Effect of Diabetes Mellitus on Gastric Motility: an EGG Study

by

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ABSTRACT

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Longstanding diabetes mellitus is associated with gastrointestinal symptoms and disturbances of gastrointestinal motility. Diabetic patients with a history of microvascular and macrovascular complications such as retinopathy, nephropathy, and neuropathy frequently have diabetic gastroparesis. Diabetic gastropathy includes a number of neuromuscular dysfunctions of the stomach, including abnormalities of gastric contractility, tone, and myoelectrical activity in patients with diabetes. The main pathogenetic factors in diabetic gastroparesis are vagal autonomic neuropathy and, interstitial cells of cajal pathology. Slow waves and spike activities are the well-known components of stomach myoelectricity. Electrogastrography, a technique using electrodes positioned on the abdominal skin records gastric myoelectrical activity, or the gastric electrical slow wave, which is responsible for controlling the maximal frequency and the propagation of distal gastric contractions. Electrogastrography is one of the many tests of gastrointestinal function which were proposed to evaluate patients with unexplained nausea, vomiting and other dyspeptic symptoms. Understanding of the gastric neuromuscular function in diabetic patients may be an important component to consider in therapy, selecting appropriate drugs to regulate gastric emptying, and designing therapy for individual patients. However EGG has not been used commonly in clinical practice in order to diagnose or screen diabetic gastropathy. Therefore the main objective of this study is to record gastric myoelectrical activity of diabetic patients and healthy person with EGG in order to evaluate the impact of diabetes mellitus on gastric myoelectrical activity. Another objective of this study is to detect gastric spike potentials by using surface electrodes. At present, recording of the spike potentials from human by using surface electrodes are not reported while it was reported that cutaneous recording from dogs was achieved. In this study with a different approach from conventional EGG, the power spectrum was further analyzed for its major two peaks in the slow wave (2-15 cpm) and spike activity (50-100 cpm) ranges in order to show that high frequency waves may reflect peristaltic contractions.

Keywords: Diabetic gastroparesis, electrogastrography (EGG), gastric slow waves, spike potential, gastric motility.

ÖZET

Diabetes Mellitus'un Gastrik Motilite Üzerindeki Etkisi: bir EGG Çalışması

Uzun süreli diabetes mellitus gastrointestinal motilite bozukluğu ve gastrointestinal semptomlar ile seyreder. Retinopati, nefropati ve nöropati gibi mikrovaskuler ve makrovasküler komplikasyon hikayesi olan diabetik hastalarda sıklıkla diabetik gastroparezi gözlenir. Diabetik gastropati diyabet hastalarında gastrik kasılma, tonus ve mide kas hücrelerinin elektriksel aktivitesinde meydana gelen bir takım nöromusküler disfonksiyonu içerir. Diabetik gastroparezide gözlenen majör patoloji vagusa ait otonomik nöropati ve interstisyel cajal hücre patolojileridir. Yavaş dalga ve diken dalga potansiyelleri mide elektriksel aktivitesinin çok iyi bilinen unsurlarıdır. Abdominal deri üzerine yerleştirilen elektrodların kullanıldığı bir teknik olan Elektrogastrografi (EGG) mide elektriksel aktivitesini yani distal gastrik kasılmaların yayılımını ve maksimum frekansı kontrol eden gastrik elektriksel yavaş dalgaları kayıt eder. Elektrogastrografi açıklanamayan mide bulantısı, kusma ve diğer dispeptik şikayetleri bulunan hastaları değerlendirmede kullanılan gastrointestinal fonksiyon testlerinden biridir. Diabetik hastalarda gastrik nöromuskuler fonksiyonları anlamak gastrik boşalmayı düzenleyen ilacı seçmede ve kişiye uygun tedaviyi planlamada önemli katkı sağlayabilir. Ancak EGG klinik pratikte diabetik gastropatinin tanısı veya tarama amacıyla yaygın olarak kullanılmamaktadır. Bu yüzden bu çalışmanın ana amacı diyabetik hastalarda ve sağlıklı kişilerde mide elektriksel aktivitesini EGG ile kaydetmek ve diabetin mide elektriksel aktivite üzerine etkisini değerlendirmektir. Bu çalışmanın diğer bir amacı yüzey elektrotları kullanarak gastrik diken dalga potansiyellerini tespit edebilmektir. Bu güne kadar diken dalga potansiyellerinin kutanöz elektrodlar ile kaydedilebildiği köpeklerde gösterilmişken henüz insanlarda bildirilmemiştir. Bu çalışmada konvansiyonel EGG'lerden farklı bir yaklaşımla güç spektrumunda major iki zirve, yavaş dalga (2-15 dalga/dakika) ve diken dalga aktivitesi (50-100 dalga/dakika) analiz edilerek, tespit edilen yüksek freakanslı dalgaların peristaltik kasılmaları yansıtabileceği gösterildi.

Anahtar Sözcükler: Diabetik gastroparezi, elektrogastrografi (EGG), gastric yavaş dalgalar, diken dalga potansiyeli, gastrik motilite.

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DM	Diabetes Mellitus
EGG	Electrogastrography
ICC	Interstitial Cells of Cajal
SW	Slow Wave
CNS	Central Nervous System
VIP	Vasoactive Intestinal Peptide
GIS	Gastrointestinal System
FDA	Federal Drug Administration
FFT	Fast Fourier Transform
RSA	Running Spectral Analysis
AMS	American Motility Society
DF	Dominant Frequency
PDF	Power of Dominant Frequency
DFIC	Instability Factors of the Dominant Frequency
DPIC	Instability factors for the Dominant Power
ICD	International Classification of Diseases
HbA1c	Glycated Hemoglobin
cpm	cycles per minute

1. INTRODUCTION

1.1 Diabetes Mellitus

Diabetes mellitus (DM) is characterized by chronic hyperglycemia with disturbances of carbohydrate, fat, and protein metabolism resulting from defects in insulin secretion, insulin action, or both [3].

Type 1 diabetes is the form of the disease due primarily to β–cell destruction. This usually leads to a type of diabetes in which insulin is required for survival.

Type 2 diabetes is the most common form of diabetes. It is characterized by disorders of insulin action and insulin secretion, either of which may be the predominant feature. Usually, both are present at the time diabetes becomes clinically manifest. Type 2 diabetes frequently goes undiagnosed for many years because the hyperglycemia develops gradually and in the earlier stages is not severe enough to produce the classic symptoms of diabetes; however, such patients are at increased risk of developing macrovascular (coronary and peripheral vascular) and microvascular (optic, renal, neuropathic) complications

The effects of diabetes mellitus include long-term damage, dysfunction, and failure of various organs, especially the eyes, kidneys, heart, and blood vessels. Diabetes may present with characteristic symptoms such as thirst, polyuria, blurring of vision, weight loss, and polyphagia, and in its most severe forms, with ketoacidosis or nonketotic hyperosmolarity, which, in the absence of effective treatment, leads to stupor, coma, and death. Hyperglycemia sufficient to cause pathologic functional changes may quite often be present for a long time before the diagnosis is made. Consequently, diabetes often is discovered because of abnormal results from a routine blood or urine glucose test or because of the presence of a complication.

