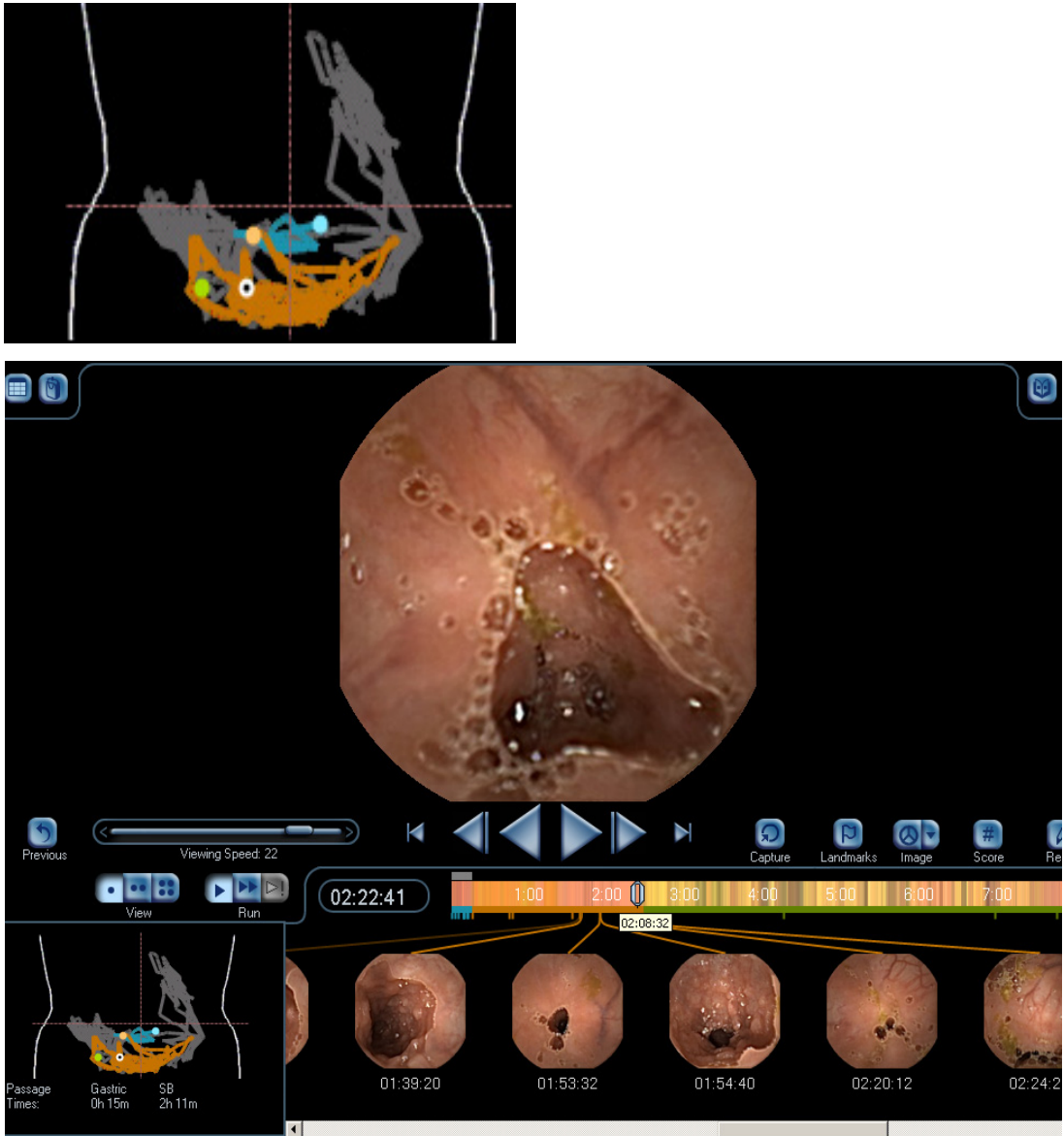
Figure 2-4: Capsule transit through the small intestine

Figure 2-4: Capsule journey marked in brown in the small intestine. The second image demonstrates pictures taken in different parts of the ileum, until the capsule is seen in the terminal ileum at 02:22:41 after ingestion. Time of entry in the duodenum is subtracted from the total time to calculate IT.
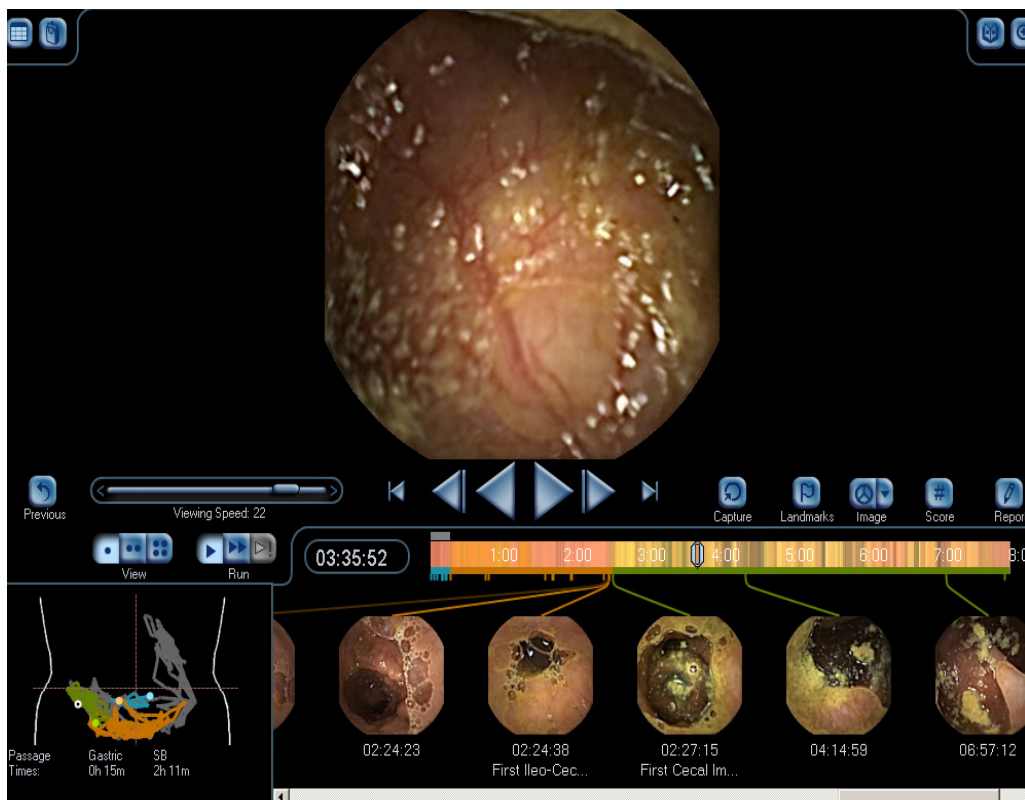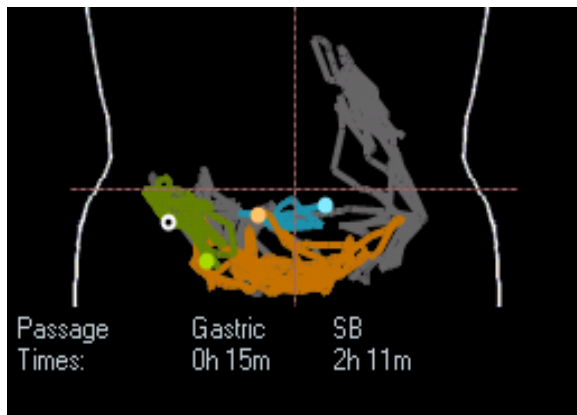
Figure 2-5: Capsule transit through the terminal ileum and into the caecum

Figure 2-5: These figures demonstrate the journey of the capsule in the terminal ileum and caecum. Images taken at 02:24:38 demonstrate the ileocaecal valve. The capsule entered the caecum at 02:27:15 as shown in the images above. The capsule continued to move in the caecum thereafter, as shown in the capsule journey (colour green) in both images.

Identification of the caecum can sometimes be difficult in CE. However, the change in villous pattern and identification of the ileocaecal valve along with identification of caecal landmarks help to identify the caecum. Figure 2-6 demonstrates the presence of submucosal blood vessels, semisolid faecal matter and loss of the villous pattern of the ileum.
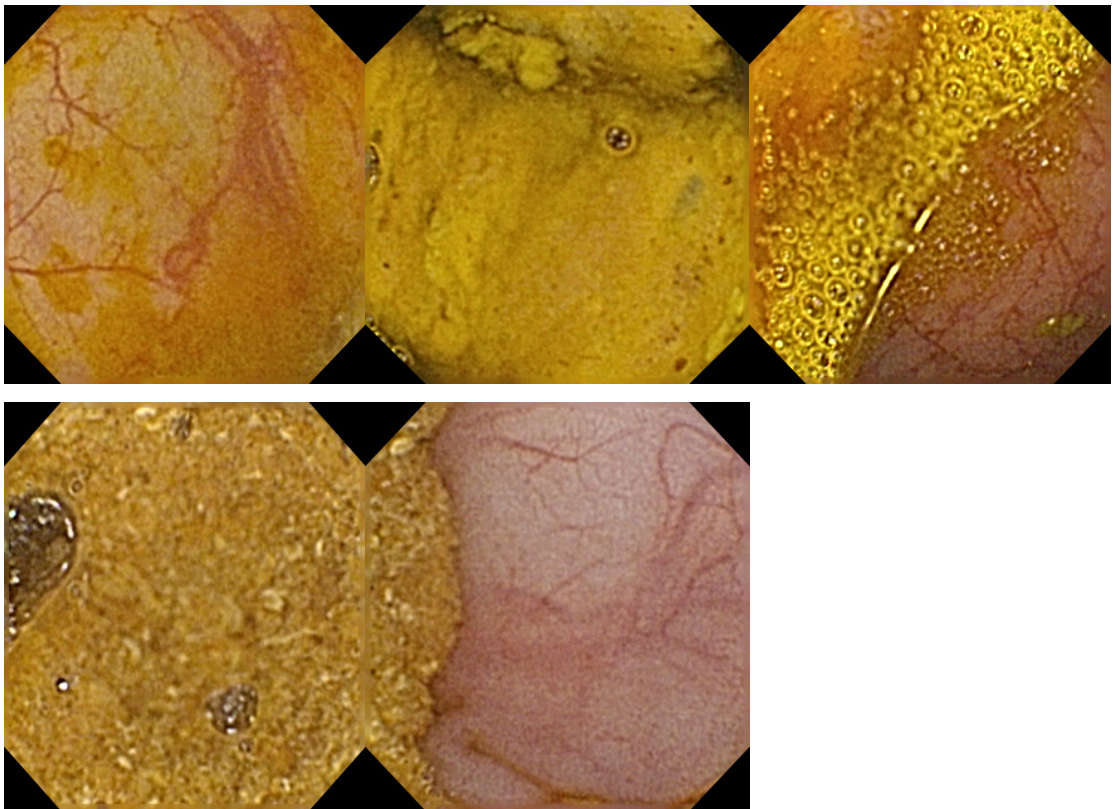
Figure 2-6: Identification of the caecum

Figure 2-6: Identification of the caecum:

1. Submucosal blood vessels
2. Semisolid faecal matter
3. Loss of villous pattern of the ileum

2.1.3 Study approval

Study approval by the hospital clinical governance department was obtained. Video, electronic and paper records were reviewed in this study.

2.1.4 Statistics

Data was entered into an Excel datasheet and statistical analysis was performed using SPSS 17. Values are expressed as mean +/- standard deviation (SD) unless otherwise stated. Significance of difference was calculated using two-tailed paired or unpaired student t tests.

2.1.5 Results

A total of 113 patients underwent CE during this period. The male to female ratio was male 61 (54%): female 52 (46%). The mean age of the patients was 56+/-17 years (range 17–84 years). ASA grade included 1 = 15 (13%), 2 = 68 (61%), 3 = 29 (25.5%), 4 = 01 (0.5%).

Indications of capsule endoscopy are explained in
Table 2-1. The majority (84%) of these patients underwent CE as a part of diagnostic process for anaemia of unknown origin/occult GI bleeding. 6 patients (5%) had a known source of GI bleeding and were further assessed by CE. Other causes included suspected or part of a work-up for inflammatory bowel disease in seven patients (6.1%) and rare indications included abdominal pain in three patients, and weight loss investigations in one patient.

Findings of CE are explained in Table 2-2. CE was reported normal in 23 cases (20%). Areas of redness or red spots of unknown origin were found in 14 patients (12%). Small bowel erosions were seen in 10 patients (8%), ulcers in the small intestine in 9 patients (7.5%) and polyps in the small intestine in 8 patients (7%). Bleeding sites were identified in the small intestine in 3 patients and in stomach in 2 patients. Crohn's work-up/evaluation was carried out in 2 patients. Angiodysplasia and telangactasia were seen in 12 patients (10%). Collectively, the findings were picked up in 68 cases (60%). In one patient, threadworms were identified as a cause of anaemia. Some of these findings are presented in the tables below.

Table 2-1: Indications of CE

Indications	N	%
Anaemia	96/113	84
Bleeding	6/113	5.3
Weight loss	1/113	0.88
Inflammatory bowel disease	7/113	6.1
Abdominal pain	3/113	2.6

Indications of CE included anaemia in 84%, inflammatory bowel disease in 6.1%.

Table 2-2: Findings of CE

Findings	N
Angiodysplasia	6
Ulcers (stomach) +/- bleeding	2
Ulcers (small bowel)	9
Erosions (stomach)	5
Erosions (small bowel)	10
Polyps in small bowel	8
Crohn's disease	2
Red spots/area of redness	14
Bleeding site (small bowel)	3
Threadworm (small bowel)	1
Telangiectasia	6
Bowel narrowing	2
Total	68 (60%)
23/113 (20%) normal	

Threadworm
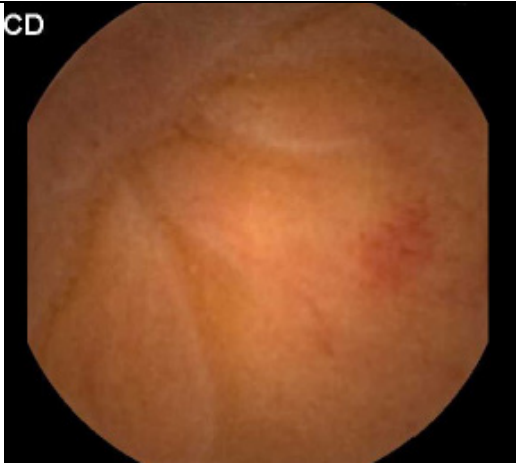
Angiodysplasia of the jejunum
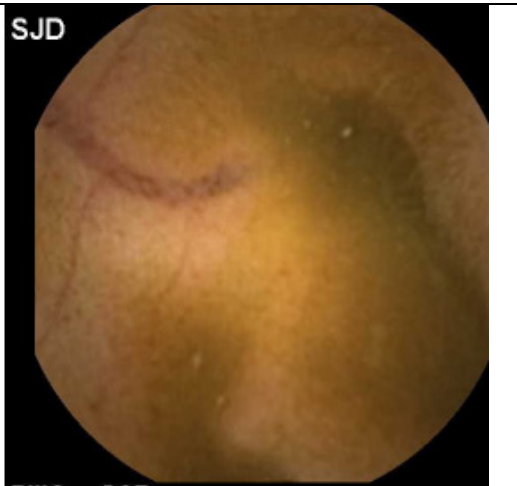
Angiodysplasia of the jejunum
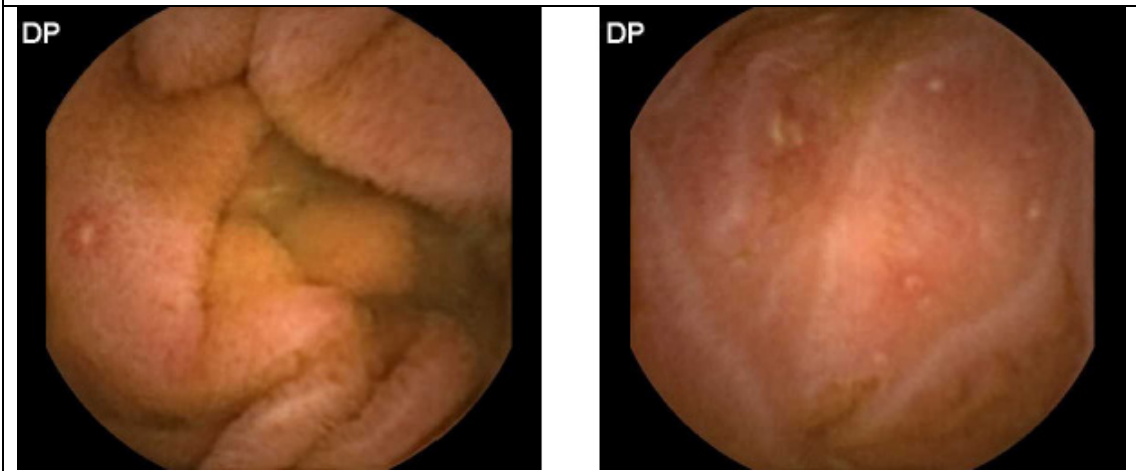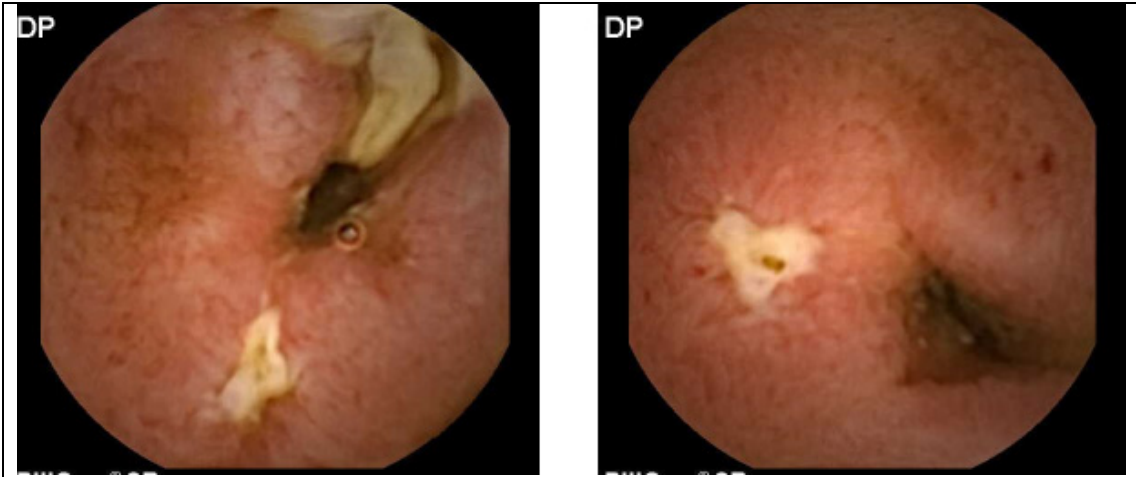
Aphthous ulcers in the jejunum and ileum
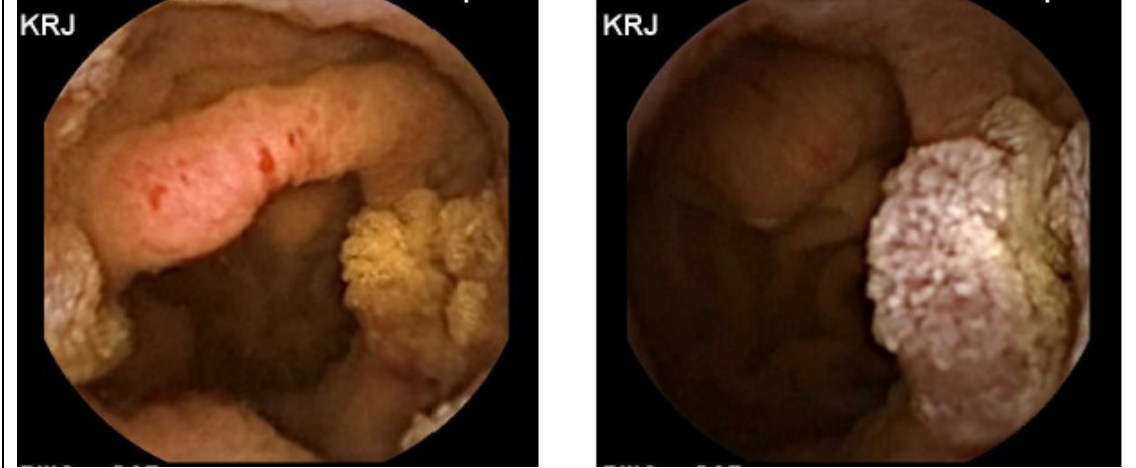
Duodenal and early jejunal polyps

Diverticuli in the jejunum and ileum

Ulcers in the distal ileum; thick oedematous mucosa – suspected Crohn's disease
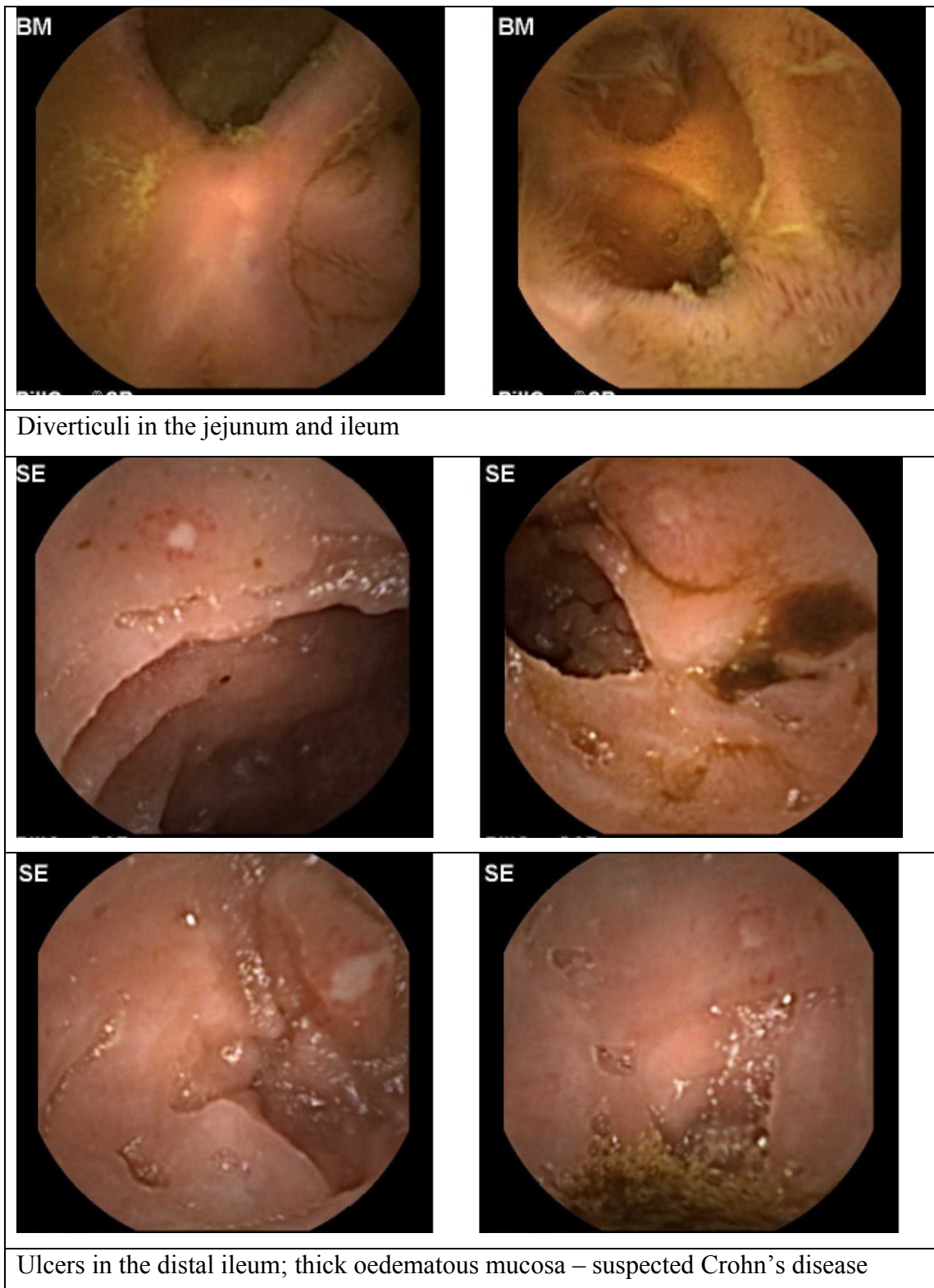
Figure 2-7: Pathologies identified with CE

Mean capsule passage time in the stomach was 00:31 (SD 39) minutes (median 00:17, range 01:00-05:00). Similarly, mean capsule transit time in the small intestine was 04:40 (SD 01:20) hours (median 04:22, range 01:02-07:44) (for details see Table 2-3). The

capsule failed to reach the caecum in 8 patients (7%). This included 2 post-surgical (Crohn's disease) patients, 1 with DM, whereas no obvious cause was seen in 5 patients. The capsule reached the caecum after > 6 hrs in 22 pts, > 7 hr in 3 pts. Capsule retention in the stomach was observed in 3 patients, including 1 post-procto-colectomy and 2 unknown causes.

A subgroup analysis of 12 patients with long-standing DM revealed gastric passage time of 00:31 (SD 39) minutes and intestinal passage time of 05:31 (SD 02:03) hours. These patients matched for age and American Society of Anesthesiologists (ASA) with non-DM group. Comparison of the DM group with the rest of the patients did not show any significant difference in gastric passage time; however, intestinal passage time was significantly prolonged in the DM group (p value 0.07, 0.004 respectively) (Mean capsule transit time through stomach was 31 minutes; intestinal transit time was 4 hours 40 minutes.

Table 2-4 Table 2-4).

Opiates or opiates derivative use was observed in 4 patients. The mean age of this group was 52 years. Gastric passage time was 00:50 (SD 00:55) and intestinal passage time was 04:14 (SD 01:38) hours. This difference was not statistically significant compared to patients not on opiate analgesia (p 0.36, p 0.29 respectively).

3   out of the 113 patients required repeat CE (1 could not swallow, 1 had poor bowel preparation). 1 patient experienced nausea 14 days after CE and an X-ray of the abdomen revealed a capsule in the small intestine. Symptoms however settled spontaneously and the patient did not require surgery. No other complications were observed in this group of patients.

Table 2-3: GE and IT passage time of CE

	Minimum	Maximum	Mean & SD (Hr: Min)	Median
Gastric passage time (N=110)	00:01	05:00	00:31 (39)	17
Intestinal passage/transit	01:02	07:44	04:40(01:20)	04:22

time (N=95)				

Mean capsule transit time through stomach was 31 minutes; intestinal transit time was 4 hours 40 minutes.

Table 2-4: Capsule passage time in diabetic patients

	Minimum	Maximum	Mean & SD (Hr: Min)	P
Gastric passage time	00:02	05:00	00:45 (1:22)	0.07
Intestinal passage/transit time	02:59	08:18	05:31(02:03)	0.004*

*Significantly short intestinal transit time in DM compared to the non DM patients.

2.1.6 Discussion

The British Society of Gastroenterology (BSG) has issued guidelines elaborating the role of CE and these were published in 2008.[124] CE uses a 26x11 mm disposable capsule containing a battery, camera, image transmitter, antenna and a light source (Figure 2-2). The capsule travels with GI motility. There are three major companies manufacturing CE: Pillcam SB by Given Imaging Ltd, Endocapsule by Olympus and OMOM capsule by Jinshan Science and Technology Group.[124] One of our centres used Pillcam and the other used Endocapsule. The equipment and techniques are similar for both companies. The approximate battery life is 8 hours and previous literature has demonstrated that in 85% of cases the capsule can reach the caecum by this time. In this time period, CE records approximately 50,000 images. The main limitations of CE include poor bowel preparation and incomplete examination because of limited (8 hours) battery time, and/or slow transit of the capsule through the GI tract. Based upon these limitations, CE completion rate is published between at 75–90% in different pathologies.[112, 121, 124] In a recent meta-analysis, the diagnostic yield of CE in diagnosing occult GI bleeding was reported to be better than other modalities.[124] When comparing CE with other forms of endoscopy (enteroscopy), the diagnostic yield was similar.[114, 124] Diagnosis of small intestinal Crohn's disease is difficult and previous studies have compared the other modalities with CE. 45% detection of Crohn's disease has been reported in a recent meta-analysis.[114] In another study, the yield for CE versus ileoscopy

was 61% and 46% respectively, showing CE as a better tool for investigation of small intestinal Crohn's.[113] The main complication of CE is capsule retention. It is therefore important that patients should be fully informed about the procedure. Variable results of capsule retention have been reported from 0% (health subjects) to 21% (intestinal obstruction).[112] This problem may be more common in patients with Crohn's disease as there is a high risk of ulceration and stricture formation in Crohn's disease. False negative results are reported to be around 11% (range 5–18%) because CE may miss some information.[125] Other limitations include inability to control the movement, transit through the GI tract and biopsies cannot be taken. The findings were in line with the published data, indicating total finding pick-up rate of 60% and normal CE in 20% of cases. In the rest of the patients, findings were considered not suggestive of any firm conclusions. The capsule failed to reach the caecum (incomplete CE) in 7% of cases.

GI motility depends on multiple factors, including the food composition, medications and body fluids. The results of gastric passage time and IT time in this study were comparable with a large published study to assess GE and IT using CE.[126] This study published the GI motility data of 790 patients using CE and reported GE time of 0:41 ± 0:49 and IT time of 4:22 ± 1:30 hours in subjects over 40 years of age. There was no significant difference in GE time; however, IT time was prolonged in the >40 years age group. A subgroup analysis of health volunteers revealed GE time of 0:39 ± 0:43 and IT time of 3:56 ± 1:22 in 87 subjects. GI motility results are comparable between healthy subjects and patients with celiac disease, obscure GI bleeding, PAF (familial adenomatous polyposis), intestinal lymphoma and ulcerative colitis. In this study, gastric passage time was 00:31+/-00:39 minutes which demonstrates fast GE comparable with this published data.[126] In addition, we noticed a wide range in our gastric passage time data (range 01:00-05:00) and in 3 patients the capsule failed to leave the stomach without any obvious reason. In patients with very short gastric passage time, the capsule fell into the pylorus and passed quickly through the duodenum. This cannot be representative of true GE in these patients.

However, mean capsule transit time in the small intestine (04:40+/-01:20 hours) was comparable with the largest published study,[126] suggesting that the assessment of IT may be more reliable using CE. In our experience, the gastric passage time in patients with DM was unaffected; however, IT time was significantly prolonged in those patients

(Mean capsule transit time through stomach was 31 minutes; intestinal transit time was 4 hours 40 minutes.

Table 2-4 . There is no published available data to compare this finding. In addition, we noticed that gastric passage time was prolonged in patients with opiate use but their results should be cited with caution as the number was very low (n=4).

In 1 of our patients there was severe oesophageal spasm and the capsule failed to progress three hours after ingestion Figure 2-8 (pictures taken after every 30 minutes). In another patient, the capsule was retained in the stomach (Figure 2-9). This patient was suspected with Crohn's disease and subacute bowel obstruction. Food and bile were visible in the stomach and the capsule remained in the stomach during the study time. The patient later underwent small bowel resection for a terminal ileum stricture. The capsule passed spontaneously through the small intestine after the operation. Some unusual findings like diverticuli of the small intestine and ringworm were also identified.

Limitations of CE.
Battery life is approximately 8 hours. In some cases, the capsule may not reach the caecum during this time, and therefore the test will be classified as incomplete. In our study, the capsule failed to reach the caecum in 8 cases (7%). This represents slow GI transit as no other cause of obstruction was identified.

Another limitation of CE is inability to take biopsy of lesions found in small intestine. This may necessitate enteroscopy in such patients; however, this may also fail to obtain biopsy or resection subject to the distance and length of scope, technical inability and patient factors.

Inability to manoeuvre the capsule may result in missing some part of the mucosa. Based upon the previous studies, 10–15% missed mucosa was reported. This may result in missing some important information which may lead to false negative results.

Bowel preparation can hamper the image quality and therefore result in incomplete tests or inaccurate results. This can be rectified by bowel preparation and a repeat examination. In our study, 2 patients required a repeat test on these grounds.

Conclusion:

The role of CE is well established in obscure GI bleeding. It is also a valuable tool in assessment of Crohn's disease, celiac disease and other small bowel pathologies. We propose that it can be used as a tool to assess IT. It may not be a true representative of GE.
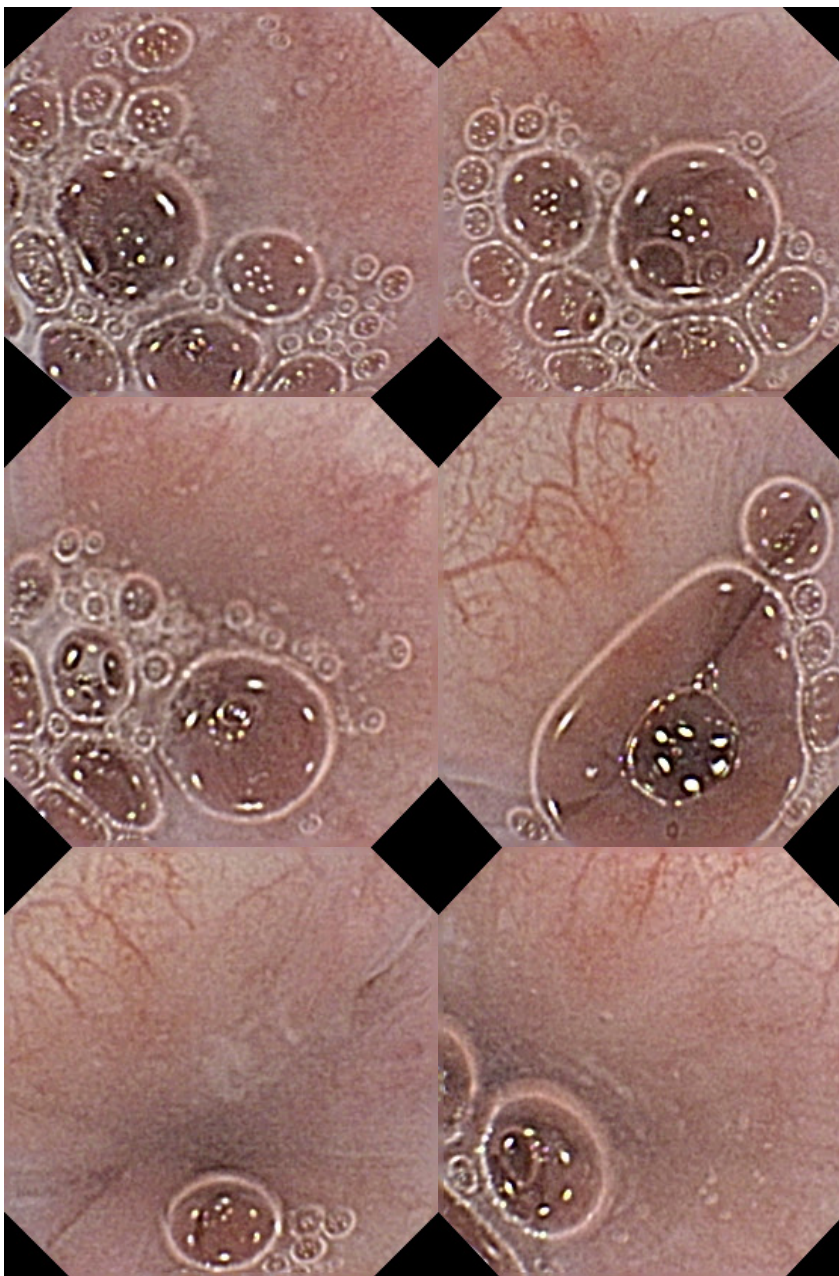
Figure 2-8: Oesophageal sphincter spasm

Oesophageal sphincter spasm. Capsule failed to progress until 3 hours after ingestion. 6 pictures taken at 30-minute intervals.
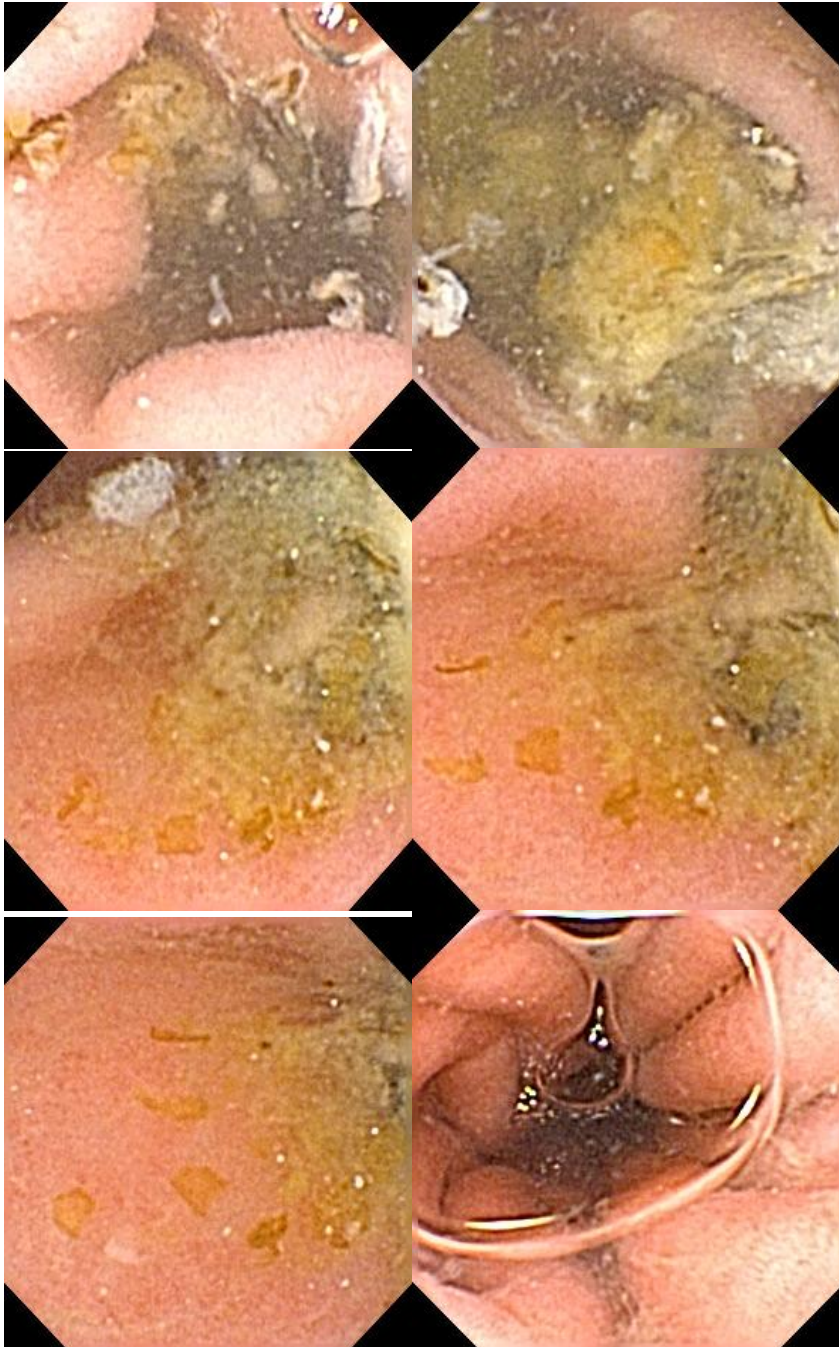
Figure 2-9: Crohn's stricture on CE

A patient with Crohn's stricture and subacute small bowel obstruction. Food and bile is visible in the stomach. The capsule failed to progress in the small intestine and was retained in the stomach.

2.2 Role of lactulose breath test in assessment of GI motility

2.2.1 Introduction

Hydrogen breath test is a non-invasive and safe investigation. In a hydrogen breath test, patients are asked to take a test solution to drink after they have fasted overnight. The concentration of hydrogen (measured in parts per million (ppm)) in the breath is then measured using a breath test machine. If the breath contains a large amount of hydrogen (more than 20 ppm above the baseline) it is classified as a positive test. The baseline amount of hydrogen present in the breath before drinking the test solution is also measured. Hydrogen breath tests have been in practice for a long time; however, their utility is not fully explored. They are used for the assessment of GI metabolic disturbance (lactose and fructose intolerance) and assessment of bacterial overgrowth.[127-130]

The time between ingestion and first rise of hydrogen in the breath is considered as a positive test.[131, 132] Further interpretation of the results is controversial. Although generally accepted, interpretation of a positive test is >20 ppm rise in hydrogen in the breath; however, some studies have used more flexible definitions such as simply a rise of hydrogen within 90 minutes as positive test.[133-135] In a recent review article about methods of GI motility assessment, a rise of above 10 ppm was considered as a positive test.[136]

Castle Hill Hospital is a tertiary referral hospital and breath tests are regularly performed for suspected metabolic disorders, bacterial overgrowth and impaired GI transit. The aim of this study was to evaluate our practice and interpretation of the hydrogen breath test and evaluate the results of consecutive patients. In addition, we wanted to critically review the use of the hydrogen breath test in OCTT.

Figure 2-10: Breath test analyser

Gastro+ Gastrolyzer® analyser for lactulose breath test as used in our department

2.2.2 Methodology

Apparatus:

The breath test machine used in our centre was Bedfont Gastro+ Gastrolyzer made by Bedfont Scientific Ltd, Maidstone, Kent, UK (Figure 2-10). It is a user-friendly apparatus which measures the end expiratory breath using single-use disposable cardboard Flatpak™ mouthpieces or disposable face masks. The instrument is calibrated regularly. The calibration gas settings were kept at 100 ppm.

Hydrogen Breath Tests Protocol

Patient preparation:

1.   Patients were asked to fast from 6pm the night prior to the study (water allowed up to 4 hours prior to the study). They were asked not to take any

antibiotics 6 weeks before the test. In addition, motility agents or laxatives were also stopped 5 days prior to the study. They were suggested to take a restricted diet 24 hours prior to the test (no roughage or complex carbohydrates) with a suggested menu sent to the patient with their appointment letter. Furthermore, they were requested not to smoke on the morning of the test.

2.   The patients were asked to inhale as deeply as possible and hold their breath throughout the on-screen countdown. After the audio beep, they exhaled slowly but gently into the mouthpiece, aiming to empty the lungs as much as possible.

Test description:

1.   Glucose test for small bowel bacterial overgrowth

Procedure: Patients were fasted overnight (from 6pm). Prior to the procedure, patients had 3 measurements of hydrogen breath. (If the baseline average exceeded 5 ppm, the test was abandoned.) The patients were given the 200 ml test solution to drink **(50 grams of glucose dissolved in 200 ml of lemon spirit, sorbic acid and citric acid).** Breath hydrogen was then measured at x − 15, 30, 60, 90, 120, 150, 180, 210 and 240 minutes. The hydrogen breath data were plotted in a software programme (Microsoft Access) or written on a results sheet.

Interpretation: Under normal circumstances, the amount of hydrogen in a breath sample will remain unchanged as the glucose is absorbed in the small intestine. However, in patients with bacterial overgrowth the glucose will be digested by the bacteria, producing hydrogen, which is released in the breath. In general, a rise of 20 ppm above the baseline is taken as a positive hydrogen breath test; this must be seen on two consecutive hydrogen breath measurements before the test can be stopped or at the 240-minute point, whichever comes first.

2.   Lactulose breath test for the measurement of oral-caecal transit time

Patients were fasted overnight (from 6pm). Prior to the procedure, patients had 3 measurements of hydrogen breath. (If the baseline average exceeded 5 ppm, the test was abandoned.) The patients were given **30 ml of lactulose** solution taken orally. Breath hydrogen was then measured at x − 15, 30, 60, 90, 120, 150, 180, 210 and 240 minutes.

The hydrogen breath data was plotted in a software programme (Microsoft Access) or written on a results sheet.

Interpretation: The rise in breath hydrogen, which reflects delivery of lactulose to the caecum was noted. This is taken as the oral-caecal transit time. In general, a rise of 20 ppm above the baseline is taken as a positive test in our centre.

3.   Lactose test for diagnosis of intestinal lactose deficiency

Patients were fasted overnight (from 6pm). Prior to the procedure, patients had 3 measurements of hydrogen breath. (If the baseline average exceeded 5 ppm, the test was stopped.) The patient was given the **200 ml test solution to drink (50 grams of lactose dissolved in 200 ml of lemon spirit and sorbic acid).** Breath hydrogen was then measured at x − 15, 30, 60, 90, 120, 150, 180, 210 and 240 minutes. The hydrogen breath data was plotted in a software programme (Microsoft Access) or written on a results sheet. Interpretation: Under normal circumstances, the amount of hydrogen in a breath sample will remain unaltered as the lactose is absorbed in the small intestine. However, if a patient has lactose intolerance, the lactose will not be absorbed and hydrogen will be produced, which is released in the breath sample. In general, a rise of 20 ppm above the baseline is taken as a positive test.

2.2.3   Statistics

Data was entered in an Excel sheet and analysed using SPSS 19. Mean +/- standard deviation was used.

2.2.4   Results

A total of 495 patients underwent hydrogen breath tests from march1998 to August 2010. 217 patients (43%) had a glucose test for suspected bacterial overgrowth, 114 (23%) had lactose test for suspected lactose intolerance. The remaining 164 patients (33%) had a lactulose test for suspected impaired OCTT.

Presenting complaints included constipation (90%) and diarrhoea (4%), and rare indications included scleroderma in 1 patient, cystic fibrosis in 1 patient, high output

from iliostomy in 1 patient, and 2 diabetic patients presented with constipation (Table 2-5: Indications of breath test).

Normal OCTT was observed in 67 patients (40%) (20 ppm rise within 0–90 minutes), blunted in 10 patients (0.6%) (0–19 ppm rise within 0–90 minutes). In another 20 patients (12%) the OCTT increased by >20 ppm; however, this was demonstrated after 90 minutes (Figure 2-11). A rise 100 ppm was observed in 2 patients (Figure 2-11). A mean increase was 2 +/- 5 to 19 +/- 20 from baseline to 120 minutes (Figure 2-11,

Table 2-6, Figure 2-12, Figure 2-13). Patients with scleroderma and cystic fibrosis demonstrated slow OCTT; however, it was blunted in diabetes.

Table 2-5: Indications of breath test

Indications of lactulose breath test	N (%)
Constipation/decreased bowel frequency	148 (90%)
Diarrhoea/increased bowel frequency	7 (4%)
DM, suspected decreased OCTT*	2 (1%)
Scleroderma**	1 (0.6%)
Cystic fibrosis***	1 (0.6%)
High output from iliostomy (post Crohn's surgery)****	1 (0.6%)
Indication not documented	4 (2%)

In patients with scleroderma,** and cystic fibrosis*** the OCTT was 150 minutes. Fast OCTT was noticed in patients with high-output iliostomy**** (< than 60 minutes). It was inconclusive in DM.*
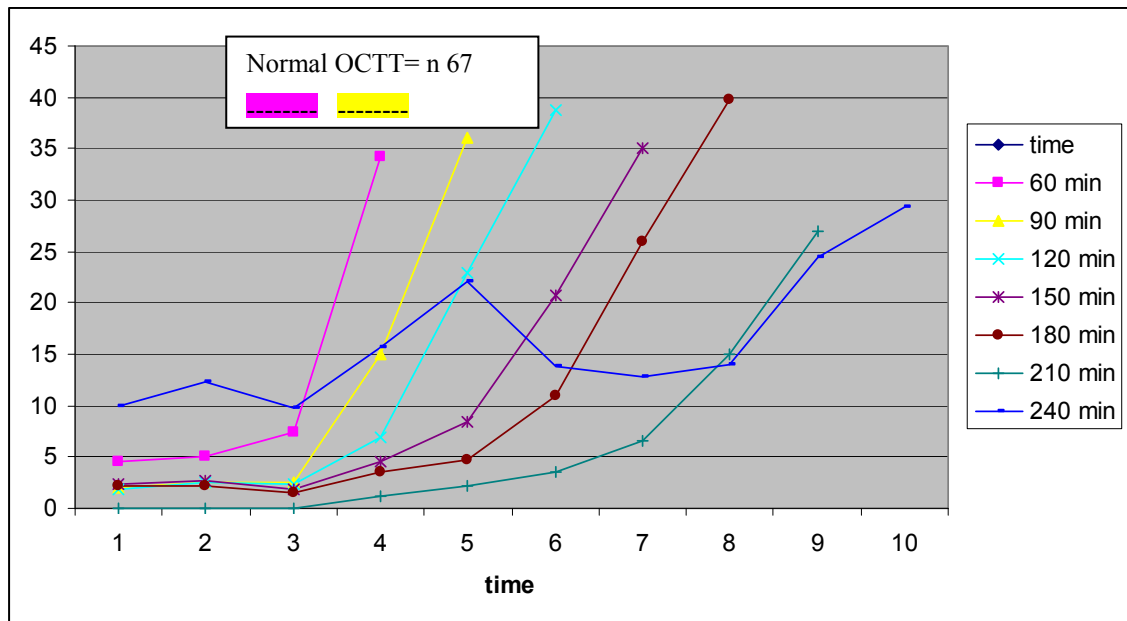
Figure 2-11: Categorical results of breath test

This figure demonstrates the categorical data of patients with normal OCTT.

Labels

X axis: (1=O MINUTES, 2=15 MINUTES, 3=30 MINUTES, 4=60 MINUTES, 5=90 MINUTES, 6=120 MINUTES, 7=150 MINUTES, 8=180 MINUTES, 9=210 MINUTES, 10=240 MINUTES)

Y axis: ppm

Number of patients demonstrating >20 ppm rise from baseline=119 (72%)

Number of patients demonstrating >20 ppm rise within 0–60 minutes=32

Number of patients demonstrating >20 ppm rise within 0–90 minutes=67(40%)

Number of patients demonstrating >20 ppm rise after 90 minutes=20 (including 4 @ 240 minutes and 5 @ 210 minutes).

Blunted response ppm rise of 10–19 from baseline=10

Early rise within 30 minutes noted in only 1 patient.

Table 2-6: Cumulative OCTT data

Baseline mean breath test = 2+/-5(range 0–30) ppm, maximum at 90 minutes 16+/-18
(range 0–83) ppm.

Time (minutes)		0	15	30	60	90	120	150	180	210	240
N	Valid	164	158	158	158	151	125	91	68	46	13
	Missing	0	6	6	6	13	39	73	96	118	151
Mean		2	2	3	9	16	19	18	18	10	14
Median		0	0	1	2	8	13	14	12	8	12
Std. Deviation		5	5	6	13	18	21	18	21	11	14
Range		30	30	31	63	83	136	97	114	54	50
Minimum		0	0	0	0	0	0	0	0	0	0
Maximum		30	30	31	63	83	136	97	114	54	50
Percentiles	25	0	0	0	0	1	2	4	3	0	2
	50	0	0	1	2	8	13	14	12	8	12
	75	1	2	3	12	26	29	25	27	16	22
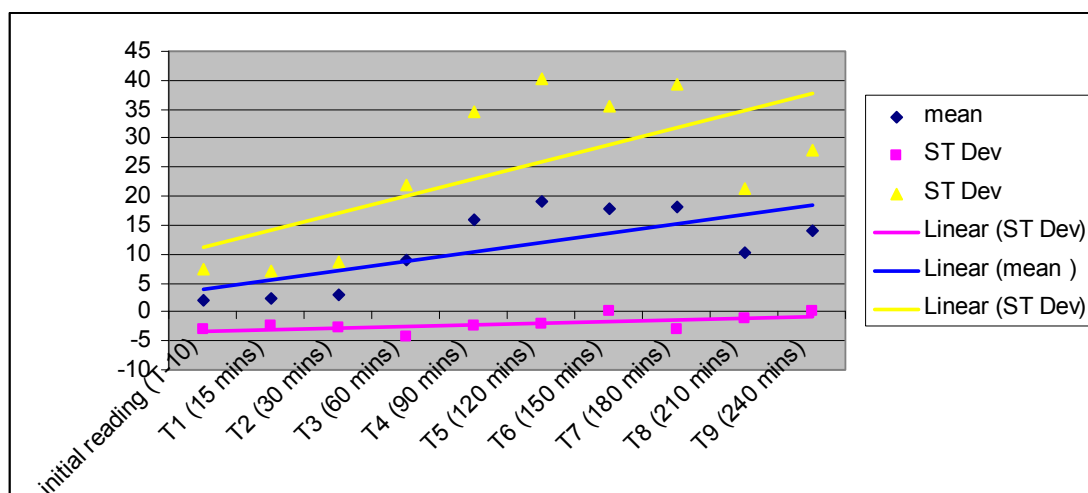
Figure 2-12: OCTT (mean)

This figure demonstrates the mean (blue**)** + Standard deviation of OCTT in all patients.
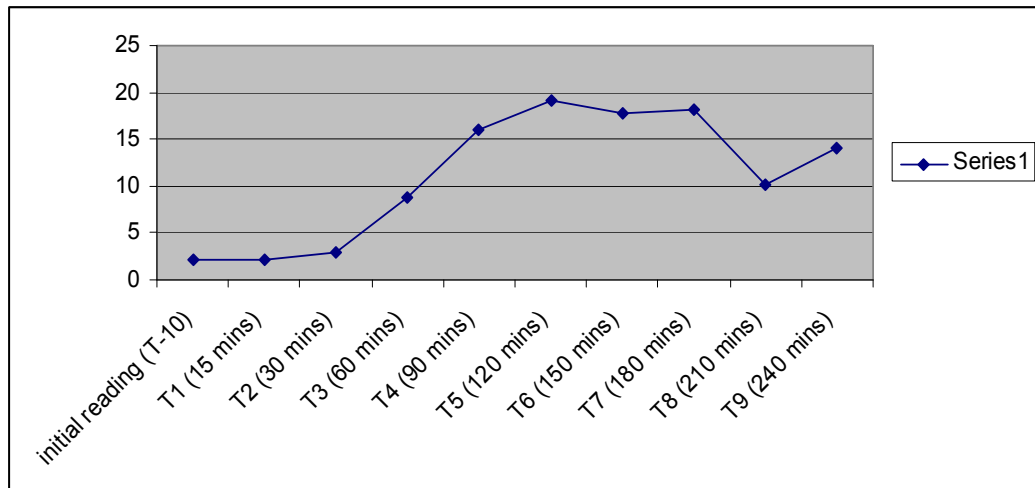
Figure 2-13: Minimum and peak value of OCTT

Graphic representation of OCTT in all patients. Highest levels observed from 90 minutes to 180 minutes.