1.2 Gastrointestinal Function in Diabetes Mellitus

The stomach is a hollow organ composed primarily of muscle that serves as a storage container for food. The essential muscular functions of the stomach are to receive ingested foodstuffs, to mix the food with acid and pepsin, and to empty the nutrient suspension (chyme) with rhythmic peristaltic waves from the stomach into the small bowel for absorption. The ingested solid foods must be triturated, or broken down, into particles of less than 1 mm in diameter and then emptied in a coordinated manner for optimal digestion [4]. When the stomach's muscles are paralyzed, food is not thoroughly ground and does not empty into the intestine normally. The control of motility is performed by neuronal and hormonal factors that modulate the smooth muscles in generating muscular contractions. Likewise the diseases of stomach, some systemic diseases like diabetes mellitus may alter the gastrointestinal motility. Diabetes may be associated with several effects on gastrointestinal motor function. Diabetes mellitus is frequently associated with symptoms and disturbances of gastrointestinal motility and/or sensation. These include gastroparesis, accelerated emptying of liquids, oesophageal dysmotility, small intestinal dysmotility (including the pseudo-obstruction syndrome), delayed colonic transit, megacolon and fecal incontinence. The digestive system dysfunction in diabetes may result from diabetes itself or, more often, from diabetes-associated complications. Diabetic neuropathy plays an important role in motor and secretory abnormalities in the GI tract, in nausea, vomiting, and the syndrome of abdominal pain [5].

1.3 Diabetic Gastroparesis

Diabetic gastropathy is a term that encompasses a number of neuromuscular dysfunctions of the stomach, including abnormalities of gastric contractility, tone, and myoelectrical activity in patients with diabetes. These abnormalities range from tachygastria to antral hypomotility and frank gastroparesis [4]. Diabetic gastropathy is common and has been reported in up to 50% of patients with long-standing type 1 diabetes

mellitus. While most prevalent among those with type 1 diabetes, it is clear from recent studies that gastropathy may be equally prevalent among those with type 2 disease. In the general population, therefore, type 2 related gastropathy will be most common [6]. A substantial proportion of patients with either type 1 or type 2 diabetes mellitus have scintigraphic evidence of delayed gastric emptying of radiolabeled solid meals, which may or may not manifest in clinical symptoms. Conversely, many patients may have symptoms such as nausea, vomiting, early satiety, bloating, and abdominal discomfort or pain and yet have normal gastric emptying [7].

Patients with diabetes with a history of retinopathy, nephropathy, and neuropathy frequently have diabetic gastroparesis, a syndrome characterized by delayed gastric emptying that often develops after suffering from diabetes for at least 10 years. Cardinal symptoms of diabetic gastroparesis include nausea, vomiting, postprandial fullness, and bloating, in addition to heartburn, gastroesophageal reflux, lack of appetite, weight loss, and erratic blood glucose levels [8]. Gastroporesis seriously affects quality of life. There is deterioration in glycemic control and incapacitating symptoms such as malnutrition, water and electrolyte imbalance, and aspiration may occur. Diabetic gastropathy is thought to be a manifestation of autonomic neuropathy. The underlying cause of diabetic neuropathy, as well as other complications of diabetes, is hyperglycemia. The vagus nerve controls the movement of food through the digestive tract. If the vagus nerve is damaged, the muscles of the stomach and intestines do not work normally, and the movement of food is slowed or stopped. Diabetes can damage the vagus nerve if blood glucose levels remain high over a long period of time. High blood glucose causes chemical changes in nerves and damages the blood vessels that carry oxygen and nutrients to the nerves [9]. While the entire gastrointestinal tract may be affected by autonomic neuropathy, we will point out impaired gastric motility.

1.4 Diagnosis of Gastroparesis

Numerous techniques are available to evaluate and diagnose gastroporesis which of them are mostly invasive. Gastroparesis is usually diagnosed by demonstrating

delayed gastric emptying in a symptomatic patient after exclusion of other potential etiologies of symptoms and obstruction with endoscopy and radiological imaging. Therefore, most patients with suspected gastroparesis require upper endoscopy or radiographic imaging to exclude mechanical obstruction or ulcer disease. The presence of retained food in the stomach after overnight fasting and absence of obstruction in the endoscopy suggests that there is ineffective antral interdigestive motility, and this is suggestive of gastroparesis [10].

The most common method for diagnosing gastroporesis is a nuclear medicine test called a gastric emptying study, which measures the emptying of food from the stomach. For this study, a patient eats a meal in which the solid food, liquid food, or both contain a small amount of radioactive material. A scanner is placed over the stomach for several hours to monitor the amount of radioactivity in the stomach . The antroduodenal motility study is a study that can be considered experimental that is reserved for selected patients. An antroduodenal motility study measures the pressure that is generated by the contractions of the muscles of the stomach and intestine. This study is conducted by passing a thin tube through the nose, down the oesophagus, through the stomach and into the small intestine. With this tube, the strength of the contractions of the muscles of the stomach and small intestine can be measured at rest and following a meal. Electrogastrography (EGG) is defined as the recording of myoelectric activity of the smooth muscles of the stomach by means of cutaneous electrodes attached to the epigastric skin. The EGG signal reflects the myoelectrical events occurring in the stomach, much like the electrocardiogram summarizes electrical events occurringin the heart.

It was concluded that EGG can be regarded as a powerful non-invasive tool for the study of gastric rnyoelectric activity in both health and disease.The EGG diagnosis of gastric dysrhythmias provides new insights into gastric neuromuscular abnormalities and guides therapies to improve upper GI symptoms in patients with diabetes mellitus [4].

1.5 Objectives

The main objective of this study is non-invasively record gastric myoelectrical activity in patients with diabetes mellitus and healthy person, and evaluates the impact of diabetes mellitus on gastric myoelectrical activity. This study in some extend will be a continuation of the studies of Akin and Sun, and Özcan. Akin and Sun have been presented that the possibility of detecting the spike activity of the serosa in dogs from surface electrodes (Akin and Sun, 1999) and the spike activity signals from the abdominal surface recordings in dogs detected with an accuracy of 96% using a new detection algorithm based on a continuous wavelet transform (Akin and Sun, 2002).

We will perform a new analysis method of the motility information from the electrogastrogram signal that has been recorded at a higher sampler rate than the conventional approaches. This technique utilizes a power spectrum approach to calculate the power in the the 50-80 cycles per minute (cpm) activity that was previously noted to represent the spike activity range of the cutaneous signals of dogs. Comparison of the pre and post- prandial frequencies and power at the dominant frequency at the slow and spike activity range will be performed to evaluate the performance of our fEGG technique to the conventional approaches that use the slow wave as the reference.

2. ANATOMY AND BASIC PHYSIOLOGY OF THE STOMACH

2.1 Anatomy of Stomach

The stomach is an expanded section of the digestive tube between the esophagus and small intestine. Its characteristic shape is shown, along with terms used to describe the major regions of the stomach. The right side of the stomach is called the greater curvature and the left the lesser curvature. The most distal and narrow section of the stomach is termed the pylorus as food is liquefied in the stomach it passes through the pyloric canal into the small intestine (Fig.2.1).

The wall of the stomach is structurally similar to other parts of the digestive tube, with the exception that the stomach has an extra oblique layer of smooth muscle inside the circular layer, which aids in performance of complex grinding motions (Fig.2.1) [11].

In the empty state, the stomach is contracted and its mucosa and submucosa are thrown up into distinct folds called rugae; when distended with food, the rugae are "ironed out" and flat.