2.2.5   Discussion

This study addressed the issue of OCTT in altered GI motility. If we imply the definition of a rise of hydrogen in breath at 90 minutes to a normal test, our results demonstrate that 40% of patients had normal OCTT. However, this was based upon the rise of >20 ppm above the baseline whereas some authors accept a rise of 5–10 ppm as normal.[136, 137] If we imply this definition in our study, only 23 patients (14%) had delayed OCTT although 148 (90%) suffered from symptoms suggestive of constipation or decreased bowel frequency. It is, however, important to know that 2 suspected slow OCTT patients (1 with scleroderma and 1 with long-standing cystic fibrosis) had slow OCTT. There was a wide range of results (Figure 2-12)**Figure 2-12**, (Table 2-6) which limit generalisation of this test.

Other studies and review articles have encountered these problems.[133, 136, 138] Low specificity and sensitivity have been reported for lactulose breath tests in literature. This may be because of many factors. Lactulose is not a physiological test meal and may alter the motility of the GI tract and result in false positive results. On the other hand, if part of it is absorbed by the small intestine it may show an early rise on small intestinal absorption followed by a delayed rise when reaching the caecum. This is also described

by Simre´n M et al.[133] Similarly, there are far more controversies in terms of implication of the test in malabsorption and small bowel bacterial overgrowth.[133, 136, 139]

About one third of the population suffer from symptoms of gastroparesis, irritable bowel syndrome, constipation and bloating etc. This results in significant utilisation of NHS time and resources. It is, however, well recognised that there is no single test to investigate motility disorders of the stomach, intestine and colon. In the first part of this chapter, the role of CE is described in detail. American and European neurogastroenterology guidelines about different techniques to assess GI motility were published in 2010.[136] According to these guidelines, a rise in 5–10 ppm is considered as a positive test. They also demonstrated a wide range of results in the normal population (OCTT 53–208 minutes). In addition, high variations (14%–39%) were observed when the tests were implied in subjects on two occasions. OCTT using hydrogen breath test in another study was found to be faster than the other two methods (one with blue food colour and the other with radio opaque markers).[140] Another limitation of this test is the inability to measure the solid phase OCTT as the test meal used is liquid.

There are, however, certain advantages of this test as well. These include that the test is validated and uniform across the centres of the world. It is easy to perform and well tolerated by patients. It does not require radiation as used in scintigraphy; nor is there a test meal required as some patients may not like that or may develop a reaction to certain food particles. In addition, it is less expensive than the other methods.

Limitations: This was a retrospective single centre study. In addition the implications of the test on patient's management could not be study. It is a liquid phase transit test which is not a true reflection of food transit in GUT. As there is no standardization of its interpretation in relation to other more accurate methods, more studies are required to validate this test.

Conclusion: It is concluded that the hydrogen breath test is inexpensive, easy to perform and can be used when other precise methods are not available. It may also be used in younger patients and in pregnancy because there is no risk of radiation. However, care must be taken during interpretation, and patients with a strong suspicion of GI transit problems should be considered for scintigraphy or CE.

3   Resolution of type 2 diabetes following RYGB

Excerpts of this chapter have been modified and presented in ASGBI by way of an oral presentation.

Ullah S, Meden L, Jain PK, Sedman P. Resolution of type 2 diabetes following Roux-en-Y gastric bypass. Is this mediated by changes in gut hormones? (Oral Presentation in Moynihan's prize session. ASGBI 2011).

Excerpts of this chapter have been modified and presented in ASGBI as a poster.

Ullah S, Arsalai-Zadeh R, Sedman P, G. Avery G, MacFie J. Role of gstrointestinal transit and pouch emptying in resolution of type 2 diabetes following Roux-en-Y gastric bypass. (Poster ASGBI 2011).

3.1 Introduction

Obesity is one of the leading preventable causes of death worldwide and with rates of adult and childhood obesity increasing authorities now view it as one of most serious public health problems of the 21st century. Not surprisingly, this epidemic has resulted in an exponential increase in the number of patients seeking bariatric surgery (surgical weight loss procedures). There is increasing evidence to suggest that Roux-en-Y gastric bypass (RYGB) is the operation of choice. It is associated with minimal morbidity and significant weight loss.[141,142]

Insulin resistance is a very common feature of morbid obesity which leads to hyperinsulinemia, impaired glucose tolerance and type 2 diabetes. Weight loss surgery results in 50–70% loss of excess body weight and cures diabetes in up to 77% of patients. What is most curious, however, is that resolution of diabetes frequently occurs

within seven to ten days of bariatric surgery. Clearly, therefore, weight loss alone cannot account for the improvement in glucose metabolism.[142]

Recent evidence suggests that the dramatic improvement in diabetes may be mediated by modulation of insulin secretion by glucagon-like peptide-1 (GLP-1) from the distal ileum. This mechanism is explained in detail in Chapter 1. A brief description of GLP-1 in relation to DM is given here.

This hormone possesses two important functions:

1. Insulinotropic effect: GLP-1 is secreted from the distal small intestine in response to glucose. It results in the suppression of glucagon and the increased secretion of insulin.
2. Ileal brake hormone: GLP-1 is called *brake hormone* because on stimulation it reduces GE and modulates IT to reduce food entry into the small intestine.[8, 143] There is evidence suggesting that these effects are impaired in patients with obesity and improved after obesity surgery.[8, 26, 143]

Ghrelin is another important recently identified GI hormone secreted from the empty stomach and proximal small intestine. This hormone has also been explained in detail in Chapter 1. It is a powerful appetite stimulant and levels are increased before and decreased after food intake.[142] It may also decrease insulin secretion and affect other hormones, resulting in hyperglycaemia.[142] The possible mechanism on appetite and satiety is mediated by the autonomic nervous system (the vagus and sympathetic chain) and controlled by the medulla and the hypothalamus.[142, 144] Decreased plasma levels were recorded after RYGB,[142] which may result in improved insulin secretion. Also, there are conflicting reports of increased, decreased and unchanged ghrelin levels after bariatric surgery.[142]

The action mechanism of gastrointestinal hormones and altered anatomy influence food intake and its delivery to the intestine are not fully understood. It is thought that the bypassed stomach and decreased ghrelin (appetite hormone) may result in early satiety. Early exposure of food to the distal small intestine may result in the stimulation of GLP-1, resulting in increased insulin secretion and the resolution of diabetes.[142,143] It would seem, therefore, that the nature, amount and frequency of food ingestion may influence

these gut peptide activities. In this regard, it is interesting to note that most bariatric surgical procedures will have a significant impact on both GE and intestinal motility. Many studies have investigated GE of patients with morbid obesity, some studies finding increased GE, others no change and others decreased GE.[53, 54, 58-61, 63-65, 145] The lack of consistency in results may relate to the methods employed or to a lack of standardisation of patients. There are few studies available which have specifically addressed the issue of intestinal motility, although it is interesting to note that RYGB will inevitably increase gastric motility as much of the upper gut is bypassed.

The aim of this study was to investigate changes in GLP-1 and ghrelin that occur in patients following bariatric surgery and attempt to determine whether these changes are primarily mediated by food intake (amount and volume) or changes in intestinal motility. In addition, the results of these investigations will be critically appraised in conjunction with any changes in insulin sensitivity or diabetic status.

The following two hypotheses were proposed and tested in this study:

1. Foregut hypothesis
2. Hindgut hypothesis

3.1.1 Foregut hypothesis

Following surgery (RYGB), foregut may play an important role in the resolution of type 2 DM because

1. The bypassed stomach may produce lower levels of ghrelin.
2. The small gastric pouch and hormones may influence (induce) satiety.
3. Food may reach the distal small intestine quicker (fast GE/pouch emptying), causing early release of incretins.
4. All these changes may improve glucose levels and insulin resistance (IR) following surgery.

Foregut

↓ Ghrelin————— ↓ Time taken by food to enter the small intestine and reach the distal ileum, ↑Satiety, improved IR, ↓Glucose

3.1.2 Hindgut hypothesis

The second hypothesis to be tested in this study was as follows:

1. Possible early delivery of food to the small intestine and distal ileum (fast IT).

2. There may be early and/or exaggerated GLP-1 release.

3. The above may induce hypoglycaemia and decreased IR.

<div style="background-color:#1abc9c; padding:20px; display:inline-block;">

Hindgut

</div>
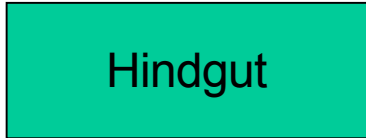
↑GLP-1──────── ↓ Time taken by food to enter the small intestine and reach the distal ileum, ↑Satiety, improved IR, ↓Glucose

3.2 AIM

The primary aim of this study was to assess IR and diabetic status in patients with morbid obesity before and after bariatric surgery, and attempt to determine whether or not this is influenced by changes in GE, intestinal motility and gut peptides.

Study design

This was a prospective observational study conducted in Hull & East Yorkshire Hospitals NHS Trust.

3.2.1 Ethical approval and ARSAC approval

This study was reviewed and approved by South Humber Research Ethical Committee in May 2009. **09/H1305/33**

ARSAC approval was obtained for this study by Dr G Avery, Consultant Radiologist, Castle Hill Hospital, Cottingham (email: ged.avery@hey.nhs.uk).

3.2.2 Informed consent

Patients with type 2 DM were identified by the clinical team. A brief discussion regarding the study was given and an information leaflet was provided containing the information set out in Appendix 1.

3.2.3 Inclusion and exclusion criteria

Table 3-1: Inclusion and exclusion criteria

INCLUSION CRITERIA	EXCLUSION CRITERIA
Patients with BMI >40, or >35 with comorbidities (NICE guidelines), undergoing surgery for morbid obesity (includes patients with type 1 and type 2 diabetes)	1. Patients requiring insulin after a 6-hour fast. 2. Hypoglycaemia requiring glucose before or during the course of study procedures. 3. Hyperglycaemia requiring insulin or oral hypoglycaemic agents during the course of study procedures.
Age >18 years	Age <18 years
Either sex	Allergies to radioactive material
Patients fit for surgery	Failure to obtain written and verbal informed consent
	Too disabled to have scintigraphy
	Inability to understand English
	Possible pregnancy

3.3 Methodology

3.3.1 IR and diabetic status

Effects of hormones and GI motility on insulin secretion, IR and the resolution of diabetes were assessed. GI motility and hormone response were also plotted on computer-generated graphs. Pre- and post-operative findings were compared with appropriate statistical tests.

Homeostatic model assessment[126] is a method of assessment of the B cell function and diabetic status of patients. This was first described in 1985 and this method can be implied to assess diabetic status and IR by using basal glucose, insulin levels/or C peptide levels. The basis of diabetic status is IR and the ability to measure it enables us to understand the diabetic status and the effect of treatment used for DM. IR is an important factor to determine the risk of ischemic heart disease, DM, hyperlipidemia, hypertension and obesity. The pathophysiology of DM in obesity demonstrates that there is higher than normal insulin secretion in type 2 DM but that it remains ineffective because of IR. There is physiological as well as pathological IR which is beyond the domain of this thesis; however, they are well described in a paper published by Wallace TM et al.[146]

The Homeostasis Model of Assessment (HOMA) is a method of assessment of IR. It is robust and requires glucose and insulin/or C peptide levels in a fasting state. Other methods include continuous infusion of glucose with model assessment (CIGMA), frequently sampled intravenous glucose tolerance test (FSIGTT), Hyperglycaemic clamp (HC) and Euglycaemic clamp (EC). All these methods require either glucose infusion and or insulin which will interfere with/influence the response of other hormones including insulin, GLP and ghrelin in our study. Therefore, HOMA-IR method was adopted in this study and other methods were deemed not to be suitable in this study. IR using HOMA-IR is calculated as follows:

Insulin resistance = fasting insulin (mIU/L) x fasting glucose (mmol/L) / 22.5

Glucose levels in this study were also checked by a glucometer (standardised and calibrated) available in radiology department. Plasma samples were taken to assess insulin, ghrelin and GLP-1 levels. These samples were stored at -70°C and transported in batches of 40 samples to the Department of Biochemistry, University of Hull, for Enzyme-linked immunosorbent assay (ELISA) analysis.

3.3.2 GI motility (scintigraphy)

Scintigraphy is a gold standard investigation for GE. Patients are fasted overnight and given a meal containing isotope 99m Tc (radioactive material). Dynamic acquisitions are taken for 100 minutes followed by static acquisitions at fixed time points such as 120, 180, 240, 360 and 480 minutes after the meal. The % of activity in stomach and % of activity in the intestine is recorded. Similarly, gastric half-emptying time (T50) is also calculated and activity is drawn on a computer-generated plot and compared with the local reference values.[147]

Scintigraphy is the only reliable method to assess both regional and total IT.[148],[149],[150] Small bowel transit is measured as the percentage of the delivered radioactivity entering the colon by a specified time (colonic filling), for example at 6 hours.[150] The technique is similar to above and in the Mayo method accelerated small bowel transit is defined as colonic filling of >70% at 6 hours and delayed small bowel transit is defined as colonic filling of <11% at 6 hours.[151] GI transit studies are regularly conducted in the Nuclear Medicine Department and results are interpreted in relation to the normal values calculated by departmental studies conducted on healthy volunteers in the past.

A very small dose of radioactive material (0.3mSv 99m Tc) was used for this study. We are all exposed to background radiation of 2.3mSv/year from the environment during day-to-day activities. In relation to background radiation, this amount is 7.5 times less than what we are exposed to in a year. It is equivalent to 45 days of background radiation and if compared with radiation exposure from a CT scan of the abdomen, it is 23–33 times less than that. The radiation dose is 10 times less than standard small bowel barium studies.[152]

3.3.2.1 Setup

This study was conducted in Castle Hill Hospital, Cottingham, and the University of Hull. Castle Hill Hospital is a tertiary hospital which provides bariatric surgery services. Patients with morbid obesity and refractory to non-operative treatments are referred to the bariatric surgery unit by their general practitioner or primary care trust (PCT). They are reviewed by one of the two bariatric surgeons in the outpatient department. They are also assessed by a dedicated bariatric nutritionist and psychologists. Initial assessments include anthropometric measurements, maintenance of food diary records, level of activity/exercise advice and medical and social history. A further six-week plan is made, including the tasks to modify food and nutrition and improvement in activity. In addition, initial information about the surgery, procedures, indications, potential complications and short- and long-term side effects are also explained. Patients who were listed for RYGB were considered for discussions to participate in this research project.

They were identified by the clinical team at this stage. They received a brief explanation about the study and an information leaflet was provided. Details of the patients interested in this project were passed on to the researcher and subsequently seen by him in further routine bariatric clinic follow-up. The aims of the study were explained together with the methods, the subject's involvement (i.e. overnight fast, fasting blood sample, test meal in the morning, followed by further blood test and GI scintigraphy). Subjects were advised to continue as per routine and continue regular medications until the night before the tests. They were advised not to take antidiabetic medicines in the morning and to attend the Nuclear Medicine Department at Castle Hill Hospital, Cottingham. On arrival the baseline data (age, gender, weight, height), other comorbidities and medication history were recorded.

Laboratory preparations: As the sample techniques were different for each hormone assay, the blood collection bottles were prepared in the morning before conducting the study. Each hormone assay required specific preparation for blood sampling.

A. Ghrelin samples: The instruction notes recommended by the assay kits were followed. We used Millipore Elisa Kits cat number EZGRT-89K for human ghrelin measurements. As ghrelin is considered an extremely unstable hormone and requires rigorous protection, the Vacutainer tubes were treated (added) with Pefabloc to a concentration of 1mg/ml.

B. GLP-1 samples: Ice-cooled Vacutanors were used. DPP-IV inhibitor (10 Ul/ml of blood) was added in vaccinators before blood sampling.

C. For glucose and insulin: No additives used.

A venflon was inserted and the first blood sample withdrawn using a syringe. Blood samples were then transferred into the vacutainers. Blood glucose levels were checked with a departmental glucometer. This glucometer is routinely calibrated by the Pathology/Biochemistry Department of the Hospital. The venflon was flushed with 1 ml normal saline (0.9%) and used again for further samples later on. Before the next blood sample, 3 ml blood was drawn and discarded to avoid any dilution secondary to the previous saline flush. The samples were immediately transferred into the laboratory and processed for centrifuge and storage. Centrifuge settings at 3,000 rev for 15 minutes at temperature 4 +/- 2 were used. Ghrelin samples were acidified by HCL to a final concentration of 0.5N. All samples were stored at -70°C and analysed on a later date in batches.

3.3.2.2 Test meal

The test meal in this study consisted of 1 scrambled egg with 1 slice of white toast and 100 ml orange juice. The approximated calories of the meal size were as follows.

1 slice of white toast = 80 calories

1 scrambled egg = 100 calories

150 ml orange juice = 70 calories

Total = 250 calories.

A small amount of radioactive material (0.3mSv 99m Tc) was used for this study. We are all exposed to background radiation of 2.3mSv/year from the environment during day-to-day activities. In relation to the background radiation, this amount is 7.5 times

less than what we are exposed to in a year. It is equivalent to 45 days of background radiation and if compared with radiation exposure from a CT scan of abdomen, it is 23–33 times less than that. The radiation dose is 10 times less than standard small bowel barium studies. Patients were explained about the amount and mode of this radiation. Radioactive Tc was added in the scrambled egg and patients were advised to consume the meal within 5–10 minutes.

The meal size was very carefully chosen based upon our departmental experience as these patients cannot consume normal-sized or large meals after RYGB. Two weeks after surgery only one fasting blood sample was taken. Six months after surgery (RYGB), the tests and test meal were repeated in accordance with the guidelines as explained for per operative studies.

ARSAC approval: In addition to ethical approval, an ARSAC approval was also obtained for this project as it involved radiation exposure to patients.

3.3.2.3 Image processing and measurement of GE

The Nuclear Medicine Department in Castle Hill Hospital is equipped with two gamma cameras which are used routinely for clinical purposes (Figure 1-11). The images of these cameras are sent to a central system and then processed for results. Multiple computers with the necessary software are installed in the Department. The researcher and consultant radiologist had access to a camera, the computers and the data of this study.

A total of 100 (1 image/minute) anterior and posterior images were recorded for each patient to measure GE (Figure 3-1, Figure 3-2, Figure 3-3). This data was recorded as dynamic acquisitions; however, it can also be used as static images. Radioactivity in the stomach represents food in the stomach. In gastric scintigraphy (GS) (pictures below), the food passing through the pylorus can be seen clearly. An area of interest (AOI) (Figure 3-4, Figure 3-5) was drawn around the stomach in both anterior and posterior images. Images were realigned to fit in the AOI to get an accurate count. This required images to move up, down, left, right or rotate as shown in Figure 3-5. In this picture, the patient during the 5th minute of the study may have moved towards the head end of the

camera. This resulted in the image falling outside the AOI, which required readjustment into the AOI for further calculations. All the images (100 anterior and 100 posterior) for each patient were readjusted according to the movement and then a geometric mean was calculated using software. T50 and % emptying at different time points were calculated, and computer-generated time vs. activity graphs were generated (Figure 3-6, Figure 3-7).
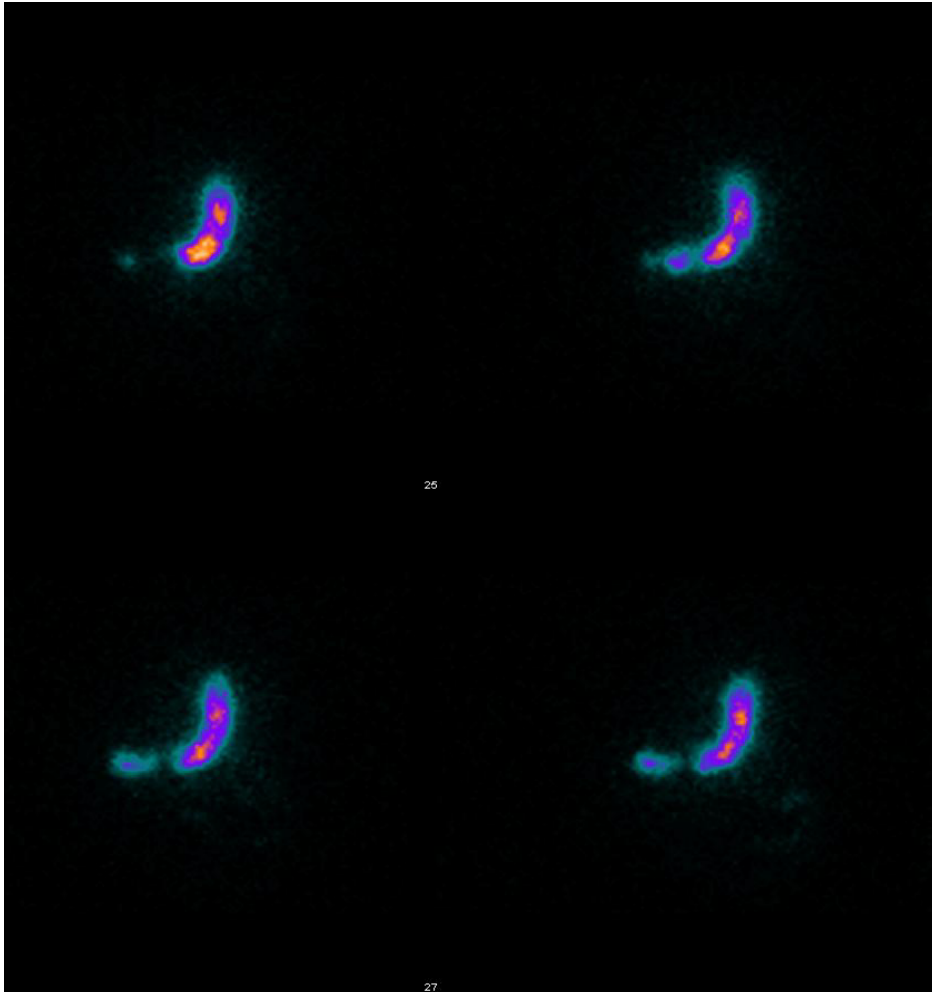
Figure 3-1: GE on anterior images

Image of stomach with radioactivity representing food in it.

Note: GE can clearly be demonstrated by passage of food/bolus through the pylorus.
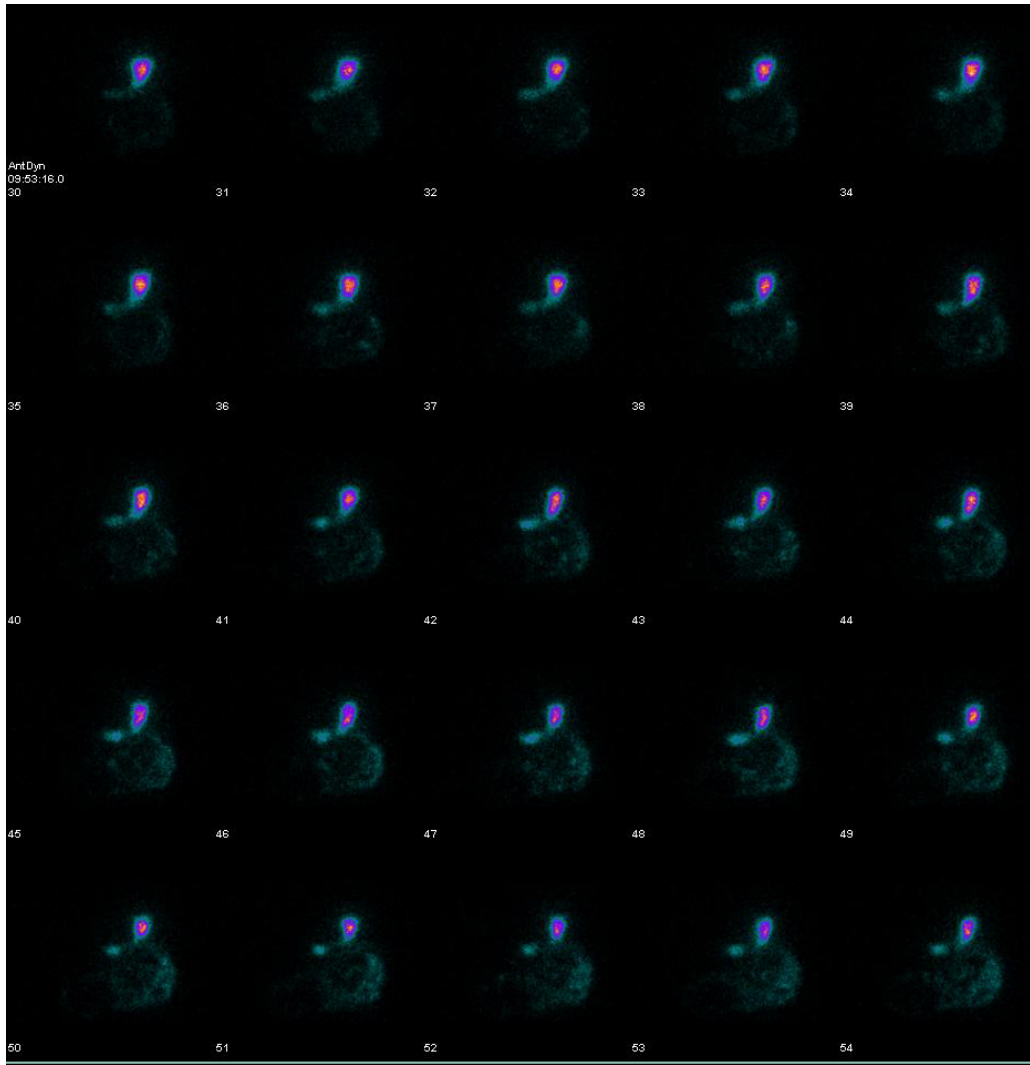
Figure 3-2: GE and intestinal appearance of radioactivity

Anterior acquisitions (images) taken every minute showing the radioactivity in the stomach and small intestine.
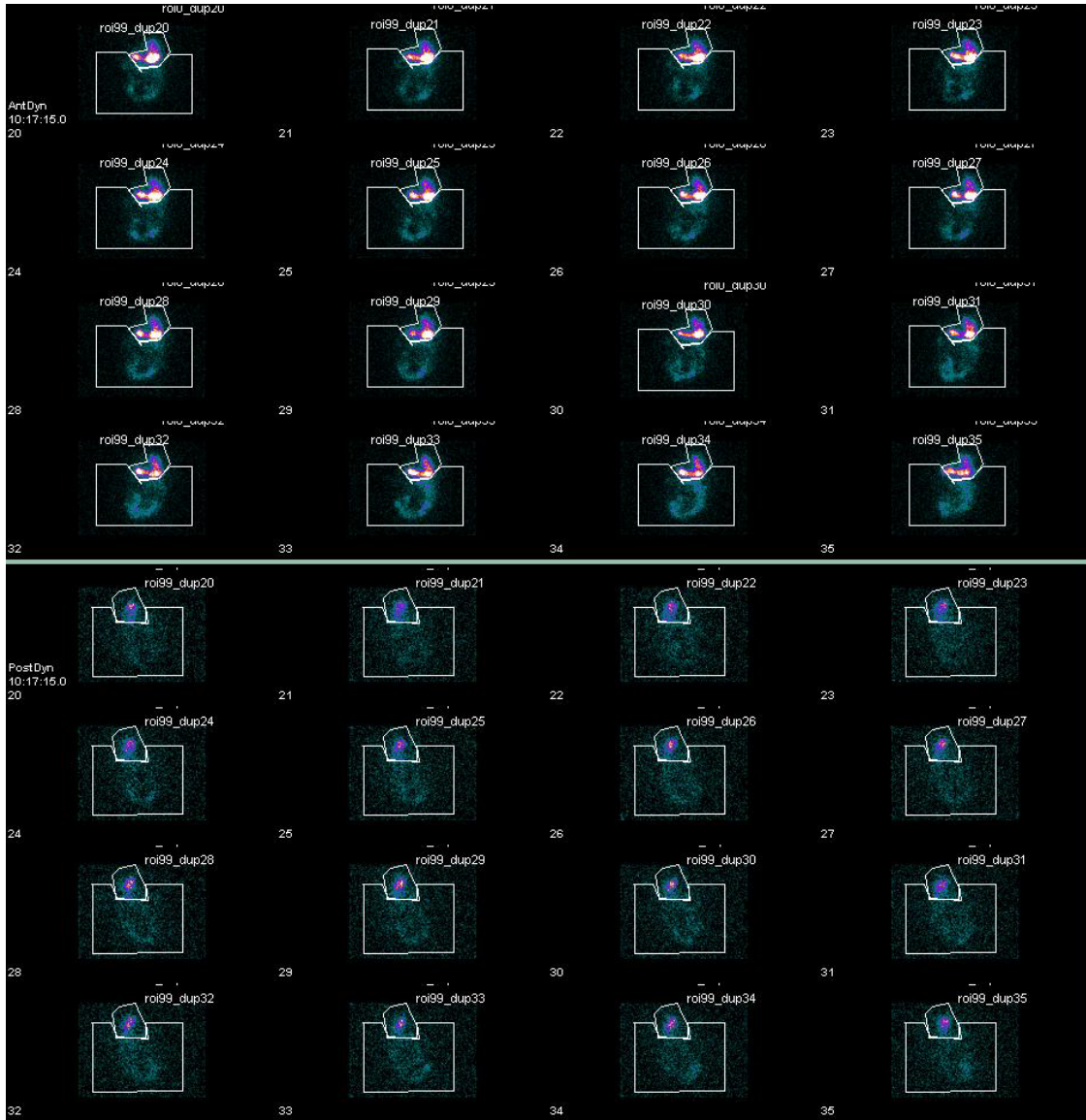
Figure 3-3: Marking the AOI around the stomach and intestine

Area around the stomach is marked on anterior images and posterior images.
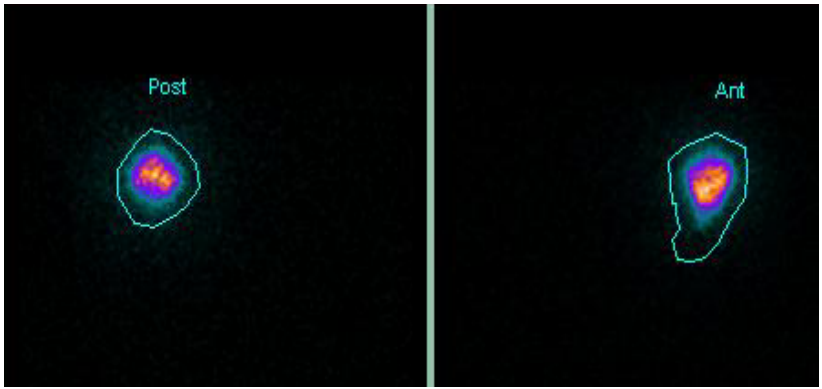
Figure 3-4: Marking AOI

Image processing for GE. AOI marked around the stomach in both anterior and posterior images.
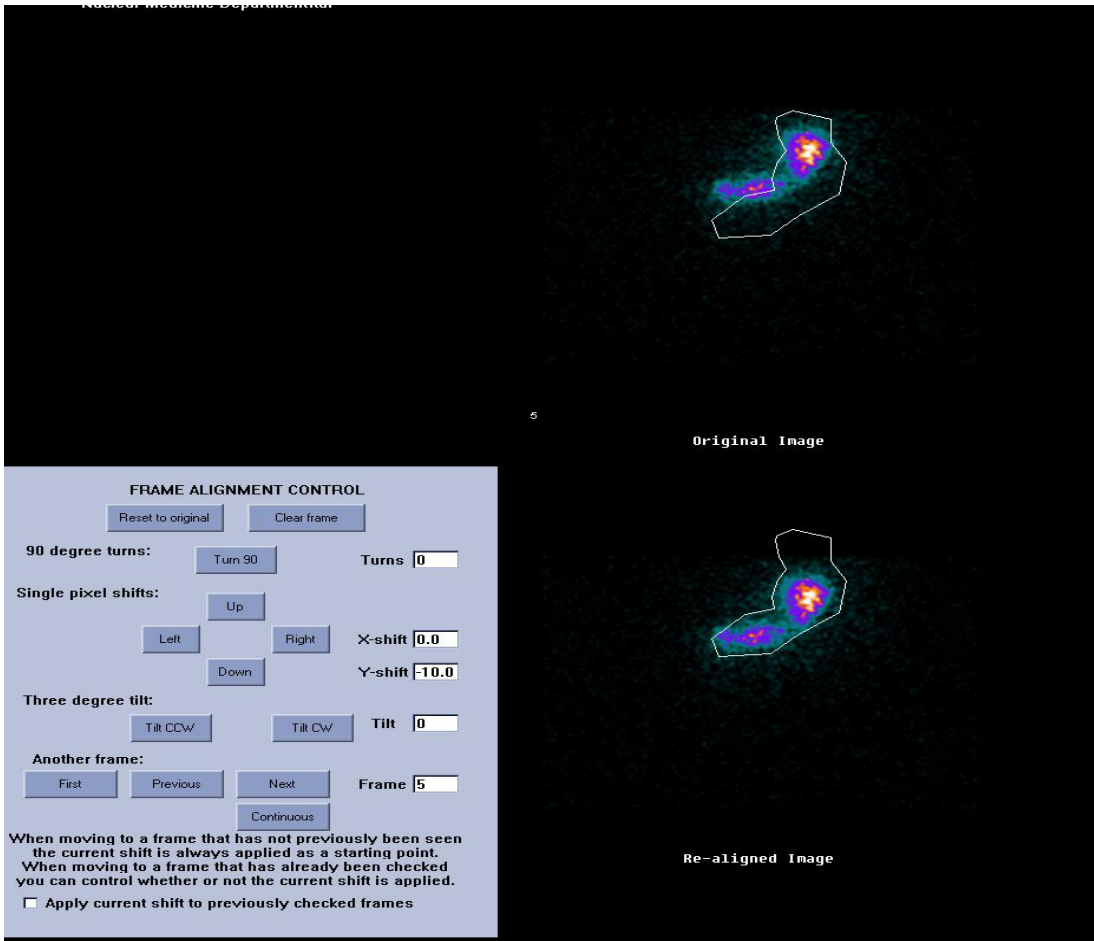
Figure 3-5: Image realignment for GE

This figure represents the patient movement which resulted in the image being partially or completely outside the AOI. Images were readjusted for alignment manually using the software as shown above.
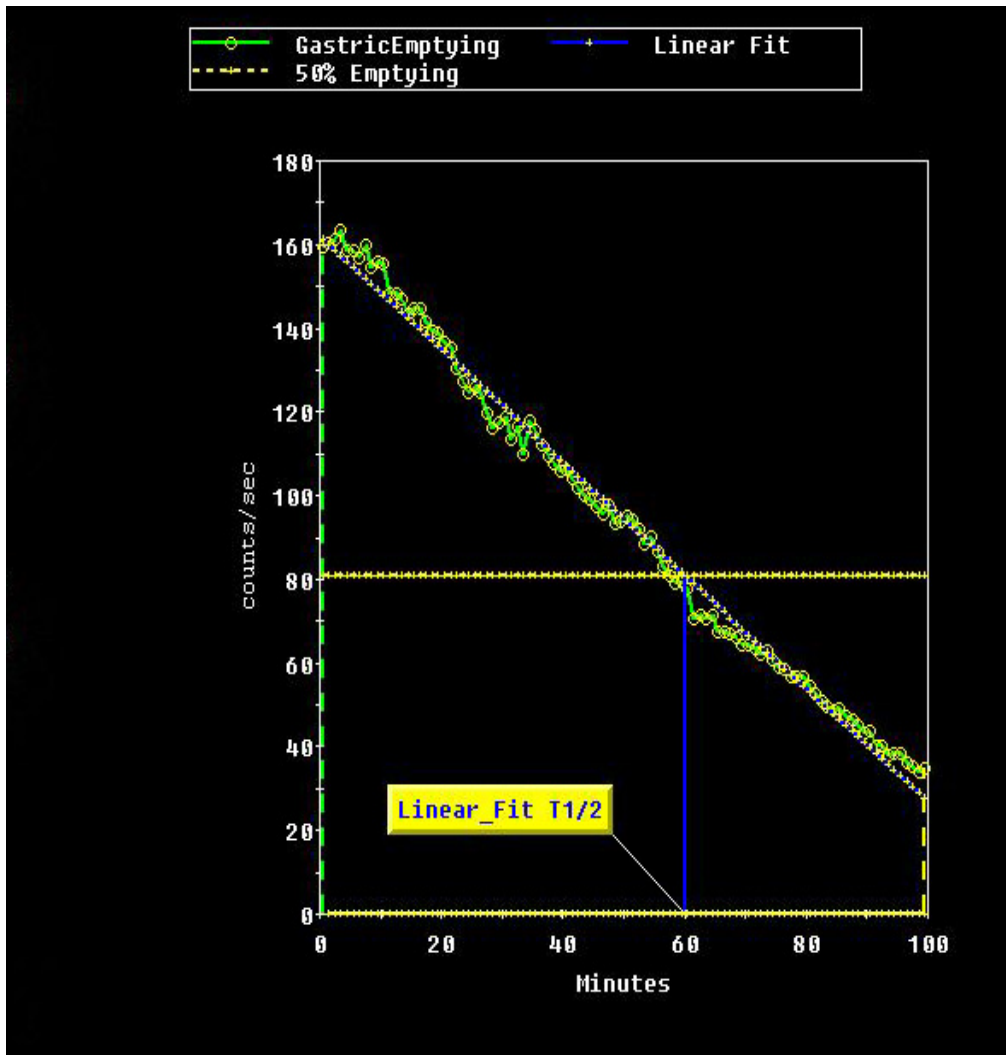
Figure 3-6: Time vs. radioactivity curve

Time vs. activity graph. X axis representing time (minutes) and Y axis representing the counts/sec radioactivity in the AOI. A geometric mean was calculated from anterior and posterior acquisitions.

Green line represents absolute data.

Dotted white line represents linear fit on absolute data.

Blue line marks the half-emptying time in this patient (T50 = 59.6 minutes)

Frame/Time		Fit / Raw % Empty		Kcounts**	Anterior / Post	
10	9.5	8	2	0.156	0.190	0.128
20	19.5	16	13	0.139	0.188	0.103
30	29.5	24	26	0.118	0.163	0.085
40	39.5	33	34	0.106	0.165	0.068
50	49.5	41	41	0.094	0.148	0.060
60	59.5	49	50	0.080	0.135	0.047
70	69.5	58	60	0.064	0.108	0.038
80	79.5	66	64	0.057	0.098	0.033
90	89.5	75	73	0.044	0.078	0.024
100	99.5	83	78	0.035	0.068	0.018

Linear Fit T 1/2 (min) = 59.66
Linear Fit Slope (%/min) = 0.84
Raw Data T 1/2 (min) = 57.65
Tc_99m
** Geometric Mean

Figure 3-7: % GE at 10-minute intervals

Time vs. radioactivity and % emptying at 10-minute intervals.

Linear fit T50 (half-emptying) of this patient=59.6 minutes.

Post-operatively the stomach was bypassed, therefore food (containing radioactivity) could only be seen in the gastric pouch, and gastric pouch emptying was calculated using the same method as implied for GE measurement (Figure 3-8, Figure 3-9, Figure 3-10).

As most of the stomachs were bypassed, the gastric pouch was small compared to the stomach size, and food entry into the small intestine was seen during the procedure. However, we noticed that at a later stage it was difficult to identify the pouch (after emptying); therefore, a skin marker (on the right side and next to the pouch) was applied to keep a reference point during the time of IT calculation (Figure 3-8 and Figure 3-9).
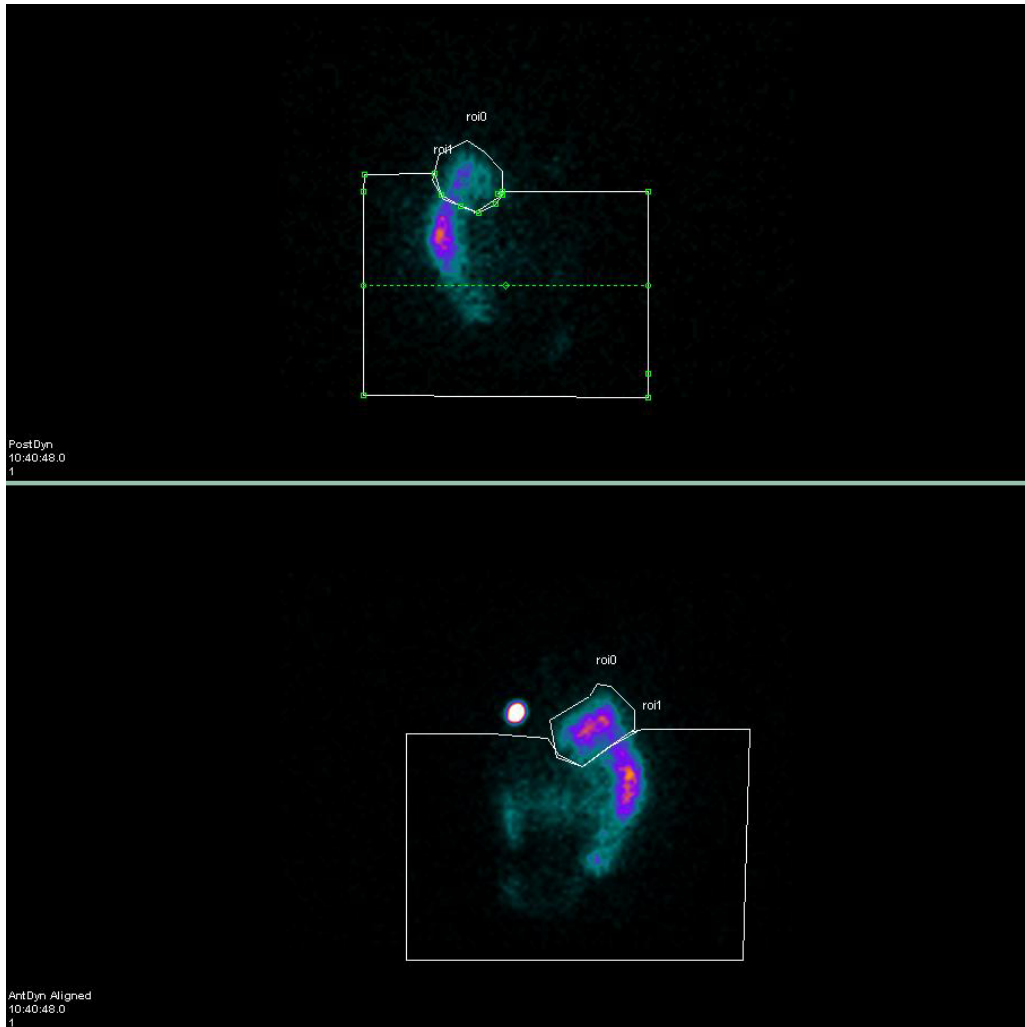
Figure 3-8: Post-operative gastric pouch AOI

Post-operative (RYGB) gastric pouch in one patient (posterior and anterior views on GI scintigraphy. AOI is marked around the pouch. A small marker was placed next to the pouch to keep a reference point during the study as at a later stage (IT) pouch identification was difficult after emptying of food. Times vs. radioactivity computer-generated graphs were made for each patient on the same lines as GE (Figure 3-10).
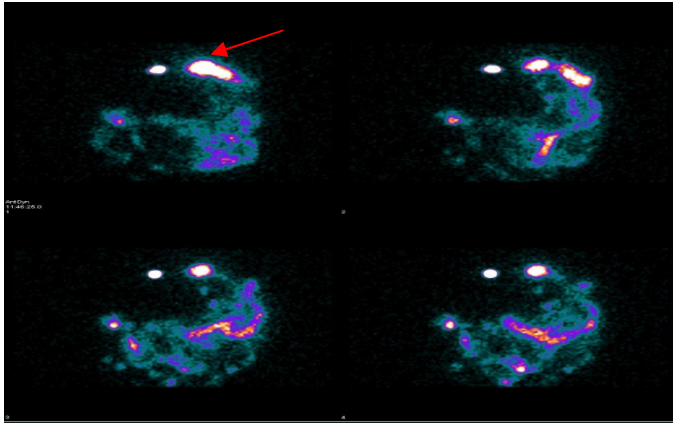
Figure 3-9: Pouch identification and marker

This figure demonstrates the gastric pouch emptying (anterior images) during 4 consecutive minutes. Pouch is marked with red arrow. Small dot next (right) to pouch is a marker for future pouch site reference during IT time calculation.
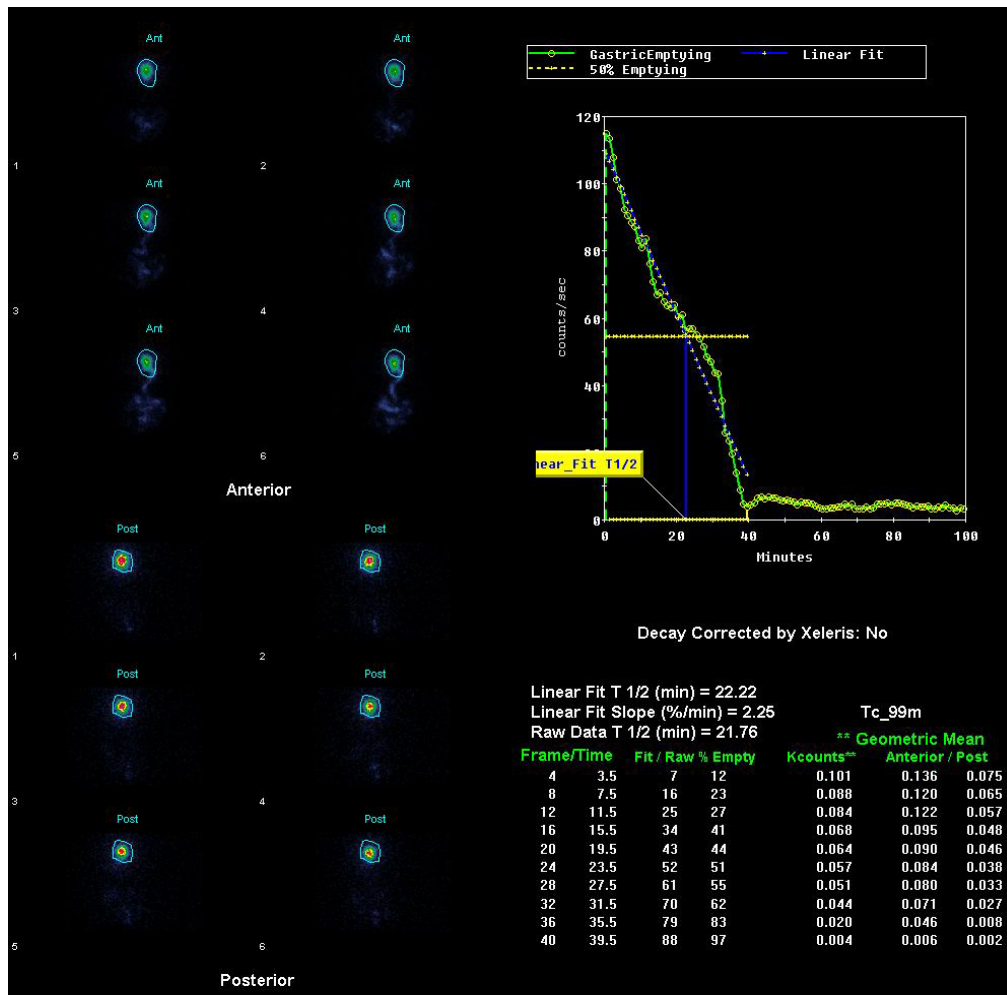
Figure 3-10: Measurement of pouch emptying following RYGB

AOI drawn around the pouch (anterior and posterior images). Time vs. activity graphs were computer generated. In this patient, pouch half-emptying time was 22.2 minutes.

3.3.2.4 Measurement of IT

GI scintigraphy was continued after GE studies. A marker (a very small amount of radioactivity covered in a double plastic sticker and secured with tape on the skin) was placed on the epigastric region next to the stomach for a reference point. (Figure 3-11, Figure 3-12, Figure 3-13). This reference point was crucial in calculations of IT at a later stage. This is demonstrated in the following figures showing the food entry into the small intestine which resulted in an empty/invisible stomach at a later stage. This is also demonstrated on another patient's images in Figure 3-14.
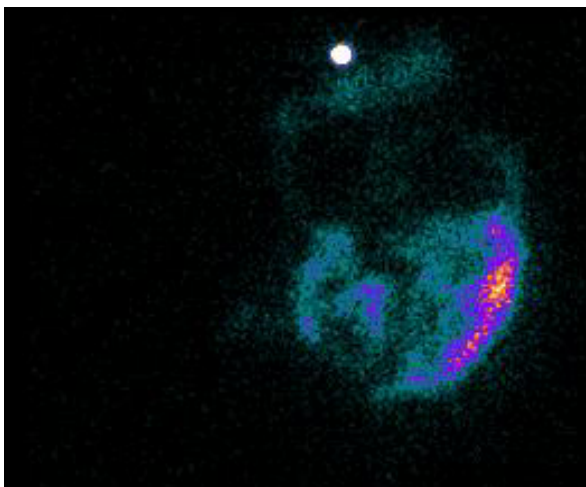
Figure 3-11: GS at 100 minutes (anterior view)
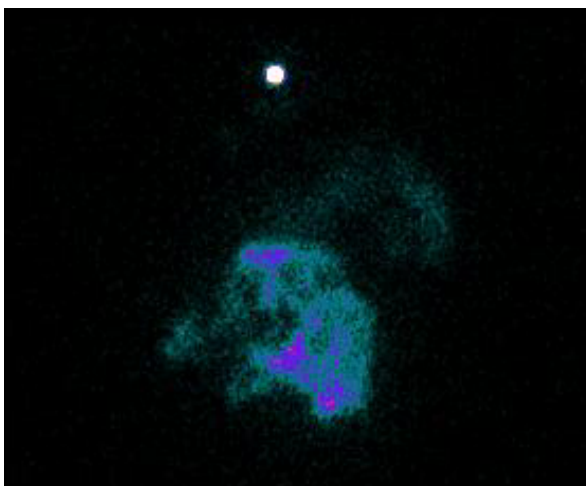
Figure 3-12: GS at 130 minutes

Note that the stomach is not visible and there was a negligible amount of radioactivity/food left in the stomach. The marker indicates the reference point of the stomach for calculation.
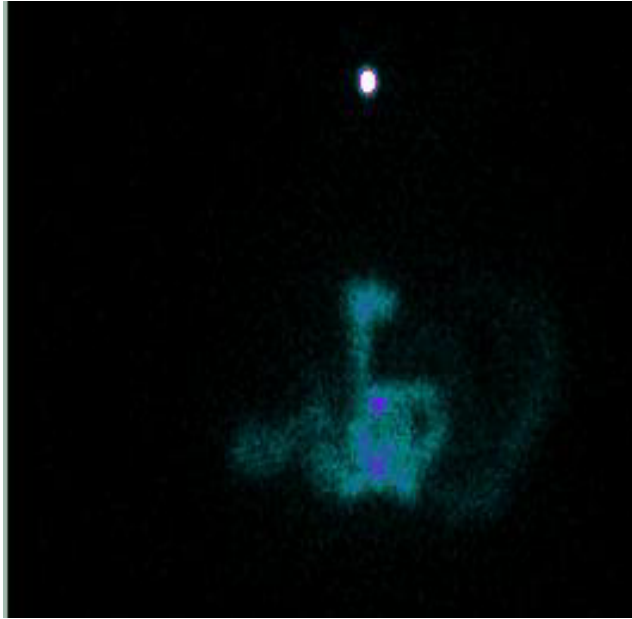
Figure 3-13: GE at 160 minutes

GI motility of the same patient at 160 minutes. No food is left in the stomach and most is visible in the intestine.
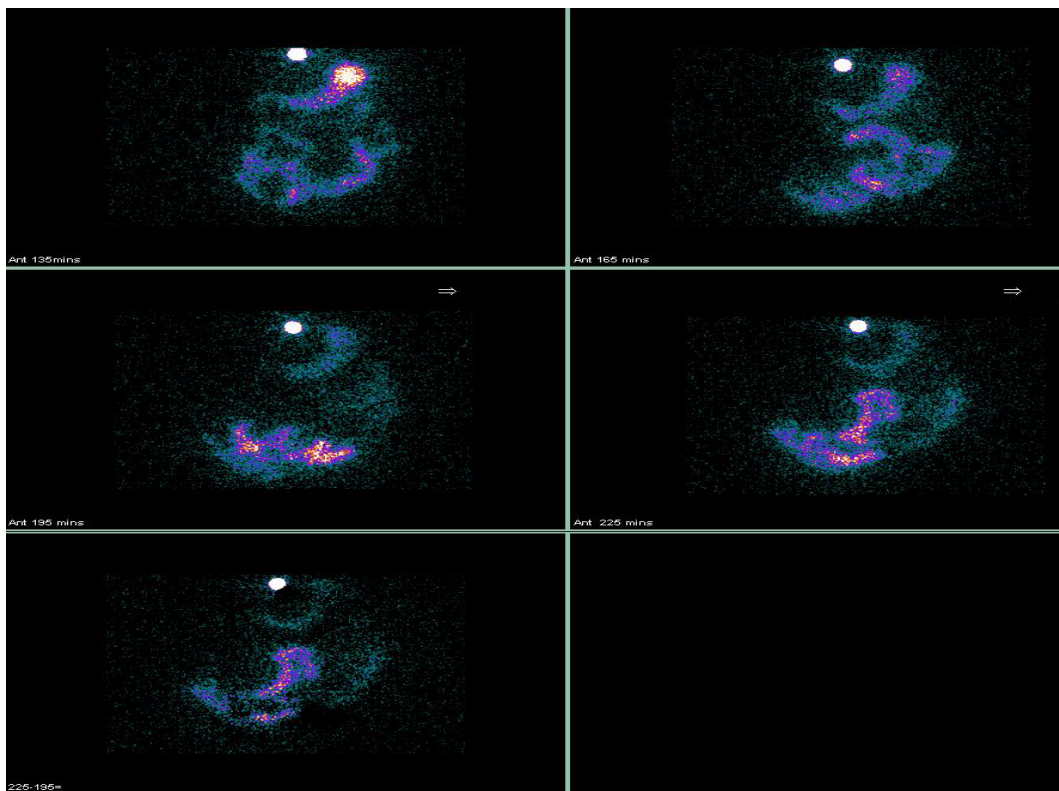
Figure 3-14: Intestinal radioactivity in reference to the skin marker

GE resulting in the disappearance of the stomach image on anterior acquisition. The marker (on the right side of the stomach) is used as a reference point for calculations.