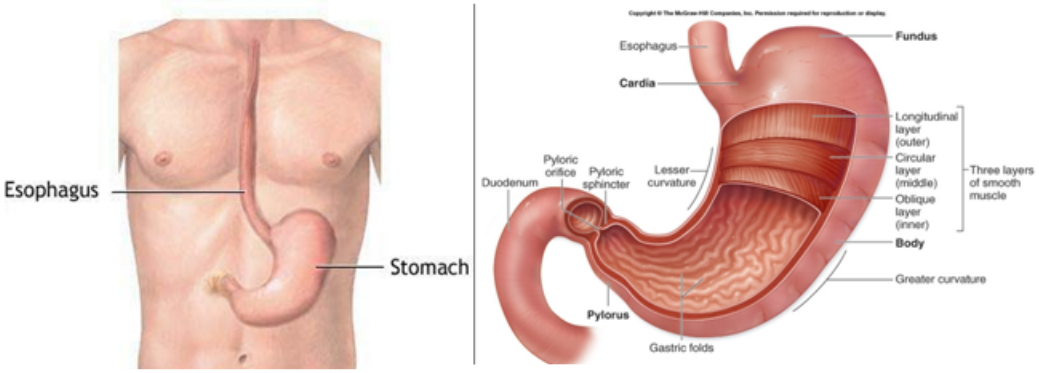

Figure 2.1 (A) Location and (B) Anatomy of Stomach

2.2 Functions of Stomach

The stomach is a sophisticated muscle with intrinsic rhythmicity. The essential muscular functions of the stomach are to receive ingested foodstuffs, to mix the food with acid and pepsin, and to empty the nutrient suspension (chyme) with rhythmic peristaltic waves from the stomach into the small bowel for absorption. The ingested solid foods must be triturated, or broken down, into particles of less than 1 mm in diameter and then emptied in a coordinated manner for optimal digestion. Healthy individuals experience pleasant, satisfying sensations in the epigastrium after meals. These pleasant postprandial sensations occur while the stomach is performing the muscular work of gastric emptying. In contrast, many patients with diabetic gastropathy experience dyspepsia-like symptoms of nausea, unpleasant epigastric fullness, early satiety, vague epigastric discomfort, and intermittent vomiting after meals [10].

2.3 Neuromuscular Activity of Stomach

The purpose of stomach physiological functions includes secretion, digestion, mixing and emptying. In order to achieve this, controlled mechanisms are required to coordinate ordered movement. Efferent signals from the higher neuronal levels of central, spinal and enteric nervous systems determine stomach motility. These systems also modulate reflex responses following stimulation in the afferent pathways including the emotional and humoral states.

During ingestion of a meal, the fundus or proximal stomach must relax to receive or accommodate the volume of food. Relaxation of the fundus is mediated by vagal efferent fibers via nitric oxide pathways. Receptive relaxation is the initial neuromuscular activity of the proximal stomach as a meal is ingested (Fig.2.2) [4].

During and after ingestion of the meal, regular gastric contractile activity begins in the body-antrum (the distal stomach) to mix and triturate the ingested food

(Fig.2.2). The period before emptying begins lasts about 30-40 min depending on caloric and physical characteristics of the food. This period is the lag phase. For example, hyperosmolar and fatty foods delay the rate of gastric emptying and prolong the lag phase. Once gastric emptying begins, nutrients are emptied by recurrent peristaltic contractions of the body/antrum. This is the linear phase of gastric emptying. Roughage in the form of salad vegetables and fiber require prolonged trituration and are emptied very slowly. These materials are retained and emptied last or during phase III of the fasting interdigestive period of gastric motility [12].

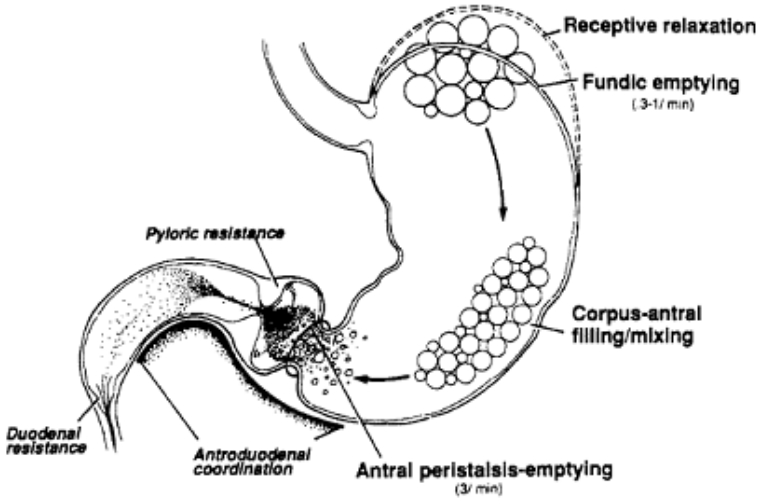

Figure 2.2 Neuromuscular Work Performed by the Stomach. Postprandial gastric motility events include fundic receptive relaxation to accommodate the ingested food, and recurrent gastric peristaltic contractions in the corpus and antrum for mixing and emptying the chyme into the duodenum. Gastric peristalsis occurs at approximately 3/min. Antroduodenal coordination is necessary for efficient emptying.

Gastric peristalsis is controlled by the intrinsic electrical activity of gastric pacemaker cells, the interstitial cells of Cajal (ICC). The gastric pacemaker area is located in a region at the junction of the fundus and body on the greater curvature (Fig.2.3). Gastric pacesetter potentials or slow waves depolarize and repolarize at a frequency of approximately 3 cycles per min (cpm) as recorded by serosal or cutaneous electrodes. The slow waves coordinate the frequency and propagation of circular muscle contractions in the body and antrum. Circular muscle contractions occur during plateau and action potentials, which are affected by ongoing neural and hormonal inputs as well as physical characteristics of the meal (Fig.2.4) [4].

The results of normal postprandial gastric neuromuscular activity are the regulated presentation of nutrients to the duodenum (2-4 mL of chyme/antral peristaltic wave) and pleasant epigastric sensations. In the duodenum, the chyme stimulates appropriate release of gastric inhibitory polypeptide and glucagon-like polypeptide, cholecystokinin and secretin to ensure optimal secretion of insulin, pancreatic enzymes and bile, respectively, to complete the digestion and absorption of ingested nutrients-the carbohydrate, fat, and protein in the meal [4].

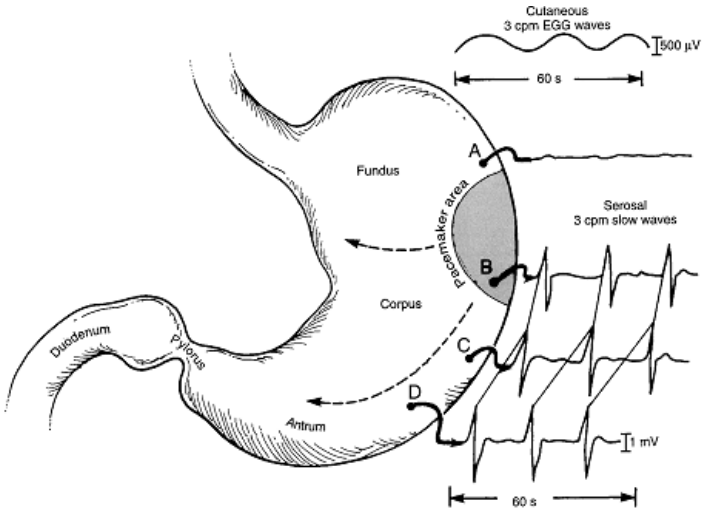

Figure 2.3 Gastric Pacemaker Area. Gastric pacesetter potentials or slow waves originate from the pacemaker area on the greater curve. Pacesetter potentials travel in a circumferential and aboral direction at a rate of approximately 3 cycles per minute (cpm). The cutaneously recorded electrogastrogram shows a 3-cpm wave pattern. The fundus has no rhythmic electrical activity.

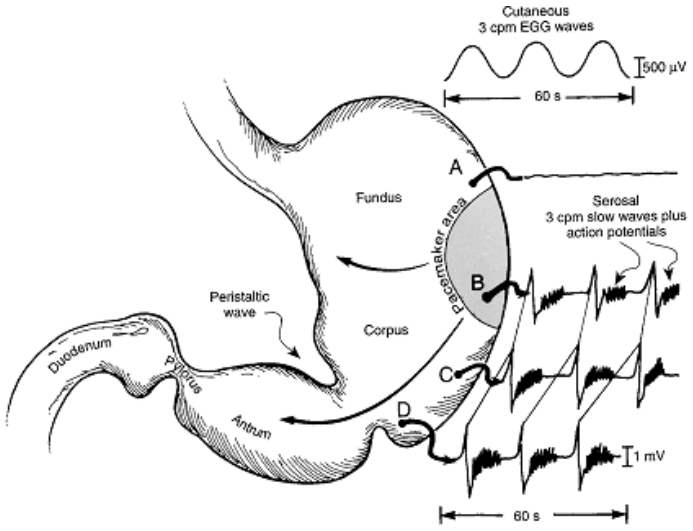

Figure 2.4 Potentials or Action Potentials are linked to the propagated pacesetter potentials to produce gastric peristaltic contractions. The amplitude of the electrogastrogram waves is increased during these myoelectrical events.

2.4 Myoelectrical Activity of Stomach

The stomach muscle itself presents a myogenic character to mediate stomach motility. Both slow wave (SW; electrical control activity) and spike (electrical response activity) are the well-known components of stomach myoelectricity [2].

2.4.1 Slow Waves

Most gastrointestinal contractions occur rhythmically and this rhythm is determined mainly by the frequency of the so-called "slow waves" in the smooth muscle membrane potential (Fig 2.3). These waves are not action potentials. Instead, they are slow, undulating changes in the resting membrane potential. Their intensity usually varies between 5 mV and 15 mV and their frequency ranges in different parts of the human GI tract between 3 cycles per minute (cpm) and 12 cpm: about 3 cpm in the body of the stomach., as much as 12 cpm in the duodenum and changing about 8 or 9 cpm in the terminal ileum. The slow waves themselves do not directly cause muscle contraction. However, they do control the appearance of intermittent spike potentials and the spike potentials in turn cause the muscle contraction [13].

2.4.2 Spike Potentials

The spike potentials are true action potentials. They occur automatically when the resting potential of the gastrointestinal smooth muscle becomes more positive than about -40mV (the normal resting potential is between -50 and -60mV). Thus, each time the peaks of the slow waves rise temporarily above the -40mV, spike potentials appear on these peaks. Also, the higher the slow wave potential raises above this level, the greater the frequency of the spike potentials, usually ranging between 1 and 10 spike per second (Fig 2.4). The spike potentials last 10 to 40 times as long in the gastrointestinal muscle as the action potentials as the action potentials in large nerve fibers each lasting as long as 10 to 20msec [13].

2.5 Neural Control of Gastrointestinal Function

The gastric myoelectrical and contractile activities that occur during these physiologic functions are controlled by extrinsic (parasympathetic and sympathetic) and intrinsic (enteric) nervous system activity. The autonomic nervous system links the activity of the central nervous system (CNS) and the enteric nervous system in order to modulate gastrointestinal motility [2].

The gastrointestinal system has a nervous system all its own called the enteric system. It lies entirely in the wall of the gut, beginning in the esophagus and extending all the way to the anus. The number of the neurons in this enteric system is about 100000000, almost exactly equal to the number in the entire spinal cord; this illustrates the importance of the enteric system for controlling gastrointestinal function. It especially controls the movements and secretion [14].

The digestive system is innervated with nerve fibres of both the sympathetic and parasympathetic divisions, although the parasympathetic control dominates. Movements of the gastrointestinal tract are brought about by smooth muscle activity. There is an outer longitudinal layer, an inner circular layer, and a submucosal muscle layer (muscularis mucosae) with both circular and longitudinal fibres that moves the villi of the mucosa. The inner surface is lined with mucosal epithelium. The outer muscle layer is covered by the serosa, which is continuous with the mesentery containing blood vessels, lymph vessels and nerve fibres [14].

The parasympathetic system increases digestive activity (secretion and motility), and the sympathetic system has a net inhibitory effect. The generally inhibitory digestive effects of the sympathetic nervous system are caused indirectly by vasoconstriction, which reduces blood flow in the digestive tract [14].

The intrinsic, enteric nervous system consists of two sets of nerve plexi. The submucosal Meissner plexus mainly regulates the digestive glands, whereas the myenteric Auerbach plexus, located within the muscle layers, is primarily connected with gut

motility. The nerve plexi contain local sensory and motor neurons as well as interneurons for communication. Motor neurons in the myenteric plexus release acetylcholine and Substance P. Acetylcholine contracts smooth muscle cells, when bound to muscarinic receptors. Inhibitory motor neurons release vasoactive intestinal peptide (VIP) and nitric oxide (NO). These molecules relax smooth muscle cells [14].

3. GASTROINTESTINAL FUNCTION IN DIABETES MELLITUS

Diabetes mellitus is frequently associated with symptoms and disturbances of gastrointestinal motility and/or sensation. The reported prevalence of delayed gastric emptying in patients with longstanding diabetes has ranged from 28-65%; however, the relationship between symptoms and delayed emptying is variable. Some studies have shown that the prevalence of symptoms was not generally higher in patients with diabetes compared to volunteers without diabetes; indeed, some patients with delayed gastric emptying are asymptomatic [5].

Patients with diabetes mellitus have reduced frequency of antral contractions, antroduodenal incoordination, and pyloric spasm. Increased compliance of the proximal stomach and abnormal postprandial proximal gastric accommodation and contraction may contribute to the development of delayed gastric emptying. Since delays in gastric emptying rates are commonly observed in patients with diabetes, clinicians may find it difficult to differentiate gastroparesis from the functional delay in gastric emptying that often occurs in the setting of significant hyperglycaemia.

The fact that delayed gastric emptying can also be observed in nondiabetic individuals under experimental conditions in which hyperglycaemia is artificially induced suggests that a delay in gastric emptying rate when blood glucose concentrations are high is actually an appropriate physiological response to hyperglycaemia, slowing further increases in blood glucose [5]. According to these studies, increasing plasma glucose from normal levels to 230 mg/dl significantly decreased the antral motility index in healthy subjects. Also it was shown that the percentage of tachygastria activity increased signifcantly as plasma glucose was increased from normal to 230 mg/dl using the glucose clamp technique [12].

3.1 Diabetic Gastroparesis

Diabetic gastropathy is defined as a symptom complex with functional, contractile, electrical, and sensory dysfunction of the stomach associated with diabetes. In its classical form, called diabetic gastroparesis, it is associated with delayed gastric emptying [3].

The American Gastroenterological Association defines gastroparesis as a symptomatic chronic disorder of the stomach characterized by delayed gastric emptying in the absence of mechanical obstruction [5]. Diabetic gastroparesis is characterized by a significant impairment of gastric emptying, accompanied by severe nausea, vomiting, malnutrition, and often weight loss. There is deterioration in glycemic control and incapacitating symptoms such as malnutrition, water and electrolyte imbalance, and aspiration may occur. Therefore, gastroparesis seriously affects quality of life.