Both anterior and posterior acquisitions were continued at approximately 30-minute time intervals. The process was continued until the food was visible in the terminal ilium/caecum. This was confirmed by the consultant radiologist with a special interest in GI motility. All the images were realigned with AOIs around the stomach. The intestines were marked in both anterior and posterior images (Figure 3-14, Figure 3-15 and Figure 3-16). To calculate accurate radioactivity count, the markers were excluded for the count calculations on both anterior and posterior images. AOIs were drawn around the stomach and rest of the abdomen. This was performed on both anterior and posterior acquisitions. Radioactivity counts for each area (gastric and intestinal) were calculated as follows:

Geometric mean = square root of (AOI on anterior acquisition X AOI on posterior acquisitions)

The % emptying of the stomach and IT were thereafter calculated. In last images when the caecum was identified, the AOI around the caecum and or the large intestine was also drawn and the radioactivity was counted in the same way as in the stomach and small intestine (Figure 3-17, Figure 3-18, Figure 3-19).
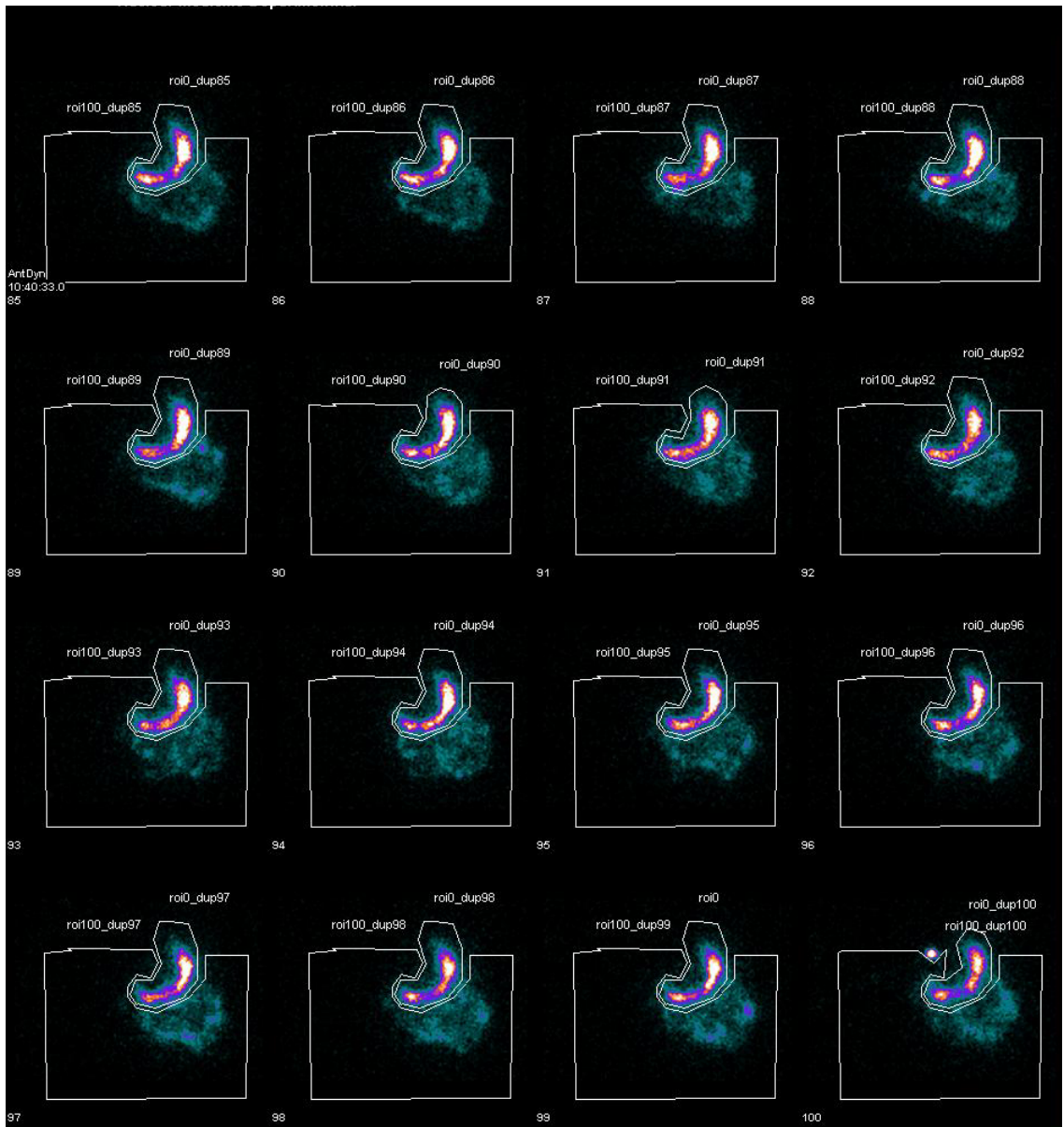
Figure 3-15: AOI around the stomach and intestine (anterior views)
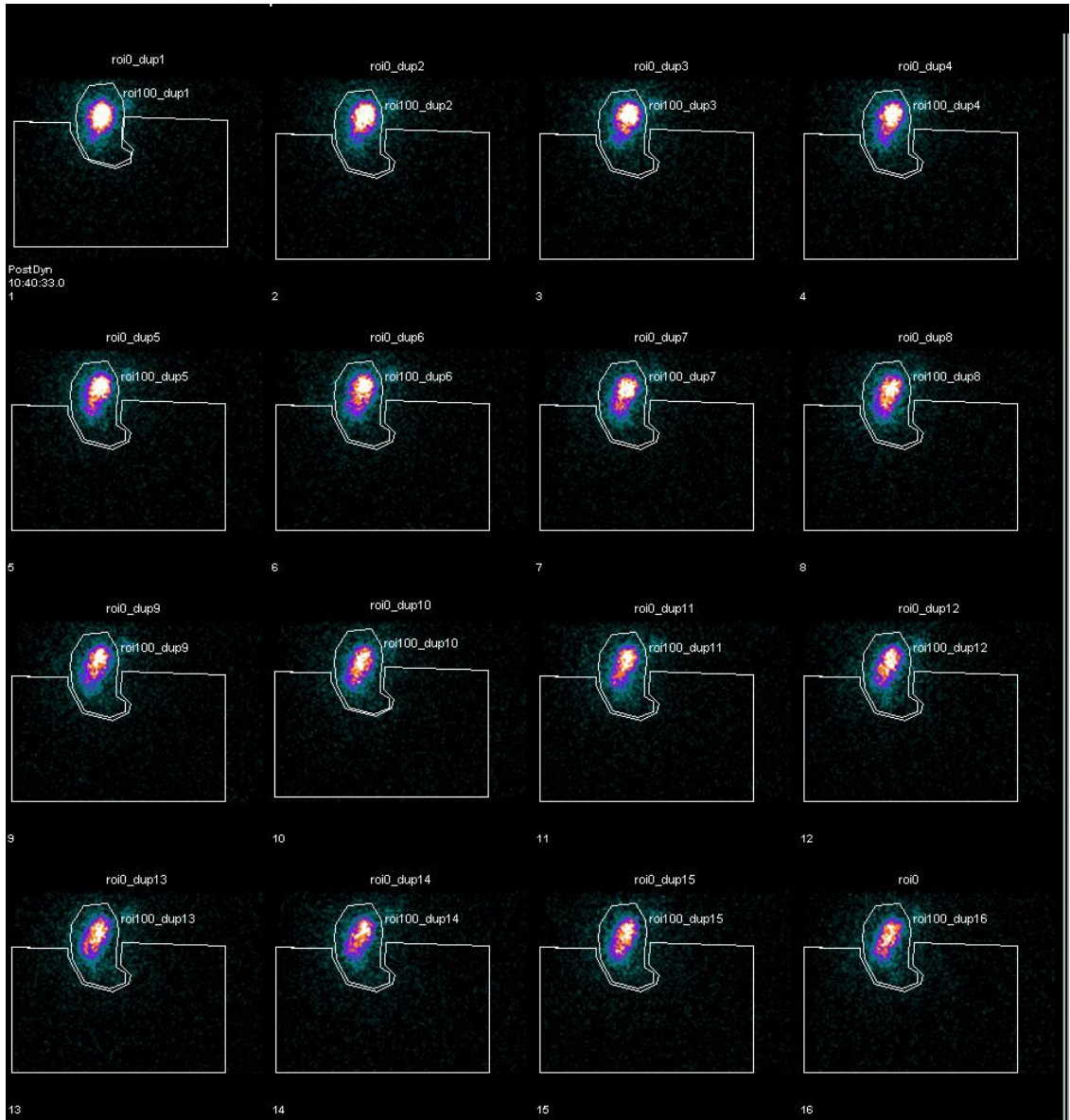
Figure 3-16: AOI around the stomach and intestine (posterior views)
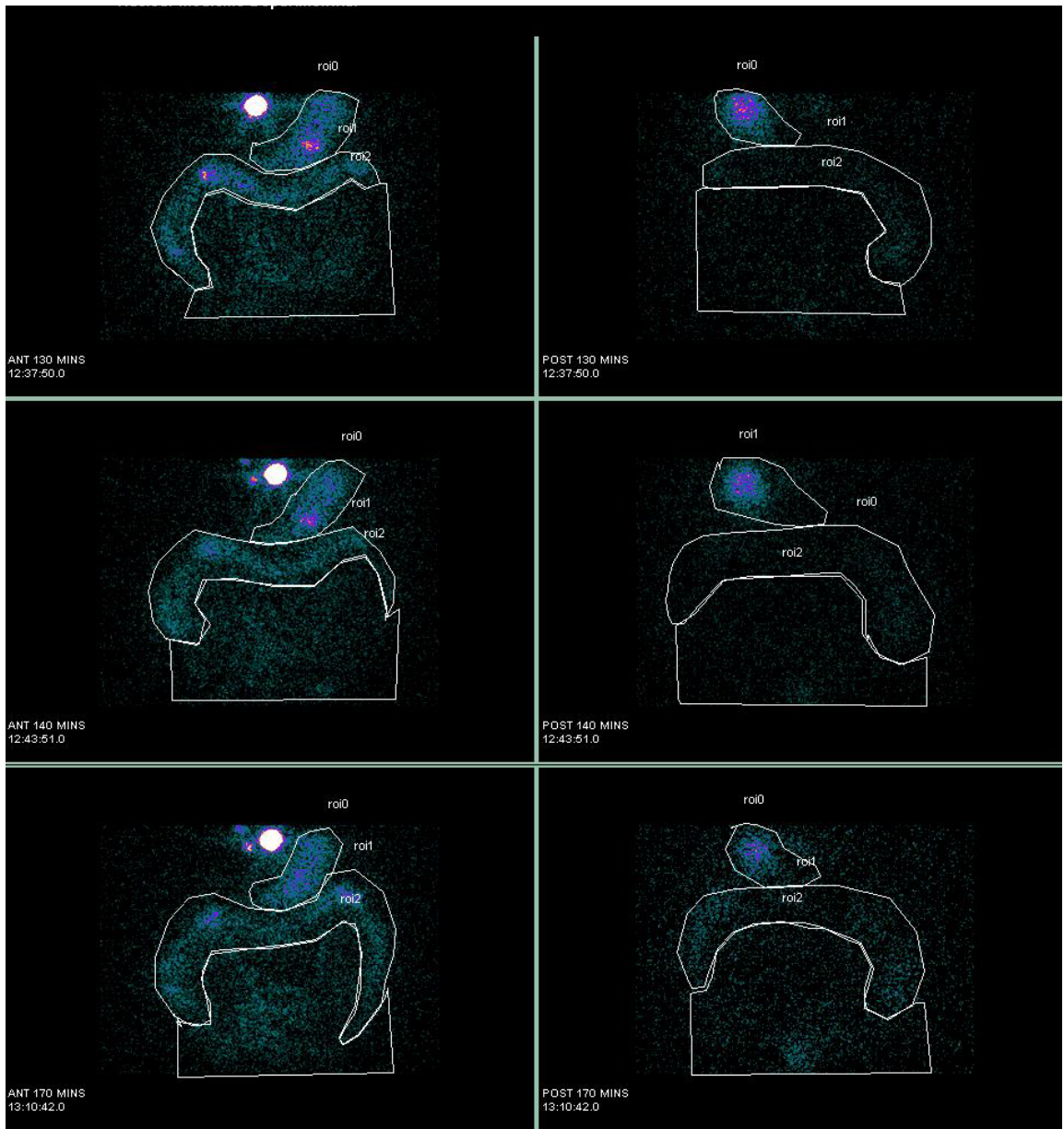
Figure 3-17: AOI around the stomach, small intestine and large intestine

(Anterior acquisitions)
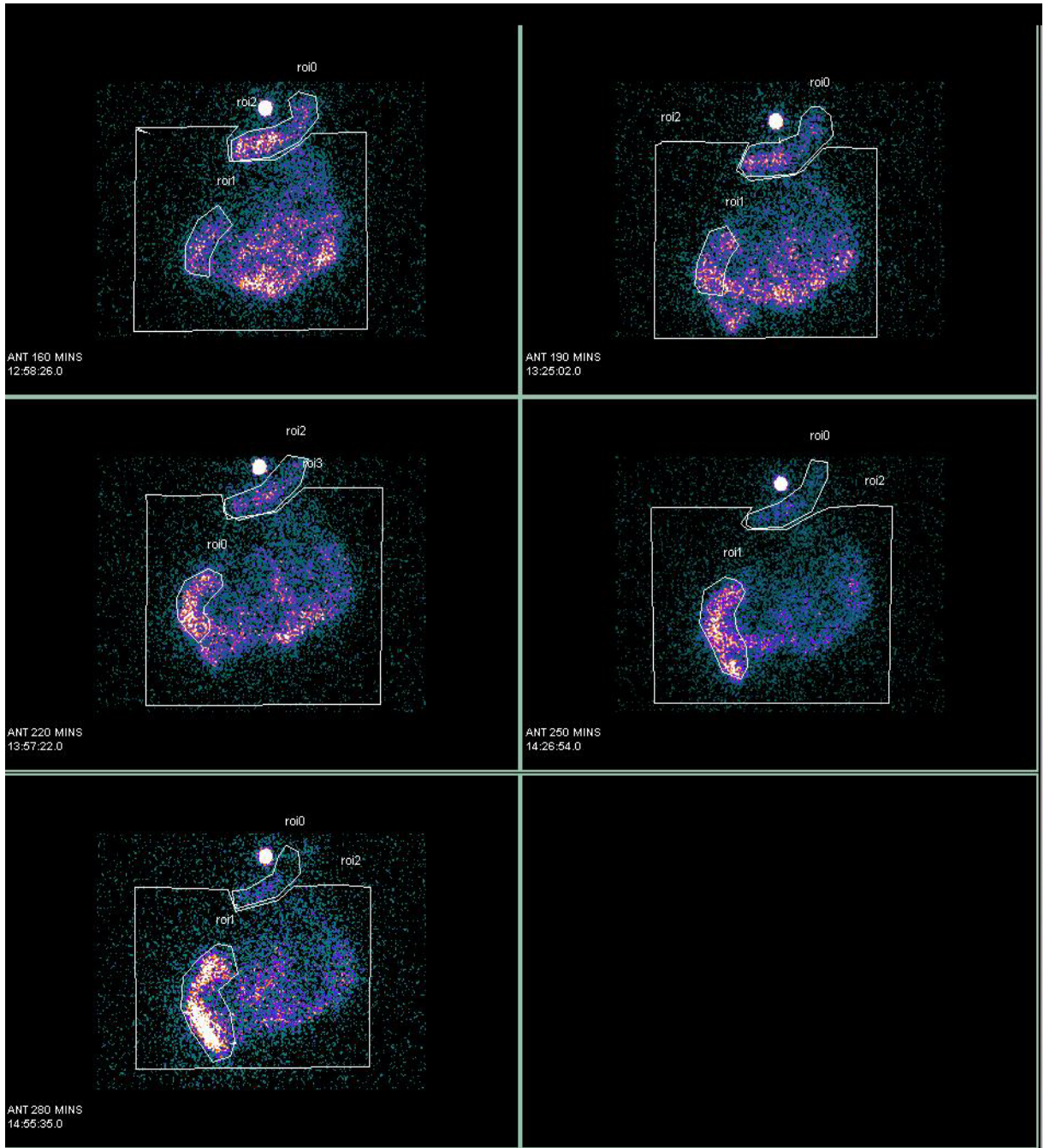
Figure 3-18: AOI around the caecum/ascending colon

This figure demonstrates the AOI around the caecum/ascending colon, small intestine and stomach. Note the gradual caecal filling from time 160 minutes to time 280 minutes. Simultaneously, the food in the small intestine and GE is also elaborated.
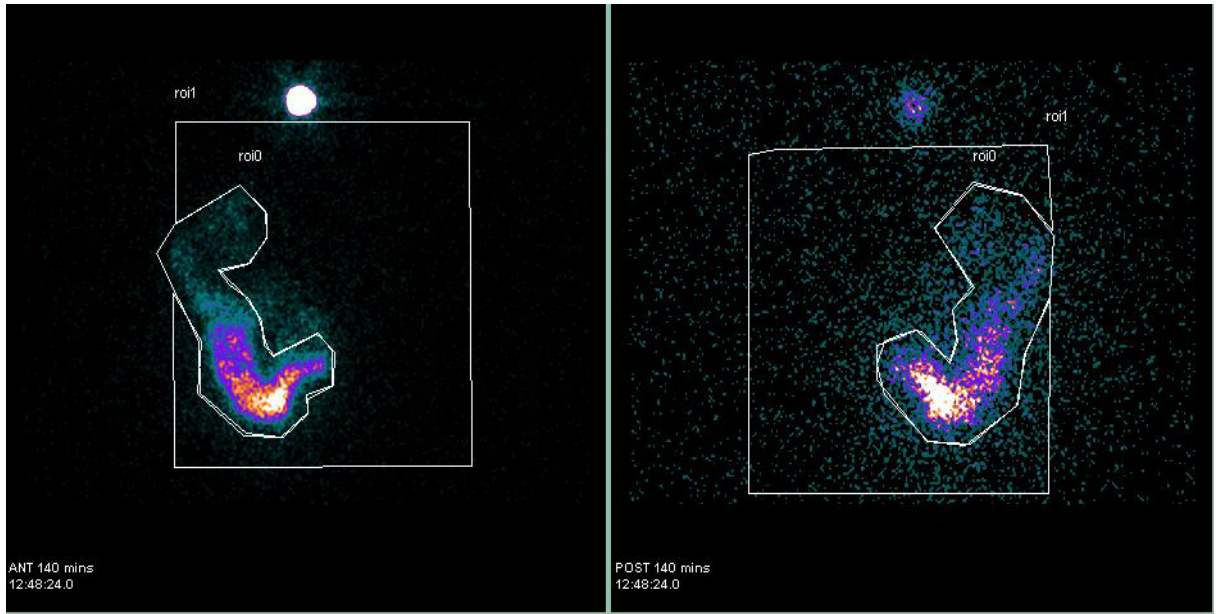
Figure 3-19: The caecum and terminal ileum

(Anterior and posterior acquisitions).

Post-operatively, IT was very fast. As the pouch was very small in size, the food quickly entered into the small intestine. The marker was placed at 0 minutes (before start of scintigraphy) as the pouch size was small and we proposed that this may result in quick pouch emptying. The rest of the procedure was as described above. Figure 3-21, Figure 3-20 and Figure 3-22 demonstrates IT following RYGB.
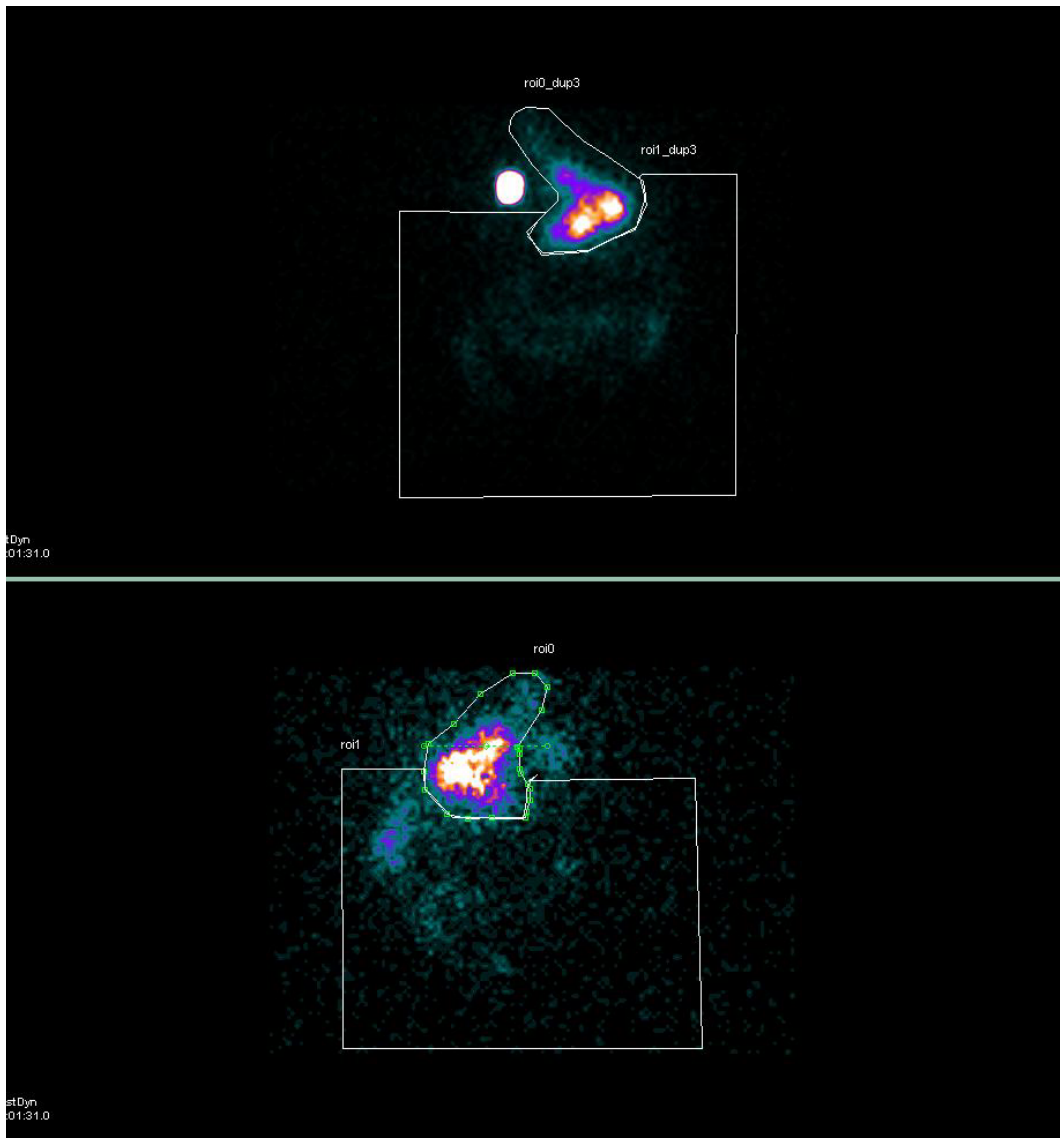
Figure 3-20: Gastric pouch emptying measurement

The AOI around the gastric pouch (anterior and posterior acquisitions) and a marker
next (right) to the gastric pouch. The AOI around the intestine is also marked.
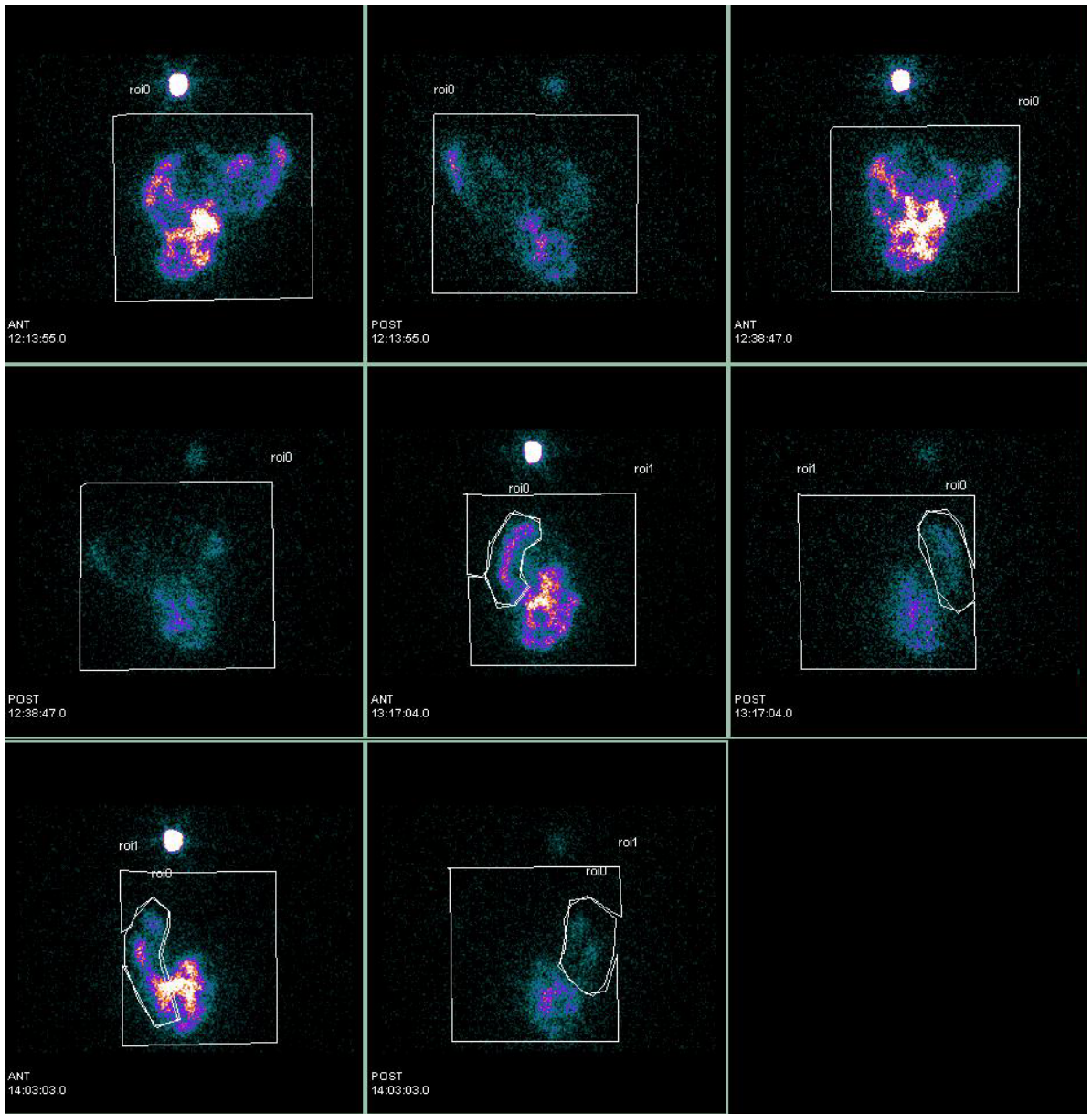
Figure 3-21: AOI around the gastric pouch, small intestine and caecum

The AOI around the caecum, intestine and gastric pouch. There is a change in GI transit as there is more radioactivity in the caecum and ascending colon in the last part of this image.
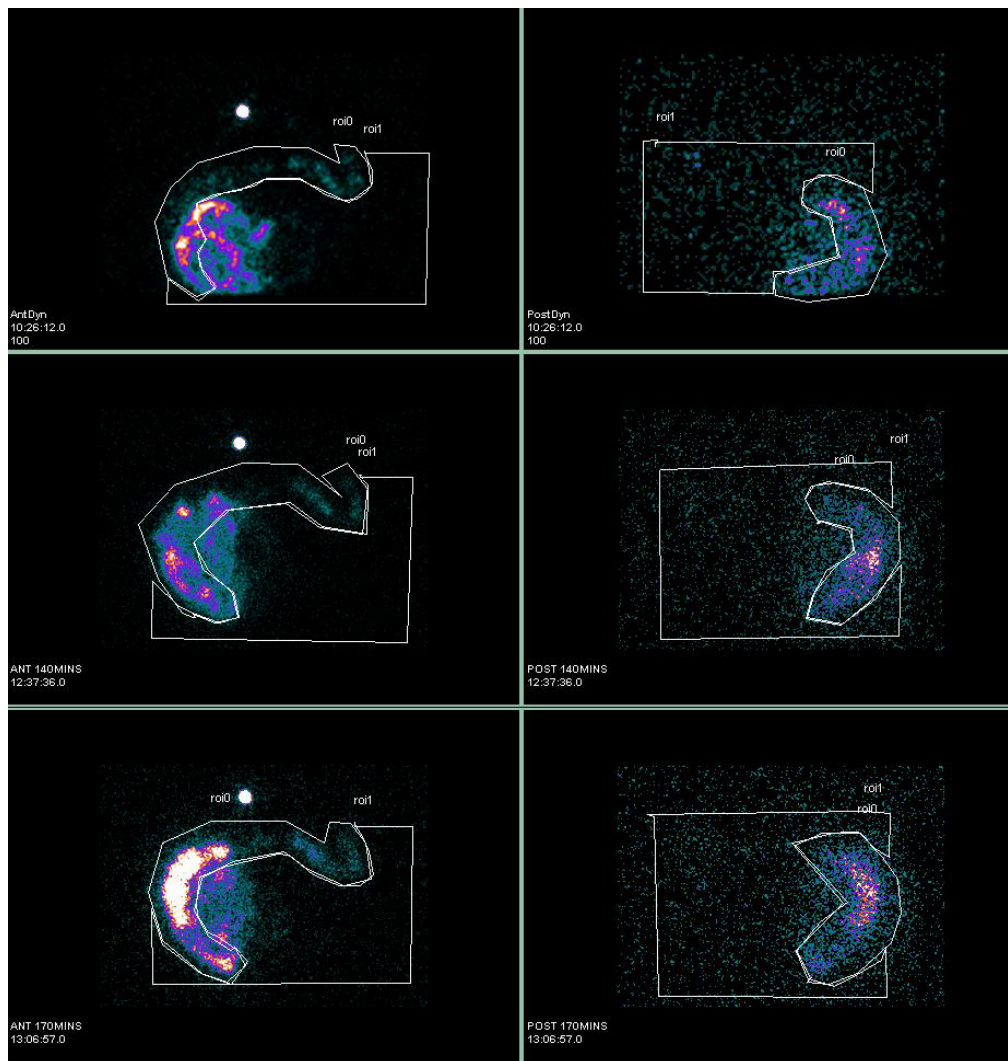
Figure 3-22: Ascending colon and transverse colon radioactivity

AOI around ascending and transverse colon. The count in the rest of the intestine (small intestine) is also elaborated.

3.3.3 Hormones

The following hormones were measured before and after bariatric surgery. Post-op samples were taken at 2 and 6 weeks after surgery (Figure 3-25).

1. Ghrelin (foregut hormone).

2. GLP-1 (distal small intestine hormone).

3. Insulin (pancreatic hormone).

4. Glucose.

Glucose levels were checked by a glucometer (standardised and calibrated) available in the Radiology Department during the time of the study. Plasma samples were taken as per the kit instructions and assessed for insulin, ghrelin, GLP-1 and glucose levels in the Biochemistry Lab in the University of Hull. These samples were stored at -70°C and then transported in batches of 40 samples to the Department of Biochemistry, University of Hull, for analysis. Hormone assays using ELISA kits are in practice and have been used in previous studies[153,154,155] (see Figure 3-25).

3.3.3.1 Ghrelin

This hormone has been described in detail in Chapter 1, Table 1-1. A brief description is as follows:[6, 142, 156, 157]
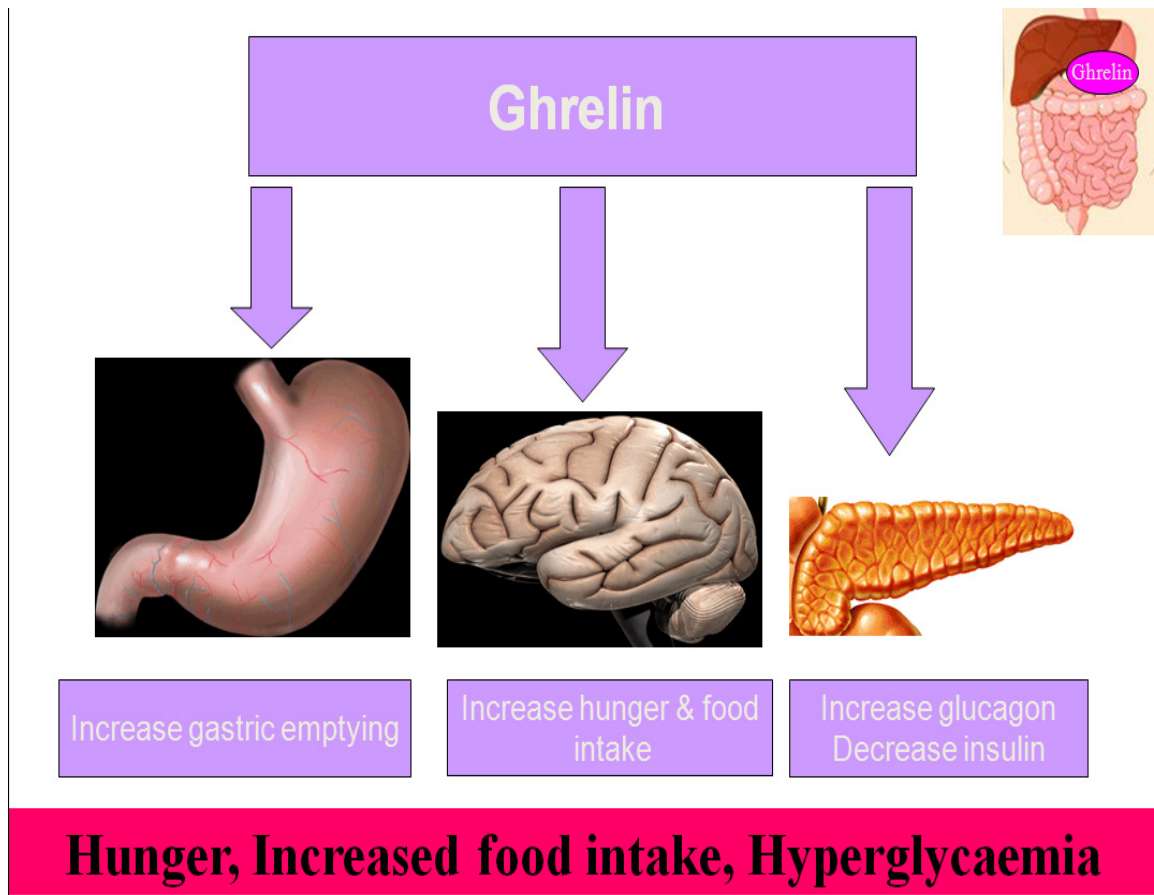
Figure 3-23: Overview of ghrelin

Source – gastric fundus

Target – hypothalamus

Actions: Stimulates appetite, levels ↑ before meal and ↓ after meal intake (30 minutes).

Acts as meal initiator.

It is proposed to increase glucagon level and decrease insulin levels.

It was proposed that post-RYGB food bypasses ghrelin-producing cells, which may result in decreased ghrelin levels.

3.3.3.2 GLP-1

GLP-1 has been described in detail in Chapter 1, Table 1-1. Here is a brief description based upon the published literature:[19, 20, 143, 158, 159]
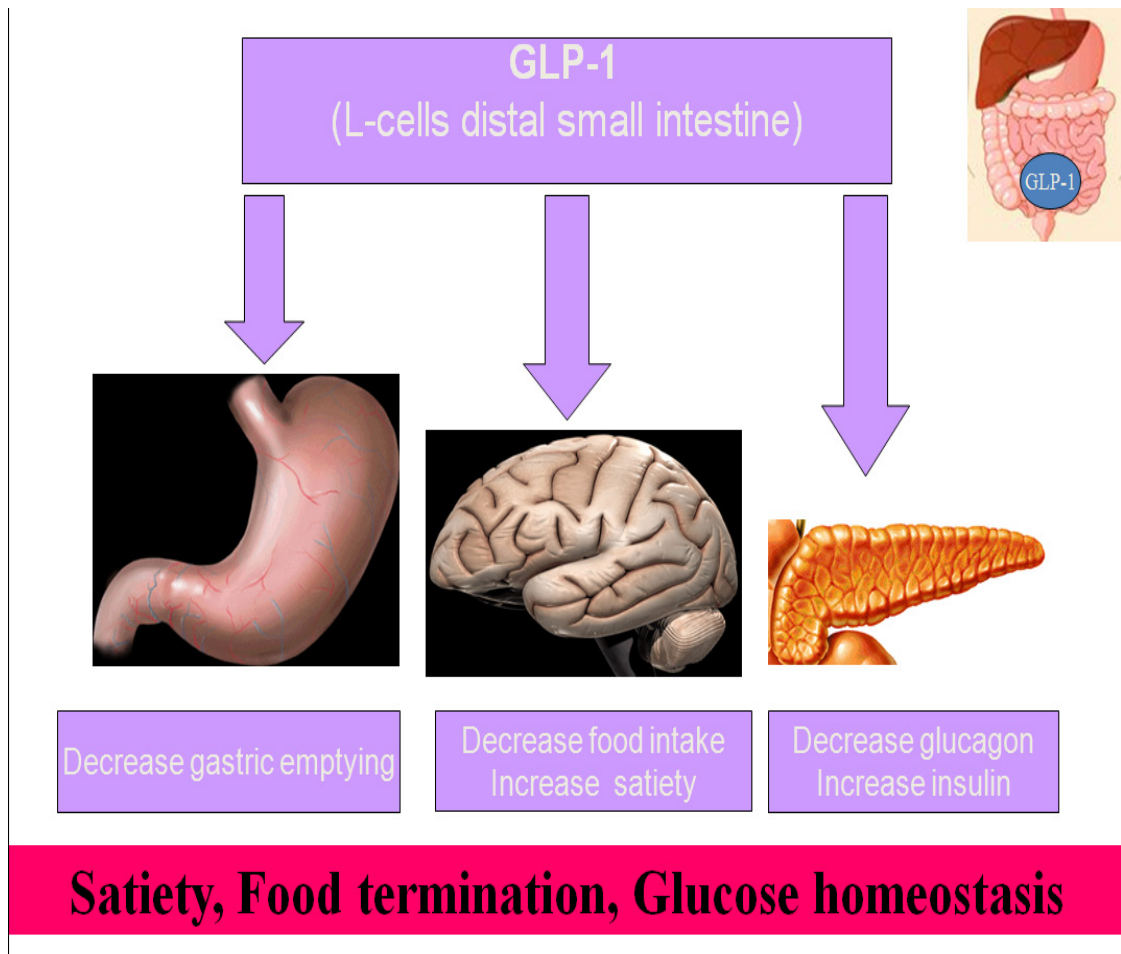
Figure 3-24: Overview of GLP-1

GLP-1 is produced by L cells in the distal ileum in response to food.

On stimulation – ↑ insulin level, ↓glucagon (Incretin Effect).

It appears to function ↓GE (Ilealbreak hormone).

Levels are considered to be ↓ in obesity

It is proposed that the levels increase after gastric bypass resulting in better glycaemic control and decreased IR.

We proposed that the increased levels may be observed after the RYGB which may influence the diabetic status of patients after surgery.

3.3.3.3 Insulin

Introduction: Insulin was discovered in the 1860s. It is produced by the pancreas and is the central regulator for carbohydrate and fat metabolism. It is produced in the beta cells of the islets of the pancreas. It is produced in proinsulin form and later the removal of C peptide results in its activated form insulin.[1, 3]

Typical normal insulin levels are 8–11 μIU/ml (57–79 pmol/L) after a meal.

Physiology:

1. Insulin controls the glucose intake in muscle and adipose cells. Lack of this function results in impaired glucose tolerance, DM.

2. Integral part of proteins, DNA and enzymes synthesis.

3. Glycogen synthesis, which is stored in the liver, is converted to glucose when required.

4. Lipids under the influence of insulin are converted to triglycerides.

5. Decreases gluconeogenesis (the production of glucose from non-carbohydrate sources).

6. K homeostasis (acts on cells to uptake the K – failure of this action results in hyperkaleamia).

7. Acts as an arterial muscle relaxant which helps in the secretion of hydrochloric acid (HCL) from stomach.

In our study, insulin levels were assessed in plasma levels before and after RYGB. We also assessed the meal-related response to insulin and IR after surgery (RYGB).

3.3.3.4 Glucose

Glucose levels were assessed with a glucometer at fasting, 30 minutes and 60 minutes after meal intake. The last blood glucose levels were checked when the food reached into the caecum.

2 weeks post-op fasting levels were checked.

6 weeks after surgery the levels were repeated as per the pre-operative protocol.

Furthermore, glucose levels were also assessed in patches in the Biochemistry Lab, University of Hull.

3.3.4 Schedule of investigations (Figure 3-25)

3.3.4.1 Pre-operative investigations

1. GI hormone studies

2. GI motility studies

The tests involved the subjects fasting overnight and attending the Nuclear Medicine Department, Castle Hill Hospital, in the morning. A Research fellow conducting all investigations helped the Nuclear Medicine Department. IV cannulas were sited and pre-procedure blood samples were taken. Cannulas were flushed with heplok (heparinised saline) to prevent clotting between blood samples.

A standard meal containing isotope 99m Tc (radioactive material) was given at this stage. Dynamic acquisitions were taken at 100 minutes followed by static acquisitions at fixed time points such as 120, 180, 240, 360 and 480 minutes after the meal. Simultaneously, three more blood samples were withdrawn from the cannula. The first two blood samples were taken at fixed time points of 30 and 60 minutes, and the last blood sample was taken at the time when food was seen in the distal ileum/iliocaecal region. All blood samples were centrifuged; serum and plasma were stored at -70°C immediately after being withdrawn. For further details, see (Figure 3-25).

3.3.4.2 Post-operative investigations

3.3.4.2.1 Two-week post-operative investigations

First follow-ups were organised 2 weeks after surgery in the outpatient clinic. Patients were requested to attend the clinic in a fasting state, where they were seen by the research fellow. Any post-op concerns were liaised with the consultant surgeon and fasting blood samples were taken, processed and stored. A two weeks post-operative follow-up was performed to investigate the early resolution of diabetes, improvement of IR and any alterations in ghrelin and GLP-1 levels.

3.3.4.2.2 Six-week post-operative investigations

Second follow-ups were organised 6 weeks after surgery. Patients were requested to re-attend at the Nuclear Medicine Department with overnight fasting. Investigations included:

1. GI hormone studies.
2. GI motility studies.

Investigations were conducted on the same lines as pre-operatively.

Also see the flow chart

```
┌─────────────────────────┐
│ Overnight fast          │
│ Patients to attend      │
│ Nuclear Medicine        │
│ Department              │
└─────────────────────────┘
             │
             ▼
┌─────────────────────────┐        ┌─────────────────────────┐
│ Cannula                 │        │ Plasma isolated and     │
│ 1st blood sample,       │───────▶│ stored at -70°C          │
│ Heplok flush            │        │                         │
└─────────────────────────┘        └─────────────────────────┘
             │
             ▼
┌─────────────────────────┐
│ Standard test meal      │
│ containing isotope      │
│ 99m Tc                  │
└─────────────────────────┘
        │           │
        ▼           ▼
┌──────────────────────────────┐   ┌──────────────────────────────┐
│ Further blood samples after  │   │ Dynamic gamma camera         │
│ 30 and 60 minutes and last   │   │ scintigraphy for 100 minutes │
│ blood sample when food seen  │   │ followed by static           │
│ in the distal                │   │ acquisitions at              │
│ ileum/ileocaecal region.     │   │ 120, 180, 240, 360 and 480   │
└──────────────────────────────┘   │ minutes.                     │
             │                      │                              │
             ▼                      └──────────────────────────────┘
┌──────────────────────────────┐
│ Plasma to be isolated and    │
│ samples stored at -70°C       │
│ immediately after            │
│ being withdrawn from cannula.│
└──────────────────────────────┘
```

Figure 3-25: Flow chart showing the investigations

3.3.5 Hormone assays
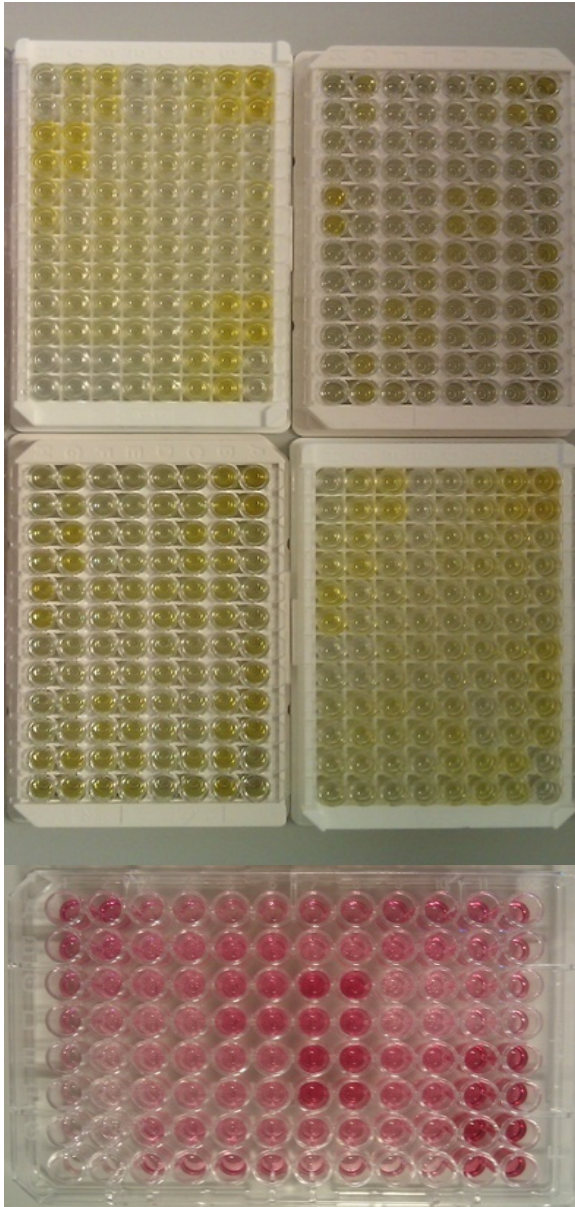
Figure 3-26: Assays

General principles: Every effort was made to protect the hormones/peptides from withdrawal from the patients to assays. Preservatives were used as per the kits. The samples were stored at −70°C, and transported in an ice-cooled container to the central Biochemistry Lab, University of Hull. They were stored until the day of assays in duplications. The samples were defrosted immediately before the assays.

Glucose: Cayman's glucose assay kits, Cat number 1009582 were used for this assay. These kits are simple, reproducible and highly sensitive for assaying glucose in plasma, serum and urine.

This kit implies **Glucose Oxidase-Peroxidase reaction** for determination of glucose concentration. In this assay, glucose is oxidised to δ-gluconolactone. The reduced form of glucose oxidase is regenerated to its oxidised form by molecular oxygen to produce hydrogen peroxide. Finally, with horseradish peroxidase as a catalyst, hydrogen peroxide reacts with 3,5-dichloro-2-hydroxybenzenesulfonic acid and 4-aminoantipyrine to generate a pink dye with an optimal absorption at 514 nm.

Plate setup and procedure:

1. Plate setup used duplicated samples on the plate.
2. Assay buffers were thawed and equilibrated to 4°C. All samples and reagents were equilibrated at 4°C.
3. The final volume of assay was 150 uL in each well.
4. The incubation temperature was 37°C.
5. All samples and standards were assayed in duplication.
6. Absorbance was monitored at 500–520 nm using a plate reader.

Table 3-2: Glucose standards used in assay

Tube	Glucose Stock(pi) (1000 mg/dL)	Assay Buffer (pi)	Glucose Concentration (mg/dL)
A	0	200	**0**
B	2	198	12.5
C	5	195	25
D	10	190	50
E	20	180	100
F	30	170	150
G	40	160	200
H	50	150	250

Standard preparation: Eight clean 12 x 75 mm glass test tubes were taken and labelled A-H. The amount of glucose standard and assay buffer to each tube were added as described in the table above. The diluted glucose standards are stable for two hours at room temperature.

Performing the assay:

1. 5 ul sample or standard was added in labelled tubes.

2. 500 ul of the enzyme mixture was added to the tube. The tubes were taped and mixed.

3. The tubes were placed in an incubator for 10 minutes at 37°C.

4. After that 150 ul was placed in each well (in duplication).

5. Absorbance was read at 500–520 nm using a plate reader.

Calculations:

1. The average absorbance of each standard and sample was calculated.

2. The absorbance value of the standard A (0 mg/dL) was subtracted from itself and all other values (both standards and samples). This is the corrected absorbance.

3. Corrected absorbance values of each standard as a function of the concentration of glucose were drawn.

The concentration of glucose for each sample from the standard curve was calculated as follows:

Glucose (mg/dl) = [corrected absorbance – (y-intercept)]

Slope

Assay range 0–250 mg/dl.