Gastroparesis has been found in up to 50% of patients with type 1 diabetes mellitus and 30% of patients with type 2 diabetes mellitus [4]. While most prevalent among those with Type I diabetes, it is clear from recent studies that gastropathy may be equally prevalent among those with Type II disease

3.2 Hyperglycemia and Diabetic Autonomic Neuropathy

Diabetic gastropathy is thought to be a manifestation of autonomic neuropathy. The underlying cause of diabetic neuropathy, as well as other complications of diabetes, is hyperglycemia [7].

The digestive system dysfunction in diabetes may result from diabetes itself or, more often, from diabetes-associated complications. Diabetic neuropathy plays an important role in motor and secretory abnormalities in the GI tract, in nausea, vomiting, and the syndrome of abdominal pain. Diabetic angiopathy and vascular

complications play a role in the pathogenesis of intestinal ischemia, and in the nerve and muscle dysfunction of diabetic gastroenteropathy [3].

In diabetes, any one or several of the various components of the nerve elements that control gut function may be involved. The extent of neuropathy appears related to the duration of diabetes and the age of patients. Diabetic enteric neuropathy is responsible for many of the GI abnormalities in these patients. The wide spectrum of possible enteric neuropathies may explain the wide range of GI dysfunction in the patient with diabetes.

The vagus nerve controls the movement of food through the digestive tract. Loss of vagal tone and increased sympathetic nervous system activity has been associated with gastric dysrhythmias, and this may be a factor in the development of gastric dysrhythmias in some diabetic patients. Damage to enteric neurons or interstitial cell of Cajal or subtle dysfunction of these elements may also be mechanisms of diabetic gastropathy.

Diabetes can damage the vagus nerve if blood glucose levels remain high over a long period of time. High blood glucose causes chemical changes in nerves and damages the blood vessels that carry oxygen and nutrients to the nerves [9].

The pathophysiology of the neuropathic complications of diabetes follows one of at least two pathways. The first is nonenzymatic glycosylation, which occurs when a persistently elevated blood glucose level results in the excessive glycosylation of proteins such as hemoglobin, other circulating molecules, and cellular structures. This leads to the development of advanced glycosylation end products, impairing the normal function of tissues including collagen and basement membranes of cells and capillaries [7].

The second pathway is enhanced activity of the polyol pathway, in which glucose is converted to sorbitol via the enzyme aldose reductase. This results in a decrease in tissue myoinositol, with far-reaching effects throughout the nervous system. As the integrity of cellular information, including the sodium-potassium ATPase system is

disrupted, nerve conduction velocity is diminished and the anatomy of nerve fibers is altered [7].

Diabetic neuropathy can impair function anywhere in the nervous system. In the gastrointestinal tract, it causes, in effect, an autovagotomy. In addition, hyperglycemia results in cellular anatomic disruption throughout the gastrointestinal tract, but especially in the stomach. Nerve cells may swell with the loss of myelinated fibers, and smooth muscle cells may become rounded and hyalinized. In the stomach, motility may be reduced in the antrum and proximal stomach and there may also be pylorospasm.

Hyperglycemia also has secretory effects in the stomach, including decreased secretion of hydrochloric acid. The net result of these changes is a reduction in effective emptying, starting first with indigestible solids, then progressing to digestible solids, and eventually to liquids. The myoelectric and neuroanatomic consequences of hyperglycemia may be accentuated by abnormal secretion of various hormones, including glucagon, gastrin, cholecystokinin, and gastric inhibitory peptide in patients with diabetes.

3.3 Gastric Motor Abnormalities in Diabetes Mellitus

Vagal dysfunction can result in abnormal receptive relaxation of the stomach, decreased gastric antral contractility with failure of the antral pump, and prolonged contraction of the pylorus resulting in pylorospasm. Neuropathy of the gastric enteric nervous system can exacerbate vagal dysfunction and may contribute to gastric myoelectric dysrythmias. Hyperglycemia itself can disrupt normal gastric motility and delay gastric emptying [15].

Various neuromuscular and myoelectrical abnormalities may afflict the stomach in patients with diabetes mellitus as summarized in Table 3.1.

Table 3.1
Gastric Motor Abnormalities in Diabetes Mellitus

Gastric Contractions
1.Reduced amplitude of fundic contractions
2.Reduced amplitude of antral contractions
3.Reduced frequency of antral contractions
4.Absence of antral interdigestive migrating motor complex(IMMC)
5.Periods of sustained high-frequency, nonpropagated contractions
6.Pylorospasm
Electrogastrographic findings
1.Tachygastria
2.Bradygastria
3.Flat Pattern
4.Absence of postprandial increase in strength of slow waves
Delay in gastric emptying
1.Liquids:variable
2.Digestible solids:frequent
3.Indigestible solids:very frequent

3.3.1 Gastric Dysrhythmias

Gastric dysrhythmias are defined as bradygastrias (1.0±2.4cpm activity), tachygastrias (3.6±.9 cpm activity) or tachyarrhythmias, which are a combination of both bradygastrias and tachygastrias. Gastric dysrhythmias interfere with the normal 3-per-minute gastric peristaltic contractions, which mix and empty food from the stomach [12].

3.3.2 Antral Hypomotility

Antral hypomotility has been recorded with intraluminal pressure transducers in patients with diabetes mellitus. Poor antral contractility results in delayed emptying of food from the stomach and gastroparesis. Low amplitude or irregular contractions of the antrum also lead to poor antral- duodenal coordination in the function of providing the proper peristaltic waves to empty chyme into the duodenum [12].

3.3.3 Antroduodenal Coordination

The most efficient movement of chyme from the stomach to the duodenum requires antroduodenal coordination. The pylorus and duodenum offer resistance to emptying of chyme from the antrum. Pylorospasm or uncoordinated pyloric contractions provide resistance to gastric emptying and has been reported as a cause of delayed gastric emptying in diabetic patients [12].

3.3.4 Gastric Tone

In diabetic patients the fundic tone does not relax normally in response to balloon distension when compared with control subjects. Fundic tone abnormalities may also have a role in dyspepsia-like symptoms experienced by diabetic patients. Figure 3.1 illustrates and Figure 3.2 summarizes the various neuromuscular abnormalities that may afflict the stomach in patients with diabetes mellitus. In the patient at the extreme end of the spectrum, diabetic gastroparesis, gastric dysrhythmias, dilated antrum, and antral hypomotility may all be present and represent the underlying pathophysiology of symptoms. Pylorospasm and duodenal resistance may contribute to the delay in gastric emptying. Other patients may have predominantly dilated antrum or gastric dysrhythmias as the primary pathophysiologic event that correlates with meal-related symptoms.

3.3.5 Delay in Gastric Emptying

Some patients with diabetes mellitus and dysmotility-like dyspepsia have gastric dysrhythmias but normal gastric emptying. While gastric dysrhythmias were associated with upper GI symptoms, the dysrhythmia did not necessarily indicate or result in delayed gastric emptying. Thus, there is a spectrum of neuromuscular disorder of the stomach that ranges from gastric dysrhythmia alone to gastric dysrhythmia with delayed gastric emptying [4].

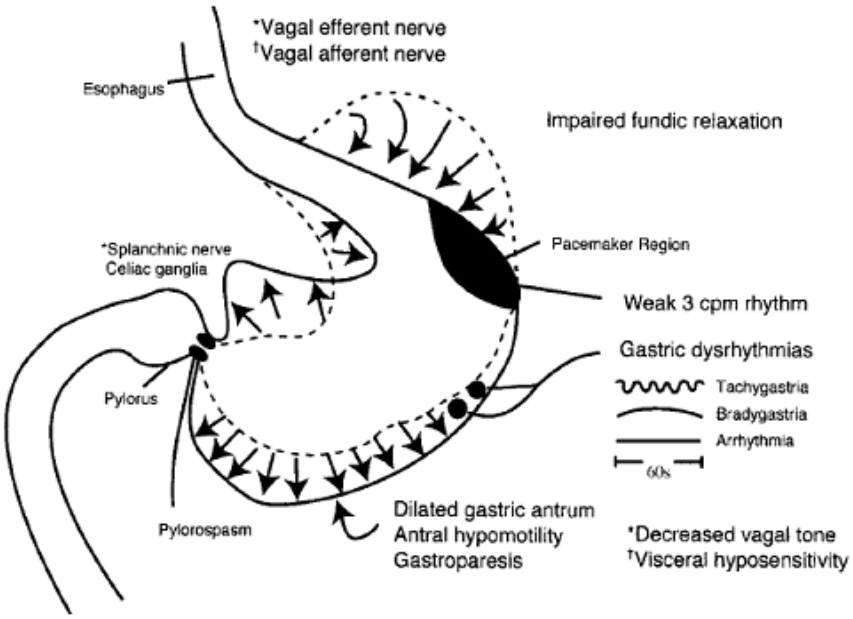

Figure 3.1 The Spectrum of Gastric Neuromuscular Abnormalities in Diabetic Gastropathy.

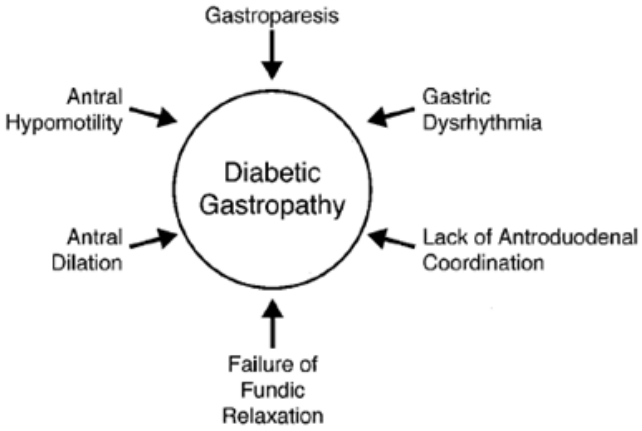

Figure 3.2 Elements of Diabetic Gastropathy

Gastric dysrhythmias and delayed gastric emptying may also be intermittent and reversible, even in patients with diabetes. In healthy individuals in whom the plasma glucose is increased to over 240 mg/dL, tachygastrias develop and the rate of gastric emptying is slowed. Hyperglycemia (.240 mg/dL) also decreases gastric emptying in patients with diabetes. A vicious circle may develop wherein disordered neuromuscular function of the stomach is acutely worsened by hyperglycemia [4].

The motor activities of various parts of the stomach are well designed to regulate the emptying of different physical constituents of food, so that the liquid and digestible solid components are emptied in the digestive period (within 2 to 3 hours after ingestion) and indigestible solids are emptied from the stomach during the interdigestive period (2 to 3 hours after a meal). In diabetic gastroparesis, gastric emptying of all these components is affected to varying degrees, depending upon the stage of the disease and the underlying pathophysiologic defects. Figure 3.3 shows patterns of gastric emptying of liquids and solids in one patient with diabetic gastroparesis and in a normal control. Figure 3.4 shows patterns of gastric emptying of indigestible solids in normal and diabetic subjects [3].

3.4 Diagnosis of Gastroparesis

Understanding of the gastric neuromuscular function in the patient with type I or type II diabetes mellitus is an important component to consider in dietary therapy, selecting appropriate drugs to regulate gastric emptying, and designing insulin therapy for individual patients

Diagnostic tests that measure gastric myoelectrical activity and gastric emptying are indicated when the results of standard diagnostic tests are negative and symptoms persist. There are a number of methods available for assessing gastric myoelectrical and contractile events shown in Figure 3.5 [12]. Some tests are invasive and are used primarily for research studies, others are noninvasive and available for clinical use.

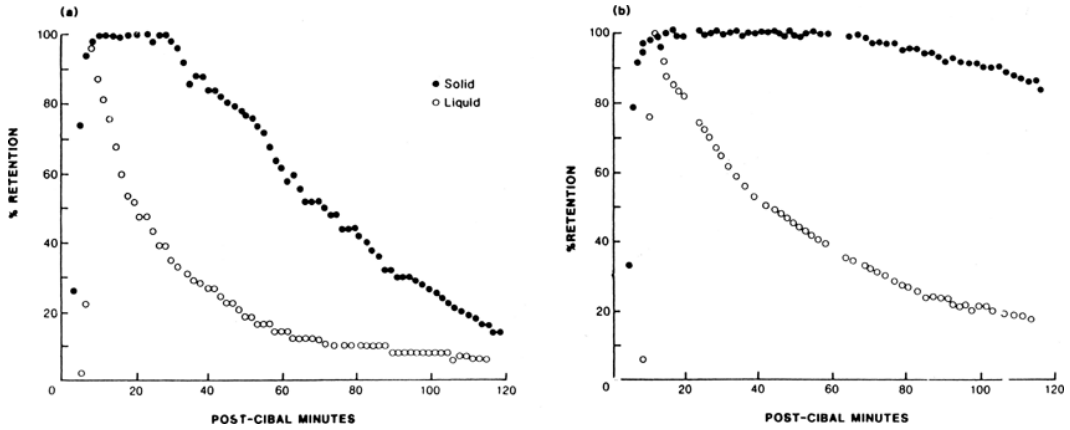

Figure 3.3 Gastric Emptying of (A) Healthy Subject and (B) Diabetic Patient. Gastric emptying of solids and liquids in one control subject (A) and a diabetic patient with autonomic neuropathy (B). Note that emptying of solids is slower than that of liquids and both solid and liquid emptying are slower in the diabetic patient.

The most common method for diagnosing gastroparesis is a nuclear medicine test called a gastric emptying study, which measures the emptying of food from the stomach. For this study, a patient eats a meal in which the solid food, liquid food, or both contain a small amount of radioactive material. A scanner is placed over the stomach for several hours to monitor the amount of radioactivity in the stomach [10].

The noninvasive 13C-labeled breath test is an indirect means of measuring gastric emptying. 13C-labeled foods are ingested and the 13C exhale d in breath is determined. For the 13C to be present in the breath, it must be emptied from the stomach, absorbed from the intestine, metabolized by the liver, secreted into the blood, and finally expired from the lungs for measurement. The rate of emptying of the food from the stomach is then estimated [10].

Ultrasonography is a noninvasive tool for evaluating gastric wall motion and gastric emptying of liquids, but considerable expertise in stomach imaging and interpretation is required. The emptying of liquids from the stomach can be measured with this technique [12].

Magnetic resonance imaging can accurately measure gastric emptying rates but is expensive, time consuming, and facilities are limited.