Standard curves: The following standard curves were generated:

X axis representing glucose concentration (mg/dl)

Y axis representing absorbance (514 nm)

134

Standard Curve

Standard Curve
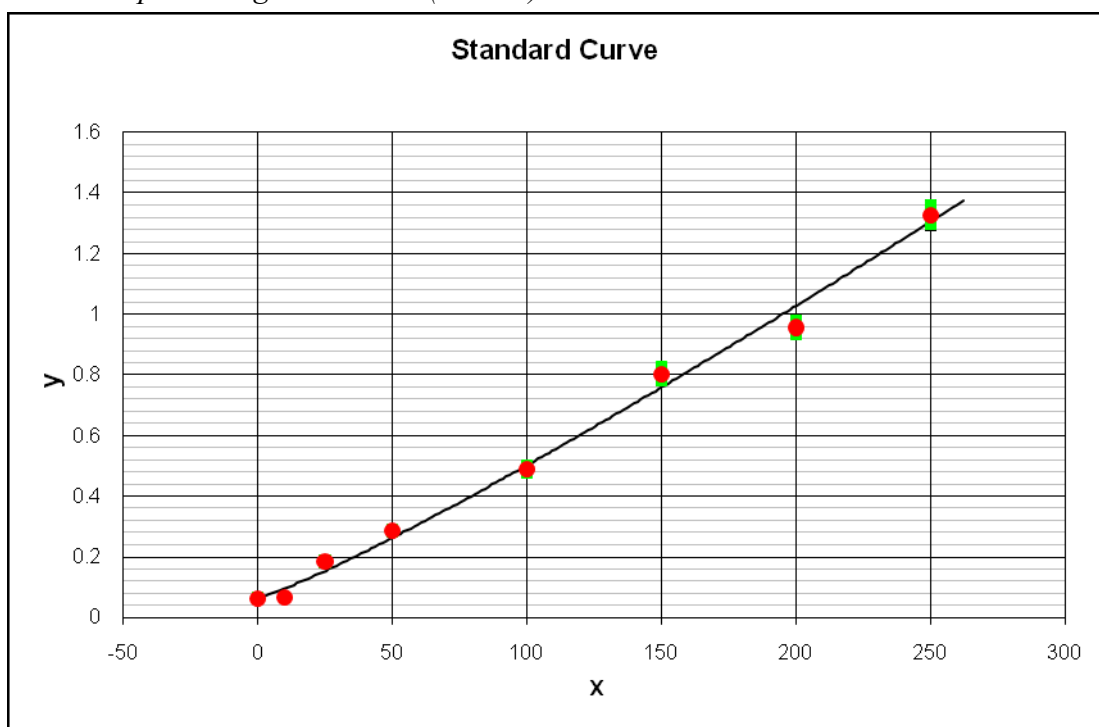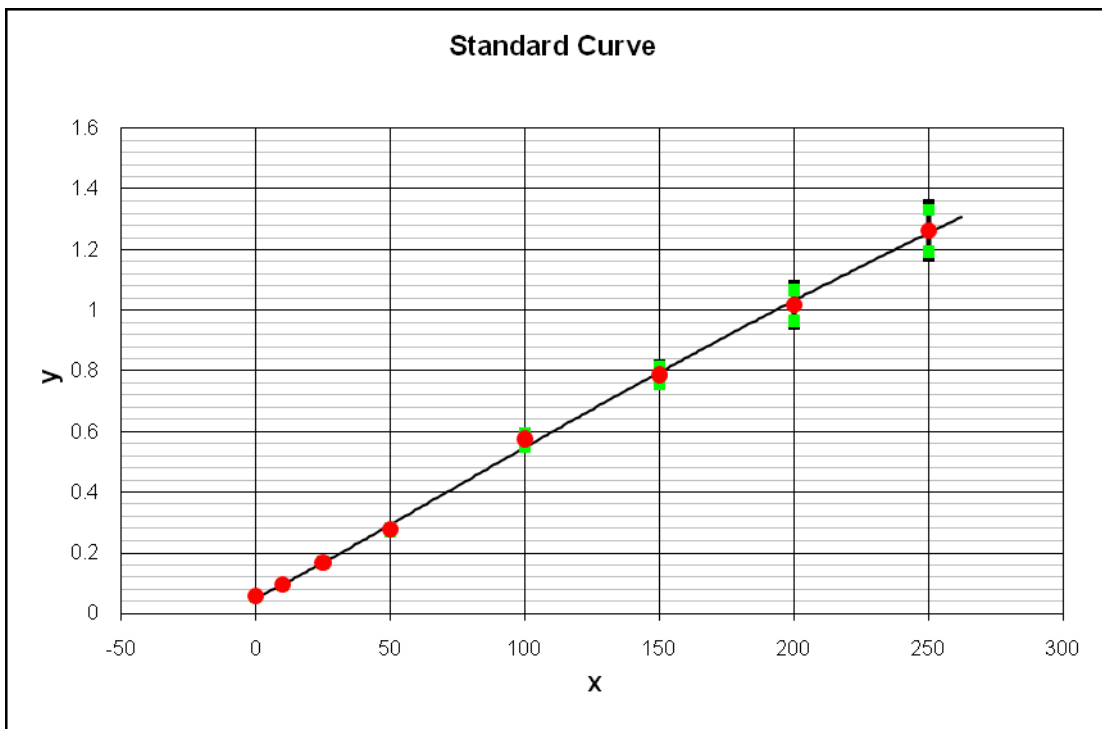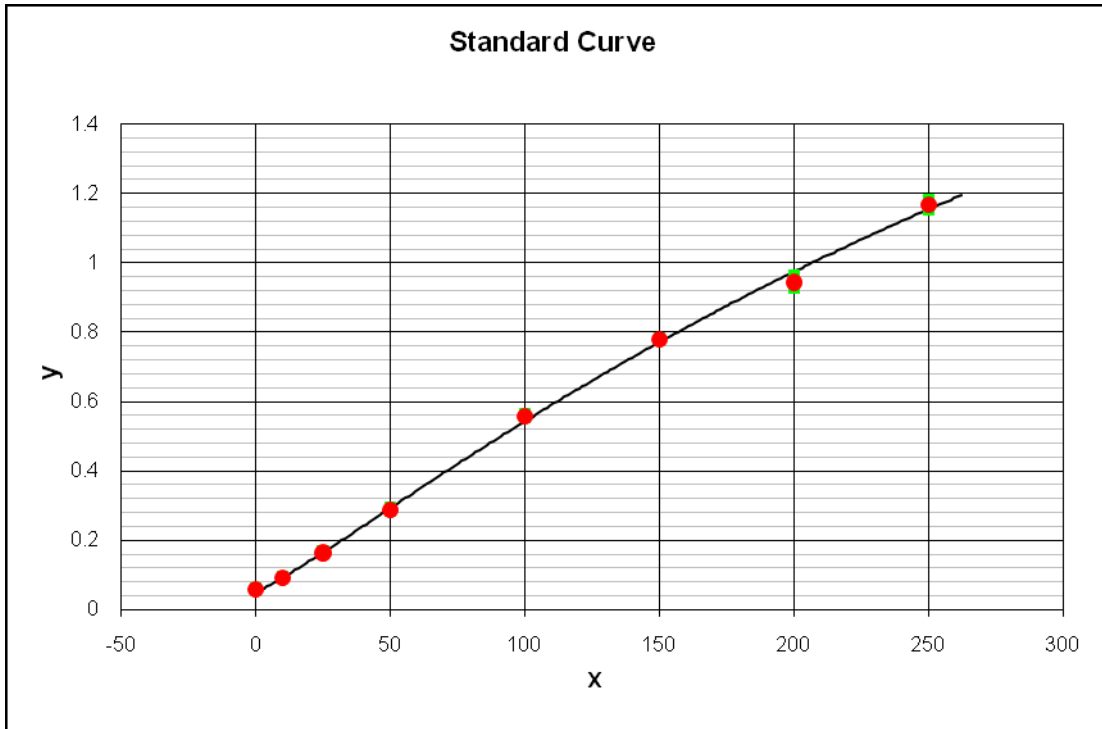
Insulin:

Insulin Elisa tests were performed with INVITROGEN kits, catalogue number KAQ1251, on pre-collected plasma samples.

Principle: The assay uses monoclonal antibodies directed against insulin. Samples including standards of known insulin content, control specimens and unknowns were pipetted into the wells. A detector monoclonal antibody labelled with horseradish peroxidase (HRP) was added. After an incubation period, the plate was washed to remove unbound enzyme-labelled antibody and the substrate solution was added. This was followed by incubation. The reaction was stopped with HCl and the plates read spectrophotometrically. The intensity of colour in this method is directly proportional to the concentration of insulin in the original specimen.

Procedure:

1.   After defrosting the samples and preparing standards, 50 µl of each standard, control or sample were added into the appropriate wells.
2.   50 µl of Anti-Insulin-HRP conjugate was added into all wells.
3.   The plates were covered with a plate cover and incubated for 30 minutes at room temperature.
4.   Fluid from the wells was aspirated and plate wells washed 3 times with wash solution.
5   100 µl of chromogen solution was added into each well.
6.   Plates were incubated for 15 minutes at room temperature in the dark.
7.   100 µl of stop solution was added into each well. Plates were gently mixed. The solution in the wells changed from blue to yellow (see the figure below).
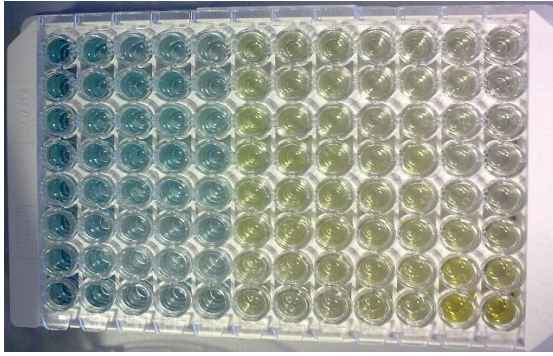
8.   The absorbance of each well was read at 450 nm.

9.   Standard curves were plotted as below.
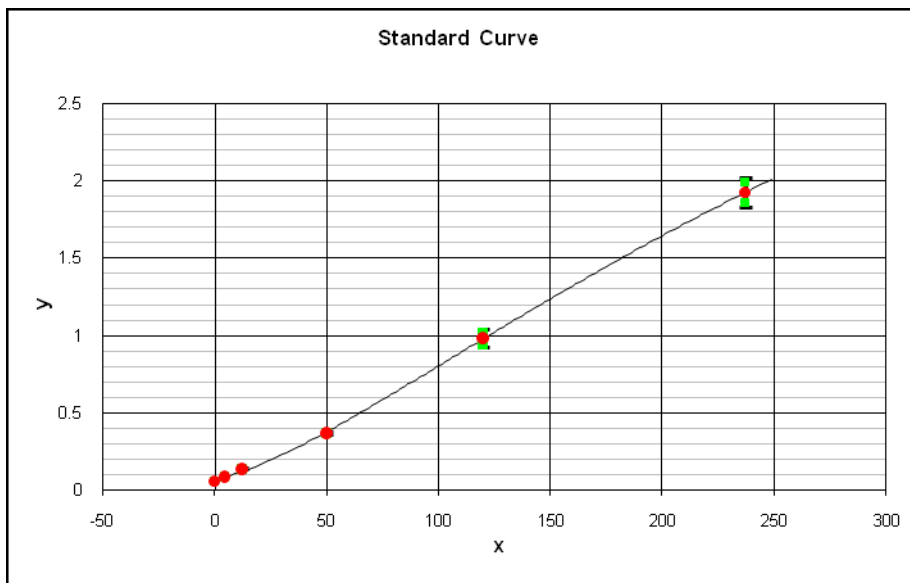
Figure 3-27: Insulin standard curve
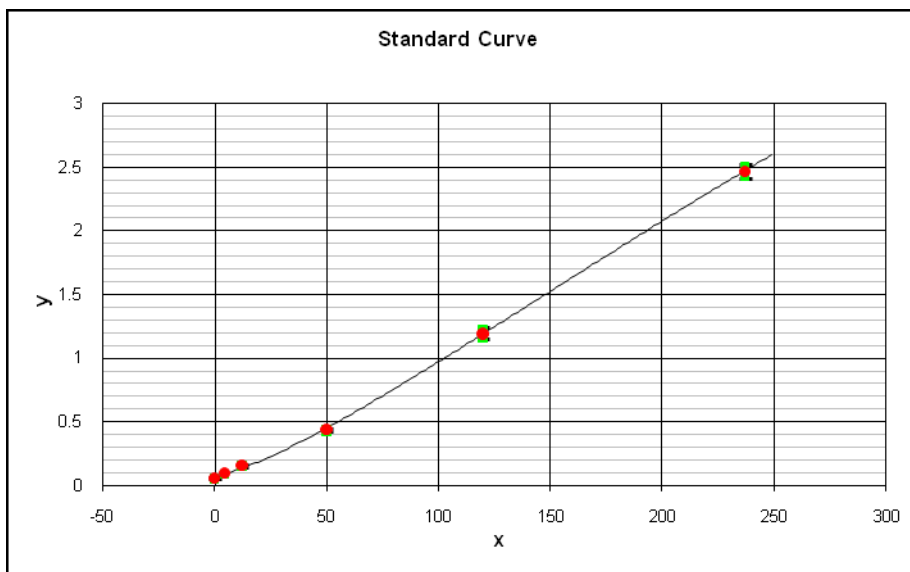
10.	Concentrations for unknown samples and controls from the standard curve were read.

Typical example data for the assay was as follows:

Table 3-3: Insulin reference values

Assay reverence values **between 0–250 μIU/ml**

Standard Insulin (μIU/ml)	Optical Density (450 nm)
250	2.34
128	1.31
44.4	0.51
13.8	0.13
5.1	0.07
0	0.03

GLP-1:

GLP-1 assays were performed with ALPCO Elisa kits, cat number 43-GPTHU-E01. Pre-collected plasma samples were defrosted immediately before the assays.

Principle: This test is designed for the quantitative measurement of GLP-1. The assay is based upon a two-site "sandwich" technique with two selected GLP-1 antibodies. Assay standards, controls and test samples are added directly to the wells of a microplate that is coated with streptavidin. Subsequently, a mixture of GLP-1 specific antibody and a horseradish peroxidate (HRP) conjugated GLP-1 specific antibody is added to each well. After the incubation period, a "sandwich" immunocomplex of "streptavidin–biotin-antibody–GLP– HRP conjugated antibody" is formed and attaches to the walls of the plate. The unbound HRP conjugated antibody is removed in a subsequent washing step. For the detection of this immunocomplex, each well is then

incubated with a substrate solution in a timed reaction and then measured in a spectrophotometric micro plate reader. The enzymatic activity of the immunocomplex bound to GLP-1 on the walls of the microtiter wells is directly proportional to the amount of GLP-1 in the sample.

Procedure: Antibody mixture was prepared by 1:21 fold dilution of the Tracer Antibody and by 1:21 fold dilution of the biotinylated Capture Antibody with the Tracer Antibody Diluent. For each strip, a mix of 1 ml of the Tracer Antibody Diluent (30017) with 50µL the Capture Antibody (30361) and 50µL of the Tracer Antibody (30360) were added in a clean test tube.

100 µL of standards, controls and test samples were added to the designated micro wells. 100 µL of Antibody Mixture was added to each well. The plates were covered with plate sealer and incubated at 2–8°C, static for 20–24 hours. The next day (i.e. after 24 hours) the plate sealer was removed and the contents of the wells were aspirated.Wash with wash buffer was performed with an automated micro plate washer. 200 µL of HRP Substrate was added to each well. The plate was covered with aluminum foil to avoid exposure to light. The plates were incubated at room temperature for 20 minutes. Aluminum foils were removed and 50 µL of stop solution was added to each well. The contents were mixed gently and the plates were read for absorbance at wavelength 450 nm/620 nm or 450 nm/650 nm within 10 minutes in a micro plate reader.

Interpretation of results: The average absorbance for each pair of duplicate tests was calculated .The standard curves were generated by the average absorbance of all standard levels, including the zero standard, on the ordinate against the standard concentrations on the abscissa using point-to-point or log-log paper. The GLP-1 concentrations for the controls and test samples were read directly from the standard curve using their respective absorbance.

Absorbance

(unknown)

Value of unknown = Absorbance (unknown) / absorbance (2nd standard) x Value of 2nd STD)

Standard curves were as follows:
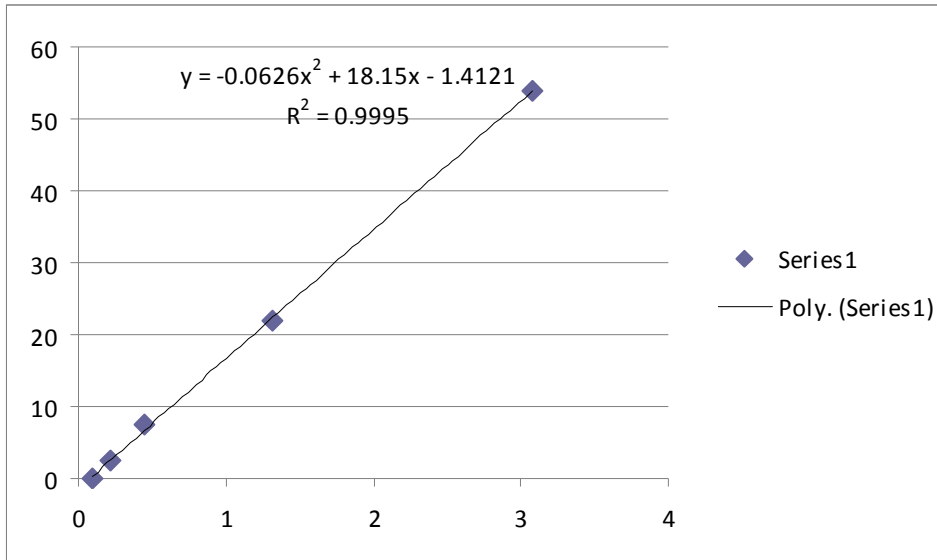
Figure 3-28: Standard curve for GLP
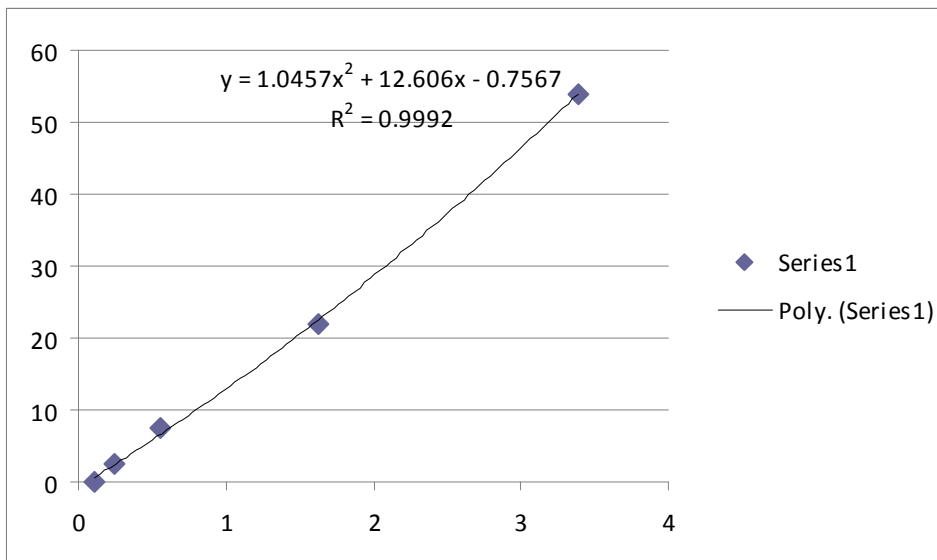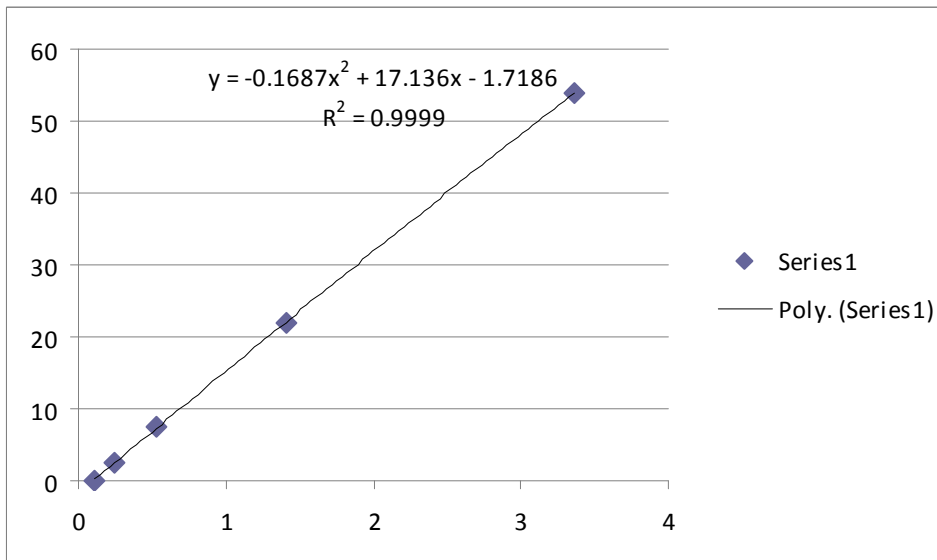
Reference values were GLP-1 were **0–54pmol/L** using this assay.

Ghrelin:

Ghrelin assays were performed with Millipore HUMAN GHRELIN (TOTAL) ELISA KIT, 96-Well Plate (catalogue number EZGRT-89K).

Principles:

1.   This assay is also a "sandwich" ELISA based on the capture of human ghrelin molecules in the sample by anti-human ghrelin IgG and the immobilisation of the resulting complex to the wells of a microtiter plate coated by a pre-titered amount of anchor antibodies.

2.   In addition, there is simultaneous binding of a second biotinylated antibody to ghrelin and then the washing away of unbound materials, followed by conjugation of horseradish peroxidase to the immobilised biotinylated antibodies.

3.   The washing away of free enzyme, and quantification of immobilised antibody-enzyme conjugates by monitoring horseradish peroxidase activities in the presence of the substrate 3,3',5,5'tetra methylbenzidine.

4.   The enzyme activity is measured spectrophotometrically by the increased absorbency at 450 nm.

Procedure:

After the preparation of standards and defrosting the stored samples the following steps were followed for the measurement of ghrelin levels in plasma samples:

1. Wash buffer was mixed in 900 ml distilled water.
2. Each well was washed with 300 Pl diluted wash buffer.
3. 20 µL matrix solution was added to blank, standards and quality control wells.
4. 30 µL assay buffer was added to each of the blank and sample wells.
5. 10 µL assay buffer added to each of the standard and quality control wells.
6. 20 µL ghrelin standards was added in duplicate in the order of the ascending concentrations to the appropriate wells.
7. 20 µL QC1 and 20 µL QC2 were added in duplicate to the appropriate wells.
8. 20 µL of the Plasma samples were added in duplicate to the remaining wells.

9. 50 µL Antibody Solution Mixture (1:1 mixture of capture and detection antibody) was added to each well.

10. The plates were covered with plate sealer and incubated at room temperature for 2 hours on an orbital microtiter plate shaker set to rotate at moderate speed (about 400–500 rpm).

11. The plate sealer was removed and decanted solutions were removed from the plates.They were tapped as before to remove residual solutions in the wells.

12. The wells were washed 3 times with diluted Wash Buffer, 300 µL per well per wash.

13. There was decanting and tapping after each wash to remove residual buffer.

Calculations: Graph of reference curve was generated by plotting the absorbance unit of 450 nm, less unit at 590 nm, on the Y axis against the concentrations of ghrelin standard on the X axis. The dose–response curve of this assay fits best to a sigmoidal 4- or 5-parameter logistic equation. The results of plasma samples were calculated with any computer programme having a 4- or 5-parameter logistic function.

The theoretical minimal detecting concentration of this assay is 100 pg/ml.

Standard curves were as follows:

$y = -230.04x^2 + 3020.6x - 813.1$
$R^2 = 0.9964$
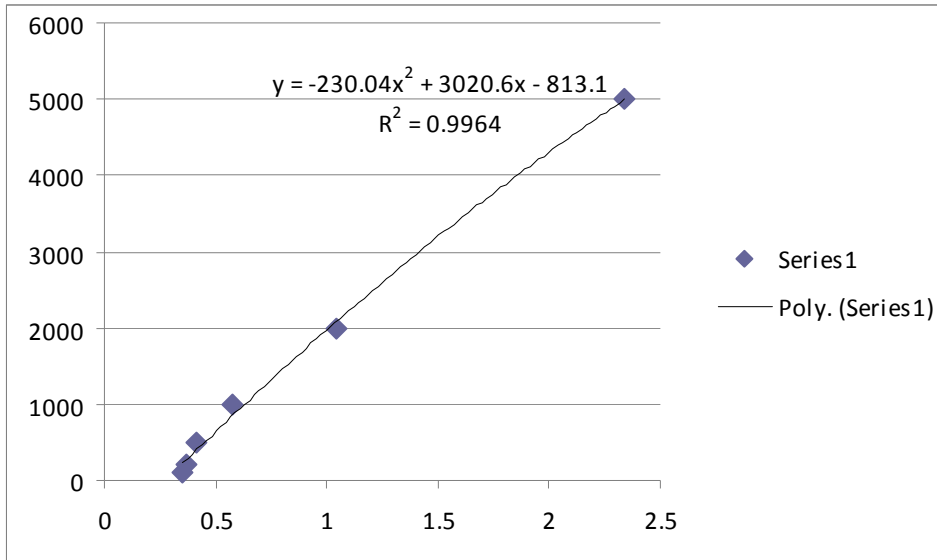
Figure 3-29: Standard curve for ghrelin

$y = -1284.5x^2 + 6114.1x - 1005.7$
$R^2 = 0.999$

$y = -1968.8x^2 + 7197.1x - 1369.7$
$R^2 = 0.9981$
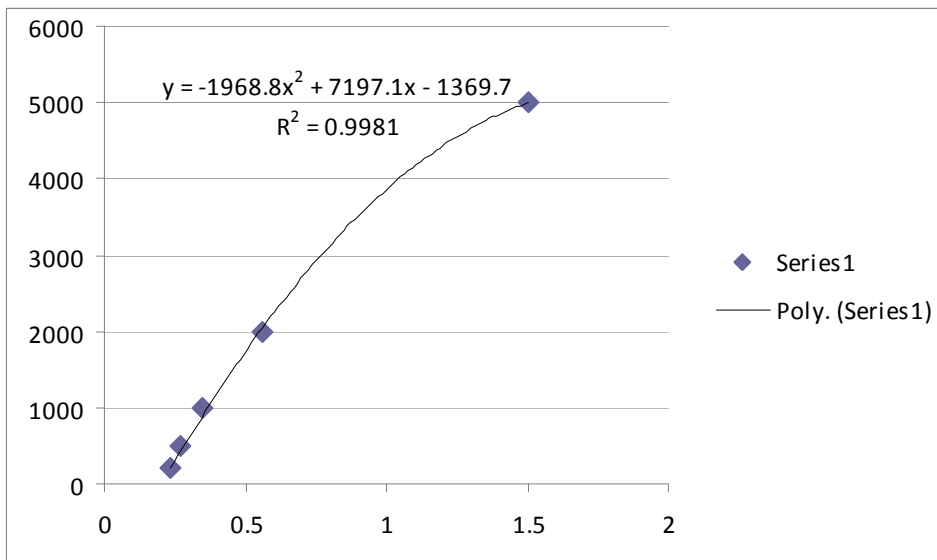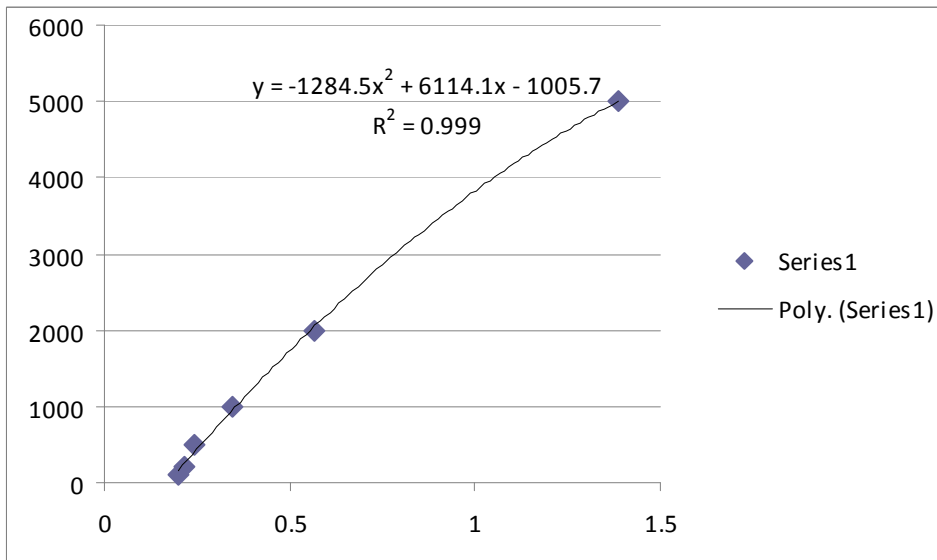
The appropriate range of this assay (total ghrelin) **is 100 pg/ml–5,000 pg/ml.**

Funding and expenditure

Source of funds: Scarborough Combined Gastroenterology Research Fund, Scarborough

The cost of the study was as follows:

1. Scintigraphy £250 x 2 (studies per patient) x 25 (number of patients) = £12,500.00

2. Hormone assays 40 assay/kit, total number of kits required=19, approximated price/kit (£350–370), total cost = £6500 (approximately).

3. Travel and refreshments for the participants.

4. Parking charges for participants.

5. Stationery and postal charges.

Total cost = approximately £21,500

6. The cost related to conduct of the study and salary to the research fellow was funded by the University of Hull.

3.3.6 Data storage and research facilities

All the collected data were anonymised and stored on computers in the Research Office in the Academic Surgical Unit at Castle Hill Hospital in a non-identifiable way. These are password protected, and part of the hospital IT network system. They are protected both by antivirus and firewall software, as with all Trust computers. Only the named investigator will have access to patient data. Transfer of electronic data was anonymised and only carried out through encrypted and password-protected USB devices provided or via www.nhs.net email accounts. Furthermore, hard copies of the forms were also filed in the Research Office in Castle Hill Hospital. A coded lock and general hospital security services protect these premises.

3.4 Statistics

Data was entered in Microsoft Excel 2007 spreadsheets and analysed by Excel 2007 and SPSS 19. Data is described as Mean + Standard deviation unless otherwise described. Paired and unpaired student t tests were used and p value of less than 0.05 was considered to be statistically significant.

3.5 Results

3.5.1 Improvement of weight, BMI and diabetic status following RYGB

Table 3-4: Change in weight, BMI, Diabetic status, GE after RYGB.

22 patients (Male 6, Female 16), Weight 1,2,3 = Pre operative, 2 weeks, 6 weeks after surgery respectively.BMI 1, 2, 3 = Pre operative, 2 weeks, 6 weeks after surgery respectively, DM 1,2 ,3= Fasting glucose levels (pre operative, 2 weeks, 6 weeks after surgery respectively) Weight improved from a mean of 130+/-22 to 111+/-18 kg 6 weeks. Fasting glucose levels improved from a mean of 11.0+/-4.3 to 8.0+/-2.3 m mol/L. GE was fast after RYGB (pre operative 94+/-74 minutes vs. post operative 21+/-21 minutes).

		Age (years)	Height (cm)	Weight 1 (kg)	Weight 2 (kg)	Weight3 (kg)	T50 (pre-op)	T50 (post-op)	BMI1	BMI 2	BMI 3	DM 1	DM 2	DM 3
N	Valid	22	22	22	22	22	22	22	22	22	22	22.00	22.00	22.00
	Missing	0	0	0	0	0	0	0	0	0	0	0.00	0.00	0.00
Mean		46	166	130.7	117.2	111.5	94	21	21	42.4	40.4	11.08	7.68	8.03
Median		46	164	127.0	113.0	107.5	69	18	18	42.2	40.3	11.01	7.75	7.41
Std. Deviation		8	9	22.5	20.8	18.8	74	21	21	5.6	5.2	4.31	2.60	2.83
Range		29	30	85.0	78.2	78.0	288	85	85	22.3	21.3	4.70	3.11	4.18
Minimum		29	152	93.0	80.8	76.0	32	1	1	34.1	32.0	19.74	11.81	16.40
Maximum		58	182	178.0	159.0	154.0	320	86	86	56.4	53.3	7.66	5.68	5.63
Percentiles	25	43	159	115.0	101.8	98.8	52	4	41.9	38.0	41.9	11.01	7.75	7.41
	50	46	164	127.0	113.0	107.5	69	18	46.4	42.2	46.4	13.19	9.96	10.02
	75	52	175	145.0	134.0	123.0	95	30	52.9	46.0	52.9	22.00	22.00	22.00

3.5.2 Change in GE following RYGB
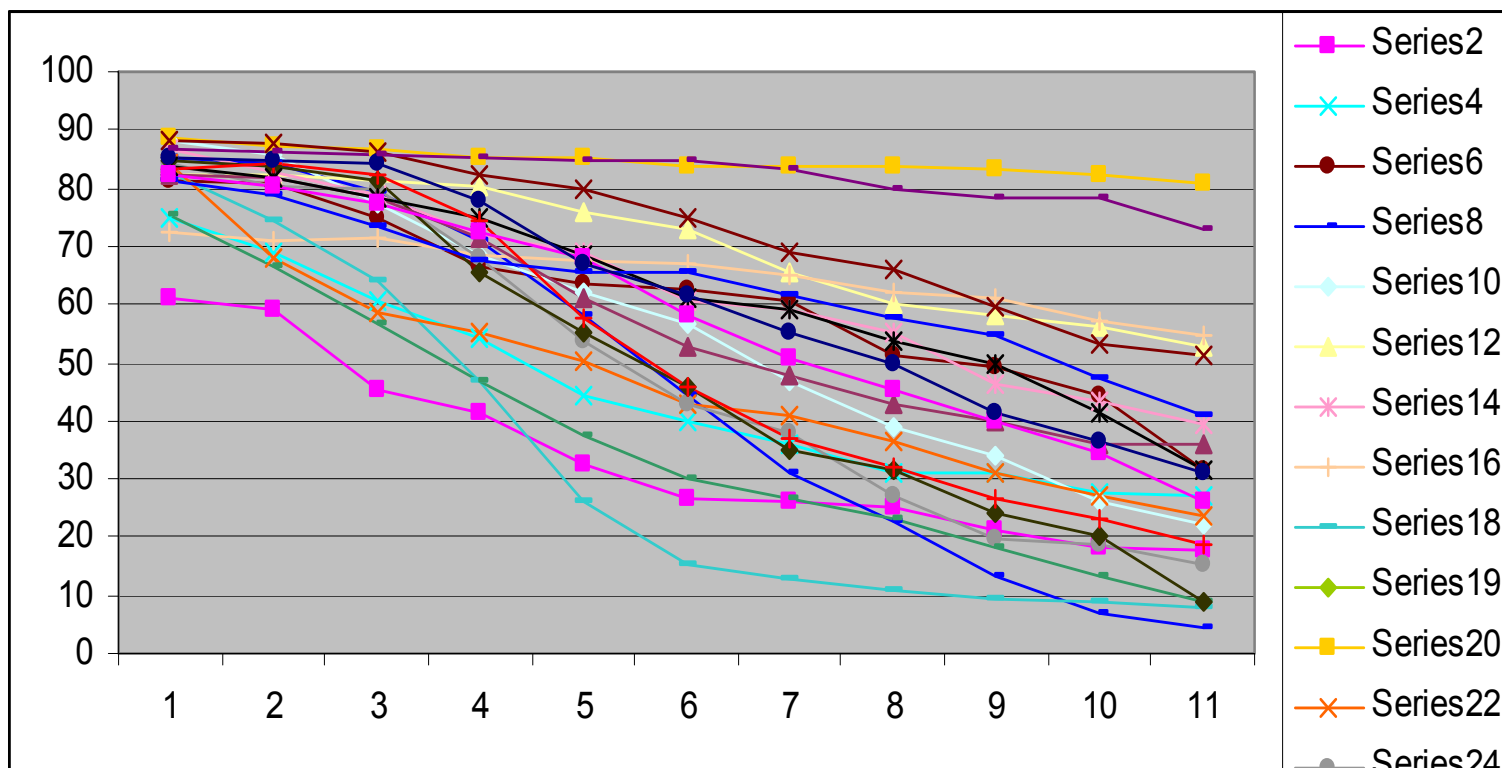
Figure 3-30: GE before surgery

Total number of patients = 22. X axis = GE emptying at (0 to 100 minutes after food intake). Y axis = food/radioactivity in gastric pouch.

A mean of 83% radioactivity (food) was seen in stomach at 0 minutes and it reduced to 32 % at 100 minutes.

Table 3-5: GE (time vs. radioactivity) for each patient

The first image was taken immediately after the food intake. Thereafter images were taken continuously for 100 minutes.

Data of images after every 10 minutes is presented for each patient.

X axis = patient number, Y axis = GE.

Over 80% radioactivity was seen in the stomach in 17 patients at the start of the test. Less than 40% left in the stomach in 15 patients at the end of the test (100 minutes).

time (minutes)	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22
0	61.02	74.92	81.11	85.29	88.09	82.23	86.57	72.65	82.77	88.72	84.03	84.21	75.24	84.87	82.49	83.79	83.12	81.14	82.21	88.18	85.46	86.49
10	58.99	69.16	80.93	84.45	85.62	82.19	82.81	71.03	74.46	87.41	68.16	80.35	66.61	83.79	81.95	81.98	84.33	78.64	80.42	87.48	84.76	86.24
20	45.32	60.83	74.94	79.50	77.27	81.32	78.91	71.66	64.06	86.77	58.80	79.61	56.52	81.17	78.18	78.09	82.32	73.49	77.27	86.17	84.07	85.53
30	41.40	53.94	66.48	70.72	68.58	80.12	71.97	68.48	46.93	85.07	55.26	68.16	46.80	65.61	71.39	74.83	74.21	67.27	72.25	82.28	77.92	85.45
40	32.56	44.10	63.39	58.30	61.87	75.76	69.01	67.60	25.97	85.42	50.36	53.75	37.47	55.20	60.95	68.38	57.84	65.42	67.87	79.97	66.97	84.71
50	26.64	39.95	62.51	44.49	56.56	73.03	60.82	66.91	15.12	83.71	42.93	43.03	30.02	45.72	52.61	61.04	45.73	65.45	58.02	74.95	61.77	84.57
60	26.29	36.17	60.35	30.82	47.00	65.53	59.19	64.80	12.64	83.71	40.66	37.82	26.67	34.86	47.62	59.21	36.73	61.45	50.58	68.75	55.01	83.28
70	25.05	30.96	51.21	22.42	38.97	59.94	55.00	62.06	10.67	83.69	36.29	27.11	23.38	31.31	42.92	53.63	32.12	57.46	45.21	66.12	49.51	79.65
80	21.39	31.19	49.03	13.50	34.15	58.19	46.49	60.91	9.28	83.49	31.20	19.83	18.21	24.19	39.99	49.57	26.36	54.84	40.00	59.62	41.56	78.51
90	18.12	27.69	44.53	6.67	26.25	56.25	43.44	56.97	8.95	82.14	27.02	18.87	13.16	20.13	36.01	41.33	23.10	47.10	34.57	53.22	36.46	78.32
100	17.61	27.04	31.75	4.67	22.04	52.75	39.58	54.66	7.74	80.72	23.80	15.28	8.62	8.81	35.78	31.46	18.80	41.09	25.96	51.09	31.13	72.70

Table 3-6: GE before surgery (mean).

Mean and Std Deviations of radioactivity at each data point (10 minute intervals). 82+/-6 % radioactivity at the start of the test, 54+/-17 % after 50 minutes and 32+/-20% at 100 minutes.

Time		0	10	20	30	40	50	60	70	80	90	100
N	Valid	22.00	22.00	22.00	22.00	22.00	22.00	22.00	22.00	22.00	22.00	22.00
	Missing	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Mean		82.03	79.17	74.63	67.96	60.59	54.34	49.51	44.76	40.52	36.38	31.96
Std. Deviation		6.29	7.73	10.89	12.25	15.58	17.82	18.52	19.01	20.07	20.39	20.47
Range		27.70	28.49	41.45	44.05	59.45	69.45	71.07	73.02	74.21	75.47	76.05
Minimum		61.02	58.99	45.32	41.40	25.97	15.12	12.64	10.67	9.28	6.67	4.67
Maximum		88.72	87.48	86.77	85.45	85.42	84.57	83.71	83.69	83.49	82.14	80.72
Percentiles	25	81.13	73.60	69.76	63.02	52.90	43.01	35.84	30.00	23.49	19.82	17.03
	50	83.46	81.97	78.14	69.65	62.63	57.29	49.10	44.07	40.00	35.29	29.09
	75	85.72	84.53	81.57	75.60	68.54	65.82	62.29	58.08	55.68	48.63	43.59
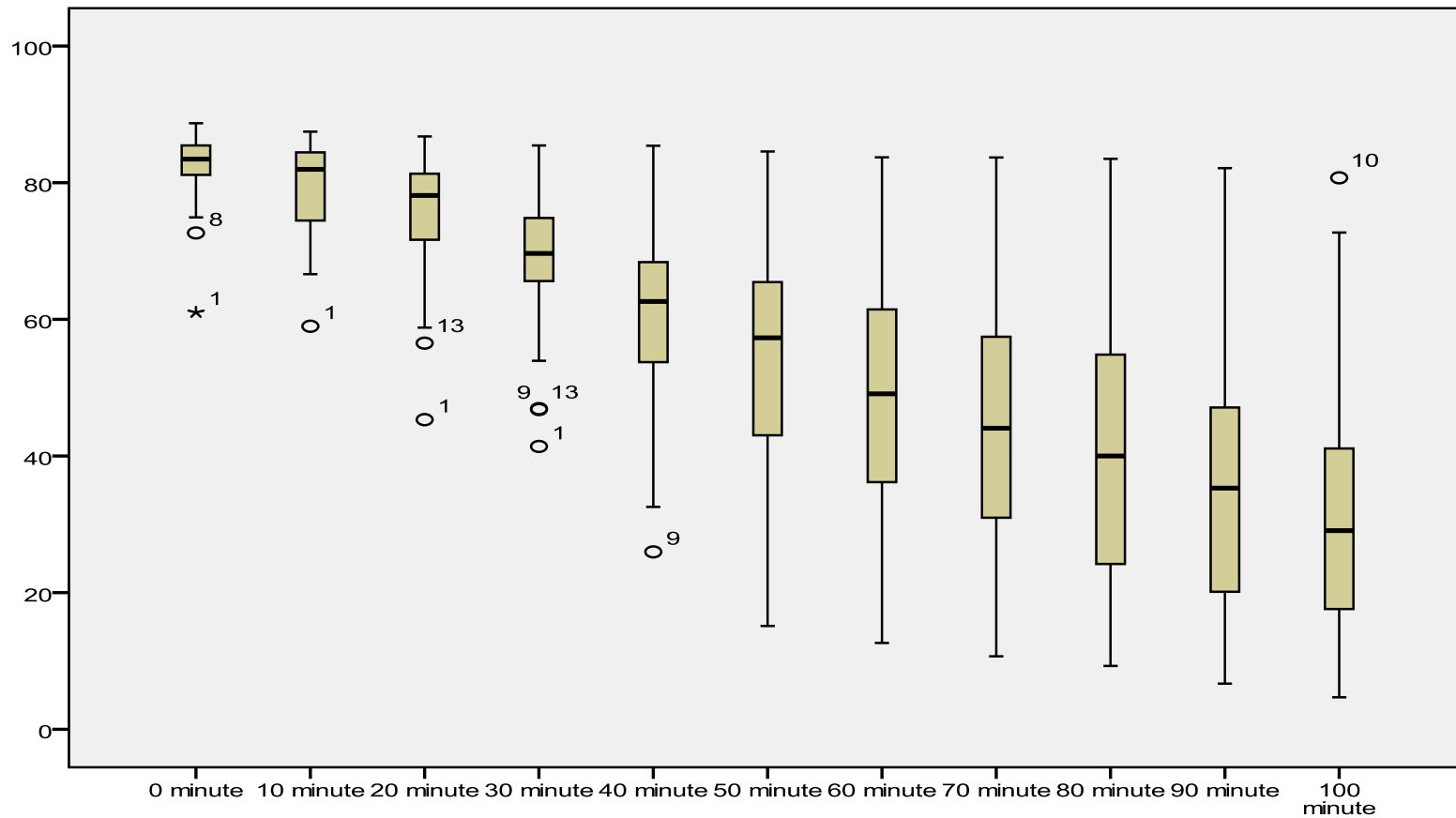
Figure 3-31: Box plot representing GE before RYGB

Y axis = % GE, X axis = Time

Mean GE + St Deviation presented in box plot. 82+/-6 % radioactivity at the start of the test, 54+/-17 % after 50 minutes and 32+/-20% at 100 minutes.

Post-Operative Pouch Emptying
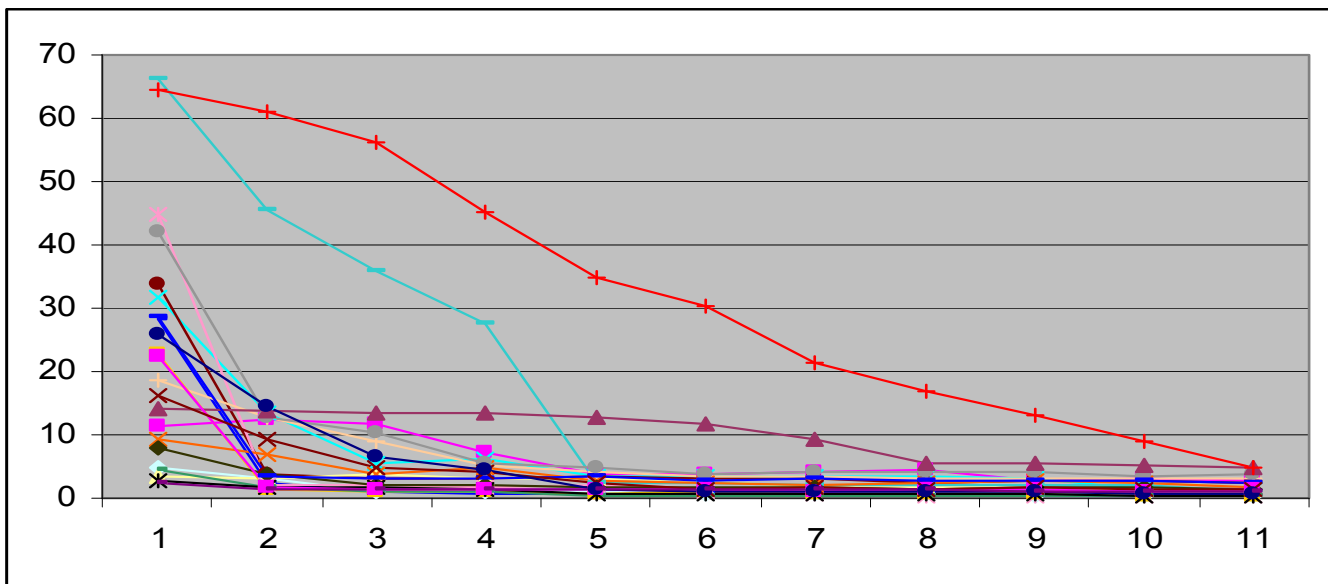
Figure 3-32: Post-operative GE (pouch emptying)

Total number of patients = 22

X axis = pouch emptying at (0 to 100 minutes after food intake).Y axis = food/radioactivity in gastric pouch.

Patient number 9 and 17 had over 60% radioactivity in the pouch at the start of the test compared to patient number 5, 6,13,16,22 with less than 5% radioactivity in the pouch

Table 3-7: Pouch emptying for individual patients

Time (Y Axis) vs. Radioactivity (X Axis) in gastric pouch following RYGB. Wide variation in pouch retention and pouch emptying noted. Patient number 9 and 17 had maximum (over 60%) radioactivity in the pouch at the start of the test compared to patient number 5, 6,13,16,22 with less than 5% radioactivity in the pouch.

Time	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22
0	11.25	31.79	33.64	28.24	4.78	3.31	44.91	18.76	66.21	22.91	9.25	41.95	4.31	7.86	14.08	2.77	64.56	28.75	22.29	16.34	26.03	2.48
10	12.25	13.52	3.73	2.58	2.94	3.12	2.15	12.79	45.65	1.44	6.75	12.66	1.60	3.95	13.96	1.82	61.19	3.34	1.56	9.22	14.60	1.26
20	11.61	5.63	3.16	1.03	1.11	3.74	2.04	9.04	35.90	1.08	3.72	10.36	0.92	2.19	13.55	1.66	56.12	2.99	1.43	4.93	6.54	1.34
30	7.07	6.05	3.13	0.86	1.02	2.99	1.76	5.22	27.73	1.10	4.66	5.68	1.03	1.93	13.43	1.34	45.09	3.16	1.35	4.00	4.36	1.48
40	3.75	3.40	3.29	0.80	0.99	2.96	1.90	4.10	2.51	0.79	2.59	4.71	0.41	1.83	12.66	0.84	34.95	3.32	1.44	2.42	1.54	1.43
50	3.85	3.56	3.22	0.64	0.56	2.66	1.14	3.54	2.48	0.96	2.31	3.66	0.45	1.56	11.65	0.70	30.42	2.91	1.30	1.25	1.10	1.23
60	4.30	3.43	3.05	0.68	0.59	1.74	0.58	3.46	2.09	0.77	2.21	4.05	0.45	1.64	9.42	0.56	21.44	3.12	1.06	1.65	1.06	1.31
70	4.32	3.54	2.56	0.60	0.52	1.81	0.51	3.02	2.08	0.79	2.53	4.07	0.36	1.55	5.63	0.56	16.80	2.72	1.24	1.50	1.00	1.36
80	2.64	2.94	2.77	0.42	0.48	1.58	0.43	3.02	2.02	0.62	2.60	4.17	0.44	1.58	5.52	0.54	13.00	2.80	1.29	1.60	1.14	0.93
90	2.95	1.32	2.78	0.37	0.46	1.49	0.44	3.09	2.00	0.46	2.41	3.56	0.37	1.59	5.14	0.51	9.07	2.68	1.02	1.28	0.85	1.10
100	2.85	1.26	2.29	0.50	0.49	1.28	0.43	3.17	1.16	0.42	1.72	3.91	0.27	1.24	4.72	0.50	4.85	2.55	1.47	1.27	0.80	1.14

Table 3-8: Post-RYGB pouch emptying (mean)

77% of food/radioactivity had left the pouch and were seen in the small intestine immediately after food intake. A mean of 23+/-18% radioactivity was noticed in gastric pouch at the start of the test and it reduced to 1.7+/-1.3% at 100 minutes.

		0 minute	10 minute	20 minute	30 minute	40 minute	50 minute	60 minute	70 minute	80 minute	90 minute	100 minute
N	Valid	22.00	22.00	22.00	22.00	22.00	22.00	22.00	22.00	22.00	22.00	22.00
	Missing	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Mean		23.02	10.55	8.19	6.57	4.21	3.69	3.12	2.69	2.39	2.04	1.74
Std. Deviation		18.63	14.89	13.16	10.43	7.31	6.42	4.56	3.46	2.72	2.01	1.39
Range		63.73	59.93	55.20	44.23	34.53	29.97	20.99	16.44	12.57	8.70	4.58
Minimum		2.48	1.26	0.92	0.86	0.41	0.45	0.45	0.36	0.42	0.37	0.27
Maximum		66.21	61.19	56.12	45.09	34.95	30.42	21.44	16.80	13.00	9.07	4.85
Percentiles	25	7.09	2.07	1.41	1.35	1.32	1.06	0.75	0.74	0.60	0.50	0.50
	50	20.52	3.84	3.44	3.15	2.46	1.93	1.69	1.68	1.59	1.41	1.26
	75	32.25	12.97	9.37	5.77	3.49	3.54	3.44	3.15	2.84	2.82	2.62
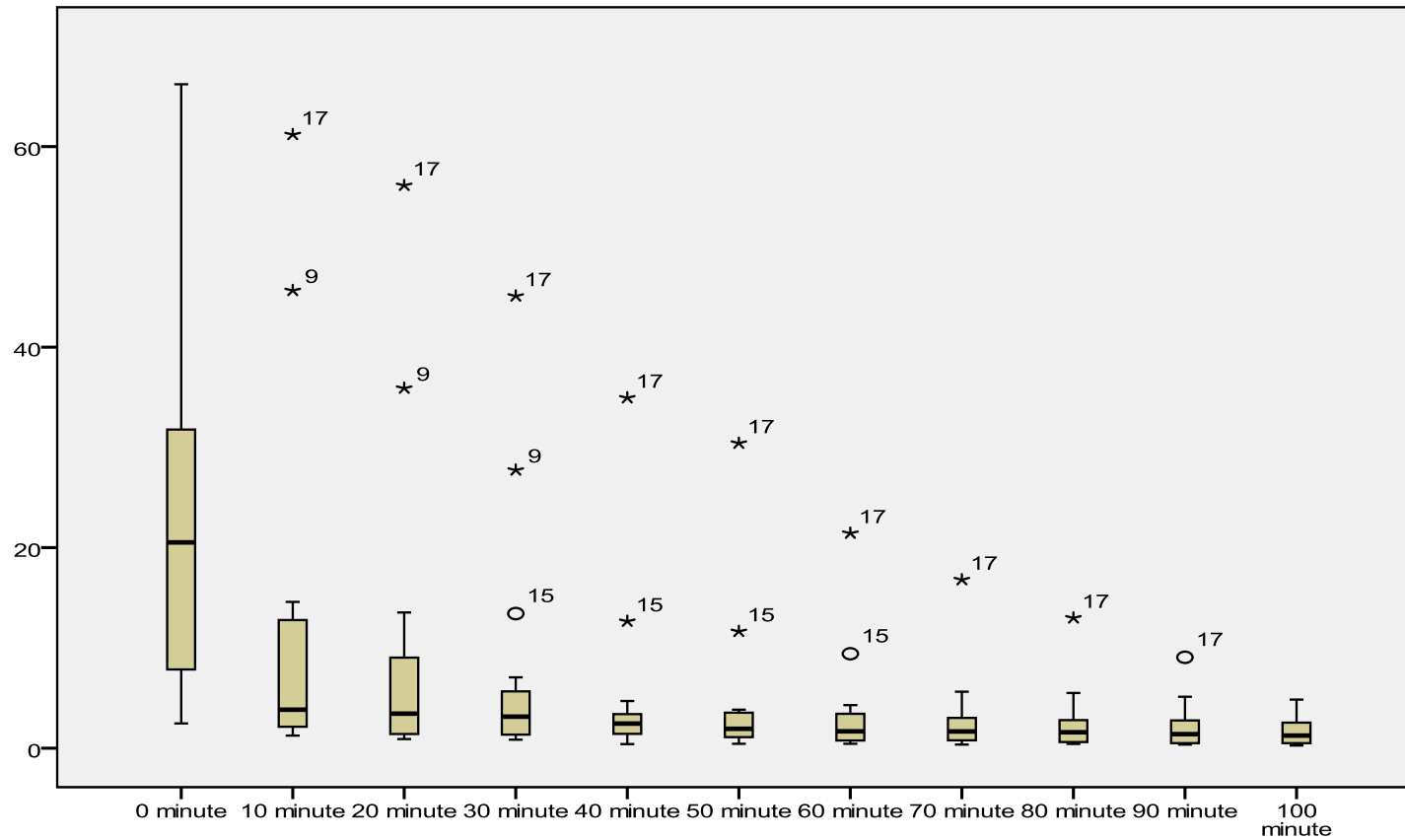
Figure 3-33: Box plot representing pouch emptying

X axis = time, Y axis = radioactivity. Small amount of radioactivity (23%) noted at the start of the test and it reduced to 1.7% at 100 minutes.

Change in GE following RYGB.
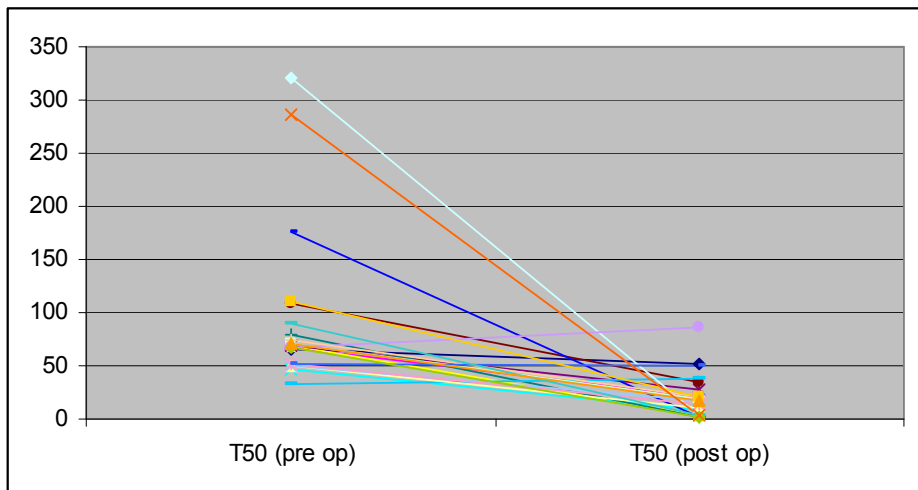
Figure 3-34: Change in GE following RYGB

X axis = Comparison of T50 (pre and post RYGB). Y axis = time. The graph above shows that all patients had fast pouch emptying compared to their pre-operative GE.
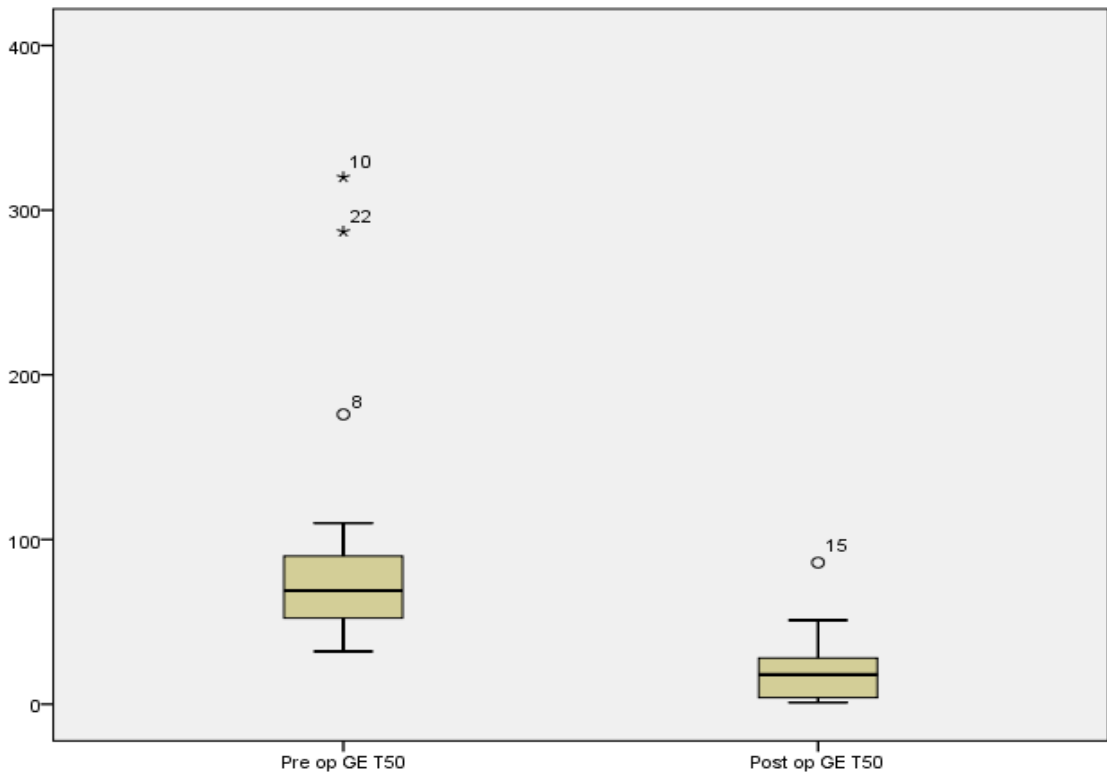
Figure 3-35: Box plot representation of pre- and post-op GE

X axis = Pre and post operative GE, Y axis = GE time. Box plot representing GE before surgery and gastric pouch emptying after RYGB. There was significantly fast pouch emptying when compared with pre-operative GE ($p < 0.01$).

A total of 25 patients were recruited. Three patients were excluded due to the following reasons:

1. Post-operative complications and the patient not being able to complete the research.

2. Failing to comply pre-operatively with the nutritional instructions and being withdrawn from the operative waiting list.

3. Funding for the procedure being refused by the PCT for one patient and not operated on for RYGB and consequently dropped from the study.

The final data of the 22 patients is included in this study (Table 3-4). This included 6 male and 16 female diabetic patients with morbid obesity. GE was assessed in a total of 22 patients. The basic demographic data is presented in Table 3-4. The mean age was 46 ± 8 years (range 29–58). The mean height was 166 ± 9 cm, pre-operative weight 130 ± 22.5 kg (range 178–93) and corresponding BMI was 47.3 ± 6.3. Post-operatively, all patients lost weight and their weight and BMI decreased and the corresponding values were as follows:

2 weeks after surgery = mean weight 117 ± 20, BMI 42.4 ± 5.6
6 weeks after surgery = mean weight 111 ± 8, BMI 40.4 ± 5.2

GE before surgery was calculated continuously for 100 minutes and individual patient data is presented above (32 % at 100 minutes.

Table 3-5, Table 3-6, Figure 3-30, Figure 3-31). The half-emptying time (T50) of the stomach before surgery was 94 minutes. A mean 82 ± 6% of food was seen in the stomach after meal intake (Table 3-4, 32 % at 100 minutes.

Table 3-5, Figure 3-31). The rest of the food was already seen in the intestine.

Post-operatively, most (approximately 90–95%) of the stomach was bypassed. A small pouch size (approximately 50 ml) and stoma (approximately 1cm diameter) were created during surgery. A post-operative pouch emptying is described in Figure 3-33**Figure 3-33**, Figure 3-34**Figure 3-34**, Table 3-7**Table 3-7** and Table 3-8. A total of 23 ± 18% of food was retained in the pouch at the end of the meal intake. The

remainder had already entered into the jejunum. This further emptied quickly to a mean 10 ± 14% left in the pouch after 10 minutes and continued emptying quickly. Pouch half-emptying time was significantly short (p<0.01) compared to pre-operative GE (Figure 3-35, Figure 3-34).

3.5.3 Change in IT following RYGB
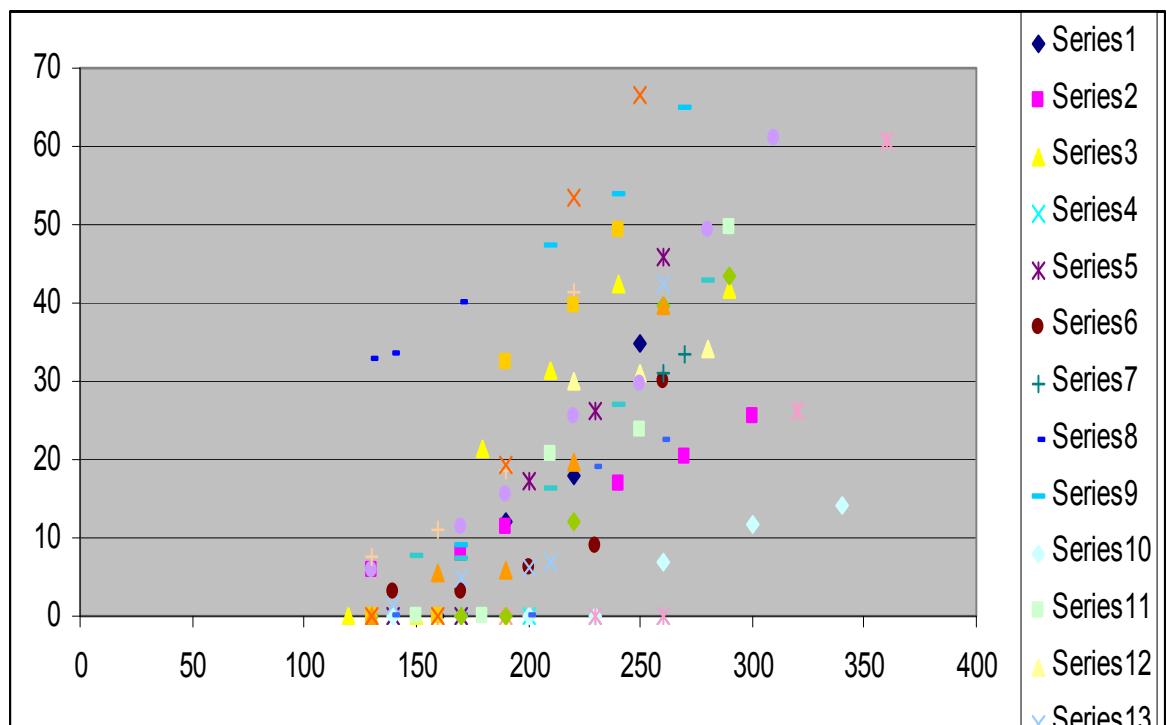
Figure 3-36: Pre-operative caecal filling time

X axis = Time, Y axis = % radioactivity. Serial calculations were performed for each patient at 30 minute intervals until Caecum was confidently identified for each patient. Each patient represented with a series of the same colour readings.

Table 3-9: Pre-operative IT time

Mean	40.21%	270 minutes
Median	41%	265 minutes
St dev	16%	39 Minutes

Pre-operative Mean intestinal transit time was 270 minutes for 40% radioactivity calculated in the caecum.
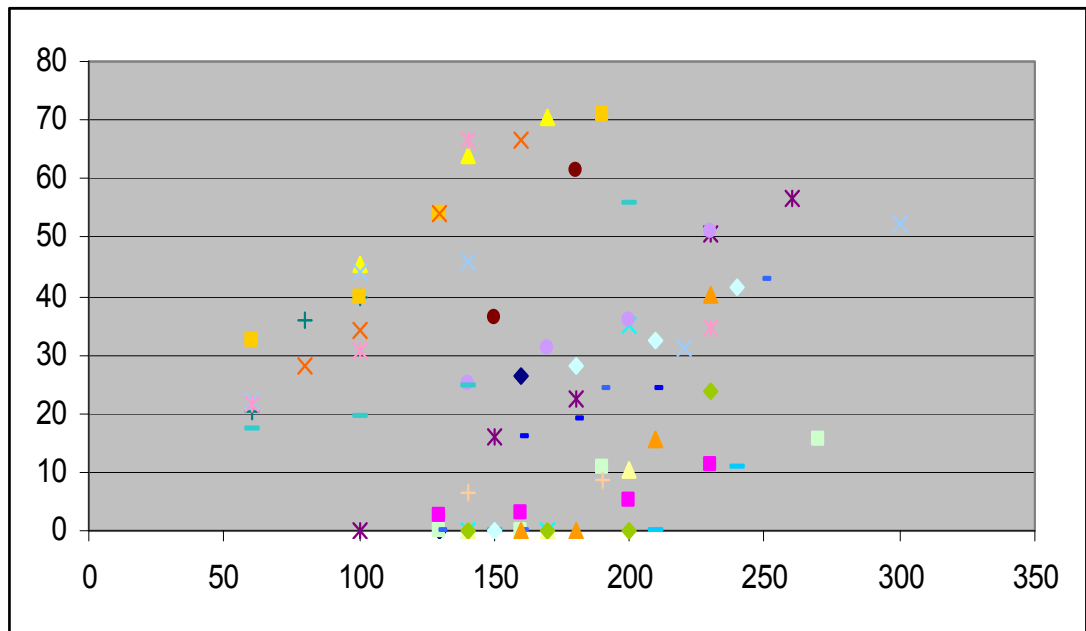
Figure 3-37: Post-operative IT time

X axis = Time, Y axis = % radioactivity. Serial calculations were performed for each patient at 30 minute intervals until Caecum was confidently identified for each patient. Each patient represented with a series of the same colour readings.

Table 3-10: Post-RYGB IT time

Mean	39%	212 Minutes
Median	40%	220 Minutes
St dev	20%	44 Minutes

Post RYGB Mean intestinal transit time was 212 minutes for 39% radioactivity calculated in the caecum

Table 3-11: Pre- and post-RYGB IT time vs. radioactivity (%)

Comparison of data of 22 patients. Pre-operative IT reduced from 271 minutes to 212 minutes for the same amount of radioactivity 40% (pre-operative) vs. 39% (post RYGB).

		IT 1 (%)	IT 2 (%)	Time 1 (minutes)	Time 2 (minutes)
N	Valid	22	22	22	22
	Missing	0	0	0	0
Mean		40	39	271	212
Median		42	40	265	220
Std. Deviation		16	20	39	44
Minimum		0	9	170	100
Maximum		67	71	360	300
Percentiles	25	33	22	250	188
	50	42	40	265	220
	75	49	56	290	240

Table 3-12: comparison of IT following RYGB

Paired t test showing significantly short IT (271 minutes vs. 212 minutes p < 0.05) for the same amount of radioactivity (40% vs. 39% P > 0.05) after RYGB.

		Paired Differences							
		Mean	Std. Deviation	Std. Error Mean	95% Confidence Interval of the Difference Lower	Upper	t	df	Sig. (2-tailed)
Pair 1	% - %	-1.59	24.36	5.19	-12.39	9.21	-.306	21	.762
Pair 2	minutes - minutes	-58.64	52.22	11.13	-81.79	-35.48	-5.267	21	.000
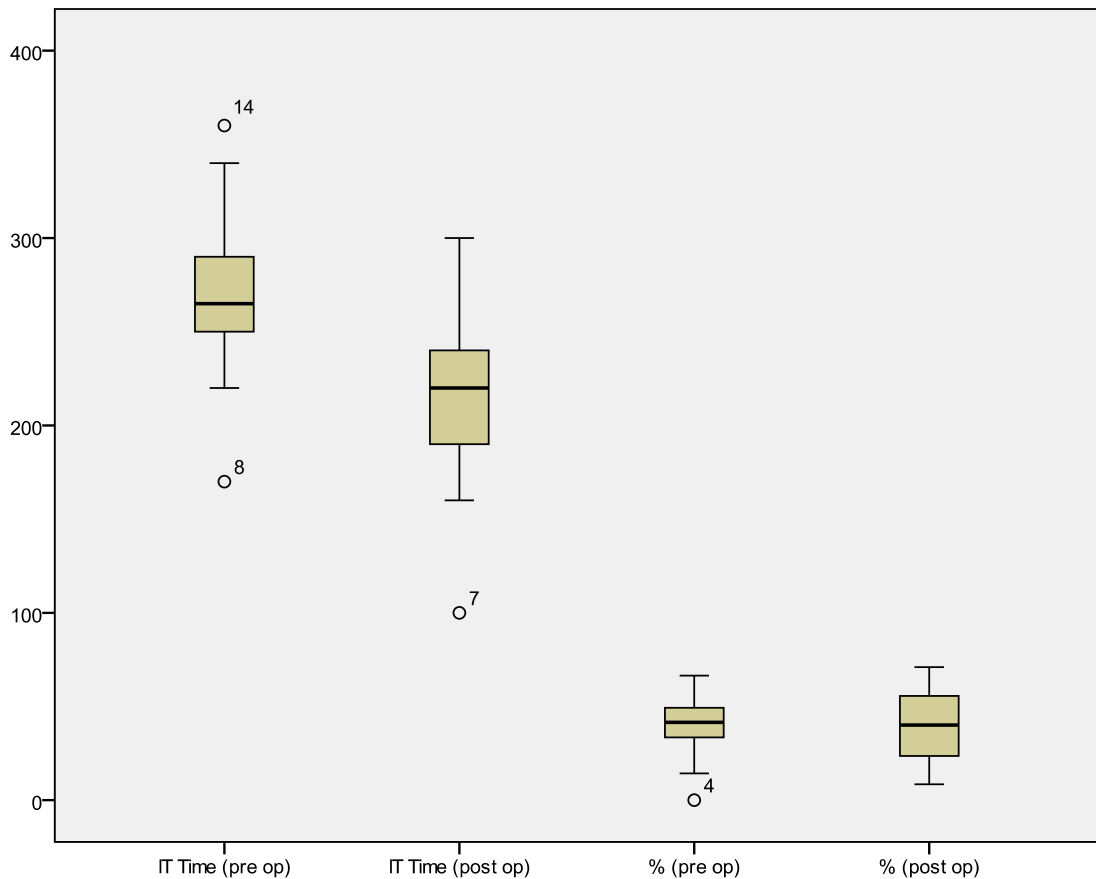
Figure 3-38: Box plot comparison of pre- and post-RYGB radioactivity in the caecum vs. filling time

Significantly ($P < 0.01$) improved IT (271 minutes vs. 212 minutes) for the same amount of radioactivity (40% vs. 39% $P > 0.05$) calculated in caesium after RYGB

IT time is described in Figure 3-36, Figure 3-38, Table 3-9, Table 3-10, and Table 3-12. Pre-operative mean IT time was 270 ± 39 minutes for 40.2 ± 16 % radioactivity/food recorded in the iliocaecal region. Post-operatively, fast IT time was recorded of 212 ± 44 minutes for 39 ± 20 radioactivity/food in iliocaecal region. There was no significant difference (p 0.76) for the amount of radioactivity/food noticed in the iliocaecal region on the last scan; however, the IT time was significantly decreased after RYGB (p <0.01), as shown in Table 3-12.

3.5.4 Change in gut hormones (ghrelin & GLP-1) following RYGB

1. **<u>Diabetic status before and after RYGB</u>**

   a. Fasting glucose levels

   <u>Glucose levels described in m mol/L</u>

Table 3-13: Fasting glucose levels before and after RYGB

Pre-operative fasting glucose levels 11.08+/-4.31 reduced to 7.68+/-2.60 at 2 weeks follow up and 8.03+/-2.83 at 6 weeks follow up after RYGB.

		Pre-op	Two weeks	Six weeks
N	Valid	22.00	22.00	22.00
	Missing	0.00	0.00	0.00
Mean		11.08	7.68	8.03
Median		11.01	7.75	7.41
Std. Deviation		4.31	2.60	2.83
Minimum		4.70	3.11	4.18
Maximum		19.74	11.81	16.40
Percentiles	25	7.66	5.68	5.63
	50	11.01	7.75	7.41
	75	13.19	9.96	10.02

Fasting glucose levels before and after RYGB: Post-operative low glucose levels were recorded. One patient adopted a different pattern of eating behaviour following RYGB as this patient was not able to take the similar amount of solid meal. However, the patient developed a habit of taking lots of fluids (milk, juice, sugary drinks), resulting in high glucose levels.

Table 3-14: Change in fasting glucose after RYGB

A significant improvement in fasting glucose levels was observed after surgery when compared with the corresponding pre-operative levels (p 0.001 and 0.01).

		Paired Differences							Sig. (2-tailed)
					95% Confidence Interval of the Difference				
		Mean	Std. Deviation	Std. Error Mean	Lower	Upper	t	df	
Pair 1	Pre-op two weeks	3.40	4.43	0.94	1.44	5.36	3.60	21.00	0.00
Pair 2	Pre-op six weeks	3.05	4.69	1.00	0.97	5.13	3.05	21.00	0.01
Pair 3	Two_weeks Six weeks	-0.35	3.45	0.74	-1.88	1.18	-0.48	21.00	0.64
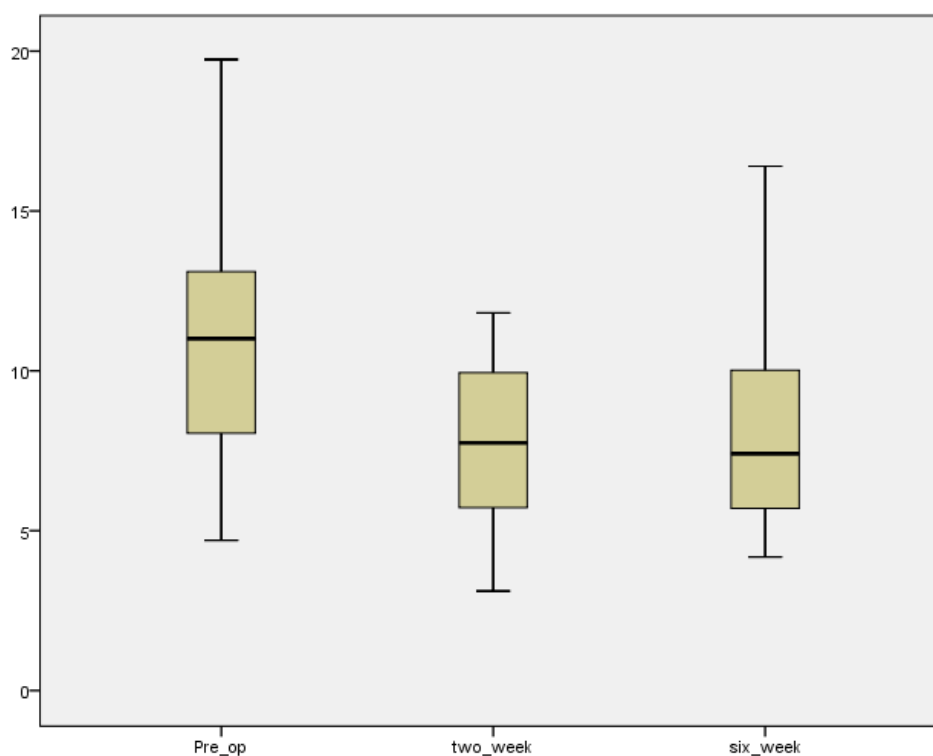
Figure 3-39: Box plot representing fasting glucose levels pre- and post-RYGB

Improvement in fasting glucose levels (Y axis) was observed after surgery (2 weeks, 6 weeks in X axis) when compared with the corresponding pre-operative levels (p 0.001 and 0.01).

Table 3-15: Pre-operative meal-related glucose response

This included fasting samples. Further samples were taken at 30 minutes and 60 minutes after food intake. The last sample was taken when food reached the iliocaecal region. Meal intake resulted in an increase in mean glucose level from fasting levels 11.0+/-4.3 to 12.6+/-4.4 at 30 minutes, 12.6+/-4.5 at 60 minutes and then reduced to 10.2+/-4.1 when food reached in caecum.

		Pre-op fasting	30	60	caecum
N	Valid	22	22	22	22
	Missing	0	0	0	0
Mean		11.08	12.69	12.68	10.24
Median		11.01	12.05	12.01	9.11
Std. Deviation		4.31	4.48	4.54	4.13
Range		15.04	17.43	16.96	14.49
Minimum		4.70	7.25	5.72	5.54
Maximum		19.74	24.68	22.68	20.03
Percentiles	25	7.66	9.01	8.64	7.17
	50	11.01	12.05	12.01	9.11
	75	13.19	14.77	14.99	12.32
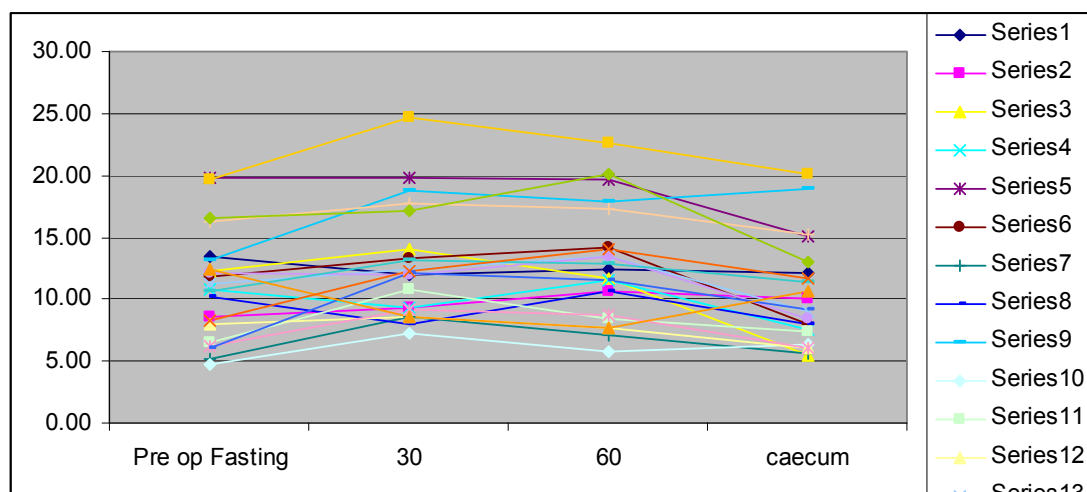
Figure 3-40: Serial pre-operative meal-related response in individual patients

Graphic representation of serial glucose tests and results on 22 paterients before surgery.
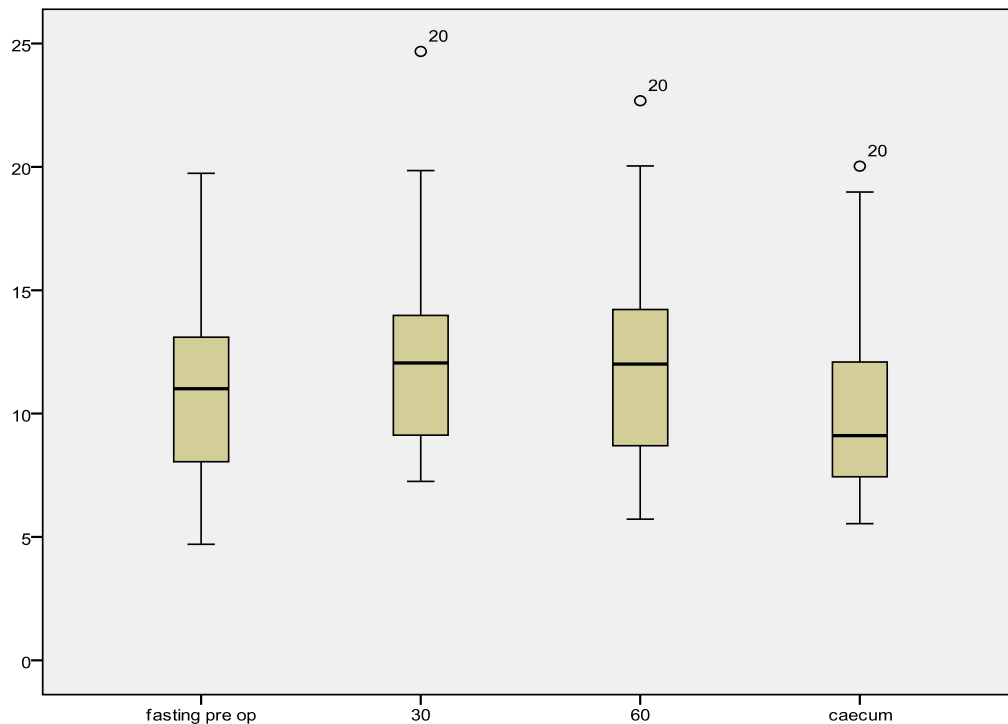
Figure 3-41: Box plot representing pre-operative meal-related glucose response
Y axis = glucose levels, X axis = time since food intake. Meal intake resulted in an increase in mean glucose level from fasting levels 11.0+/-4.3 to 12.6+/-4.4 at 30 minutes, 12.6+/-4.5 at 60 minutes and then reduced to 10.2+/-4.1 when food reached in caecum.

Table 3-16: Post-RYGB meal-related response
Improved fasting glucose levels 8.0+/-2.8 mmol/l compared to pre operative fasting levels. Meal intake resulted in an increase to 11.1+/-3.2, 10.7+/-3.7 at 30 and 60 minutes respectively.

		Fasting post-op	30.	60	caecum
N	Valid	22	22	22	22
	Missing	0	0	0	0
Mean		8.03	11.14	10.70	8.43
Median		7.41	11.64	10.48	8.07
Std. Deviation		2.83	3.27	3.75	3.13
Range		12.22	13.75	14.95	12.14
Minimum		4.18	6.25	5.05	4.46
Maximum		16.40	20.00	20.00	16.60
Percentiles	25	5.63	8.41	8.26	5.74
	50	7.41	11.64	10.48	8.07
	75	10.02	12.86	12.98	11.08
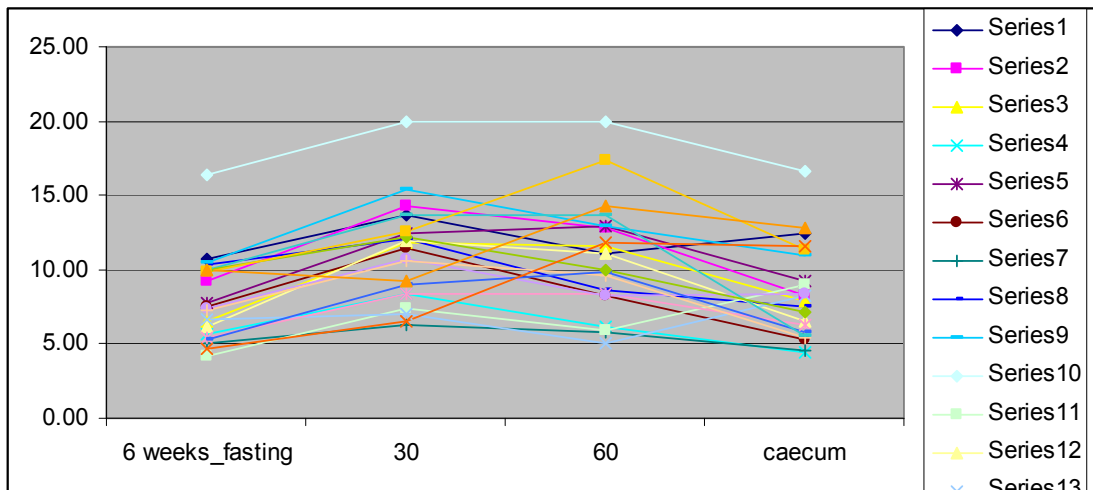
Figure 3-42: Meal-related glucose response in individual patients.

Graphic representation of serial glucose tests after meal intake in 22 patients at 6 weeks following RYGB. Increase at 30 and 60 minutes demonstratd.
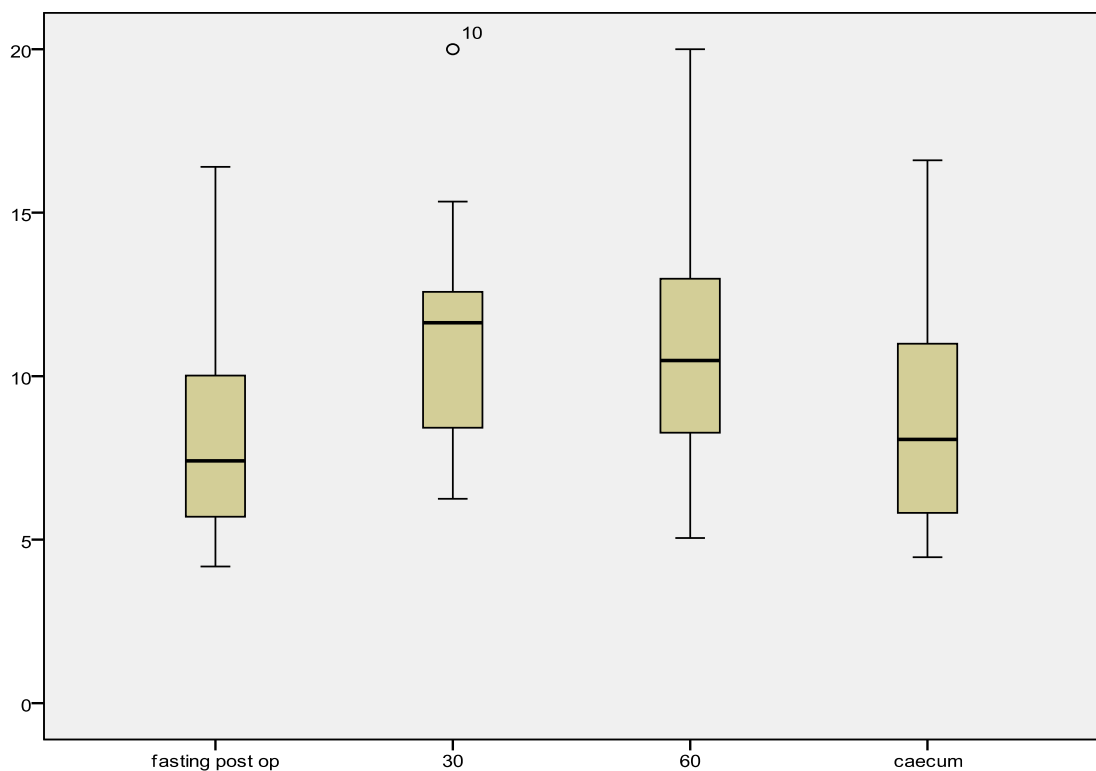
Figure 3-43: Box plot representing post-RYGB meal-related response

Improved fasting glucose levels 8.0+/-2.8 mmol/l compared to pre operative fasting levels. Meal intake resulted in an increase to 11.1+/-3.2, 10.7+/-3.7 at 30 and 60 minutes respectively.

Change in glucose levels after RYGB

Table 3-17: Comparison of pre-RYGB and 6 weeks post-RYGB meal-related glucose response

Fasting glucose levels significantly decreased after surgery (p = 0.01). No significant change in meal related response after RYGB (glucose levels at 30 minutes, 60 minutes and food in caecum).

		Paired Differences							Sig. (2–tailed)
					95% Confidence Interval of the Difference				
		Mean	Std. Deviation	Std. Error Mean	Lower	Upper	t	df	
Pair 1	fasting pre-op fasting post-op	3.05	4.69	1.00	0.97	5.13	3.05	21.00	0.01
Pair 2	30 – 30	1.55	5.13	1.09	-0.73	3.82	1.42	21.00	0.17
Pair 3	60 – 60	1.98	5.44	1.16	-0.43	4.39	1.71	21.00	0.10
Pair 4	caecum - caecum	1.82	4.45	0.95	-0.16	3.79	1.92	21.00	0.07

Glucose levels were converted to mmol/L. Fasting glucose levels reduced from 11.0±4.3 to 7.6±2.6 at 2 weeks after surgery and at the 6-week follow-up to 8.0±2.8. This change was significant p 0.01 at 2 and 6 weeks respectively after surgery (Table 3-13, Table 3-14, Figure 3-39). The standard meal resulted in an increase in glucose from 11.0±4.3 to 12.6±4.4 at 30 minutes, sustained at 12.6±4.5 at 60 minutes and reduced to 10.2±4.1 when food reached into the caecum (Table 3-15).

Following RYGB, the fasting levels 8.0±2.8 increased to 11.1±3.2 at 30 minutes, and continued to decrease thereafter to 10.7±3.7 at 60 minutes after food intake and to 8.4±3.1 when the food reached into the caecum (Table 3-17). Although decreases over all postprandial responses were seen after RYGB, it was statistically significant in the fasting state only.

2. **Change in insulin and IR before and after RYGB**

2a. Change in insulin levels

Insulin levels described in mIU/L.

Table 3-18: Fasting insulin levels before and after RYGB

A constant decrease in fasting insulin levels after surgery was recorded. Pre operative 60.7+/- 64.4, 2 weeks after RYGB 48.0+/-54.4, 6 weeks after surgery 41.6+/-55.8

		pre-op fasting	2 weeks post-op fasting	6 weeks post-op fasting
N	Valid	22	22	22
	Missing	0	0	0
Mean		60.71	48.01	41.67
Median		33.44	27.00	16.46
Std. Deviation		64.47	54.41	55.88
Range		220.24	179.21	182.24
Minimum		15.52	5.24	6.10
Maximum		235.76	184.45	188.34
Percentiles	25	23.81	11.21	11.68
	50	33.44	27.00	16.46
	75	65.17	43.83	35.00
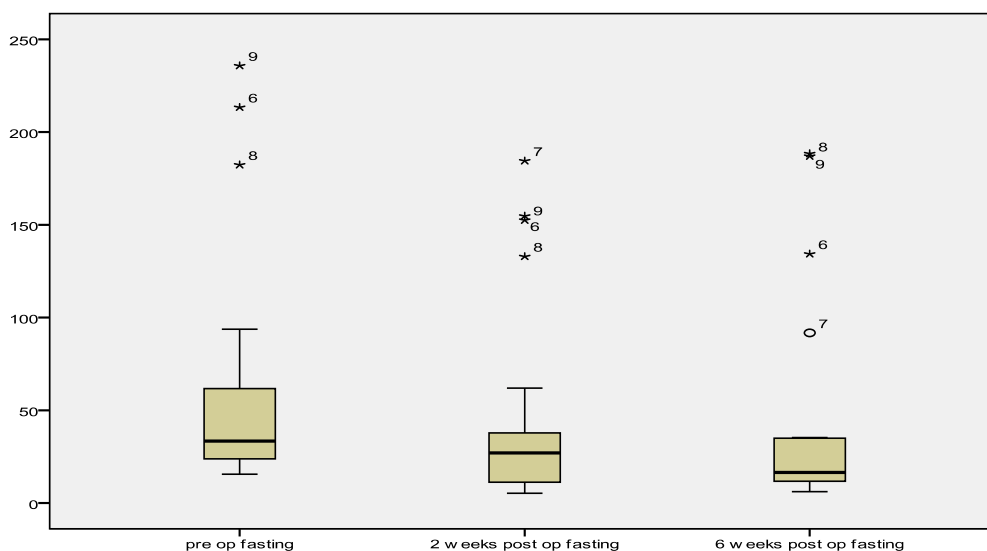
Figure 3-44: Box plot representing fasting insulin levels before and after RYGB

X axis = Time of measurement, Y axis = levels. Continuous decline noticed as pre operative 60.7+/- 64.4, 2 weeks after RYGB 48.0+/-54.4, 6 weeks after surgery 41.6+/-55.8.

Table 3-19: Comparison of fasting insulin levels

Significant improvement in fasting insulin level at 6 weeks follow-up compared with pre-operativefasting insulin level (p= < 0.01).

		Paired Differences			95% Confidence Interval of the Difference				Sig. (2-tailed)
		Mean	Std. Deviation	Std. Error Mean	Lower	Upper	t	df	
Pair 1	pre-op fasting – 2 weeks fasting	12.70	32.53	6.94	-1.72	27.13	1.83	21.00	0.08
Pair 2	pre-op fasting – 6 weeks fasting	19.04	20.85	4.45	9.79	28.28	4.28	21.00	0.00
Pair 3	2 weeks fasting – 6 weeks fasting	6.33	26.88	5.73	-5.59	18.25	1.10	21.00	0.28

Table 3-20: Pre-operative meal-related insulin response

Following meal intake insulin levels increased to 86.3+/-75.8 at 30 minutes and 95.3+/-75.7 at 60 minutes. Levels decreased to 63.4+/-75.4 when food reached in the caecum

		pre-op fasting	30	60	caecum
N	Valid	22	22	22	22
	Missing	0	0	0	0
Mean		60.71	86.38	95.31	63.48
Median		33.44	63.51	67.72	35.69
Std. Deviation		64.47	75.85	75.70	75.48
Range		220.24	329.30	305.08	334.62
Minimum		15.52	8.95	15.49	7.02
Maximum		235.76	338.25	320.57	341.64
Percentiles	25	23.81	45.43	48.81	18.23
	50	33.44	63.51	67.72	35.69
	75	65.17	91.84	115.42	92.84
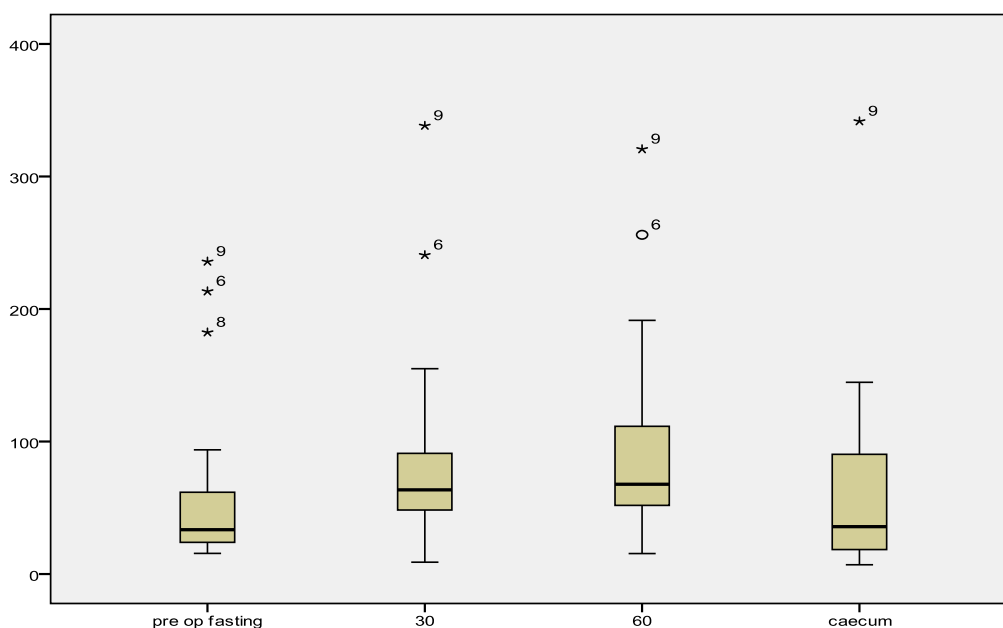
Figure 3-45: Box plot representing pre-operative meal-related response

X axis = time since food intake, Y axis = Insulin levels. Following meal intake insulin levels increased to 86.3+/-75.8 at 30 minutes and 95.3+/-75.7 at 60 minutes. Levels decreased to 63.4+/-75.4 when food reached in the caecum

Table 3-21: Post-operative meal-related insulin response

Lower fasting levels, exaggerated post postprandial response noted after RYGB. Levels (fasting 41.6+/-55.8, 30 minutes 110.2+/-67.5, 72.3+/-52.7 at 60 minutes, 38.4+/-47.8 when food in caecum)

		6 weeks fasting	30	60	caecum
N	Valid	22	22	22	22
	Missing	0	0	0	0
Mean		41.67	110.24	72.36	38.45
Median		16.46	97.85	62.62	22.02
Std. Deviation		55.88	67.52	52.70	47.88
Range		182.24	254.95	219.93	197.75
Minimum		6.10	21.08	13.70	0.00
Maximum		188.34	276.03	233.63	197.75
Percentiles	25	11.68	52.45	33.76	14.94
	50	16.46	97.85	62.62	22.02
	75	35.00	150.32	88.48	33.87
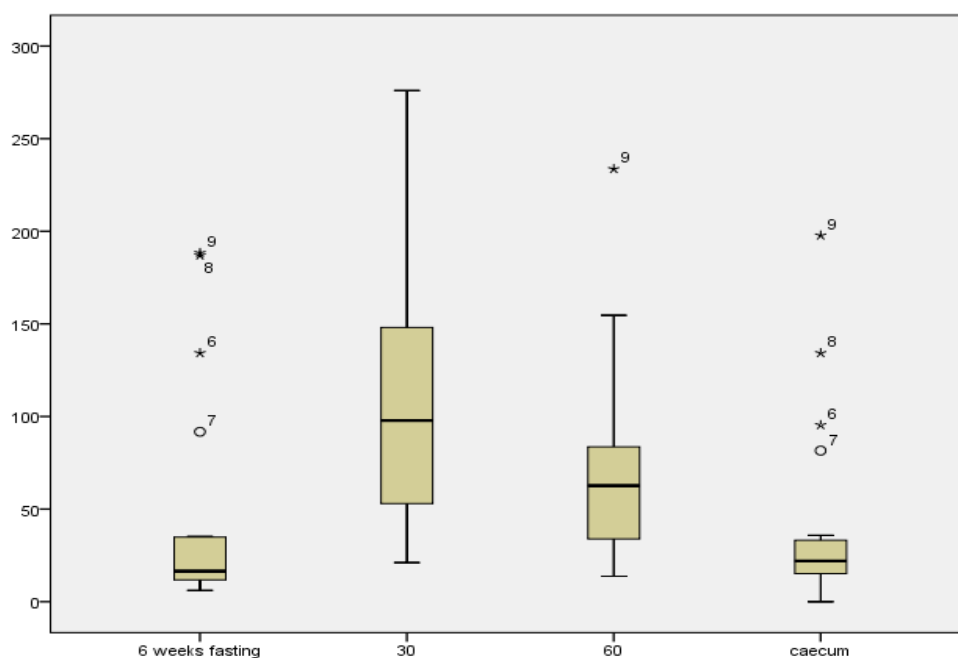
Figure 3-46: Post-operative meal-related insulin response

X axis = time since food intake, Y axis = Insulin levels. Exaggerated and early response of insulin after RYGB. Levels (fasting 41.6+/-55.8, 30 minutes 110.2+/-67.5, 72.3+/-52.7 at 60 minutes, 38.4+/-47.8 when food in caecum)

Table 3-22: Comparison of pre- vs. post-RYGB meal-related response

Post-operative meal-related insulin response was significantly higher compared to pre-operative meal-related response (all p values < than 0.05).

| | | | Paired Differences | | 95% Confidence Interval of the Difference | | | | |
		Mean	Std. Deviation	Std. Error Mean	Lower	Upper	t	df	Sig. (2-tailed)
Pair 1	pre-op fasting – 6 weeks fasting	19.04	20.85	4.45	9.79	28.28	4.28	21.00	0.00
Pair 2	30 – 30	-23.85	44.62	9.51	-43.64	-4.07	-2.51	21.00	0.02
Pair 3	60 – 60	22.95	44.31	9.45	3.30	42.60	2.43	21.00	0.02
Pair 4	caecum - caecum	25.04	36.59	7.80	8.81	41.26	3.21	21.00	0.00

2b. Change in insulin resistance following RYGB

Insulin resistance was calculated with **HOMA-IR method** = fasting insulin (mIU/L) x fasting glucose (mmol/L) / 22.5

Table 3-23: IR before and after RYGB

Decreased IR after RYGB. IR1= fasting IR before surgery, IR2= fasting IR 2 weeks after surgery, IR3= fasting IR 6 weeks after surgery. Fasting values (pre-operative fasting 30.0, at 2 weeks post RYGB 17.5, 6 weeks post RYGB 15.8).

		IR1	IR2	IR3
N	Valid	22	22	22
	Missing	0	0	0
Mean		30.07	17.51	15.82
Median		18.95	7.42	6.76
Std. Deviation		34.95	22.53	24.78
Range		133.89	83.15	85.05
Minimum		3.35	0.85	2.54
Maximum		137.24	84.01	87.59
Percentiles	25	10.09	4.65	3.10
	50	18.95	7.42	6.76
	75	30.78	19.28	12.18

Table 3-24: Comparison of pre- vs. post-RYGB IR

Significant improvement in IR after surgery at 2 weeks after surgery and 6 weeks after surgery compared with pre-op IR (p 0.03, < 0.01 respectively).

		Paired Differences							
				Std. Error Mean	95% Confidence Interval of the Difference				Sig. (2-tailed)
		Mean	Std. Deviation		Lower	Upper	t	df	
Pair 1	IR1 - IR2	12.56	25.53	5.44	1.24	23.87	2.31	21.00	0.03
Pair 2	IR1 - IR3	14.25	17.12	3.65	6.66	21.83	3.90	21.00	0.00
Pair 3	IR2 - IR3	1.69	18.71	3.99	-6.60	9.98	0.42	21.00	0.68
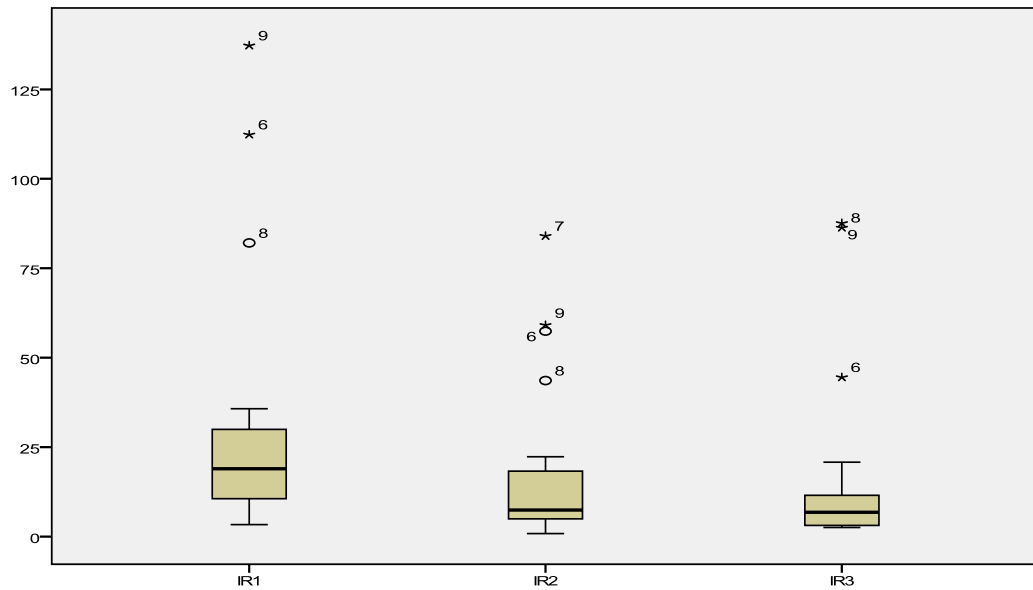
Figure 3-47: Box plot representing fasting IR before and after RYGB

X axis = Timing (IR1=pre operative, IR2=2 weeks, IR3= 6 weeks after RYGB). Y Axis = Levels. Significant improvement in IR after surgery at 2 weeks after surgery and 6 Weeks after surgery compared with pre-op IR (p 0.03, < 0.01 respectively).