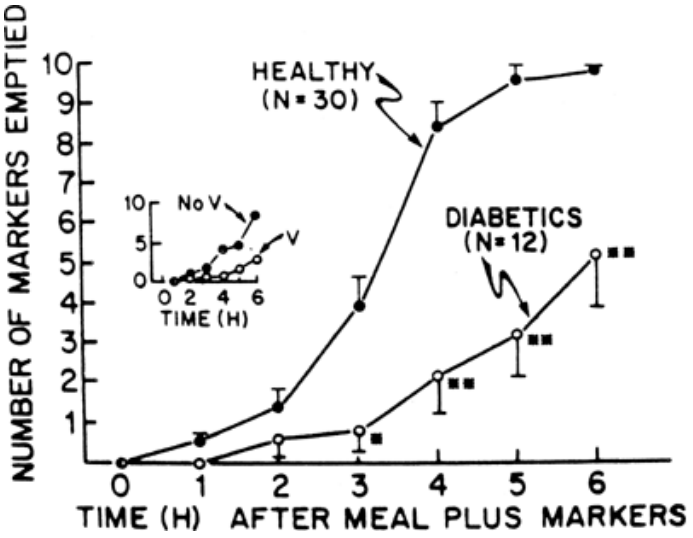

Figure 3.4 Emptying of Solid Radiopaque Markers in 30 healthy subjects and 12 patients with diabetes. Emptying of solid radiopaque markers was significantly delayed in diabetic patients ($p < 0.01$ vs. controls at 3 hours; $p < .001$ at 4, 5, and 6 hours).

Test	*Measures*	*Advantages*	*Disadvantages*
Gastric scintigraphy	Rate of stomach emptying	Noninvasive; solid- and liquid-phase studies; assesses global stomach neuromuscular activity	Wide normal range; radiation exposure; takes 2–4 hr
Electrogastrography	Gastric myoelectrical activity	Noninvasive; easily repeated	Movement artifact; difficult to interpret
Ultrasonography	Rate of emptying; antral diameter	Noninvasive	Requires expertise in imaging and interpretation; more accurate for liquid than solid emptying
Magnetic resonance imaging	Rate of emptying	Noninvasive	Time-consuming; expensive
Breath tests ^{13}C	Indirect measure of emptying	Noninvasive	Requires normal intestinal absorption, liver metabolism, lung function
Antroduodenal manometry	Assesses lumen-occluding contractions	Distinguishes fasting and postprandial contraction patterns	Invasive; radiation exposure; time-consuming (>4 hr); stressful for patient; recordings difficult to interpret

Figure 3.5 Methods for Evaluating Gastric Myoelectrical Activity and Motility

Antroduodenal manometry involves the positioning of a cathetering the antrum and duodenum with fluoroscopic guidance for intraluminal pressure measurements during fasting and postprandial periods. Small intestinal manometry can detect patterns reflecting disorders of neuropathic versus myopathic origin. Antroduodenal and intestinal motility tests are invasive, require fluoroscopy, are stressful for patients, and recordings can be difficult to interpret [12].

Electrogastrography (EGG) noninvasively measures fasting and postprandial gastric myoelectrical activity. EGG records gastric myoelectric activity via electrodes placed on the skin in the epigastrium. EGG accurately reflects the normal 3 cpm

electrical rhythm and abnormal gastric dysrhythmias termed tachygastrias (3.6 ± 9.9 cpm) and bradygastrias (1.0 ± 2.4 cpm) [12].

4. ELECTROGASTROGRAPHY

Electrogastrography (EGG) is a technique for recording gastric myoelectrical activity using cutaneous electrodes placed on the anterior abdominal wall overlying the stomach. The recorded signal is called an electrogastrogram. Direct comparisons with serosal electrodes have demonstrated that surface electrogastrography accurately records a representation of gastric slow wave activity. The greatest advantage of EGG is its non-invasiveness.

The first human EGG was recorded by Alvarez as early as 80 years ago. Unfortunately, EGG progress in clinical medicine had been slow compared to the marked success achieved by the electrocardiography. A major breakthrough in EGG evolution occurred in the last two decades due to the rapid development in computer science and medical engineering. Today EGG is popular throughout the world for clinical medicine and investigators. The Federal Drug Administration (FDA) approved EGG as a test for patient evaluation in 2000. The FDA statement on EGG concluded that EGG is a noninvasive test for detecting gastric slow waves and is able to differentiate adult patients with normal myoelectric activity from those with bradygastrias and tachygastrias. EGG can be considered as part of a comprehensive evaluation of adult patients with symptoms consistent with gastrointestinal motility disorders [1].

The limitations of EGG evolution include difficulties in recording and acquisition of very weak-amplitude signals due to the paucity of standardized methodology in terms of electrode positions, recording periods, test meals, analytic software and normal reference values.

Appropriate application of non-invasive EGG can provide more information and insight in understanding the mechanisms that regulate stomach motility.

4.1 Measurement and Recording of the EGG

Gastric myoelectrical acivity can be measured serosally, intraluminally, or cutaneously. Serosal or intraluminal electrodes can record both slow waves and spikes, since these recordings represent myoelectrical activities of a small number of smooth muscle cells. As these methods are invasive, their application is limited to the laboratory animal studies.

A weighed summation of gastric myoelectrical activity of various regions of the stomach is represented in an EGG recording. The weight is dependent on the distance between the signal source and recording electrodes.

Non-invasive EGG recording does mainly provide the SW information in terms of rhythmicity, frequency, amplitude and propagation Although some studies have shown that cutaneous electrodes are only able to pick up the rhythm of the slow waves, but not the spikes, a few study has shown that (Akin and Sun 1999, 2002), there is a possibility of detecting the spike activity of the serosa from the surface electrodes using the appropriate equipment (fEGG) and analytic algorithm[16][17].

4.1.1 Equipment

Several components are necessary for the performance of EGG. The EGG signals are acquired using electrocardiographic electrodes affixed to the skin of the abdominal wall. Pregelled adhesive Ag/AgCl electrodes frequently are employed because they facilitate reliable acquisition of the cutaneous signal for the duration of a typical clinical study. Amplifiers and filters are needed to process the EGG signal for subsequent analysis; usually these are in one unit. Amplifiers are required because of the relatively weak gastric signal acquired by the cutaneous electrodes (200-500 μV). Low and high band pass filters at 0.016 and 0.3 Hz, respectively, help to eliminate baseline drift, exclude signals from other sources (heart, small intestine and some colonic frequencies), and remove some artefacts occurring as a consequence of respiration and movement.

Computers employed for EGG analysis must possess specific characteristics. An analogue to-digital (A-D) board is needed to digitize the signal at frequencies ranging from 1 to 4 Hz. Software has been developed for preprocessing excision of motion or respiratory artefacts. Signal analysis is performed with Fast Fourier transformation (FFT) and running spectral analysis (RSA) or adaptive running spectral analysis [1].

4.1.2 Patient Preparation

EGG recordings most often are performed after overnight fasting. Some institutions have advocated ingestion of a pretest meal including four ounces of apple juice and one slice of toast 2 h before testing to enhance detection of the basal waveform, however this practice does not permit recording of a true fasting signal. Medications that might modify gastric myoelectrical activity (prokinetic and anti-emetic agents, narcotic analgesics, anticholinergic drugs, non-steroidal antiinflammatory agents) should be stopped at least 48 h prior to testing. Other medications which influence slow wave activity, such as anti-depressants and oral contraceptives, may be difficult to stop for the purposes of EGG recording. Hyperglycaemia in excess of 230 mg/ dL has been demonstrated to disrupt normal EGG rhythm in healthy volunteers [18]. Furthermore, normalization of blood glucose levels prior to testing reduces gastric dysrhythmic activity in patients with type I diabetes. For these reasons, it is reasonable to recommend performance of EGG under conditions of euglycaemia to better gauge underlying gastric myoelectric properties in the absence of modulating metabolic factors.

4.1.3 Electrode Replacement

Proper EGG electrode placement is important to ensure acquisition of a high quality gastric myoelectric signal. Any hair on the skin overlying the stomach should be shaved to improve conduction. The skin should be gently abraded with gauze or a specific electrode paste. Fresh disposable electrocardiographic electrodes that adhere securely to the skin are employed often in concert with an electrode cream to improve

signal transmission.