3. <u>Change in ghrelin after RYGB</u>

		pre-op fasting	30	60	caecum
N	Valid	22	22	22	22
	Missing	0	0	0	0
Mean		789.19	801.98	716.73	777.28
Median		665.51	684.88	650.67	773.03
Std. Deviation		493.09	483.24	405.96	495.51
Range		2014.61	1639.01	1761.47	2054.10
Minimum		308.40	289.73	189.41	96.23
Maximum		2323.01	1928.74	1950.89	2150.33
Percentiles	25	434.17	417.83	456.02	383.96
	50	665.51	684.88	650.67	773.03
	75	944.46	974.55	824.64	953.45

Table 3-25: Pre-operative meal-related ghrelin response

Pre operative Meal related Ghrelin levels (fasting 789+/-493, 30 minutes post prandial 801+/-483, 60 minutes post prandial 716+/-405, food in caecum 777+/-495.
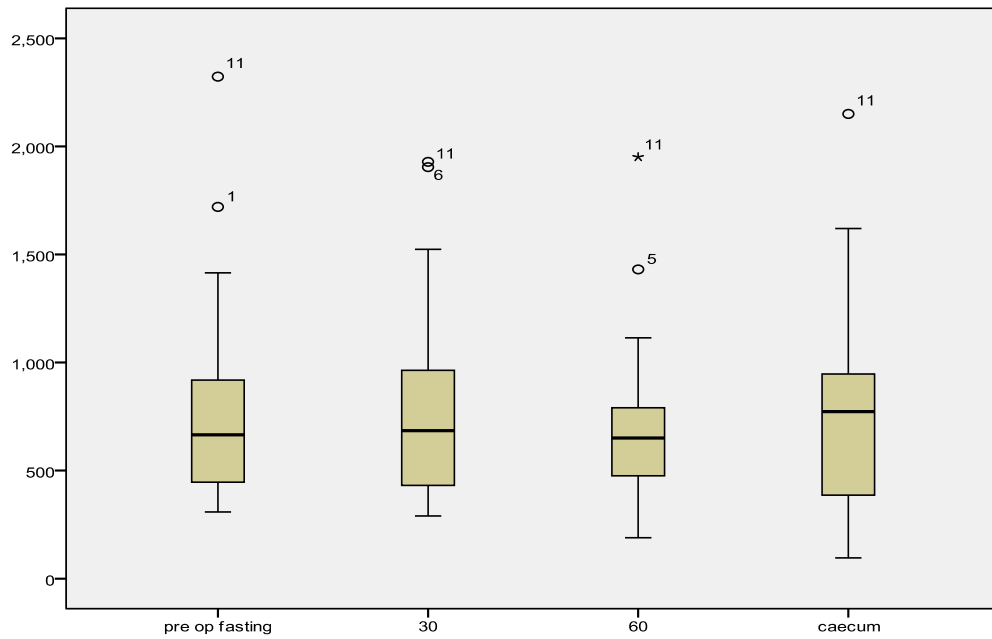
Figure 3-48: Box plot representing pre-operative meal-related ghrelin response

X axis= Timing in relation to food, Y axis = levels. Meal related response was blunted before surgery (p > 0.05)

Table 3-25: Fasting ghrelin levels before and after RYGB

A continuous decrease in fasting gherkin levels noticed at 2 weeks and 6 weeks after surgery. (Levels 789 vs. 599, 532 at 2 weeks and 6 weeks respectively)

		pre-op fasting	2 weeks fasting	6 weeks fasting
N	Valid	22	22	22
	Missing	0	0	0
Mean		789.19	599.99	532.17
Median		665.51	640.82	521.72
Std. Deviation		493.09	275.52	261.12
Range		2014.61	966.70	1271.86
Minimum		308.40	127.17	147.64
Maximum		2323.01	1093.88	1419.50
Percentiles	25	434.17	347.21	339.45
	50	665.51	640.82	521.72
	75	944.46	818.45	599.55
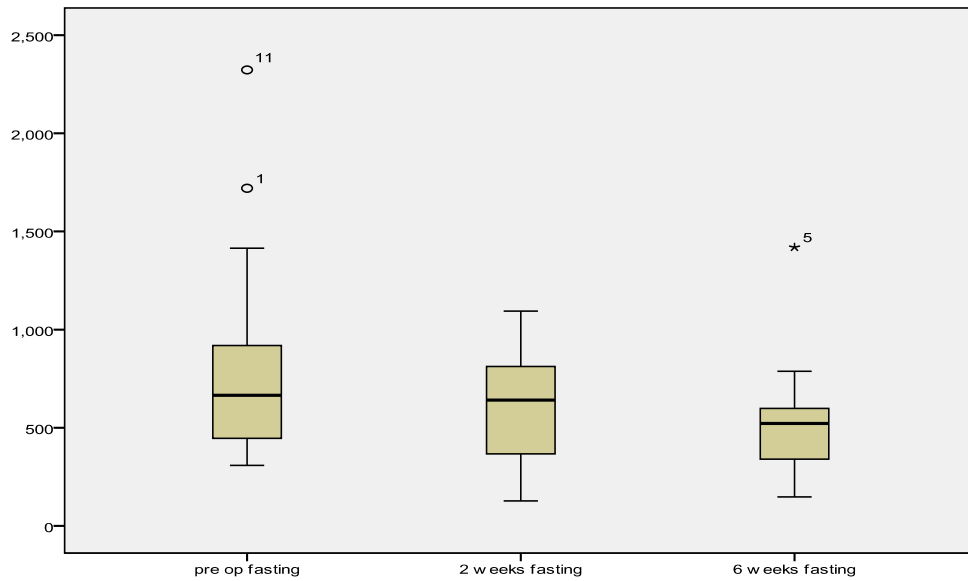
Figure 3-49: Box plot representing fasting ghrelin levels before and after RYGB

X axis = Timing in relation to food, Y axis = levels. A continuous decrease in fasting ghrelin levels noticed at 2 weeks and 6 weeks after surgery. (Levels 789 vs. 599, 532 at 2 weeks and 6 weeks respectively)

Table 3-26: Comparison of fasting ghrelin levels before and after RYGB

Significant decrease in fasting plasma ghrelin levels after surgery at 2 weeks and 6 weeks after surgery (p 0.05, 0.01 respectively).

| | | Paired Differences | | | | | | | |
| | | | | | 95% Confidence Interval of the Difference | | | | |
		Mean	Std. Deviation	Std. Error Mean	Lower	Upper	t	df	Sig. (2-tailed)
Pair 1	pre-op fasting – 2 weeks fasting	189.21	434.11	92.55	-3.27	381.68	2.04	21.00	0.05
Pair 2	pre-op fasting – 6 weeks fasting	257.02	424.71	90.55	68.72	445.33	2.84	21.00	0.01
Pair 3	2 weeks fasting – 6 weeks fasting	67.82	214.83	45.80	-27.44	163.07	1.48	21.00	0.15

Table 3-27: Post-RYGB meal-related ghrelin response

No significant change noticed on meal related response after surgery (fasting 523+/-261, 30 minutes 518+/-277, at 60 minutes 558+/-407, food in caecum 544+/-284).

		6 weeks fasting	30	60	caecum
N	Valid	22	22	22	22
	Missing	0	0	0	0
Mean		532.17	518.77	558.40	544.65
Median		521.72	466.13	431.66	485.45
Std. Deviation		261.12	277.37	407.35	284.22
Range		1271.86	1186.64	1905.67	1313.25
Minimum		147.64	138.76	147.64	244.15
Maximum		1419.50	1325.40	2053.31	1557.40
Percentiles	25	339.45	315.05	313.94	328.46
	50	521.72	466.13	431.66	485.45
	75	599.55	710.08	637.91	678.17
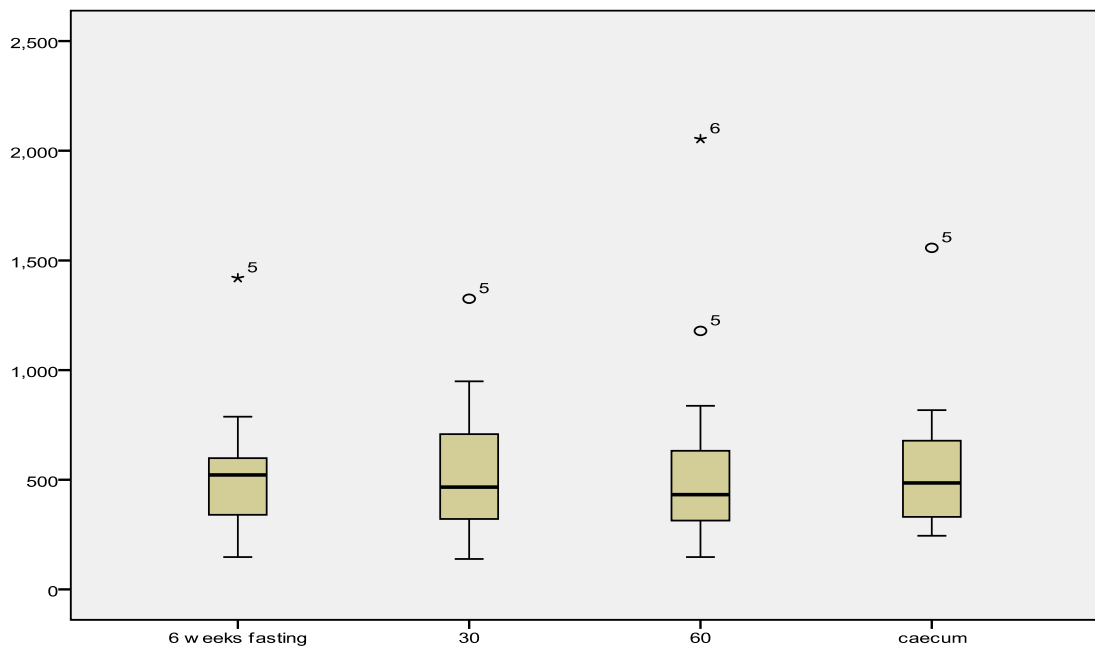
Figure 3-50: Post-RYGB meal-related ghrelin response

X axis = Timing in relation to food, Y axis = levels. Meal-related ghrelin response remained blunted after the surgery ($p > 0.05$)

Table 3-28: Comparison of pre- and post-RYGB meal-related response

Significantly lower levels of ghrelin at fasting, 30 minutes after meal intake and when food reached into the caecum were observed after RYGB.

		Paired Differences							
					95% Confidence Interval of the Difference				Sig. (2-tailed)
		Mean	Std. Deviation	Std. Error Mean	Lower	Upper	t	df	
Pair 1	pre-op fasting – 6 weeks fasting	257.02	424.71	90.55	68.72	445.33	2.84	21.00	0.01
Pair 2	30 – 30	283.21	401.80	85.66	105.06	461.35	3.31	21.00	0.00
Pair 3	60 – 60	158.33	431.22	91.94	-32.86	349.52	1.72	21.00	0.10
Pair 4	caecum – caecum	232.63	400.42	85.37	55.10	410.17	2.73	21.00	0.01

4. Change in GLP-1 following RYGB

Table 3-29: Pre-operative meal- related GLP-1 response

Highest levels of GLP were noticed at 60 minutes and decreased when food reached in the caecum.

		pre-op fasting	30	60	caecum
N	Valid	22	22	22	22
	Missing	0	0	0	0
Mean		4.96	4.56	5.74	5.05
Median		2.95	3.25	3.10	3.24
Std. Deviation		6.50	4.53	9.65	5.60
Range		29.77	19.62	46.24	25.32
Minimum		1.21	1.24	1.15	1.71
Maximum		30.98	20.86	47.39	27.03
Percentiles	25	1.75	2.54	2.40	2.57
	50	2.95	3.25	3.10	3.24
	75	5.52	4.14	4.67	5.53
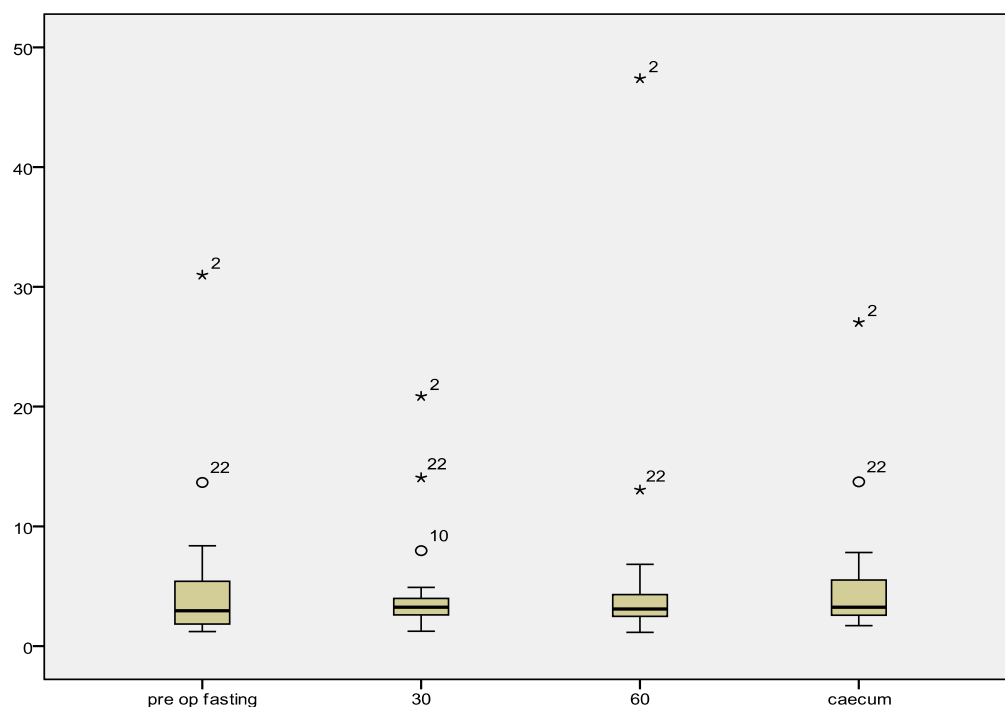
Figure 3-51: Box plot representing ppre-operative meal-related GLP-1 response

X axis= Timing in relation to food, Y axis = levels. Highest levels of GLP were noticed at 60 minutes (5.7+/-9.6) and decreased when food reached in the caecum.

Table 3-30: Fasting GLP-1 levels before and after RYGB

Fating GLP-1 levels continued to decrease following RYGB (mean values 4.96+/- 6.50 vs. 3.29+/-3.02, 3.03+/-4.76).

		pre-op fasting	2 weeks fasting	6 weeks fasting
N	Valid	22	22	22
	Missing	0	0	0
Mean		4.96	3.29	3.03
Median		2.95	2.52	1.94
Std. Deviation		6.50	3.02	4.76
Range		29.77	14.58	23.34
Minimum		1.21	0.82	0.42
Maximum		30.98	15.40	23.76
Percentiles	25	1.75	1.64	0.94
	50	2.95	2.52	1.94
	75	5.52	4.24	3.19

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Table 3-31: Comparison of fasting GLP-1 levels before and after RYGB

Significantly lower GLP levels at 6 weeks when compared with pre-operative fasting levels (p = 0.01).

| | | Paired Differences | | | | | | | |
		Mean	Std. Deviation	Std. Error Mean	95% Confidence Interval of the Difference		t	df	Sig. (2-tailed)
					Lower	Upper			
Pair 1	pre-op fasting – 2 weeks fasting	1.67	4.36	0.93	-0.26	3.60	1.80	21.00	0.09
Pair 2	pre-op fasting – 6 weeks fasting	1.92	3.14	0.67	0.53	3.32	2.87	21.00	0.01
Pair 3	2 weeks fasting – 6 weeks fasting	0.26	2.21	0.47	-0.72	1.23	0.54	21.00	0.59
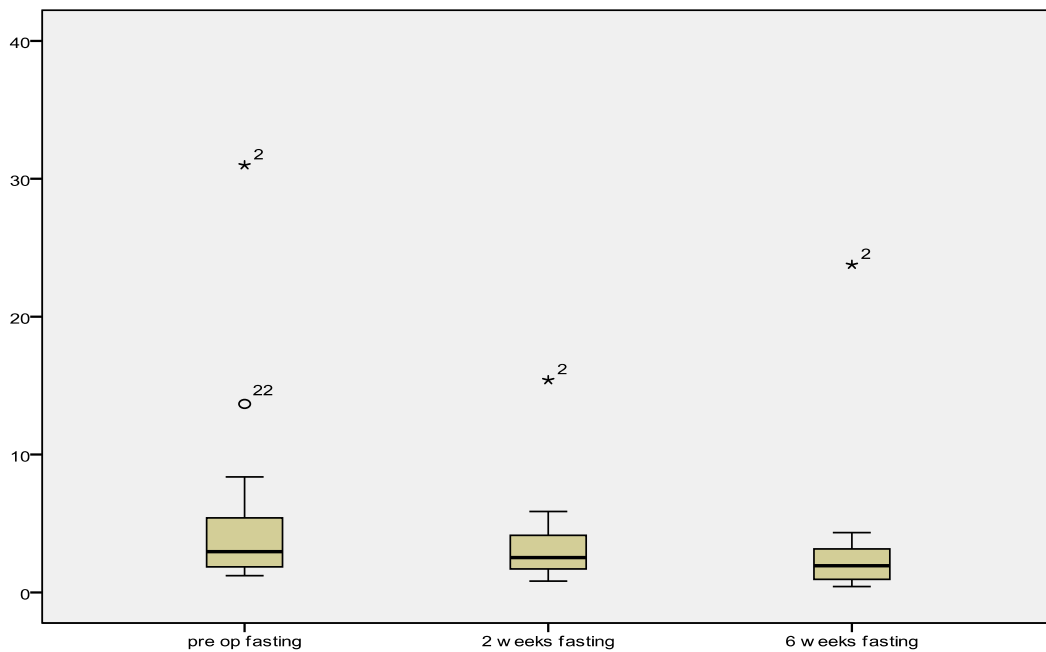
Figure 3-52: Box plot representing fasting GLP-1 levels before and after RYGB

X axis= Timing in relation to food, Y axis = levels. Fating GLP-1 levels continued to decrease following RYGB (mean values 4.96+/- 6.50 vs. 3.29+/-3.02, 3.03+/-4.76).

Table 3-32: Meal-related GLP-1 response after RYGB

Highest levels of GLP-1 noticed at 30 minutes after surgery (3.03+/-4.76, 13.53+/-7.90, 10.41+/-7.56, and 6.11 +/- 10.52).

		6 weeks fasting	30	60	caecum
N	Valid	22	22	22	22
	Missing	0	0	0	0
Mean		3.03	13.53	10.41	6.11
Median		1.94	10.80	7.78	4.04
Std. Deviation		4.76	7.90	7.56	10.52
Range		23.34	29.40	26.67	51.23
Minimum		0.42	1.54	1.57	1.19
Maximum		23.76	30.95	28.25	52.41
Percentiles	25	0.94	8.09	4.17	2.40
	50	1.94	10.80	7.78	4.04
	75	3.19	19.11	15.64	6.05
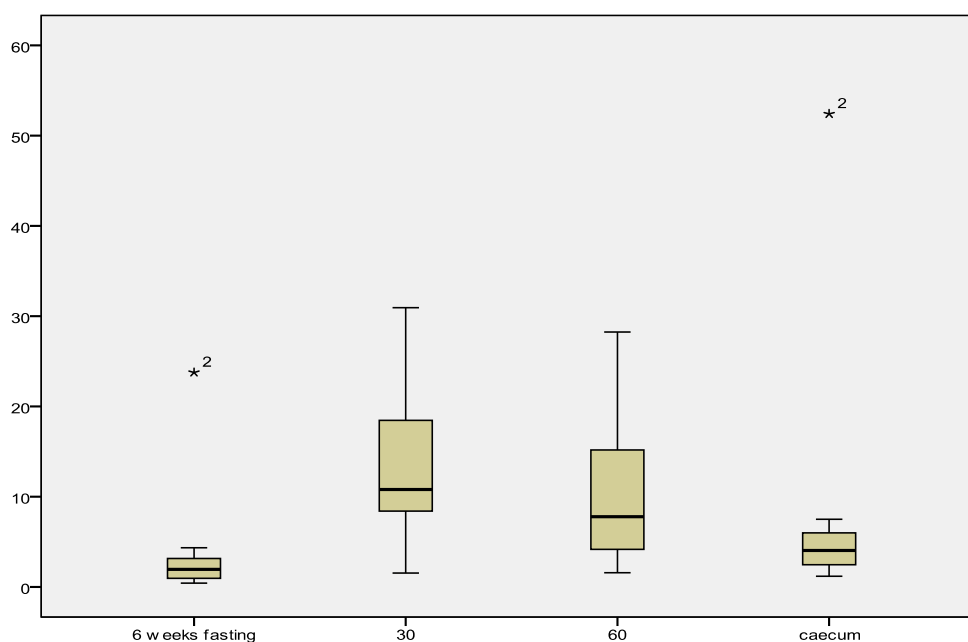
Figure 3-53: Box plot representing post-RYGB meal-related GLP-1 levels

X axis= Timing in relation to food, Y axis = levels. An early and exaggerated post prandial response after RYGB. Highest levels of GLP-1 noticed at 30 minutes after surgery (3.03+/-4.76, 13.53+/-7.90, 10.41+/-7.56, and 6.11 +/- 10.52).

Table 3-33: Comparison of pre- and post-RYGB meal-related GLP-1 levels.

Post-operative meal-related response was significantly early and exaggerated after RYGB (P values fasting 0.01, 30 minutes after meal intake <0.01, 60 minutes after meal intake 0.01).

		Paired Differences							
				Std. Error Mean	95% Confidence Interval of the Difference				Sig. (2-tailed)
		Mean	Std. Deviation		Lower	Upper	t	df	
Pair 1	pre-op fasting – 6 weeks fasting	1.92	3.14	0.67	0.53	3.32	2.87	21.00	0.01
Pair 2	30 – 30	-8.98	6.31	1.35	-11.78	-6.18	-6.67	21.00	0.00
Pair 3	60 – 60	-4.67	8.22	1.75	-8.31	-1.02	-2.66	21.00	0.01
Pair 4	caecum - caecum	-1.06	5.83	1.24	-3.65	1.52	-0.85	21.00	0.40

3.6 Discussion

3.6.1 Implications of change in GI motility on resolution of DM

It is suggested that GI motility and GE are closely related to obesity. This is based upon the fact that GI motility and GE deliver the nutrients into the small bowel. Altered GI motility in obesity is also speculated; however, in our systematic review of literature (Chapter 1, section 1.3) we have demonstrated mixed results in favour of altered (increase/decrease) or normal GE in obesity. A well-designed, controlled study is required to clarify this issue.

In our study the gastric half-emptying (T50) in 22 morbidly obese type 2 diabetic patients before surgery was 94 minutes. This is comparable with our departmental reference value for T50 = 99 minutes (based upon a study conducted upon 27 healthy normal weight, non-diabetic subjects).[147]

It is, however, important to note the post-operative (post-RYGB) findings of our study. A small-size gastric pouch was created during the surgery (size 50 ml). Although this restricted the food to be accommodated in the pouch, the pouch filled and emptied quickly (T50 = 21 minutes). It is also important to note that although the stoma of the pouch size was kept very small (1 cm), this did not entirely restrict the food from emptying into the jejunum. The possible explanations of quick pouch emptying are as follows:

1. Loss of pyloric control may result in pouch emptying under the influence of gravity.
2. The cylindrical narrow passage of the pouch may exhibit more tension on pouch wall compared to the wide pouch (like the original stomach), resulting in a quicker contraction to empty.

IT in obesity was not investigated in the past. Our study is a rare one of its kind to focus on IT in obesity and the first one to demonstrate the change in IT following RYGB. This is an important part of this study as we wanted to assess the hormonal response (ghrelin, insulin and GLP-1) along with the GE and IT. IT was normal in obesity (IT time 270 minutes). IT time was, however, quicker following RYGB (IT time 212 minutes); however, it has previously been demonstrated that there could be a very wide range of IT time and only extremes of the slow transit time should be considered significant.[160] The possible explanations of slightly fast post-operative IT may be as follows:

1. Bypassed stomach and loss of pyloric control resulted in early food entering into the intestine.
2. A small part of the small intestine was bypassed, which may have contributed to a relatively short intestinal segment for food to reach into the caecum.
3. It may have been influenced by enteric hormones influencing GI transit.

Early entry of food into the intestine may have several implications in the regulation of metabolism and the secretion of GI hormones. On the one hand, this may have resulted in early excitation of some of the foregut hormones; however, on the other hand, RYGB results in bypassing the metabolically active duodenum, and secretions from the pancreas, liver and bile. This may result in an overall decreased CCK, GIP and other

foregut hormones and, on the other hand, may have an excitatory effect on intestinal mucosa to secrete hormones necessary to absorb the nutrients.

The vagus nerve is the main afferent nerve supply from the GI tract to the brain; however, the role of this nerve in processing the nutritional information from the GI tract mucosa to the brain is not understood. It is therefore assumed that the vagus nerve has a very small role in processing this information and hormones like GIP and CCK are considered as the most potent hormones to detect glucose, lipids in the intestine and the regulation of nutritional capacity and absorption in the proximal small intestine. Bypassing the stomach and the metabolically active proximal small intestine, along with quick eating of food into more distal parts of the small intestine, will result in less exposure of food to the hormones. Glucose is, however, sensed by GIP-secreting cells and a quick response is generated in the form of exaggerated insulin release. GIP function is not effected by vagotomy and vagus stimulation;[144] therefore, glucose haemostatic function remains preserved following RYGB. It is possible that this function is enhanced because sudden glucose entry into the small intestine may result in an exaggerated proximal small intestinal hormone response compared to a pulsatile release after a controlled GE before RYGB.

3.6.2 Implications of change in gut hormones

The food is detected in the stomach by the muscle wall by stretch receptors and these signals are transmitted to the brain (the medulla, hypothalamus and cerebral cortex). These afferent fibres also innervate the mucosa of the stomach and the food in the stomach stimulates the gastric hormones like leptin and ghrelin. Ghrelin is considered as an appetite regulatory hormone, and a previous study by Le Roux et al[161] demonstrated that, in patients with post-vagotomy, the food intake was not stimulated by ghrelin. Food behaviour is an important factor in obesity and it plays an important role in obesity treatment. It is, however, interesting to note that the stomach can only detect the volume of the food, and the calorimetric analysis of the food is performed by the small intestine. With the findings that ghrelin possibly plays an important role in food and appetite regulation along with the twist that the stomach only regulates the volumetric aspects of food intake, bariatric surgery (RYGB) may show some interesting findings

when the stomach is bypassed along with, presumably, ghrelin-producing cells. Our study looked into these aspects as we investigated the change in fasting ghrelin levels along with the change in the meal-related response following RYGB.

GLP-1 was also the focus of our attention as it is considered as an incretin hormone. In addition, its role in ileal brake activity and its release is considered to be mediated by not only the direct contact of food with the L cells but also by neural reflux in the GI tract.[162, 163] The insulinotropic effect of GLP-1 has been studied in the past;[22, 159, 164, 165] however, there is very little data in support of its secretion in conjunction with GI motility. Similarly, ileal brake activity has not been studied completely. We looked into these aspects as we investigated the change in fasting GLP-1 levels along with the change in meal-related response in GLP-1 levels following RYGB. Ileal brake activity was studied indirectly as the last plasma samples for GLP-1 were taken when food was seen in the iliocaecal region directly observed by GI scintigraphy.

Results of our study were, however, very interesting as we also noticed a constant decline in ghrelin levels of 789.19 (fasting pre-op), 599.99 (fasting at 2 weeks after RYGB) and 532.17 (fasting at 6 weeks after RYGB) consistent with some previous studies;[98, 166, 167] however, the expected higher fasting levels in obesity (presumed satiety hormone) were not seen in our study as described by Cummings et al in their papers.[13, 142] The decrease in fasting ghrelin levels were statistically significant (p value 0.05, 0.01); however, these finding were contrary to the fact that most (90% or more) of the stomach was bypassed and the decline in ghrelin levels only reached a fraction of the expected (90% or more) decline. The possible explanations of these findings are that ghrelin may not be produced solely by the stomach and other parts of the GI tract or body may continue to produce ghrelin. Other possible reasons include hyperstimulation of the gastric pouch and/or bypassed stomach, which may still produce ghrelin as it may not be totally denervated (vagotmised) by RYGB. More work is required to prove or reject these hypotheses.

Pre-operative meal-related response of 789.19 (fasting), 801.98 (30 minutes following food intake), 716.73 (60 minutes following food intake) and 777.28 (food seen in the iliocaecal region) was blunted before surgery as none of these changes reaches a statistical significance. This finding is also contrary to the previous papers suggesting

higher fasting plasma ghrelin levels and proposed decrease levels after surgery suggesting the role of this hormone in satiety.[7, 13, 142, 168] In addition, we did not observe the higher expected fasting levels as we presumed that ghrelin levels would be high in a fasting state to demonstrate its role of being a satiety hormone. This may demonstrate that ghrelin is not a sole satiety signal but an important component of satiety mechanism. On the other hand, the lack of significant change following food intake could not be explained. Following surgery and a significant weight loss, improved IR and diabetic status were observed. At 6 weeks follow-up, meal-related ghrelin levels were as follows: 532.17 (fasting), 518.77 (30 minutes following food intake), 558.40 (60 minutes following food intake), 544.65 (food in the iliocaecal region). These findings were also consistent with the pre-operative findings, as the expected higher fasting levels were not observed and a blunted meal-related response was observed. This justifies more research in this field before including or excluding the role of ghrelin in obesity and the management of obesity. There was, however, a limitation of our research as we focused on the meal-related response of ghrelin and exogenous administration was not intended.

GLP-1 response, however, is very closely related to insulin, elaborating the incretin effect as reported in the previous studies.[9, 19, 26, 142, 159, 164, 169] There was a continuous decline in fasting GLP-1 levels noticed following RYGB as mean values decreased from 4.96 (pre-operative fasting levels) to 3.29 (2 weeks after RYGB fasting levels) and 3.03 (6 weeks after RYGB fasting levels). These changes were statistically significant ($p < 0.05$). Meal-related response before RYGB revealed the highest concentration when most of the food was in the small intestine (t 60 minutes after food intake). This response was, however, exaggerated and an earlier response (peak values) was observed after RYGB. This was in conjunction with early food entry into the small intestine observed with GI scintigraphy (GE and IT) as the gastric pouch emptied quickly. This is possibly mediated by the gut-brain-peripheral axis and considered to act as a paracrine hormone as short half-life may not make it possible to reach the beta cell receptors in the pancreas to secrete insulin. We noticed a very close relation/response of GLP-1 to insulin levels (before and after RYGB) as others have also reported the similar response; however, the use of GLP-1/GLP-1 analogue as a treatment option remains a question to be answered. This is because of its short half-life, easy degradability, availability in only injectable form and the dilemma of who will respond to this

treatment. NICE has therefore recommended to use GLP-1 analogues only as a second-line treatment option and to closely monitor HbA1c. If patients do not respond after 6 months, it is advised to withdraw this treatment. In a recent review by Burcelin et al,[169] the current evidence of GLP-1 in its therapeutic strategies was evaluated. It was concluded that more pharmacological evidence is required to validate GLP-1 as cardioprotective, beta cell-regenerative and anti-apoptotic functions.[169]

3.6.3 Role of GLP-1 as intestinal brake hormone

The inhibitory effect of food in the terminal ileum resulting in modulation of GE by pyloric control, gastric acid and other enteric peptides is called *ileal brake*. It is believed that GLP-1 acts as a potent mediator to enhance the ileal brake activity, which may play an important role in weight loss following bariatric surgery.[170] There is, however, no study to prove this theory that GLP-1 potentiates this important enteric reflex.[170] This is, in fact, based upon the studies showing the endocrine suppression by food in the ileum.[19, 171] It is also demonstrated that GLP-1 can completely eliminate the acid production in the stomach by vagus nerve stimulation.[19, 172] Schirra et al used GLP-1 receptor antagonist exendin and demonstrated that it markedly stimulated the pyloric contractility, suggesting that GLP-1 has an inhibitory effect on antroduodenal motility in addition to its insulinotropic effect.[32]

In our study, the last blood samples were taken when the food was seen in the terminal ileum/ileocaecal region. We wanted to assess the change in GLP-1 levels in conjunction with GI motility and food in iliocaecal region. Similarly we also wanted to assess the change in GLP-1 levels in conjunction to food in the iliocaecal region following RYGB. A continuous decline in GLP-1 was observed when the food was seen in the terminal ileum/ileocaecal region. This was not associated with any change in GE or intestinal motility before RYGB (Figure 3-30,Figure 3-31, Figure 3-36,Table 3-6) and post-operative early and exaggerated GLP-1 was not correlated to pouch emptying or IT (Figure 3-32,**Figure 3-32**Figure 3-36),(Table 3-8, Table 3-51, Figure 3-53)

3.7 Conclusions

1. GE may be normal in obesity, contrary to previous data suggesting impaired GE in obesity.

2. Post-operatively, the gastric pouch empties quickly, resulting in an early nutrient supply to the gut which potentiates the important incretin hormone GLP-1.

3. Although lower levels of ghrelin were observed following RYGB, they could not be causally related to the change in their production as opposed to gastric size and change in diabetic status.

4. This study has established the average IT time in morbid obesity (270 +/- 39 minutes) and that the IT time does not significantly change subject to the short segment of the small intestine bypassed during RYGB (post-RYGB IT transit time is 212 +/- 44 minutes).

5. Early and uncontrolled (lack of pyloric control) food delivery to the intestine results in an exaggerated GLP-1 response which potentiates the insulin-contributing resolution of diabetes following RYGB.

Limitations: It is, however, important to note the limitation of this study as we did not intend to use GLP-1/analogue or ghrelin analogue to see the pharmacological effect of these hormones on GI motility and change in diabetic status. In addition, we did not focus on the metabolic role of liver, muscles and fat (change in protein, fat and glucose metabolism); however, we feel that it is important to assess these functions at cellular levels as well as at hormonal levels to establish the improvement in diabetic status following RYGB. Furthermore, the important part of food restriction and the exclusion of the metabolically active duodenum (along with a change in other upper GI hormones) play an important role in the improvement of diabetic status. The impact of these changes on the hypothalamus and other food and satiety centres in the brain also needs to be explored.

4 Gastroparesis and modulation of gastric function

Excerpts of this chapter have been modified and published as:

Excerpts of this chapter have been modified and presented in ASGBI, ESSR

4.1 Definition

Gastroparesis is a chronic motility disorder of the stomach, defined by delayed GE of a solid meal in the absence of mechanical obstruction.

Although the epidemiology of the disorder is not well known, the majority of patients presenting with its symptoms are young and middle-aged women.[43] Gastroparesis in these patients interferes with oral drug absorption and impairs blood glucose levels, leading to further complications as a result of problems with ineffective blood sugar control.

Gastroparesis is a debilitating condition, which can reduce a functional individual to an existence tied to hospitals and emergency rooms. Gastroparetic patients have no good long-terms solutions and death can result from interventions and life-threatening

complications, such as electrolyte imbalance, dehydration and malnutrition. Soykan et al, in their analysis of 146 patients seen over 6 years in 2 centres,[173],[2] indicate that 10% of patients died during the follow-up period. They describe gastroparesis as "far from being a benign disorder".

4.2 Background and disease prevalence

The true prevalence of gastroparesis is not known; however, it has been estimated that up to 4% of the population experiences symptomatic manifestations of this condition.[174] Prevalence of gastroparesis is increased in diabetic patients and may occur in 30–50% of patients with diabetes mellitus (DM).[175,176]

The most frequently reported symptoms of gastroparesis include nausea, vomiting, early satiety and postprandial fullness. Abdominal discomfort and pain are also reported. Weight loss, malnutrition and dehydration may be prominent in severe cases.

In addition to having a highly negative impact on a patient's quality of life, gastroparesis is associated with significant costs both to patients and to healthcare services. In addition to the cost of drug therapy, patients with severe symptoms face repeated hospitalisations and often rely on expensive supplemental feeding.[177,178,179,180,181,182]

In 2002 Aamir et al reviewed medical charts of 236 patients with symptomatic gastroparesis and found that 24.8% of the patients were hospitalised at least once for symptoms of gastroparesis and 36.8% of those patients required 4 more hospitalisations. The same study reported that 18% of the studied patients stopped working because of their symptoms.

Hospitalisation was also highlighted in several clinical trials of Enterra Therapy. Forster et al[178] reported that gastroparesis patients involved in their study were hospitalised an average of 6 times in the year before Enterra Therapy treatment. The patients involved in McCallum et al's study were hospitalised for a mean of 31 days (range 0–200 days) in the year prior to Enterra Therapy treatment.

In addition to hospitalisation, many gastroparesis patients required regular nutritional report. The main categories of support are Total Parenteral Nutrition (TPN) or Parenteral Nutrition (PN). A few studies examined the cost of nutritional support in the UK and the USA from the health service perspective.[43] Their results clearly demonstrate that **nutritional support (even if delivered in a home setting) required very significant expenditure**. The alternative hospital treatment (TPN) is even more costly.

Finally, severe gastroparesis has a negative impact on the patient's ability to perform regular activities, including work. Revicki et al, in their 2003 study,[183] reported statistically significant positive correlation between patient-reported symptom severity (measured by the Gastroparesis Cardinal Symptom Index) and the number of disability days and number of days with restricted activity. **The lost productivity is an additional cost borne both by the patient (lost earnings) and society**. Furthermore, the majority of patients are young women who, in addition to professional work, would likely be responsible for caring for their children/family and who are unable to do so due to the disabling symptoms.

There is, therefore, a clear need for cost-effective alternative treatment for these severely sick patients who are not responding to current therapies and who could only be managed with nutritional support (which is expensive and carries a high risk of infection) or irreversible surgery.

Gastric electrical stimulation is a safe, reversible and cost-effective treatment alternative for patients suffering from chronic, drug-refractory nausea and vomiting secondary to gastroparesis. It has been shown to significantly:

- Reduce nausea and vomiting and improve quality of life.[184,178,179,182, 185,186,187, 188,189,90]

- Improve glucose control in diabetic patients.[189,185,179]

- Reduce the use of nutritional support and health care costs needed for hospitalisations.[184,178,179,180,182,186]

4.3 Types of gastroparesis

Gastroparesis can result from several causes. The three most common aetiologies are: DM, gastric surgery involving vagotomy and idiopathic (no identified cause).[173]

Diabetic gastroparesis: Gasatroparesis in diabetic patients has been well documented. Most often it affects patients with long-term diabetes. This may result in poor glycaemic control, persistent nausea and vomiting, which may lead to poor overall nutritional status and worsening of DM.[185]

Post-surgical gastroparesis:
Post-surgical delayed GE is another problem which clinicians face in day-to-day practice. Treatment is based on medical therapy including prokinetics and antiemetics. Some of them require long-term enteral or total parenteral feeding. Drug-refractory post-surgical gastroparesis can be treated with gastric electric stimulation (GES).[190,191,192]

Post-surgical gastroparesis has been treated successfully in some centres in the world. In one study,[191] six post-RYGB patients developed gastroparesis. They were treated successfully with GES and it resulted in improved symptoms of nausea and vomiting. Furthermore, improved GE was also recorded.[191]

In another study,[190] gastric electric stimulators were implanted in patients with gastroparesis after gastric surgery for various reasons. This study revealed improved nausea, vomiting, quality of life and GE after a long-term follow-up.

Post-esophagectomy delayed GE was treated with GES in two patients.[192] Improved symptoms (including nausea, vomiting and total symptom score) were recorded after GES.

In such drug-refractory post-surgical gastroparesis, the only other option is completion gastrectomy, which carries significant morbidity and mortality,[190] and it is suggested that GES should be considered in such patients.[190, 192]

Idiopathic gastroparesis: Idiopathic gastroparesis is diagnosed in patients with no cause of gastroparesis identified on extensive investigations.[193, 194] The role of gastric neuromodulation in such patients has been described in published literature.[43, 189, 195]

4.4 Nutritional and economic implications of gastroparesis

In up to 40% of the patients with gastroparesis, however, drugs are ineffective or intolerable.[173,184] Treatment options for these drug-refractory patients include nutritional support (feeding tube and total parenteral nutrition (TPN), which poses a high financial burden), or gastrectomy as final resort. Soykan et al[173] showed that 22% of their patients required short- or long-term parenteral feeding via laparoscopic placement of a jejunostomy tube for nutritional support at some point during the study. The systematic review of surgical therapy for gastroparesis from Jones et al[196] shows that in some reported publications, 55% of patients undergoing gastrectomy needed admissions and subsequent surgeries. They also report a paper showing 23 complications requiring hospitalisation among 14 of 26 diabetic patients treated with surgical jejunostomy. The main categories are support (TPN and delivery of nutrients directly to the bloodstream). A few studies examined the cost of nutritional support in the UK and the USA from the health service perspective.[43] Their results clearly demonstrate that nutritional support (even if delivered in a home setting) required very significant expenditure. The alternative hospital treatment (TPN) is even more costly.

4.5 Current treatment options

4.5.1 Medical

There is currently no cure for gasteoparesis. The primary goals of existing treatments are symptom relief, and restoration and maintenance of adequate nutrition. Current treatment options include dietary modifications and the use of drugs (prokinetics and antiemetic). In up to 40% of the patients, however, drugs are ineffective or intolerable.[173, 184]

4.5.2 Nutritional

Treatment options for these drug-refractory patients include nutritional support (feeding tube and total parenteral nutrition (TPN), which poses a high financial burden), or gastrectomy as final resort. Soykan et al[173] showed that 22% of their patients required short- or long-term parenteral feeding via laparoscopic placement of a jejunostomy tube for nutritional support at some point during the study. The systematic review of surgical therapy for gastroparesis from Jones et al[196] shows that in some reported publications, 55% of patients undergoing gastrectomy needed admissions and subsequent surgeries. They also report a paper showing 23 complications requiring hospitalisation among 14 of 26 diabetic patients treated with surgical jejunostomy.

4.5.3 Gastric neuromodulation

GES is achieved by delivering low-energy, high-frequency electrical stimulation (about 4 times that of the stomach basal rate) to the lower part of the stomach via an implantable system. Although the exact mechanism of the action is unknown, the possible explanation for efficacy of GES is the following:[197]

•   Increase in GE.

•   Enhancement of fundic relaxation (accommodation).

•   Decrease in gastric sensitivity.

•   Enhancement of postprandial gastric slow-wave amplitude and velocity.

•   Activation of afferent sensory pathways to central mechanisms for nausea/vomiting control.

•   Alteration of cholinergic/sympathetic pathways.

The first report of cholinergic gastric pacing (high-energy, low-frequency stimulation) was published in the 1960s. GES with Enterra Therapy has been available in Europe since 2002.

Indication: GES is indicated for patients with severe symptoms who do not respond to conventional therapy for gastroparesis. It has been proven to be both safe and effective in long-term studies.[158, 186, 188, 190]

Procedure: The Enterra GES system (the only such commercially available product) consists of implantable components (two intramuscular electrodes and a battery-

powered neurostimulator, called an *IPG or* (*Implantable Pulse Generator*) and a non-implantable physician programmer (see pictures below showing an IPG and electrode).

Figure 4-1: IPG and electrode

Implantable IPG, elcrode wire (one end to be attached to IPG and other end in submucosa).

The system can be implanted using by way of laparotomy or laparoscopy – the decision depends on the physician's choice and the patient's medical history and status. The implantation is performed under general anaesthesia and should take around one hour. The two electrodes are fixed to the muscle layer of the great curvature of the gastric antrum approximately 10 cm above the pylorus and 1 cm away from each other. They are connected to the IPG, which is placed in a subcutaneous pocket in the abdominal wall (typically the upper right quadrant). Following the implantation and patient's recovery, the system is switched on. The rate and amplitude of the current can be non-invasively adjusted to optimise treatment for each patient.

Clinical benefits: Several clinical studies have demonstrated that GES therapy is a safe and effective treatment for chronic refractory nausea and vomiting associated with gastroparesis.

•   The therapy significantly improves symptoms of gastroparesis (chronic nausea and vomiting) and patients' quality of life (QOL) and these benefits are sustained in the long term (up to 10 years).[178-180, 182, 184, 187]

•   GES therapy reduces the use of drugs (prokinetices and antiemetic) and the need for hospitalisations.[178, 180-182]

•   GES therapy is superior to drugs in improving GI symptoms, healthcare resources and long-term healthcare benefits.[182]

•   GES therapy produces significant improvement in patients' nutritional status (increased body weight and BMI) and reduces the need for nutritional support. This benefit is also sustained in the long term (up to 5 years).[178, 179, 185, 186, 198]

Long-term GES therapy is a safe treatment option with a low rate of complications. This is particularly impressive given that patients suffering from severe gastroparesis are at high risk of infection due to malnutrition, skin contamination from enteral tube and ostomies, and the systemic effect of DM.

GES with Enterra therapy is completely reversible – if the device is unavoidable, it can be safely explanted.

Symptom relief: Reported symptom improvement following GES therapy (reduction in nausea, vomiting or total symptom score) is greater than 50% in almost 80% of patients.[184,178, 179, 186, 187, 189] In some studies, the improvement was as high as 90%.[184]

It has been reported that GES therapy could be an effective therapy for treating chronic severe vomiting and nausea whether GE is delayed or not as there seems to be no correlation between symptom improvement and improved GE.[180, 184-187]

Reduction in hospitalisation: In a study of 37 patients, Lin et al[181] showed that hospitalisation days decreased from 31 days to 14 days at one year post-implantation with 29% of patients requiring no admission, and further decreased to 6 days at 3 years with 69% of patients requiring no admission. The major reasons for hospitalisation prior to the implant surgery were complications of gastroparesis. After surgery for GES therapy, the admissions were explained by complications of diabetes (poor glucose control, ketoacidosis and infection), some recurrence of nausea and vomiting, feeding tube complications or infection or injury at the pulse generator site.

In a study of 18 patients (9 patients on drug therapy and 9 patients on GES therapy), Cutts et al showed that GES did significantly reduce hospital days, with a decrease from a baseline means of 36.4 to 2.76 days per year at the end of 36 months [182]

In a study of 16 patients, McCallum et al[90] showed that hospitalisation for gastroparesis symptoms decreased from 31 for the year before receiving GES therapy to 6 during the first year of GES. 8 patients (50%) required no hospital admissions.

In a study of 55 patients, Forster et al[178, 179] showed that days spent on hospital admissions were significantly decreased. For the year prior to placement of the GES, the average for days spent hospitalised was 57 and this fell to 17 the next year. This reduction alone could explain much of the patient's improvement in their QOL.

Reduction in nutritional support and weight gain: Lin et al[180, 181] showed that the need for nutritional support decreased from 15 patients (out of 37) at the baseline to 8 patients at one year after implant and to 5 patients at 3 years after implant. Moreover, no patient was receiving TNP after receiving GES. Compared to the baseline, the median

body weight significantly increased at 12 months and was maintained beyond 3 years of GES.

McCallum et al [90] showed that at implantation, 7 out of 16 patients required nutritional support in the form of a feeding jejunostomy tube but that of these 7 patients, 4 were able to discontinue the jejunal feeding at 2, 4, 6 and 11 months after GES, and 3 still required supplemental feeding at 12 months. They also showed that average body weight increased by more than 3 kg at 6 months and continued at 12 months.

Forster et al [178, 179] showed that BMI and body weight increased significantly. In terms of nutritional parameters, the patients' average body weight increased by almost a kilogram and the BMI by 0.4 units. The majority of patients had their jejunal feeding tubes removed by one year and no one was receiving TPN. Of the 25 patients who had a jejunal feeding tube (1 had a gastrojejunostomy) after placement of the GES, only 8 (32%) required this feeding approach at 12 months.

Reduction in the use of drugs: Lin et al[185,180] showed that the need for medication decreased. 29 patients (out of 35) were at least one prokinetic at baseline and 14 of these 29 patients were off prokinetic after 3 years of GES. Similarly, 25 of these 35 patients requiring at least one antiemetic (10 patients on two antiemetic and two on three) at baseline decreased to 19 (one on three antiemetics).

Current practice: Is the technology currently being used?
The technology has been used both in the NHS and private hospitals and currently the following UK centres are offering this therapy: Broomfield Hospital, Broomfield; Chelmsford/Royal Free Hospital, London; Aberdeen Royal Infirmary, Aberdeen; Glasgow Royal Infirmary, Glasgow; BMI Ross Hall Hospital Glasgow, Glasgow; and Cork University Hospital, Wilton.

GES is not a national priority. However, improved glucose control in patients with diabetic gastroparesis (one of the clinical benefits of the GES therapy) is a key priority of many diabetes programmes, such as the Diabetes National Service Framework. Moreover, reduction in healthcare expenditure by reducing patients' need for

hospitalisation, nutritional support and drug use is a priority for all European healthcare systems.

NICE Guidelines: NICE issued the Interventional Procedure Guidance (IPG103) in December 2004. It stated the following:

1 – "Current evidence on the safety and efficacy of gastroelectrical stimulation for gastroparesis does not appear adequate to support the use of this procedure without special arrangement for consent and for audit or research".

There have been many publications since the NICE guidance issue of 2004. Long-term safety and efficacy of Enterra therapy has been reported in several publications.[182-184, 188, 190] At the time of the NICE guidance publication, only one major publication was available.[186]

1. "The procedure should only be performed in specialist gastroenterology unit with expertise in gastrointestinal motility disorder".

2. "This therapy is indeed only performed in specialized centres".

3 "Current evidence on efficacy of the procedure relates mainly to relief from nausea and vomiting and that there was little evidence that the procedure improves gastric emptying".

GES therapy is indeed indicated for the relief of the symptoms of gastroparesis (mainly nausea and vomiting) and literature did demonstrate that symptom improvement does occur even if GE remains delayed.[178, 179, 184, 185, 187] There is no correlation between improved GE and symptom improvement. Symptom improvement is what drives improved quality of life in these patients and is what reduces healthcare costs.

A recent publication stated that Enterra therapy could be an effective treatment for the debilitating symptoms of chronic severe nausea and vomiting whether GE is delayed or not and even advocates the use of this therapy for non-gastroparetic patients with these debilitating symptoms.[197]

Finally, the significant benefit to diabetic patients has already been discussed previously in this document (improvement in symptoms and better glucose control,[179, 182, 185, 187]

and the possibility to even undergo transplant surgery[195, 199]). In their recent publication, Anand et al[188] showed that the survival rate was lower for diabetic patients not implanted with a GES device than the survival rate of diabetic patients implanted with a GES device.

GES therapy is the only available treatment to patients suffering from chronic nausea and vomiting (secondary to gastroparesis) for whom conservative therapy has failed and who do not want to undergo the irreversible gastrectomy. Given that gastrectomy is associated with very high morbidity and mortality, an increasing number of specialists agree that it should no longer be considered as a viable treatment option. Therefore, GES therapy ranks high as a treatment option for this debilitating and expensive condition.

4.6 Setting up new service and approvals

The provision of the GES service was not available in Castle Hill Hospital, Cottingham. Therefore the study proposal was prepared on the basis of background studies and published data as explained in the earlier parts of this chapter.

The proposal was submitted to a new appliances committee, trust finance committee, and medical director. It was approved based on principles that the funding will be applied to a PCT on exceptional treatment panel circumstances and procedure will be conducted in patients subject to the availability of funds.

Proposal for consideration: We would propose to use GES therapy in the treatment of patients with chronic intractable nausea and vomiting secondary to gastroparesis. GES would be offered to patients who failed or could not tolerate pharmacologic therapy before the irreversible surgery (gastrectomy). Moreover, due to the high risks of infection and the costs associated with supplemental feeding (enteral and parenteral nutrition), GES therapy should be considered before those treatments are offered.

Staffing or service implications (for new and developing centres): Appropriate surgeons underwent training in the technique of implantation and relevant staff underwent

training in the subsequent follow-up of implanted patients. The temporary GES facilities were set up in the endoscopy department with access to a double lumen endoscope and the permanent procedure would be conducted in an operating theatre under general anaesthesia. The nursing staff were also provided with necessary training and familiarised with the equipment. This training was provided by Medtronic and the surgical team.

Cost estimate for GES therapy: The price for a complete Enterra system is £8,250 (1 implantable pulse generator costing £4,500 + intramuscular leads kit costing £3,750). This is exclusive of VAT (20%) and carriage.
Surgical and hospital costs were added on top of this.

How does the treatment compare with those (of the general type) from other clinical areas?

GES therapy is indicated for severely sick patients with no good long-term solutions. Therefore, the treatment should be seen as comparable to other life-saving interventions offered to patients with chronic diseases. As stated by Soykan et al,[173] gastroparesis is "far from being a benign disorder" as 10% of their patients thought during the follow-up period. It is an extremely debilitating disorder that greatly impacts patients' QOL and carries a high risk of mortality, which can result from interventions and life-threatening complications, such as electrolyte imbalances, dehydration and malnutrition. Gastroparesis is also associated with significant financial burden, both for patients and taxpayers.

Based upon this information, the first 6 patients underwent temporary GES and their data was collected prospectively over a period of 7 days. After confirmation of the beneficial effects of GES, the funding applications were prepared and sent to the corresponding PCTs for approval.

4.7 Methodology

Six patients, (M:F=4:2, mean age 49, range 44–57 years) underwent the procedure. Three patients had confirmed slow GI transit. Aetiology included previous gastric

surgery in two, DM in one and idiopathic nausea and vomiting in three patients. Gastric neuromodulation (GNM) pacing wires were placed endoscopically and left in situ for 7 days. Patients underwent GS before and 24 hours after the commencement of GNM. Total gastroparesis symptom score (TSS), vomiting frequency score/week (VFS), health-related quality of life (QOL) using SF12 questionnaire, GE, nutritional status and weight were compared before and after GNM.

4.7.1 Patient selection and assessment

Patients with refractory nausea and/or vomiting who failed to respond to medical treatment and who were not found to have any correctable pathology were selected for consideration of GNM (Table 4-1). At least one of the two symptoms had to be severe and associated with nutritional or QOL impairment to be included for the procedure. The patients were investigated to exclude mechanical gastric outlet and bowel obstruction by endoscopy and radiological investigations including plain abdominal radiograph, CT scan and/or contrast studies. All patients had an initial trial of antiemetic and or prokinetic drugs for at least six months. After a failure with medical treatment, they were considered for a trial of temporary GNM. Baseline data such as TSS, VFS, QOL using SF12 and nutritional status were assessed in the selected patients. TSS is the sum of 5 four-point categorical scales (0 for absent up to 4 for extremely frequent and extremely severe) for symptoms such as vomiting, nausea, early satiety, bloating and abdominal pain. In addition, all the patients underwent a standard gastric scintigraphy before GNM.

Detailed descriptions of the clinical problems of these patients are as follows:

Patient 1: This 57-year-old gentleman underwent surgery (gastrojejunostomy) for an annular pancreas in 1998. Later on he had persistent symptoms necessitating surgeries including gastrectomy and RYGB in 2001 and refashioning in 2004. He had multiple inpatient admissions and outpatient follow-ups for nausea, vomiting, bloating, tiredness and early satiety. He required nutritional support and yet struggled to put on/maintain his weight. He was investigated and confirmed not to have mechanical obstruction on numerous occasions. He required prokinetics and antiemetics and was unable to eat and drink properly. Pre-operative investigations confirmed delayed gastric half-emptying

with a time of 514 minutes (Figure 4-2). A detailed description of gastric symptom severity score (GSS) is described below (Table 4-2, Table 4-8).
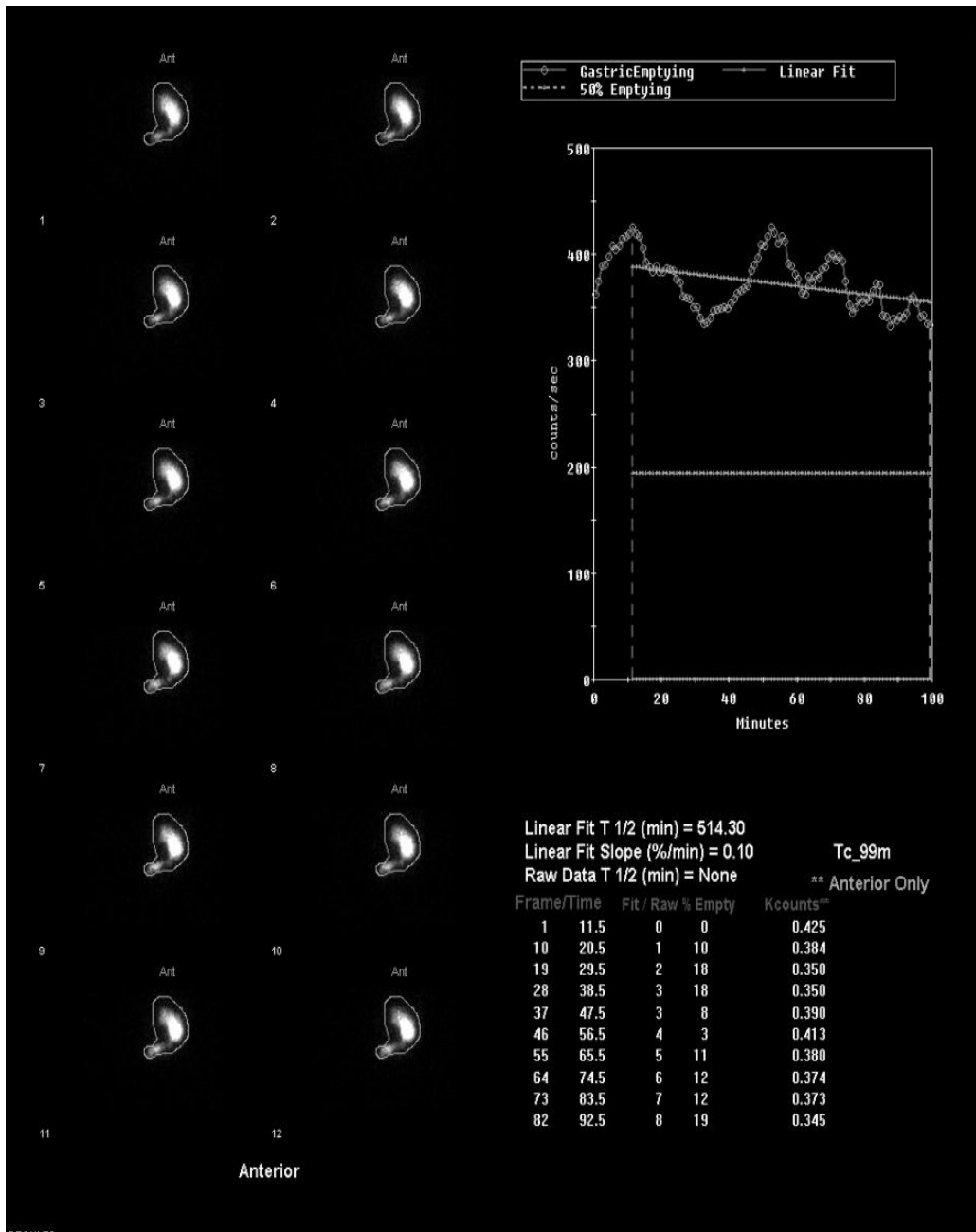
Figure 4-2: Patient 1, pre-GNM GE

Half-emptying time very prolonged (514 minutes).
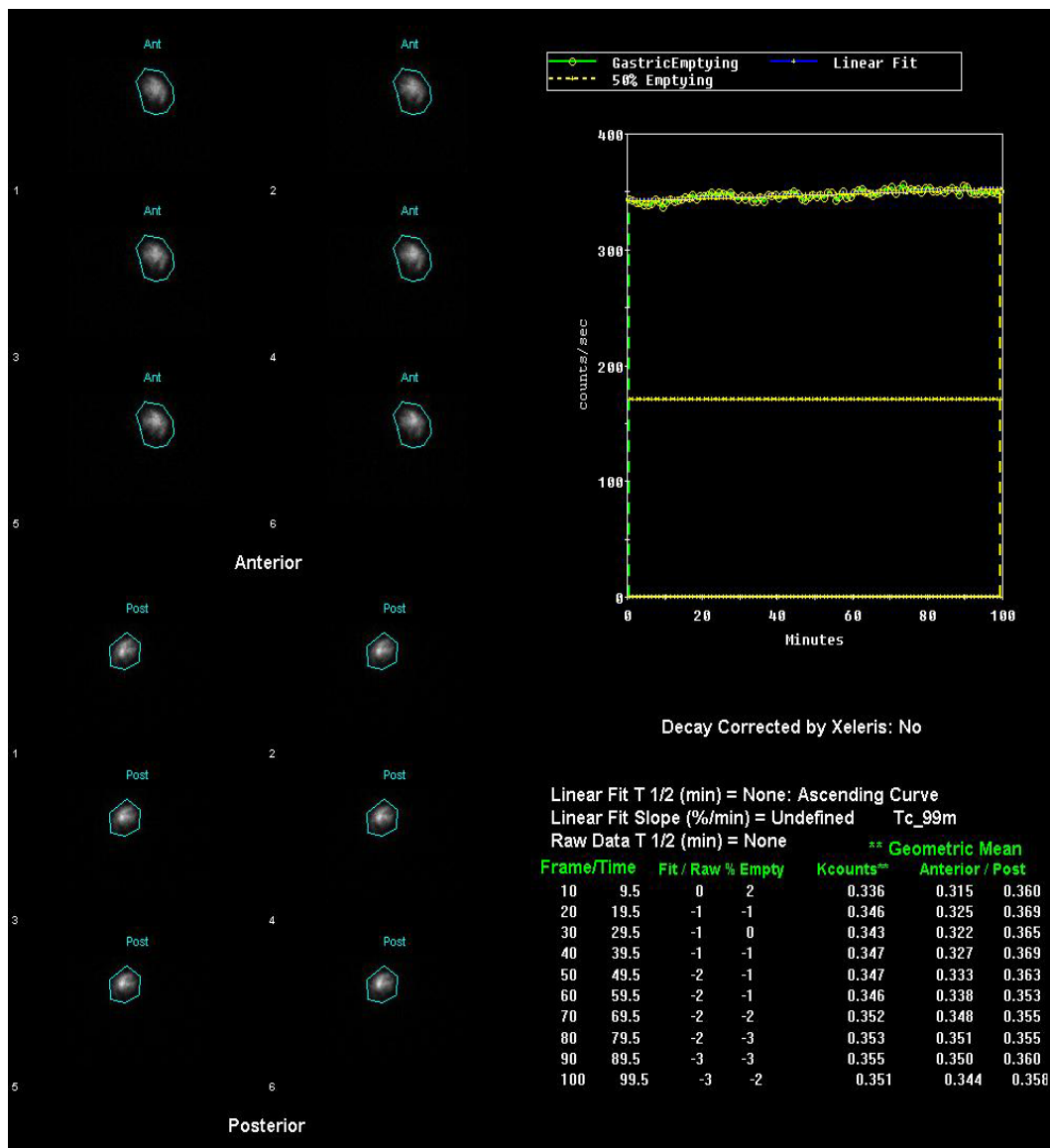
Figure 4-3: Patient 1, post-GNM GE

No change observed after GNM.

Patient 2: A 40-year-old gentleman with long-standing gastrointestinal dysmotility. He underwent an ileostomy in 2005 for intractable slow transit. Ileostomy output reduced over the period and was working only 2–3 times a week. He suffered from nausea, vomiting (20–40 times a week), bloating, early satiety and abdominal pain. He took Domperidone, an antiemetic and a very large dose of Movicol.

His work and social life was significantly limited. He had six admissions to the hospital in one year and was extensively investigated. There was no mechanical obstruction found on CT scan and other contrast studies. Subsequent GE studies revealed prolonged

GE, half-emptying time 104 minutes, (Figure 4-4) and he was considered suitable for GNM. Pre-operative GE and GSS symptoms are explained below in Table 4-3 and Table 4-8.
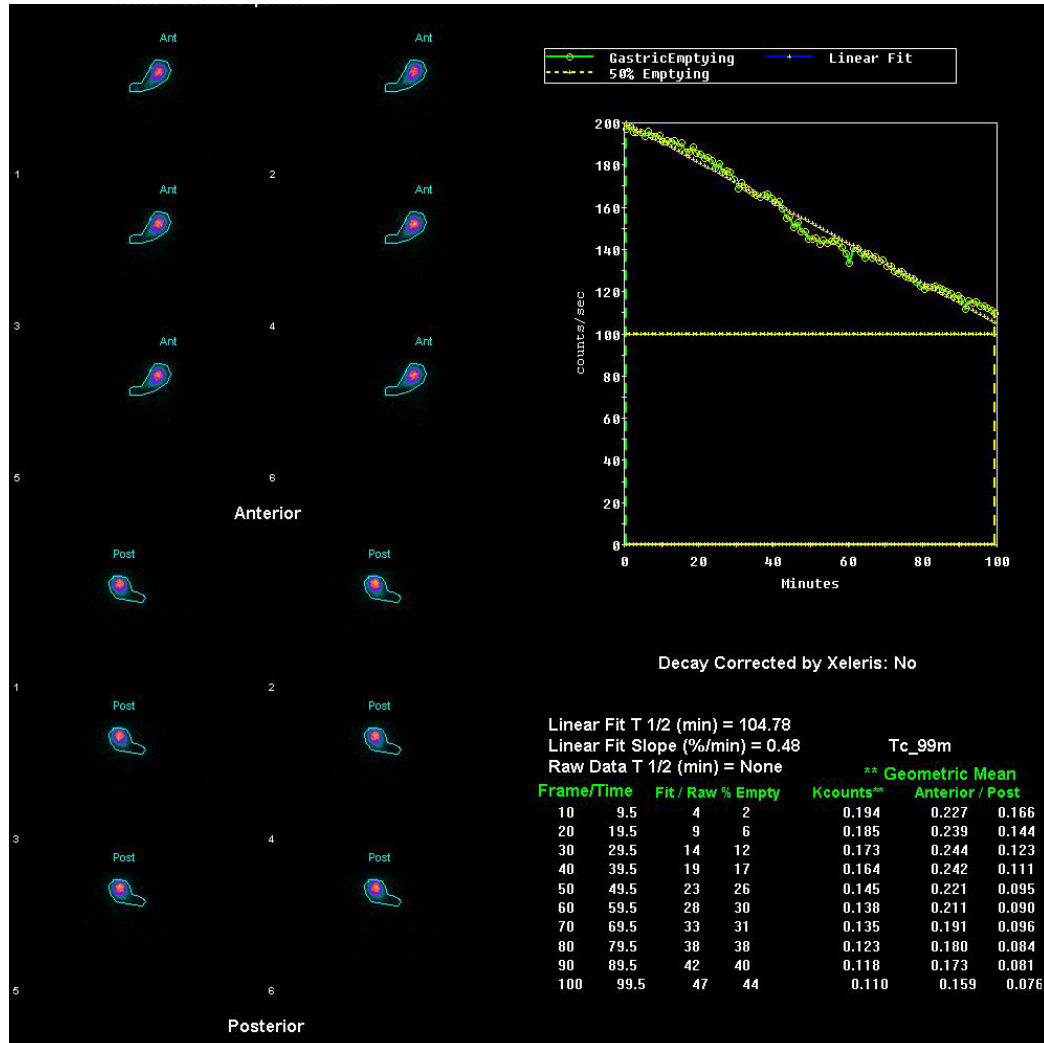
Figure 4-4: Patient 2, pre-GNM GE

GE half emptying (T50) time 104 minutes.
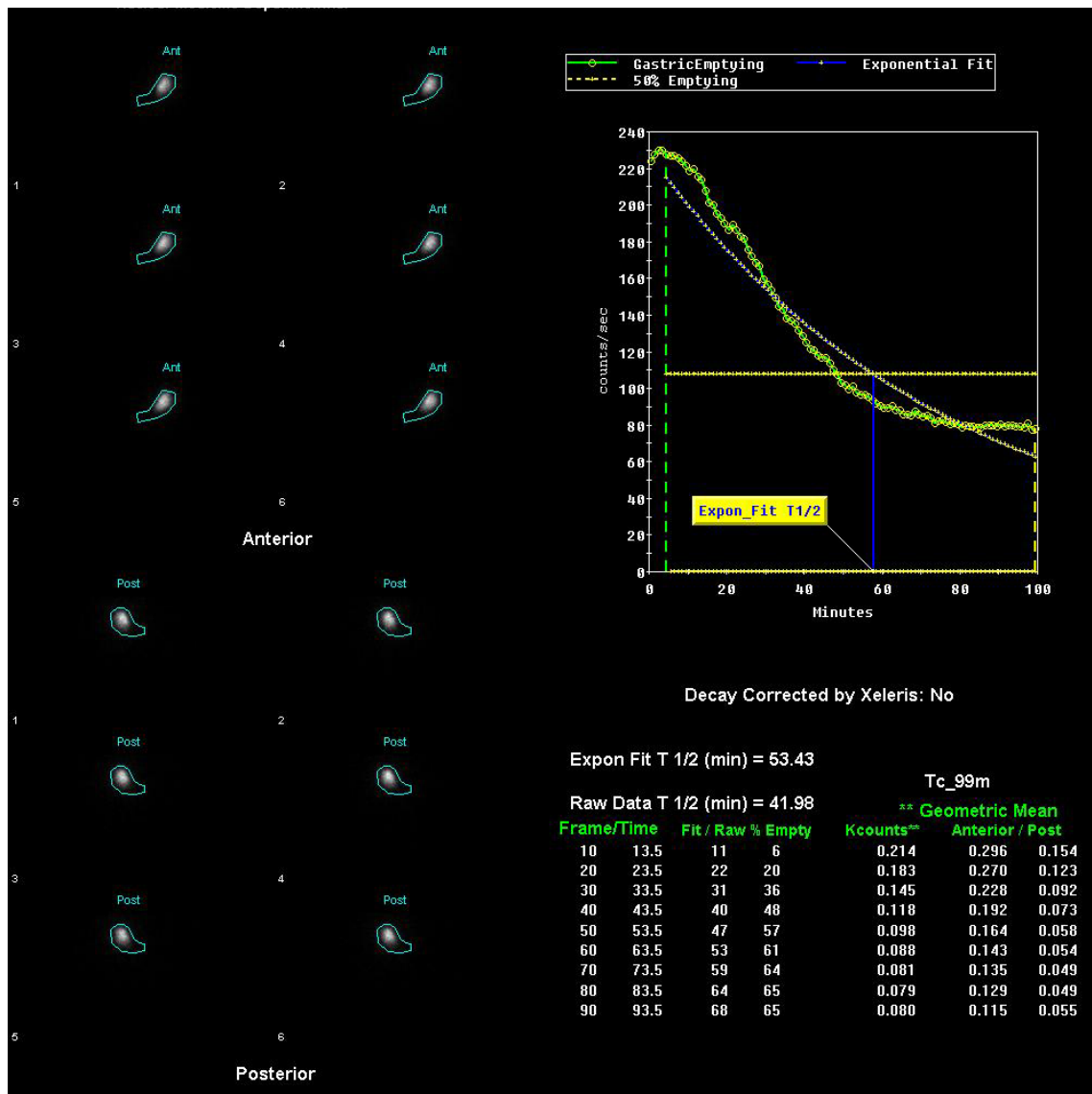
Figure 4-5: Patient 2, post-GNM GE

Post-GNM T50=53 minutes.

Patient 3: This 44-year-old gentleman presented with a long-standing history of nausea, vomiting and weight loss. He had lost 18 kg in weight and vomiting frequency was at least 20 times a week over the last four years. This had significantly limited his work and social life. He was on regular antiemetics and prokinetics without much success. He was extensively investigated under an upper GI surgeon. He had a CT scan, small bowel studies, oesophageal manometry and GE studies. All the investigations were inconclusive and based upon the nuclear scan and barium studies he was diagnosed with slow GI transit (gastroparesis). He was therefore considered suitable for GNM. His GE (Figure 4-6Figure 4-6: Patient 3, pre-GNM GE) and GSS score are described below (Table 4-4, Table 4-8) below.
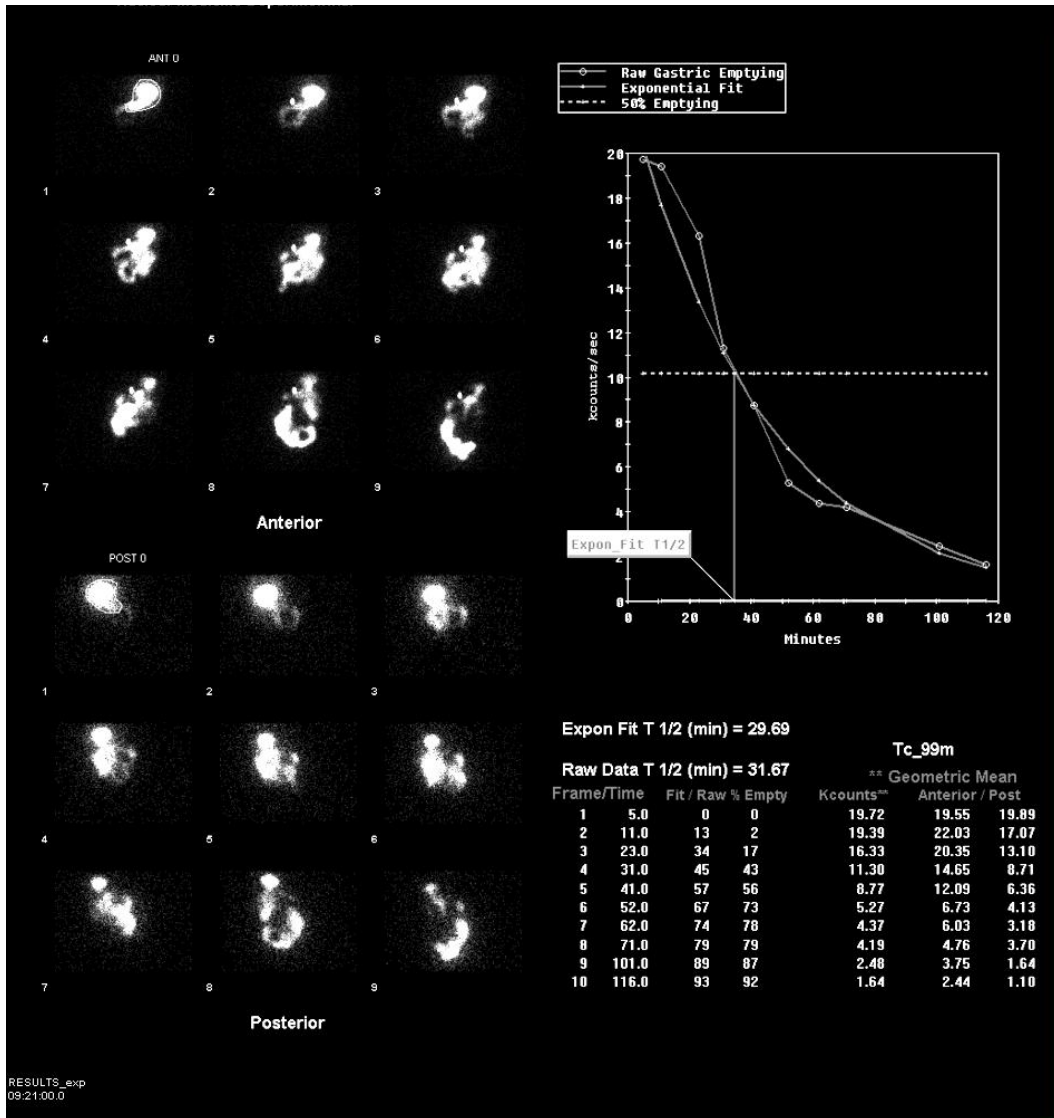
Figure 4-6: Patient 3, pre-GNM GE

GE was normal T50 = 29 minutes before GNM.
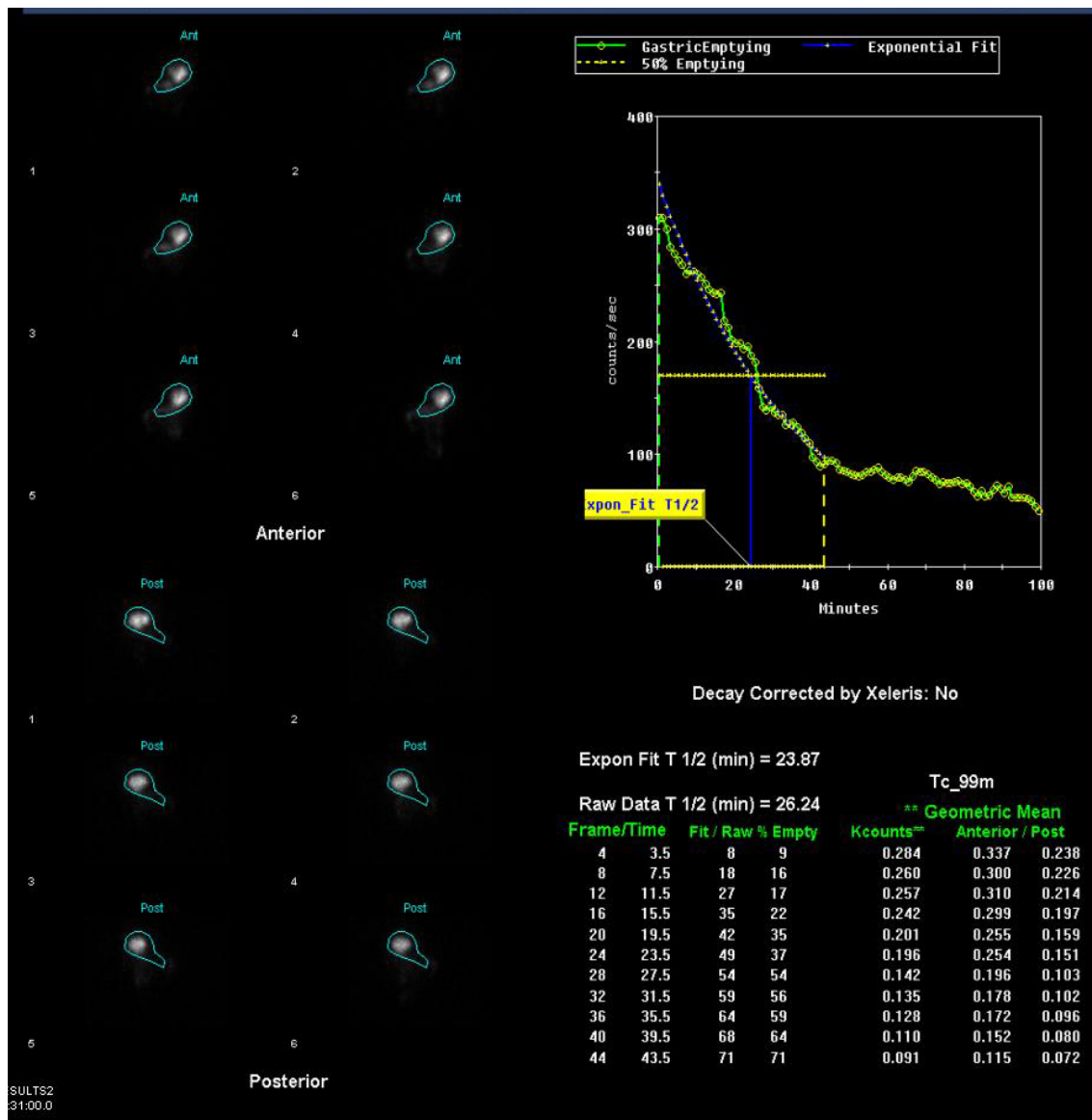
Figure 4-7: Patient 3, post-GNM GE

GNM did not result in any significant change in GNM (GE T50 = 23 minutes).

Patient 4: This 57-year-old lady was referred with severe nausea, vomiting, bloating, abdominal discomfort and early satiety for the last few years. She had lost weight (4 stone) and appetite and continued to vomit 3–4 times a week. Her past medical history included long-standing DM (15 years), arthritis and depression. Her medications included Metformin, Movicol, Dulcolax, Morphine and antidepressants. She was investigated and confirmed not to have mechanical bowel obstruction. Pre-operative investigations confirmed delayed gastric half-emptying (time 98 minutes). GE and GSS reports are described in Figure 4-8, Table 4-5 and Table 4-8.
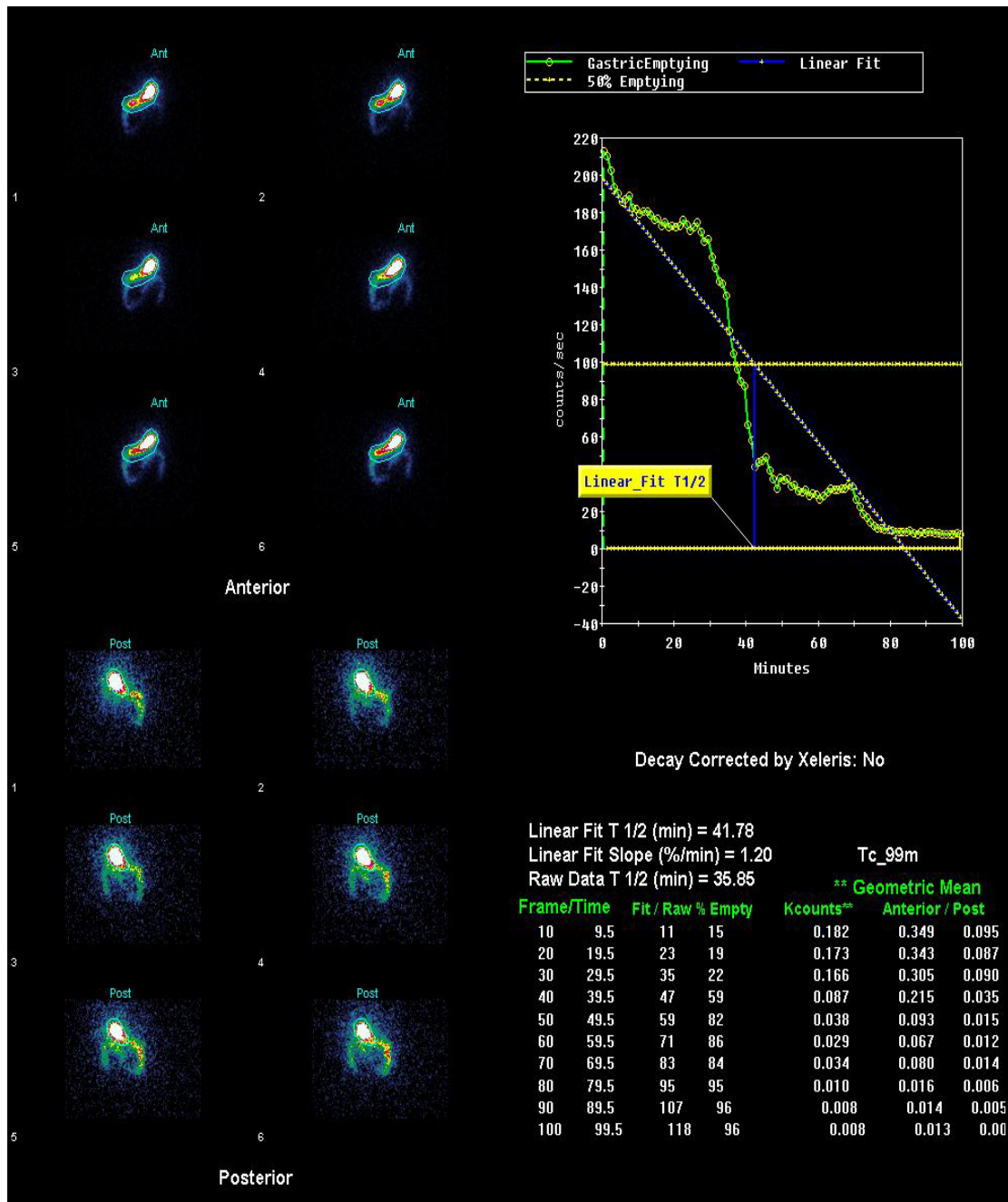
Figure 4-8: Patient 4, post-GNM GE

GE improved from 98 minutes to 41 minutes after GNM in this patient.

Patient 5: This 54-year-old lady was referred with delayed orocaecal transit secondary to gut motility failure. She suffered from intractable nausea, severe bloating, abdominal pain and early satiety since the last few years. Her past medical history included long-standing backache and hypercholesterolemia. Her medications included Tramadol, Simvastatin, Movicol and Paracetamol. She was investigated and confirmed not to have mechanical bowel obstruction on CT scan. Pre-operative investigations revealed gastric

half-emptying time of 37 minutes. GE and GSS are described in Figure 4-9,Table 4-6 and Table 4-8 respectively.

Linear Fit T 1/2 (min) = 37.52
Linear Fit Slope (%/min) = 1.33   Tc_99m
Raw Data T 1/2 (min) = 37.50
                                         ** Geometric Mean

Frame	Time	Fit / Raw % Empty		Kcounts**	Anterior / Post	
6	10.5	7	7	0.214	0.307	0.149
12	16.5	15	18	0.186	0.265	0.131
18	22.5	23	24	0.175	0.242	0.126
24	28.5	31	29	0.162	0.220	0.120
30	34.5	39	36	0.146	0.197	0.108
36	40.5	47	44	0.127	0.173	0.094
42	46.5	55	58	0.095	0.131	0.069
48	52.5	63	61	0.088	0.120	0.065
54	58.5	71	70	0.068	0.093	0.051
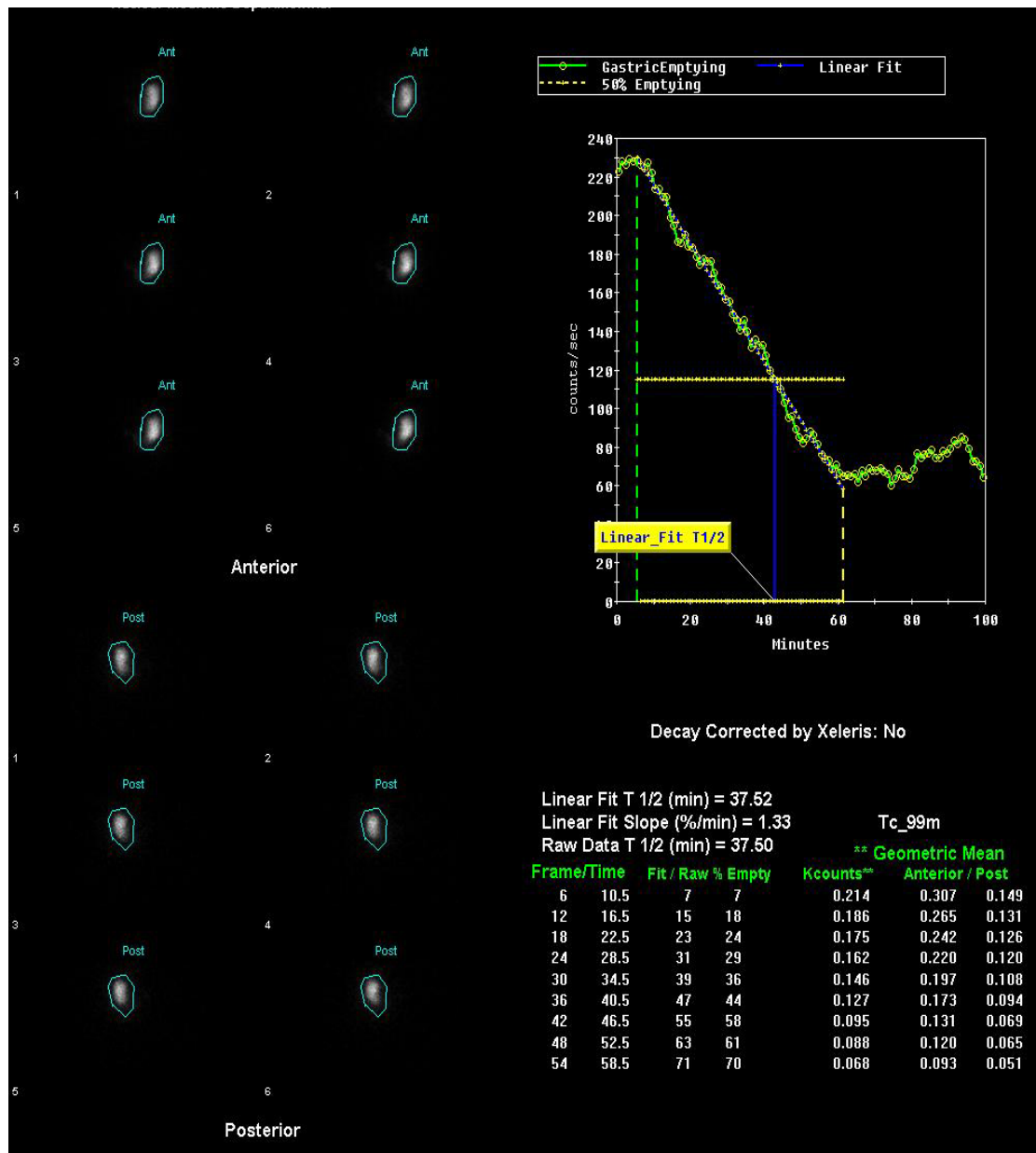
Figure 4-9: Patient 5, pre-GNM GE

Pre –GNM T50 = 37 minutes.
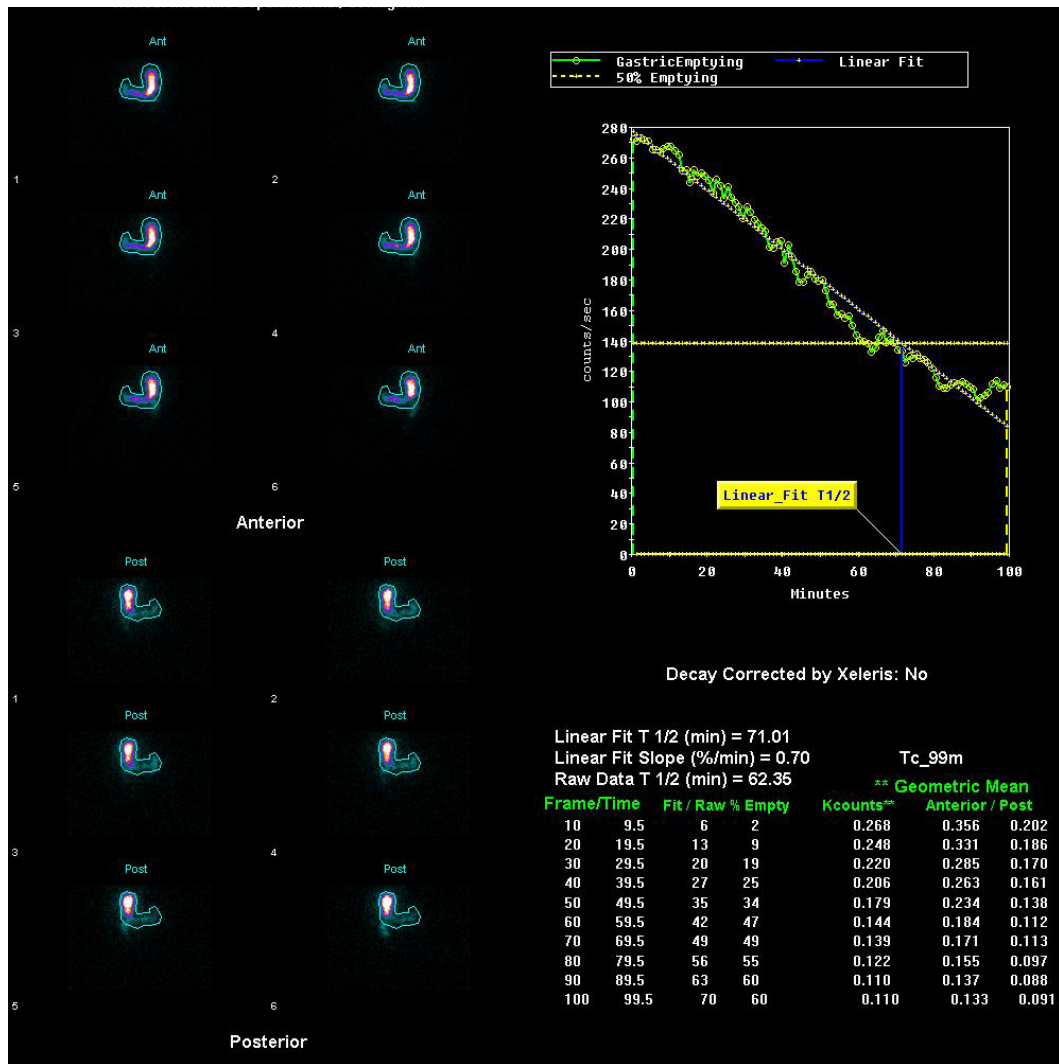
Figure 4-10: Patient 5, post-GNM GE

T50 increased but remained within normal limits of our reference value (T50=71 minutes).

Patient 6: This 44-year-old gentleman suffered from long-standing severe symptoms of nausea, eructation, bloating, abdominal pain and early satiety. He had been under the care of upper GI consultants for the last three years. He underwent a Nissen's fundoplication in Sheffield in 2006 which resulted in worsening of his symptoms and he had a reversal of this procedure in 2008. As he remained symptomatic despite being on regular metoclopramide and PPI, he was considered an appropriate candidate for GNM. He also suffered from depression and was on venlafaxine. Pre-GNM gastric half-emptying time was 65 minutes (Figure 4-11) and details of GSS are described in Table 4-7 and Table 4-8.
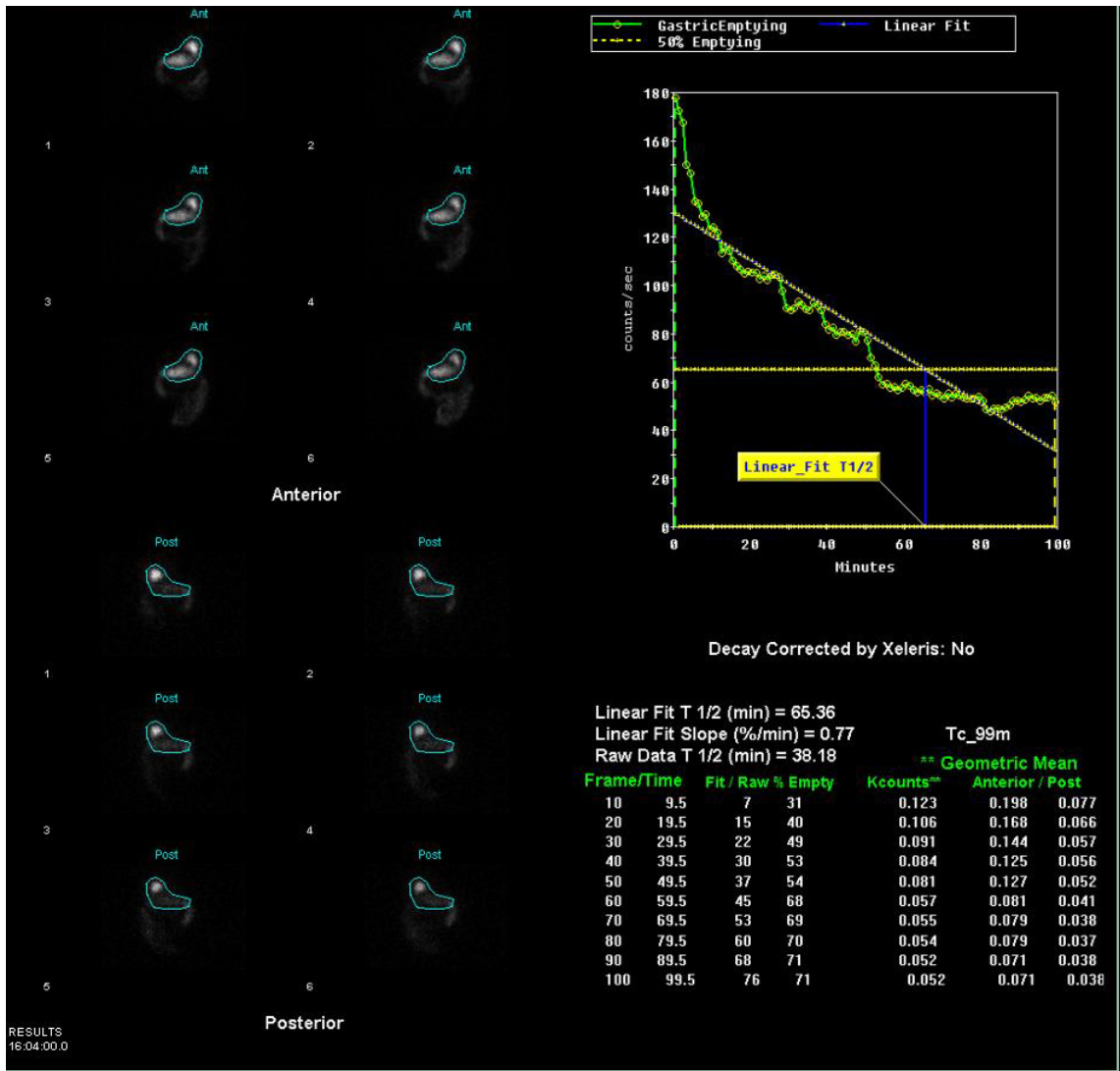
Figure 4-11 Patient 6, pre-GNM GE

Patient suffered from severe symptoms despite normal GE time (T50 = 65 minutes).
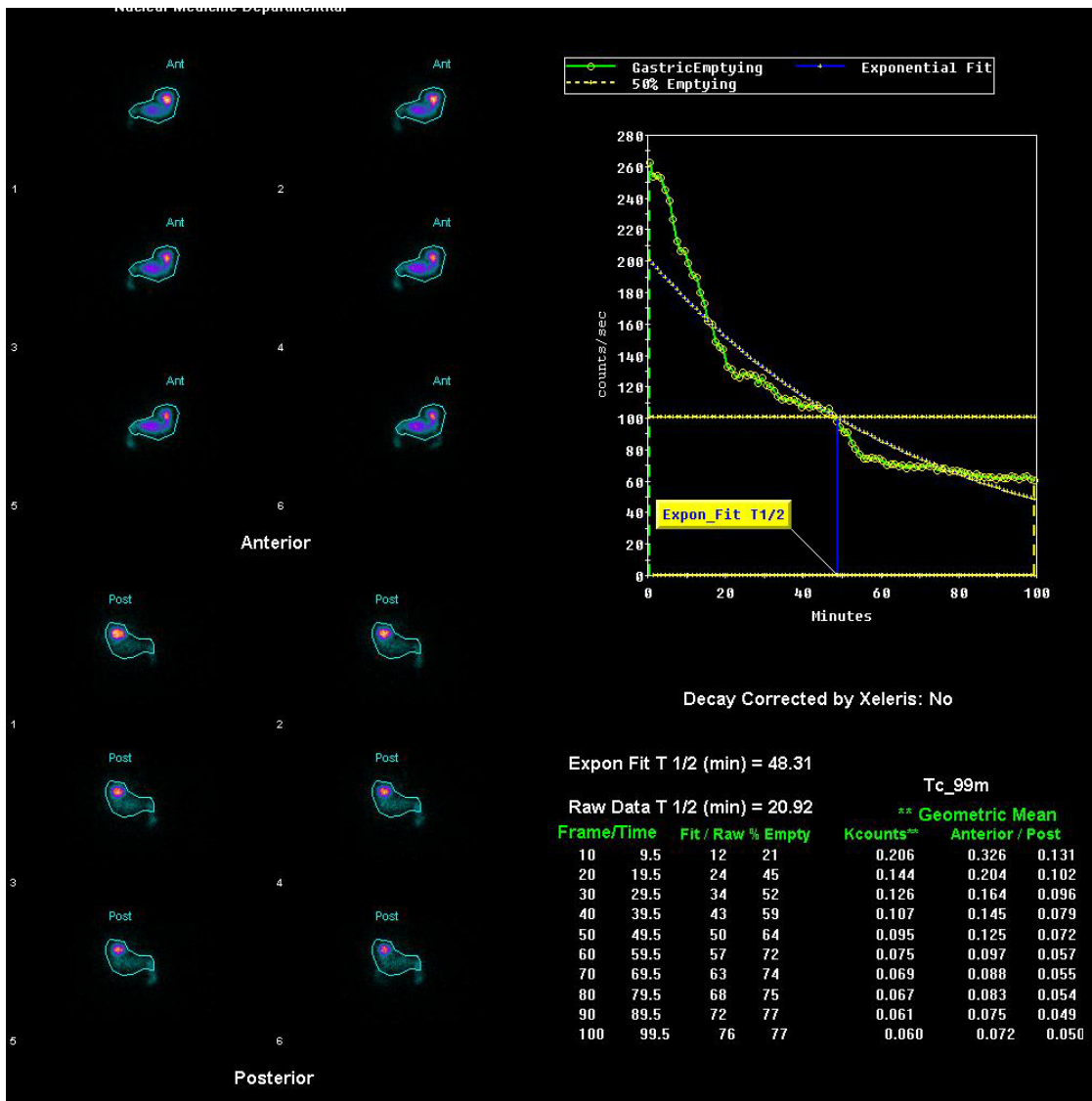
Figure 4-12: Patient 6, post-GNM GE

Improved after GNM (T50=48 minutes).

4.7.2 Patients

Table 4-1: Aetiology and patient selection

	Gender	Age	Duration of Symptoms (yrs)	Aetiology
1	M	57	12	Annular pancreas treated with subtotal (4/5th) gastrectomy, RYGB, refashioning of RYGB.
2	M	40	6	Slow pan enteric GI transit treated with iliostomy. Recurrence of symptoms.
3	M	44	3	Idiopathic nausea and vomiting.. Weight loss 15 kg.
4	F	57	3	Long-standing DM (15 years).
5	F	54	3	Idiopathic severe nausea, bloating and abdominal pain.
6	M	44	4	Long-standing nausea, acid reflux and bloating. Treated with Nissen fundoplication. Symptoms deteriorated necessitating the reversal of Nissen fundoplication.

4.7.3 Scintigraphy

Scintigraphy was used as a gold standard for measurement of GE before and after the GNM. After an overnight fast, subjects were given a test meal containing a small dose 99m Tc (0.3mSv). The meal was prepared just before the beginning of the test and consumed within 10 minutes. With the subjects lying supine, dynamic acquisitions were taken for 100 minutes and each image comprised anterior and posterior acquisitions. The areas of interest (AOI) were drawn on anterior and posterior images. Geometric means of radioactivity were calculated and computer-generated time activity curves were generated. Gastric half-emptying time (T50) was calculated and compared with our reference values (99 ± 26 minutes) based upon a study in healthy volunteers.[147]

4.7.4 Follow-up

After the application of GNM, the patients were admitted to the ward for observation for 24 hours. A repeat gastric scintigraphy (GS) was performed on the first day after GNM. Patients were then sent home and requested to keep diaries of symptoms, medication and food intake for the next seven days. The patients were reviewed in the

outpatient department for the removal of the wires seven days after the procedure. Repeat QOL, weight and nutritional assessments were recorded.

4.8 Analysis / statistics

Pre- and post-GNM data including TSS, VFS, QOL and gastric half-emptying time were entered into an Excel spreadsheet. Comparison between pre- and post-GNM was performed using SPSS version 17.0. The Wilcoxon test was used to determine the differences between medians.

4.9 Results

The GNM procedure was performed in all six patients without any complications. All six patients tolerated the wire for a week with no spontaneous dislodgement of the wire. Alterations in GE, clinical symptoms and QOL following GNM were as follows (Table 4-8, Table 4-9):

4.9.1 GE

Gastric half-emptying time improved in 4 patients and increased in 1 patient (Table 4-8). One patient with a previous history of gastrectomy and RYGB had a very prolonged GE time but there was no evidence of obstruction on endoscopic and radiological investigations. GNM did not have any effect on GE in this patient (Table 4-8, Figure 4-2, Figure 4-3).

Table 4-2: Patient 1 GSS score

	Pre-GES	**Post-GES**
Total Gastroparesis Symptom Score (a–e)	17	13
a– Nausea	2	2
b– Vomiting	4	0
c– Bloating	4	4
d– Early satiety	4	4
e– Abdominal pain	3	3
Vomiting/week	30	0
Weight (kg)	58	59

Table 4-3: Patient 2 GSS score

	Pre-GES	Post-GES
Total Gastroparesis Symptom Score (a–e)	16	0
a– Nausea	3	0
b– Vomiting	2	0
c– Bloating	4	0
d– Early satiety	4	0
e– Abdominal pain	3	0
Vomiting/week	20	0
Weight (kg)	87.1	89.5

Table 4-4: Patient 3 GSS score

	Pre-GES	Post-GES
Total Gastroparesis Symptom Score (a–e)	13	4
a– Nausea	4	2
b– Vomiting	4	1
c– Bloating	1	0
d– Early satiety	3	0
e– Abdominal pain	1	1
Vomiting/week	20	3
Weight (kg)	64	65

Table 4-5: Patient 4 GSS score

	Pre-GES	Post-GES
Total Gastroparesis Symptom Score (a–e)	11	13
a– Nausea	2	1
b– Vomiting	2	1
c– Bloating	3	1
d– Early satiety	4	1
e– Abdominal pain	0	0
Vomiting/week	3	3
Weight (kg)	85.5	85.9

Table 4-6: Patient 5 GSS score

	Pre-GES	Post-GES
Total Gastroparesis Symptom Score (a–e)	13	6
a– Nausea	2	1
b– Vomiting	0	0
c– Bloating	4	2
d– Early satiety	3	1
e– Abdominal pain	4	2
Vomiting/week	0	0
Weight (kg)	69	69.9

Table 4-7: Patient 6 GSS score

	Pre-GES	Post-GES
Total Gastroparesis Symptom Score (a–e)	14	3
a– Nausea	3	0
b– Vomiting	0	0
c– Bloating	4	0
d– Early satiety	3	1
e– Abdominal pain	4	2
Vomiting/week	0	0
Weight (kg)	83.5	84

4.9.2 Nutritional status

Results are expressed as median (inter-quartile range). The overall TSS improved after GNM in comparison with the baseline [13.5(12.5–16.25) vs. 3.5(2.25–7.75)]. VFS improved in 3 of the 4 symptomatic patients. All patients reported an improvement in oral intake and a mean weight gain of 1.02 kg (range 0.3–2.4 kg) was observed over the 7-day test period (Table 4-8).

4.9.3 Quality of life (QOL)

Health-related QOL was assessed by SF12 questionnaire. Physical Composite Score improved in 4 patients [27.5(23.3–33.9) vs. 34.3(21.6–52.8)] and Mental Composite Score improved in 5 patients [34.9(22.5–42.5) vs. 35.9(21.6–49.4)] (Table 4-9).

Table 4-8: TSS, VFS, weight and GE before and after GNM

TSS (total symptom score = sum of nausea, vomiting, bloating, early satiety and abdominal pain scores)

VFS (vomiting frequency/week score).

Patient number	TSS		VFS		Weight Gain (Kg)	GE (t 1/2)	
	Pre	*Post*	*Pre*	*Pre*		*Pre*	*Post*
1	17	13*	30	0*	1	515	600
2	16	0*	20	0*	2.4	104	42**
3	13	3*	20	3*	1	29	23
4	11	4*	3	3	0.3	98	41**
5	13	6*	0	0	0.9	37	71
6	14	3*	0	0	0.5	65	48**
Median (IQR)	13.5(12.5–16.25)	3.5(2.25–7.75)	11.5(0–22.5)	0(0–3)	1.02 (mean)	–	–
P (mean)	0.02		0.10		–	–	

*Subjects with significant improvement in symptom scores and **GE after GNM. Score are expressed as median (IQR) unless otherwise explained.

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Table 4-9: QOL before and after GNM

Patient Number	Physical Composite score		Mental Composite score	
	Pre-op	Post-op	Pre-op	Post-op
1	22.8	21.7	39.1	42.6*
2	38.8	52.4*	52.5	62.1*
3	27.2	40.5*	36.7	45.2*
4	27.9	28.1*	24.3	29.2*
5	23.4	21.1	17.1	22.8*
6	32.3	53.9*	33	18.2
Median (IQR)	27.5(23.3–33.9)	34.3(21.6–52.8)	34.9(22.5–42.5)	35.9(21.6–49.4)
P	0.24		0.34	

QOL before and after GNM; *Subjects with improved physical composite score (n = 4), mental composite score (n = 5).

4.10 Discussion

This small experience with temporary GNM demonstrates that GNM is safe and effective in improving both the clinical symptoms of gastroparesis and the objective measurements of GE.

Multiple case series have previously been published in support of the efficacy of GNM in gastroparesis and intractable nauseas and vomiting.[6–16] The larger part of the treated patients suffered from diabetics and idiopathic gastroparesis, followed by patients with

post-surgical and post-transplant gastroparesis. Recently, a systematic review of case series has been published elaborating the outcome of the procedure in different centres across the world.[200] The review demonstrated the significant benefits for high-frequency GNM in the treatment of refractory gastroparesis. Reduction in nausea and vomiting, nutritional support and an improvement in GE were also emphasised.[200] In addition to diabetic and idiopathic gastroparesis, previous studies have demonstrated promising results in post-gastric surgery gastroparesis refractory to medical treatment treated with GNM.[11,18] There are, however, only a few studies focusing on the objective changes in GE following GNM.[90, 185, 186, 200] The data is inconclusive in terms of the effect of GNM on GE. In one study, GNM in 16 post-surgical patients improved GI symptoms but did not change the GE after 12 months.[90] In another study, both liquid GE (after temporary GNM) and solid GE (after permanent GNM) improved in patients with gastroparesis secondary to diabetes, post-surgical and idiopathic cases.[201] Others have also reported improvement of GE after 6 months and 1 year.[186]

Temporary GNM electrodes can be placed using endoscopic approach where the electrode (wire) is brought out of the nose, whereas the other method involves the transperitoneal intramuscular (muscularis properia) placement using percutaneous endoscopic or laparoscopic technique.[201] The wire is then attached to an implantable pulse generator (IPG) and programmed to deliver low-energy, high-frequency GNM as described in the previous section of this paper. Endoscopic placement of temporary GNM has become a more widely established method, although both endoscopic and percutaneous methods for placement of temporary wires are safe and effective.[201] In successful cases, temporary GNM is replaced by a permanent device. In some cases permanent devices were placed without an initial trial of temporary GNM.[188] Placement of a permanent electrode is more invasive and requires open or laparoscopic abdominal surgery.[186, 202] Electrodes are attached to the IPG and after programming, the IPG is implanted in a subcutaneous pocket (generally the left hypochondrium). Permanent GNM has potential complications such as infection, device erosion, pain at the implantation site, perforation of the stomach/intestine, device migration and volvulus secondary to wires.[179, 188, 200] An overall complication rate of 8.3% has been reported in the previous literature.[200]

Our case series is of small numbers and consisted of patients with severe symptoms of mixed aetiology. We applied temporary GNM for a short period (7 days). Each subject included in this trial was selected very carefully after multiple clinical assessments and extensive investigations. In one patient (Patient 1) we recorded exceptionally prolonged GE (Table 4-8, Figure 4-2). This was also confirmed on endoscopic evaluations on multiple occasions as food was present in the gastric pouch several hours after the ingestion. Endoscopic assessment also revealed that the pouch tissue had become fibrotic, very friable and associated with multiple ulcers. This may be secondary to prolonged stasis of food and multiple surgeries. The possible mechanisms of extremely prolonged GE may be a vagotomy, loss of normal tissue and fibrotic conversion resulting in no or abnormal gastric slow waves. GE time did not improve in this patient after GNM (Figure 4-3). Slow GE following GNM, an unusual finding, was recorded in one patient and we were unable to identify any explanation for this peculiar change as GE improved in the remaining 3 patients. TSS improved in all of our patients after a GNM trial, whereas VFS did not change in one of our patients with low pre-operative VFS. The mixed response of GE in our patients may be because of the diverse and complex aetiologies. Change in GE may have been more consistent in patients with uniform aetiologies and less complex surgical history. The improvement in QOL was very subjective as the mental composite score improved in 4 patients and physical composite scores improved in 5 patients. All patients were able to eat and tolerate more food and fluids after GNM. This was confirmed with the objective evidence of increased weight after the test period.

The prompt and marked response in our patients with gastroparesis, intractable nausea and vomiting clearly suggests that permanent GNM is a potential long-term solution. The overall cost of one procedure is approximately £10,000–£15,000. Therefore, the case selection for a permanent device should be a careful process, based upon not only the subjective and objective improvements after temporary GNM, but after consideration of the overall cost and potential complications. Patient response to a temporary device can guide selection for insertion of a permanent device. Further research is justified in this field focusing on the mechanisms of GNM and long-term outcomes of the procedure.

Limitations: The mechanism underlying the clinical benefits of GNM is not fully understood. It is believed that the beneficial effects are mediated by local

neurostimulation and possibly involves the central nervous system. Other proposed mechanisms include gastric fundus relaxation and contribution of GI motility hormones.[203] Most of the studies, however, observed minimal acceleration in GE, suggesting that improved nausea and vomiting may not be due to an improvement in GE.[21,23] We observed that in only one case the clinical improvement was not associated with objective improvement in GE. However, improvement in GE time in three patients within 24 hours of GNM reflects that it enhanced the GI motility. Due to unclear mechanism of action, potential placebo effect more research is required. We propose that a study looking into the impact of placebo effect by switch off and on under close observation and blinding the patients and researcher over a period of few days may help to clear this issue. In addition the hormonal changes (Gherkin, GLP, Gastric, and CCK) in relation to switch on and off may also give valuable information.

Conclusion

Temporary GNM improved upper GI symptoms, QOL and nutritional status in patients with intractable nausea and vomiting. It does affect GE in this chronically debilitated group of patients. More research is required to determine the indications for this procedure and to understand the mechanism of action.

5 Change in energy expenditure following bariatric surgery. Implications of food intake in GI motility.

Excerpts of this chapter have been modified and published.

> **Ullah S** Arsalani-Zadeh R, MacFie John. Accuracy of prediction equations for calculating resting energy expenditure in morbidly obese patients. Ann R Coll Surg Engl. 2012 Mar; 94(2): 129–32. PMID: 22391385.

Excerpts of this chapter have been modified and presented in ASGBI as posters.

> **Ullah S**, Arsalani-Zadeh R, Jain P, Sedman P, MacFie J. Changes in resting energy expenditure following Roux-en-Y gastric bypass.

> **Ullah S**, Kirkwood B, Jain P, Sedman P, MacFie J. Accuracy of prediction equations for estimating resting energy expenditure in morbidly obese patients.

5.1 Background

Obesity is a major health issue and the prevalence of obesity and related complications is increasing worldwide.[204] According to department of health projected figures show that 60% of men, 50% of women and 25% of children will be obese by 2050. Currently obesity causes significant cost to the NHS. The direct costs caused by obesity are estimated to be £4.2 billion per year which includes the cost to treat the co-morbidities, health service expenditure, prescriptions, hospital costs and drugs. In addition the indirect costs include disability, unemployment, early retirement and 18 million sick days, 40 000 lost years working life. Over all the obese patients die 9 years early than non obese. There are Intangible additional losses including loss of self esteem, relationships, pain, depression etc.Therefore it is high in NHS agenda to control obesity and prevent related complications.

Weight management programmes are based upon estimation of energy intake and expenditure, together with appraisals of behaviour therapy and lifestyle modification. The most common way in which this is done is the use of standardised predictive equations which permit an estimate of the resting metabolic rate. The most commonly used equations by dieticians are Schofield's equation, Harris and Benedict equation. These equations are based upon age, sex, and body weight with additional factors for stress, growth and dietary-induced thermogenesis.

Harris and Benedict equation (HB): This equation was published by James Harris and Francis Benedict in 1918-1919. The baisics of this equation are as follows.

For Men: BMR = 66.4 + (13.7 x weight in kg) + (5.0 x height in cm) – 6.75 x age in years).

For Women: BMR = 65.5 + (9.5 x weight in kg) + (1.84.0 x height in cm) – 4.6 x age in years).

And enegy intake using this equation is as follows.

Little or no exercise: Daily Kilo Calories = BMR x 1.2

Little exercise (1-3 days per week): Daily Kilo Calories = BMR x 1.37

Moderate exercise (3-5 days per week): Daily Kilo Calories = BMR x 1.55

Heavey exercise (6-7 days per week): Daily Kilo Calories = BMR x 1.72

Very Heavy exercise: Daily Kilo Calories = BMR x 1.9

 Schofield Equations: Schofield's equations (SC) were published in 1985. The basis of this equstion included 50% BMR calculations on healthy army subjects in Italy.The equation is explaind as follows.

Females (kcal/day)		Males (kcal/day)	
10–17 years	13.4W + 692	10–17 years	17.7W + 657
18–29 years	14.8W + 487	18–29 years	15.1W + 692
30–59 years	8.3W + 846	30–59 years	11.5W + 873
Females over 60 years (kcal/day)		Males over 60 years (kcal/day)	
60–74 years	9.2W + 687	60–74 years	11.9W + 700
75 years +	9.8W + 624	75 years +	8.3W + 820

In addition factor for activity and diet-induced thermogenesis is added as below.

Bed-bound immobile   +10%

Bed-bound mobile/sitting   +15–20%

Mobile on the ward   +25%

The main criticism on these equations is as follows

1. The Equations are mainly based for healthy subjects.

2. They are based upon weight, height, activitivity whereas they do not take the real time acitivity, BMR, REE into account.

3. The equations were developed long time age (especially HB Equation) whereas now a days many accurate methods (Direct and indirect calorimetry) to assess the BMR and REE are available.

4. BMR is extremely difficult to measure as it requires a person in fasting for at least 12 hours, immediately after they wake up and should ideally be calculated in a dark room, without any stress, and subject in their bed. Therefore REE is more practicle and accurate method of calcutaing energy expenditure and should be used for estimation/calculation of energy intake.

In management of obesity most of the weight management programmes are based upon low-fat, low-calorie diets with a fixed amount of calories (i.e. 1000–1200 kcal for women and 1200–1600 kcal for men). Ideally, weight management programmes should be based upon individual requirements and therefore accurate assessment of energy expenditure is desirable.[205]

Prediction equations for estimating resting energy expenditure (REE) are based upon demographic information such as age, weight, height and gender.[206, 207] Previous studies have suggested they may be inaccurate in obese patients.[205, 208-210] This may result in overfeeding or underfeeding of this group of patients. The aim of this study was to compare the measured REE using a bedside indirect calorimetry (IC) device with commonly used formulae, i.e. Schofield (SC) and Harris-Benedict (HB).[211]

5.2 Methods

5.2.1 Subjects

The outpatient dietetic assessment included the measurement of energy expenditure (IC, HB, Schofield). This was performed pre-operatively, and 6 weeks and 3 months following surgery. A total of 31 morbidly obese patients undergoing RYGB surgery were assessed during the period January 2009 to March 2010.

5.2.2 Measurement of REE

REE was measured using a bedside IC device (Fitmate COSMED®). Fitmate is a small (20 x 24 cm), portable metabolic analyser designed to measure oxygen consumption and energy expenditure (Figure 5-1, Figure 5-2). This device can be used to measure REE in a resting state as well as during exercise. It contains a turbine flow meter for measuring ventilation and a galvanic fuel cell oxygen sensor for analysing the fraction of oxygen in the expired gases, and incorporates an innovative sampling technology. The device has been validated with the Douglas bag system for non-obese and obese subjects and was found to calculate REE accurately (r=0.97, P=0.579) and the results were reproducible.[212] This device also conducts a self-calibration in 20 seconds before each calorimetry.[212] Subjects were assessed in a calm place, in supine position and after 30 minutes of initial rest period. Subjects were encouraged to keep silent and breathe normally for 15 minutes during calorimetry. REE was also calculated with Schofield and HB formulae using actual body weight, gender, height and age.

Figure 5-1:Fitmate COSMED® calorimeter

Figure 5-2: Indirect calorimetry using Fitmate device

Device, screen view and print out of the result after calorimetry.

5.3 Statistics

Data was entered into an Excel datasheet and statistical analysis was performed using SPSS 17. Values are expressed as mean +/– standard deviation (SD) unless otherwise stated. Significance of difference was calculated using two-tailed paired or unpaired student t test. The Fisher exact test was used for categorical data. *P* value of < 0.05 was considered statistically significant. Pearson correlation R was also calculated.

5.4 Results

The pre-operative demographic data, REE, measured by indirect calorimetry and predicted equations are shown in Table 5-1. Comorbidities included hypertension in six patients, diabetes in nine, asthma in three, obstructive sleep apnoea in three, epilepsy in one and polycystic ovaries in one.

Three patients failed to attend the first follow-up at 6 weeks. Another 6 patients did not attend the 3-month follow-up. Follow-up data of 22 patients (15 female, 7 male) was available for the pre- and post-operative analysis (

Table 5-2).

The mean age of the patients was 47 ± 7 years (10 male, 21 female). The mean value of BMI was (46 ± 8.6) and REE measured using indirect calorimetry was 1980 ± 558 kcal/day). Estimated REE using Schofield and HB formulae was 2129 ± 449 kcal/day and 2195 ± 505 kcal/day respectively. Predicted equations overestimated the REE by 7% and 10% respectively. There was a significant correlation between measured and estimated values of REE (r=0.63, P<0.001) (Figure 5-3, Figure 5-4).

Post-operative body weight reduced from a pre-operative value of 132 ± 28 kg (mean ±SD) to 122 ± 27 kg at 6 weeks and 114 ±27 kg at 3 months after surgery < P 0.001). Corresponding values for BMI were 46±8, 42±8 and 39±8 < P 0.001). There was no significant change in measured REE over the three-month period (2039±448, 2122 ±498 and 1987±517, P 0.36, P 0.56) using indirect calorimetry (Figure5-5). In 22 patients who completed the follow-ups, pre-operative REE was overestimated by HB and Schofield equations (6.3% and 3.6%). At 6 weeks follow-up HB and Schofield equations underestimated the REE by 3.3% and 5.2% respectively. Similarly at 3 months follow-up predicted equations underestimated the REE (HB 1.2%, SC 2.7%). However, none of these differences reached statistical significance (Table 5-2)

Table 5-1: Pre-operative data and REE using IC and prediction equations

Demographic data and pre-operative REEE measured with prediction equations (HB, Schofield) and indirect calorimetry.

- HB and Schofield over-predicted by 10% and 7% respectively.

Age (years)	47 +/- 7
Male : Female ratio	10:21
Height (cm)	168 +/- 11
Weight (kg)	134 +/- 29

BMI (kg/m2)	46.6 +/- 8.6
REE using HB	
Male (10)	2195 +/- 505
Female (21)	2777 +/- 373
	1918 +/- 266
REE using Schofield	
Male (10)	2129 +/- 449
Female (21)	2666 +/–307
	1874 +/–216
REE using IC	
Male (10)	1980 +/–558
Female (21)	2329 +/–600
	1814 +/–464
Over-prediction by	
Harris-Benedict	215 +/- 458*
Schofield	149 +/- 439*

Table 5-2: Change in weight, BMI, REE (IC, HB and Schofield) after surgery

Total of 22 patients (15 female, 7 male).

* Difference in REE measurements (IC vs. HB).

**Difference in REE measurements (IC vs. Schofield)

(N 22)	Weight (kg)	BMI	REE-IC (kcal/day)	REE-HB (kcal/day)	REE-Schofield (kcal/day)	P value* (IC vs. HB)	P value** (IC vs. Schofield)
Baseline	132+/-28	46+/-8	2039+/-448	2170+/-497	2114+449	0.116	0.31
6 weeks	122+/-27	42+/-8	2122+/-498	2049+/-466	2010+/-425	0.24	0.06
3 months	114+/-27	39+/-8	1987+/-517	1961+/-450	1932+/-417	0.63	0.339
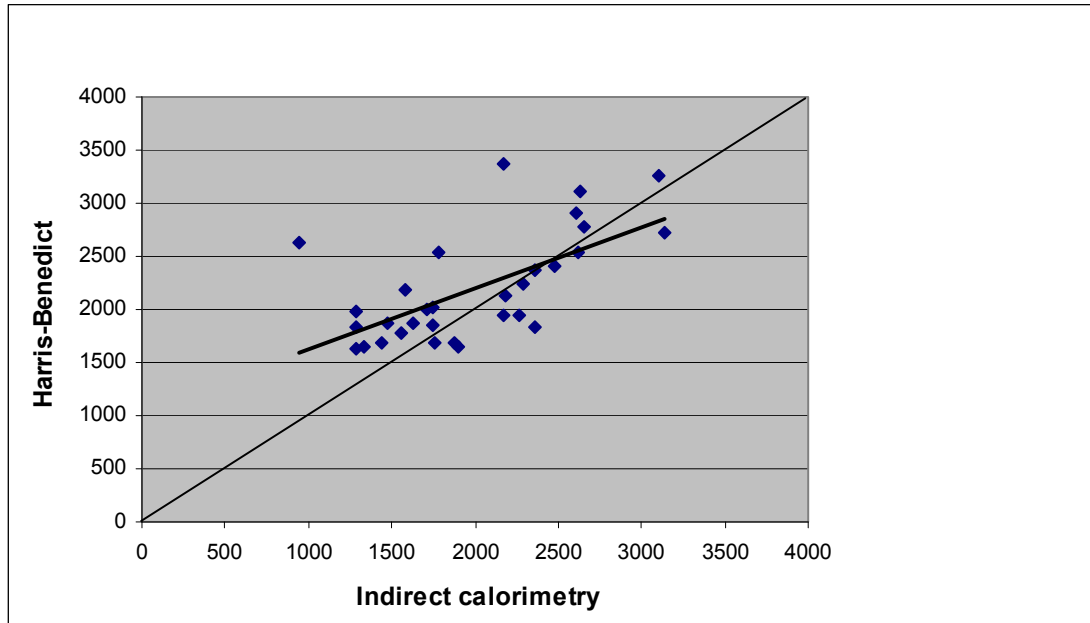
Figure 5-3: Pre-operative IC vs. HB
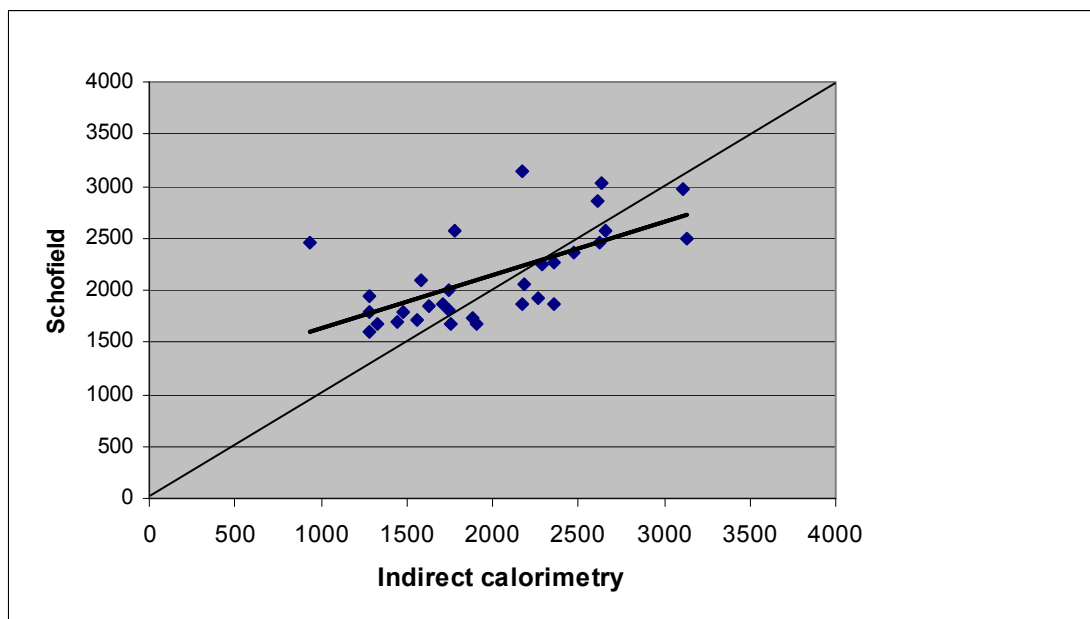
Figure 5-4: Pre-operative IC vs. Schofield

Correlation (R) of pre-operative indirect calorimetry with HB and Schofield equations. There was no strong linear correlation between IC and predicted equations (Schofield and HB); R= 0.63, p < 0.001. Similar correlation values in figures suggestive of resemblance in resting energy measurements using both predicted equations.
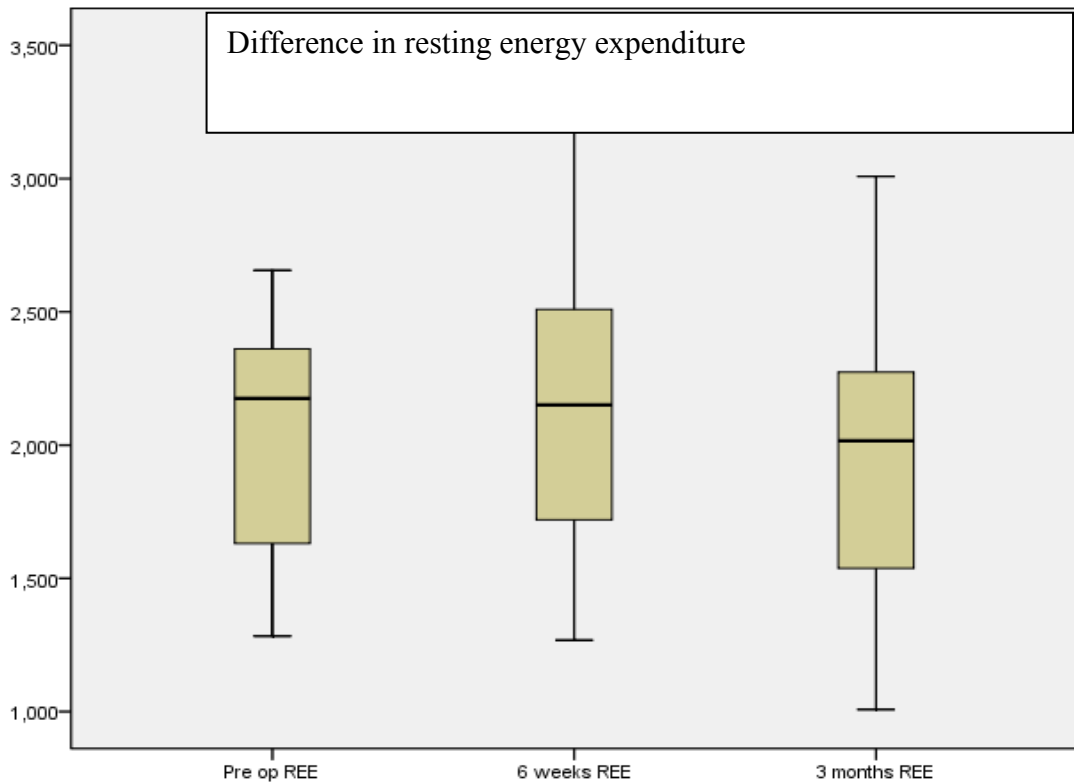
Figure 5-5: Change in REE (IC) after RYGB

Change in REE following RYGB using IC. No significant change in REE following RYGB at 6-week and 3-month follow-ups (p=0.36, p=0.56).

5.5 Discussion

Adequate nutritional assessment is important in patients with obesity. The mainstay of weight management is to reduce the energy intake and increase expenditure in an attempt to achieve a net weight reduction. Numerous prediction equations are currently used to assess REE and total energy expenditure. Amongst them HB and Schofield equations are widely used.[206, 207] These equations are based upon weight, height, age and gender. They are currently in practice for normal, overweight, obese and morbidly obese subjects. Schofield equations use body weight as the main determinant for REE measurement and have been reported to overestimate at low REE and underestimate at high REE.[213] The HB equation was derived in 1919. It has been reported that HB equation also overestimates the REE by 5–15%.[214, 215] Similarly, there are studies

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describing the inaccuracy of predicted equations in the obese population.[208,216,217] This is probably because the actual body weight is used in these formulae. Mifflin et al suggested that fat-free mass is the single best predictor to calculate the REE in healthy population.[214] Lean body mass was found to be the single predictor of basal metabolic rate in 60 lean and obese subjects.[218] Similarly, other studies also found overestimation of REE by prediction equations and suggested the use of actual measurements.[219, 220] A recently published paper looked into the variance of 27 predicted equations with IC and found the HB equation to be 69% accurate.[221] Pre-operative REE was overestimated by prediction equations in our study. The Schofield and HB equations overestimated by 7% and 10% respectively. These results are comparable with other studies as they reported 5–15% overestimation of REE using prediction equations.[214-216] There was strong linear correlation when predicted REE was analysed against measured REE (Figure 5-3, Figure 5-4).

RYGB was effective in weight reduction and improvement in BMI and related comorbidities. Post-operatively, despite the constant weight reduction, we noticed no significant change in REE (measured with IC) at 6-week and 3-month follow-ups (Figure5-5, Table 5-2).). Others have reported similar findings following gastroplasty.[222, 223] The explanation for this paradox is probably related to the fact that the bulk of tissue loss after bariatric procedures is comprised primarily of body fat rather than lean tissue (muscle). There are marked differences between rates of oxidative metabolism between fat and muscle and consequently the loss of fat has proportionally lesser impact on total REE than a corresponding loss of muscle.[224] After surgery, the estimated REE was within 1–3% of measured values, suggesting that prediction equations are more accurate in non-obese subjects.

Post-RYGB, a reduced body weight may be explained by a decreased food intake which is contributed by restricted food entry and early satiety. This may also be contributed by altered GE and increased energy expenditure through activation of the sympathetic control and breakdown of adipose tissue. The stomach, therefore, is a major regulatory factor in energy homeostasis after surgery and accurate measurements of REE and total energy expenditure are necessary for a better post-operative outcome.

5.5.1 Limitations

This study has some limitations. The sample size is relatively small but we do not consider this has adversely affected our findings as the variability of our data between patients was small. We measured REE, not basal requirements because this reflects the more usual situation. Estimation of basal requirement necessitates 24 hours of starvation and precise standardisation of conditions of measurement. However, we did ensure that patients were at rest and established a steady state before commencement of readings. Finally, we have assumed the nature of tissue loss. Ideally, future studies would need to confirm this.

5.5.2 Conclusion

Prediction equations tend to overestimate the REE. IC should preferably be used in morbidly obese patients for accurate energy calculation. Change in energy expenditure following bariatric surgery is independent of the weight loss. This might reflect losses of body fat as opposed to lean tissue. GE plays a very important role in energy intake and energy homeostasis following RYGB.

6 Assessment of energy expenditure using indirect calorimetry (IC) in patients receiving total parenteral nutrition (TPN)

Excerpts of this chapter were presented as an oral presentation in ASGBI.

Owais A, **Ullah S,** Bumby R, Coppack A. Permissive underfeeding in patients requiring parenteral nutrition. (Oral Presentation in Moynihan's prize session ASGBI 2011).

6.1 Introduction

The importance of artificial nutrition in selected patients groups is well established and could be life-saving. However, it is also well known that artificial nutrition may be associated with significant complications, such as hyperglycaemia, hyperlipidaemia and fluid retention. These, and other complications, are usually associated with overfeeding which is now recognised as the most frequent cause of morbidity in these patients. The question arises as to why is overfeeding so common?

One possible explanation is that the prediction equations which are commonly used to estimate requirements are inaccurate for use in this patient group, and frequently overestimate requirements.

The estimation of energy requirements of patients receiving artificial nutritional support is paramount for calculating their nutritional intakes, thereby avoiding significant overfeeding or underfeeding. The most common way in which this is done is the use of standardised predictive equations which permit an estimate of the resting metabolic rate. The most commonly used equations by dieticians is Schofield's equations which are based upon age, sex, and body weight with additional factors for stress, growth and dietary-induced thermogenesis.[206] Hereby this equation is briefly explained.

Schofield Equations: Schofield's equations (SC) were published in 1985. The basis of this equstion included 50% BMR calculations on healthy army subjects in Italy.The equation is explaind as follows.

Females (kcal/day)		Males (kcal/day)	
10–17 years	13.4W + 692	10–17 years	17.7W + 657
18–29 years	14.8W + 487	18–29 years	15.1W + 692
30–59 years	8.3W + 846	30–59 years	11.5W + 873
Females over 60 years (kcal/day)		Males over 60 years (kcal/day)	
60–74 years	9.2W + 687	60–74 years	11.9W + 700
75 years +	9.8W + 624	75 years +	8.3W + 820

In addition factor for activity and diet-induced thermogenesis is added as below.

Bed-bound immobile   +10%

Bed-bound mobile/sitting   +15–20%

Mobile on the ward   +25%

The main criticism on this equation is as follows

1. The equations are mainly based for healthy subjects and study population included 50% healthy army subjects.

2. They are based upon weight, height, activitivity whereas they do not take the real time acitivity, BMR, REE into account.

3. Now a days many accurate methods (Direct and indirect calorimetry) to assess the BMR and REE are available.

4. BMR is extremely difficult to measure as it requires a person in fasting for at least 12 hours, immediately after they wake up and should ideally be calculated in a dark room, without any stress, and subject in their bed. Therefore REE is more practicle and accurate method of calcutaing energy expenditure and should be used for estimation/calculation of energy intake.

An alternative approach is to measure resting metabolic rate using IC. This is based upon the principle that oxygen consumption is an indirect measure of heat production,

which is a reflection of all ongoing metabolic processes. Thus, measurement of a patient's oxygen consumption can be used to calculate resting metabolic expenditure and hence energy requirements. This method of REE calculculation is explained in detail in chapter 6 and a brief description in given in measurements section of this chapter. Until recently, measurements of oxygen consumption were only possible in dedicated research establishments with sophisticated equipment. In recent years, however, technological developments have permitted the development of easy-to-use, validated, bedside IC. These have become the gold standard in measuring energy requirements for hospitalised patients. However, the use of predictive equations is still predominant and indispensable as IC remain expensive, time-consuming and difficult to use in certain groups of patients. Therefore, the aim of our audit was to compare energy needs estimated using Schofield equations with those measured by IC.

6.2 Methods

6.2.1 Parameters

This was a prospective audit of 101 consecutive patients requiring artificial nutritional support. This audit was approved by our audit departments. Patients continued to receive their nutritional requirements according to the hospital nutrition team guidelines (Scarborough and Hull and East Yorkshire Nutrition Guidelines) using Schofield equations as illustrated in Appendix 1. Resting metabolic rate was measured using IC. The results obtained from IC were not made available to the nutrition teams and did not impact on patient care.

6.2.2 Settings

The audit was done between March 2008 and March 2010 in two hospitals, Scarborough General Hospital, Scarborough, United Kingdom, and Castle Hill Hospital, Hull, United Kingdom.

6.2.3 Sample

All patients receiving nutritional support (enteral or parenteral) were included. Patients who were ventilated or who needed oxygen supply continuously were excluded. Indications of feeding are elaborated in the figure below.
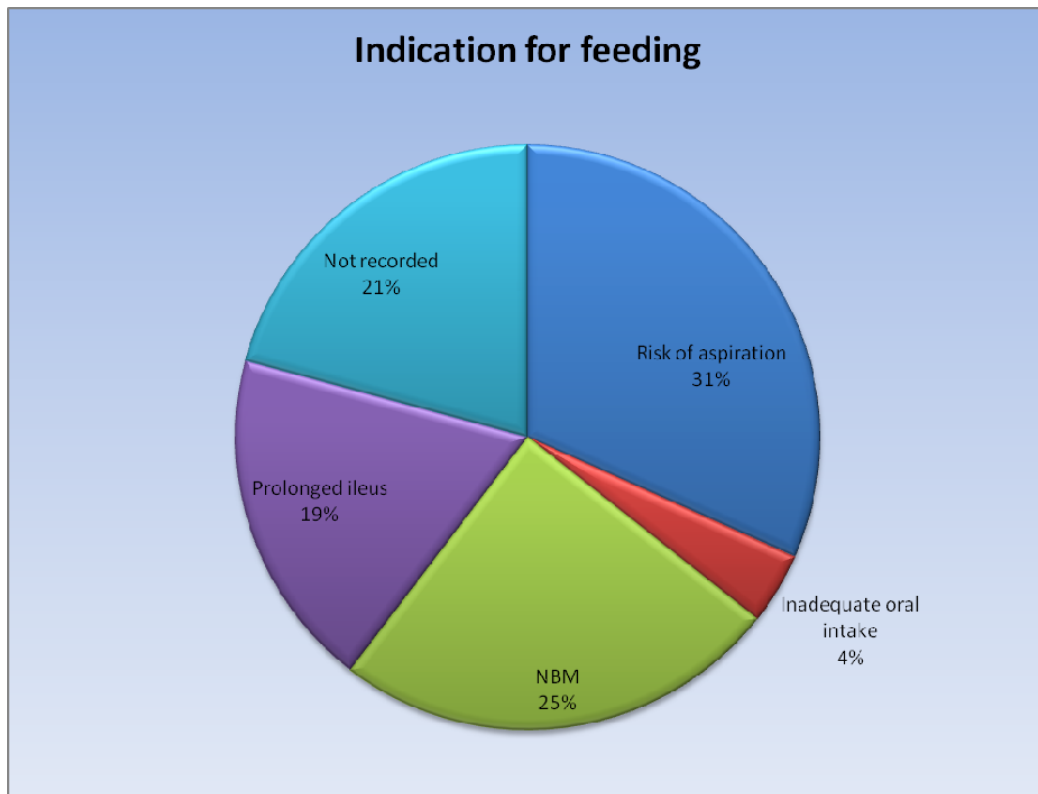
Figure 6-1: Indications of feeding groups

Indications of artificial feeding included 25% patients nill by mouth after surgery or related complications, 19% prolonged ileus, 31% at risk of aspiration.

6.2.4 Measurements

Resting metabolic rate was measured using a validated IC (Fitmate, COSMED, Italy). Measurements were standardised. All patients were in a fasting state for at least 4 hours. Patients were resting for at least 30 minutes, and measurements were taken at a standard hospital room temperature. The first 5 minutes of data were discarded to allow a steady state to be achieved. Resting metabolic rate was measured from the following 10 minutes' oxygen consumption. The device has been validated with a Douglas bag for non-obese and obese subjects. It was found to calculate REE accurately (r=0.97, p=0.579) and the results were reproducible.[212] The device calibrates itself prior to each measurement. The device displays quality control messages to enable accurate measurement and at the end of the test, results are displayed. Measurement of energy expenditure using Schofield equation was based as described in introduction part of this chapter.

6.3 Results

This audit comprised 101 consecutive patients requiring artificial nutritional support. The median age was 70 (range 21 to 94) and 65% were males. The median duration of hospital stay was 25 days (range 4 to 100). Fifty patients were receiving enteral nutrition and 51 were receiving parenteral nutrition. The median BMI for the patients included in our audit was 24 (range 16–46).

Figure 6-2 shows the distribution for the indication of feeding among patients included in this study. 32% of the patients had to be artificially fed as they were at risk of aspiration due to either a cerebrovascular accident or aspiration pneumonia. 25% of the patients were nil by mouth due to either a medical or a surgical underlying condition. Patients who suffered a prolonged ileus following a surgical procedure constituted 19% of the patients. 4% of the patients had inadequate oral intake and had to be supplemented by artificial feeding. However, in 21% of the patients the indication for feeding was not recorded.

The measured energy requirements for those patients using IC were significantly lower than the energy requirements estimated by the specialist dietitians using Schofield's equations. The median energy requirements measured by IC was 1359 (range 825–2668) kcal/day, whilst the median energy requirements estimated by Schofield was 1758 (range 1256–3048) kcal/day (P value <0.001). This is shown in the scatter plot in Figure 6-2 below.
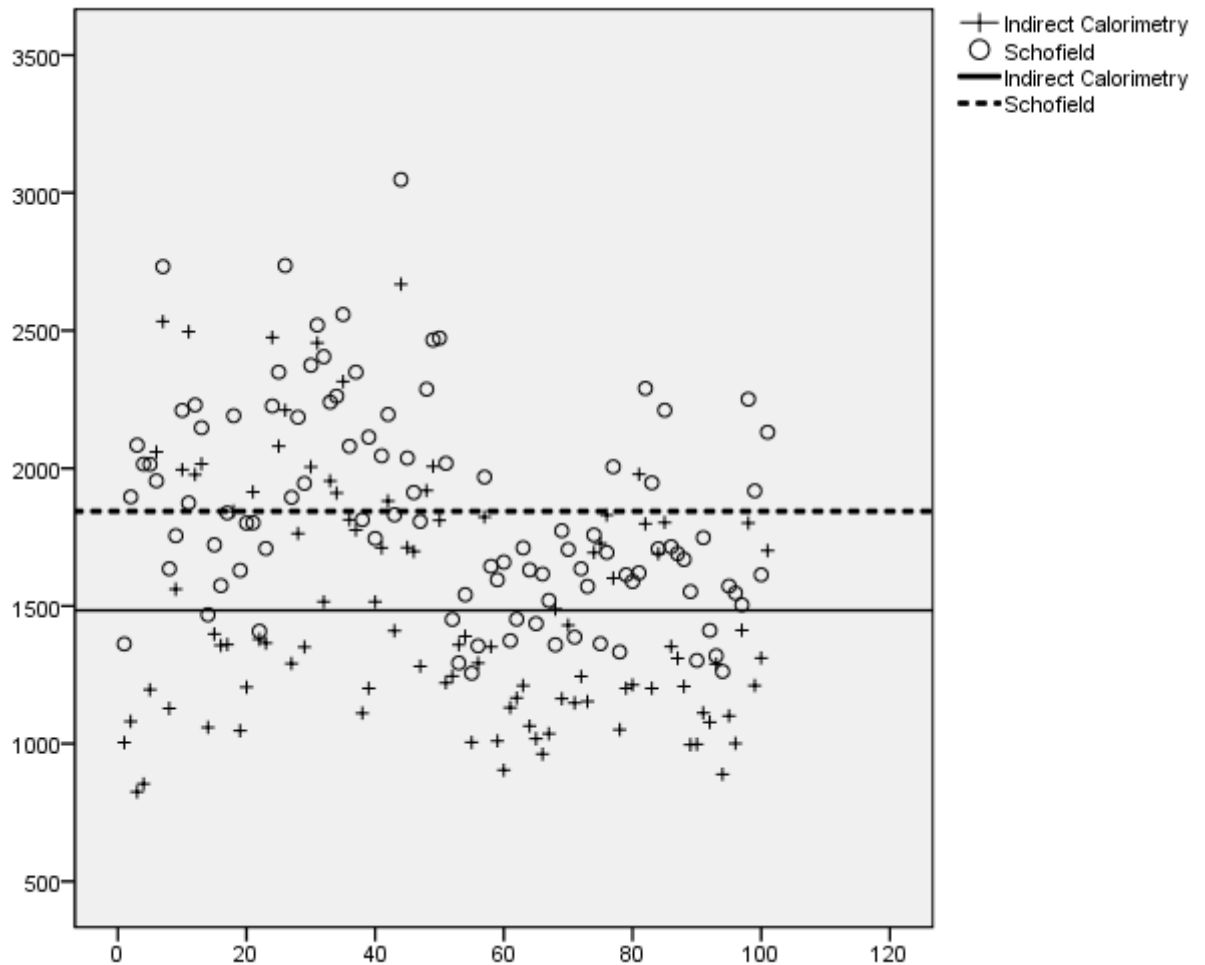
Figure 6-2: Scatter plot representing Schofield vs. IC

The median energy requirements measured by IC was 1359 (range 825–2668) kcal/day, whilst the median energy requirements estimated by Schofield was 1758 (range 1256–3048) kcal/day (P value <0.001).

6.4 Discussion and conclusion

The results of this audit show that Schofield's equations overestimate energy requirements for hospitalised patients requiring artificial nutritional support. Schofield's equations published in 1985 were a meta-analysis of several studies including over 4,000 patients.[206] These were based upon IC measurements carried out on volunteers of whom nearly 50% were healthy military Italian adults. Just over 1% of Schofield's study population were over 60 years old whilst in our study 71% of the patients were over 60 years old. This demonstrates that Schofield's study population is hardly representative of the average patient requiring adjuvant nutritional support in a hospital

setting. Muller et al[213] demonstrated that the Schofield equation overestimated REE at low REE values but underestimated REE at high REE values.

Recently, there has been an increasing interest in the concept of "permissive underfeeding". The term "permissive underfeeding" was first used by Zaloga et al in 1994.[225] They described a strategy which was based on the premise that short-term dietary restriction (but not elimination) would limit pathological processes while minimally impairing organ function. In addition, this may limit the complications relating to TPN (hyperglycaemia, hypercholestrolaemia, etc.) and delivery of TPN (sepsis). A recent study shows TPN-induced hyperglycaemia.[226] In another study, patients requiring artificial nutrition after colorectal surgery had a higher risk of infection associated with hyperglycaemia.[227] Several studies and reviews aimed to explain the rationale for permissive underfeeding and why it could confer benefit to patients. Most of these studies agreed that a possible explanation is that "permissive underfeeding" minimises complications associated with overfeeding, which offset any possible disadvantage from failing to achieve the presumed energy requirements for patients receiving artificial nutrition.

There is now overwhelming evidence to suggest that the provision of nutrients to surgical or septic patients will not reverse the gluconeogenesis that characterises the metabolic response to trauma and sepsis. Therefore, the aim of nutritional support, at least in this group of patients, is to minimise losses, accepting that these cannot be entirely prevented even if a hypercaloric diet is routinely adopted.[228, 229]

Post-operative prolonged paralytic ileus, sepsis, fistulae, gut motility disorders and patients requiring ventilator support are considered for artificial nutrition. Critically ill patients are believed to have delayed GE, putting them at risk of aspiration. In addition, they remain at risk of feed intolerance and other nutrition-related complications. The diagnosis of impaired GE in critically ill patients, sepsis, old age and multi-organ failure is important before commencement of artificial feeding.[230, 231] We propose that accurate feeding regimes should be practiced and that patients should be discussed in nutritional multidisciplinary treatment panels (MDTs) and that all these factors should be taken in account before commencement of artificial nutrition.

We recognise certain limitations to this audit. Firstly, there are relatively fewer patients in this study group in comparison to those used by Schofield's. Despite that, our study group is more representative of the actual type of patients encountered by hospital dietitians. Secondly, certain patients who were ventilated or required oxygen support continuously had to be excluded as the IC used was not validated in this type of patients. However, it is unlikely that those patients' energy requirements are any different than the rest of the patients studied here. Thirdly, Schofield's equations are not the only equations used by the dietitians, but certainly it is the most prevalent equation used among dietitians in the UK. The use of other equations might reduce the margin of error in selected patient groups, but certainly not in this group of patients. Fourthly, and most importantly, the data from this audit is limited, and it doesn't show that patients' outcome could be improved by feeding patients less than their Schofield's estimated requirements. To draw such a conclusion, a prospective randomised trial is required.

Clearly, absolute starvation is harmful. Similarly, the administration of excessive calories is detrimental. The optimal level of feeding is still unknown but must be a balance between minimising catabolism and avoiding overfeeding-related morbidity. The results of our audit suggest that Schofield's equations overestimate energy requirements, which might lead to overfeeding. Dietitians and clinicians should be cautious when using prediction equations to avoid any risk of overfeeding. Moreover, we suggest that what was termed as "permissive underfeeding" could actually be "normocaloric feeding" or "appropriate feeding". However, the actual benefit to patients should be investigated by a randomised trial of "permissive underfeeding", as defined by prediction equation. In addition, the factors like age, GE, risk of aspiration, REE and activity should be considered before the commencement of artificial feeding.[231]

7 Conclusions and future research

Conclusions

1. GE is not enhanced in morbidly obese diabetic patients. RYGB results in rearranged anatomy, resulting in fast pouch emptying and unchanged IT. RYGB results in an early and exaggerated GLP-1 response which was very closely related to post-operative insulin confirming its role as incretin hormone. Ghrelin levels reduced after surgery, but could not be causally related to weight reduction or improved diabetic status following RYGB.

2. The results of our review remain inconclusive in terms of the results and mechanism how GES may work in obesity treatment. However, GNM can be used effectively to treat gastroparesis. GNM not only improves GSS, VFS, weight and QOL; it also results in improved GE in this group of patients.

3. We elaborate the role of CE and breath test to assess IT. Hydrogen breath test is inexpensive, easy to perform and can be used when other precise methods are not available.

4. Change in REE following RYGB is independent of weight loss; therefore, accurate measurements of REE and energy intake are required for nutritional assessments of this group. Similarly, critical illness, post-operative patients with sepsis and multi-organ failure may have delayed GE, at the risk of aspiration and re-feeding syndrome. Accurate energy requirements based upon REE along with multi-disciplinary meetings may reduce the risks and complications of artificial feeding.

Future research directions

1. Fat metabolism (adeponectin, leptin), other GI hormones (PYY, GIP) may also play an important role in the resolution of DM following surgery **(prospective study)**.

2. Exogenous administration of ghrelin on GI motility and its effect on other GI hormones may elaborate its role as a satiety hormone, in resolution of DM and weight loss **(prospective study)**.

3. GLP-1 as an ileal brake hormone is not fully understood. Assessment of GI transit after exogenous GLP may elaborate this function **(prospective study)**.

4. Long-term effects of GNM in the treatment of gastroparesis need to be studied. A prospective observational study using permanent GNM and close follow-ups may elaborate this function **(prospective and retrospective)**.

5. The role of GNM in the treatment of achalasia and gastroesophageal reflux disease **(temporary GNM) (prospective and retrospective)**.

6. A prospective study is required to compare the CE and breath test to validate them against GI scintigraphy **(trial on voluntary subjects)**.

7. The role of the MR scan in the assessment of GI motility disorders **(prospective trial)**.

Appendix 1: INFORMATION FOR PATIENTS

Improvement of glucose metabolism following bariatric surgery: is this mediated by alterations in gastrointestinal motility and gut peptides? A prospective observational study.

Hull and East Yorkshire Hospitals **NHS**

NHS Trust

Castle Hill Hospital
Castle Road
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East Yorkshire
HU16 5JQ

Date: 06/04/2009

Version: 2

Appendix 1: INFORMATION FOR PATIENTS

Improvement of glucose metabolism following bariatric surgery: is this mediated by alterations in gastrointestinal motility and gut peptides? A prospective observational study.

You are invited to take part in a research study. Before you decide, it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with others if you wish. Please ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part.

You may withdraw from the study at any stage.

What is the purpose of the study?

Gastrointestinal tract hormones and GI transit (emptying of stomach and the time taken by food in the intestine) play an important role in food intake, its absorption and further processes to be used in energy expenditure. Increased food intake or less energy expenditure may result in obesity (increased body weight). Obesity is related to several diseases like diabetes, high blood pressure, high cholesterol, etc. It can also lead to impaired function of insulin and glucose without diabetes.

It is thought that there is impaired (possibly increased) stomach emptying and IT (the time food remains in the intestine) in obesity, which leads to higher amount of calories (energy) available to be used. As this function is controlled by hormones (chemicals of the gastrointestinal tract), it is thought that their function is also impaired.

Obesity surgery results in improved glucose, insulin levels and also resolves diabetes. It is thought that this dramatic effect could be a result of changes in time taken by food to reach the last part of the small intestine and changes in hormones (chemicals of the gastrointestinal tract). How all these changes have a remarkable effect on glucose, insulin and diabetes is not understood. This study is designed and being conducted to look into these aspects.

Where is the research being conducted?
The research is being conducted at Castle Hill Hospital, Cottingham.

Why have I been chosen?
You are undergoing gastric bypass surgery and, according to your clinical details, you are eligible to participate.

What will I be asked to do?
You will be seen by a research doctor in addition to your consultant. If agreed to participate, you will be reassessed and:
1. You will be requested to sign a consent form.
2. You will be requested to attend for gastrointestinal motility and hormone tests on a separate date before operation. Tests will start at 9am and you will be required to stay with us for 6–7 hours.

3. You will be requested to attend for hormone tests 2 weeks after surgery. It will take 5–10 minutes only.

4. You will be requested to attend for gastrointestinal motility and hormone tests 6 weeks after operation. Tests will start at 9am and you will be required to stay with us for 6–7 hours.

A. Tests before operation

The tests will involve an overnight fast (not eating and drinking for 6 hours), and attending the Nuclear Medicine Department, Castle Hill Hospital, in the morning. A research fellow will be conducting all investigations will the help of the Nuclear Medicine Department. The researcher will site a cannula and take pre-procedure blood samples. The cannula will be reused to take more blood samples as described below. Five ml (millilitres) of blood will be drawn each time.

A standard meal containing isotope 99m Tc (radioactive material) will be given at this stage. Dynamic acquisition (continuous imaging) will be taken for 100 minutes followed by static acquisitions at fixed time points of 120, 180, 240, 360 and 480 minutes after the meal. Simultaneously, three more blood samples will be withdrawn from the cannula, the first at 30 minutes, the second at 60 minutes and last sample at the time food is seen in last part of the small intestine.

B. Two weeks after surgery: Tests will only require a 5 ml blood sample (after an overnight fast).

C. Six weeks after surgery: Tests will be conducted on the same lines as explained in the pre-op section above (A).

Timing of investigations	Venue	Fasting investigations	Post-radioisotope meal investigations
Pre-operative	Nuclear Medicine Department, Castle Hill Hospital, Cottingham	5 ml blood sample	Gamma camera scintigraphy (GI motility studies). 5 ml blood sample at 30 minutes

			5 ml blood sample at 60 minutes
			5 ml blood sample at the time food is seen in the last part of the small intestine.
2 weeks post-operation	OPD clinic	5 ml blood sample	
6 weeks post-operation	Nuclear Medicine Department, Castle Hill Hospital, Cottingham	5 ml blood sample	Gamma camera scintigraphy (GI motility studies). 5 ml blood sample at 30 minutes. 5 ml blood sample at 60 minutes. 5 ml blood sample at the time food is seen in the last part of the small intestine.

Table of time, venue and investigations

Do I have to take part?

No, you don't have to take part. It is entirely voluntary. Your decision whether or not to take part will not influence the treatment you receive whatsoever.

Is there any possible benefit to me if I take part?

There are no benefits as such for taking part in this study. However, if you do take part, you will be seen by research doctors as well as your normal team. This will inevitably result in extra medical attention.

Are there any risks, disadvantages or costs in taking part?

There are small risks related to radiation exposure. The amount of radiation used will be very small and hereby its comparison with other routine tests is explained.

1. The dose used in this test is 23–33 times less than a CT scan of the abdomen.

2. It is equal to 45 days of background radiation to which we are all exposed on a daily basis.

3. The radiation dose is 10 times less than in standard small bowel barium studies.

You will require a venflon (cannula) on the back of the hand or arm and four blood samples will be taken. Each time 5 ml blood samples will be required. These tests will be conducted before operation and 6 weeks after operation.

Another 5 ml blood sample will be required 2 weeks after surgery.

This study will not involve any medicine.

The fee for these tests will be paid by Scarborough Combined Gastroenterology Research Fund, Scarborough, and the Academic Surgical Unit, Castle Hill Hospital, Cottingham.

Please note: travel, parking and refreshments charges will be paid to you.

Will the information about me be kept confidential?
Yes, all your information will be kept absolutely confidential.

What will happen to the information about me after the study?
All the information collated will be analysed and we intend to publish the results of this research in peer-reviewed medical journals, reports, conference papers and posters. In addition, this study will be a part of an educational qualification, an MD thesis.

Importantly, your identity will be kept confidential at all times.

Can I withdraw from the study?
Yes, you may withdraw your consent and therefore withdraw from the study at any stage without needing to give a reason. This will not affect your legal rights or medical treatment in any way.

Thank you for taking the time to read this information sheet.

Please write down any questions and contact:

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