No standardized position has been agreed on until now. Several different electrode placements have been described to reliably record gastric myoelectrical activity are shown in Fig 4.1 [1][19]. Use of a bipolar electrode system is recommended to reduce artefact and improve the signal-to-noise ratio. Because the antrum has the greatest SW amplitude among various portions of the stomach, investigators recommend that the placed electrodes should approach the antrum as close as possible along the long axis of stomach to obtain the best signals. It is uncertain how many electrodes should be used to record a fine SW. Most likely, channel number depends upon the interest of investigators and how many channels they could use for their EGG systems.

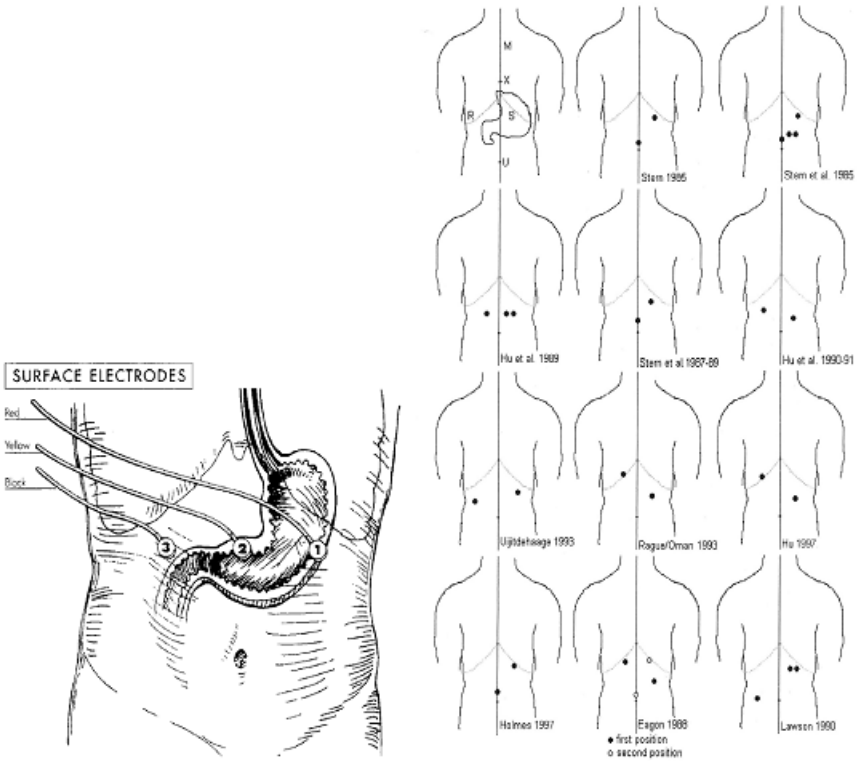

Figure 4.1 A, B Alternative Electrode Positions Used for EGG Recording

4.1.4 EGG Recording

The EGG should be recorded in a quiet room to minimize extraneous electrical signals which might be detected by the cutaneous electrodes and reduce distractions

which could promote patient movement. The patient may be placed in any conformation ranging from a supine position to a 45° inclination, as long as the patient's position and comfort are maintained for the duration of testing. Changes in position can alter EGG parameters relating to signal amplitude, thus the patient should remain motionless for the duration of the recording.

After appropriate patient preparation, EGG recording is performed. A fasting signal is acquired for 15-60 min. The patient then consumes a test meal and a stimulated EGG signal is recorded for 30-120 min. The optimal lengths of recording have not been validated in controlled investigations, however it has been observed that longer study durations enhance detection of EGG rhythm disturbances. It was the consensus opinion of the AMS (American Motility Society) Clinical GI Motility Testing Task Force that a 30-min fasting recording and a 60-min postprandial EGG recording are obtained. A variety of test meals have been employed by different institutions including water, commercially prepared balanced liquid nutritional supplements and solid meals similar to those used in gastric emptying testing (e.g., egg sandwich with orange juice). Each meal produces qualitatively similar effects on the EGG signal, although effects of water ingestion on signal amplitude are shorter in duration [1].

4.2 Interpretation of EGG Records

Analysis of a well-performed EGG examination yields specific findings which can be related to the referring clinician. A normal EGG is characterized by a waveform with a frequency of approximately 3 cpm wave activity that increases in amplitude (or power) after meal ingestion. Electrogastrography tracings from a healthy volunteer is given in Fig.4.2.

Rhythm abnormalities observed with EGG include tachygastria, bradygastria, and a non-specific dysrhythmia or lack of a single dominant frequency (DF) is given in Fig.4.3. In Table 4.1 rangesof slow wave frequency determined in various clinical studies

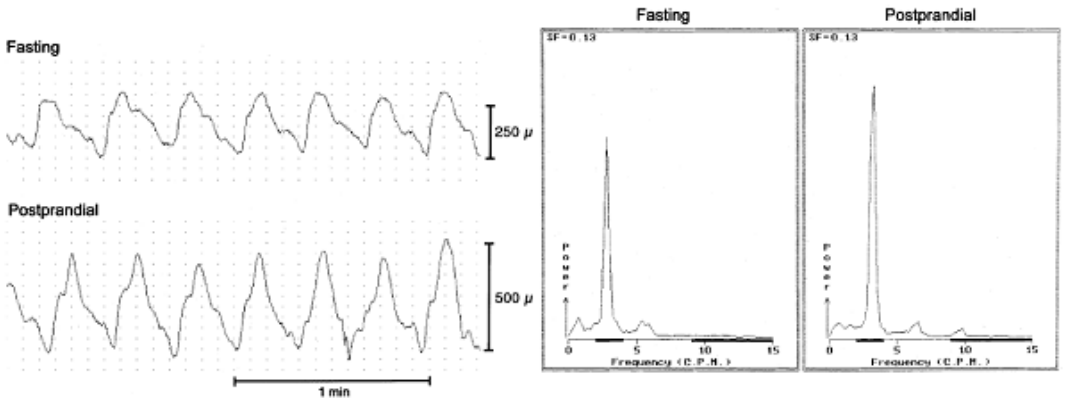

Figure 4.2 A,B Electrogastrography Tracings From a Normal Volunteer. (A)The raw tracing demonstrates a sinusoidal oscillation with a frequency of 3 cpm during both the fasting and postprandial periods. Signal amplitude increases with meal ingestion. (B)The power frequency spectrum displays the DF for the entire fasting and postprandial periods -3 cpm- [1].

The other main EGG abnormality which has been characterized is a lack of signal power increase after eating is given in Fig.4.4.

Analysis of a clinical EGG recording involves visual inspection of the raw tracing followed by computer-assisted calculation of dysrhythmic activity and postprandial power responses. Artefacts in the EGG signal must be identified and excluded from computer analysis.

Several parameters are calculated from computer analysis of the raw EGG signal. The three most commonly reported computations include: (i) the percentage of recording time with the (DF) in the normal 3 cpm, tachygastric and bradygastric frequency ranges, (ii) the percentage distributions of EGG power in the three frequency bands, and (iii) the ratio of postprandial to fasting power of the DF. Other parameters of lesser importance but often calculated with computer software programs include (i) the overall dominant EGG frequency in the fasting and postprandial periods, (ii) instability factors of the dominant frequency (DFIC) for the fasting and postprandial periods, and (iii) instability factors for the dominant power (DPIC) in the fasting period and postprandial periods [1].

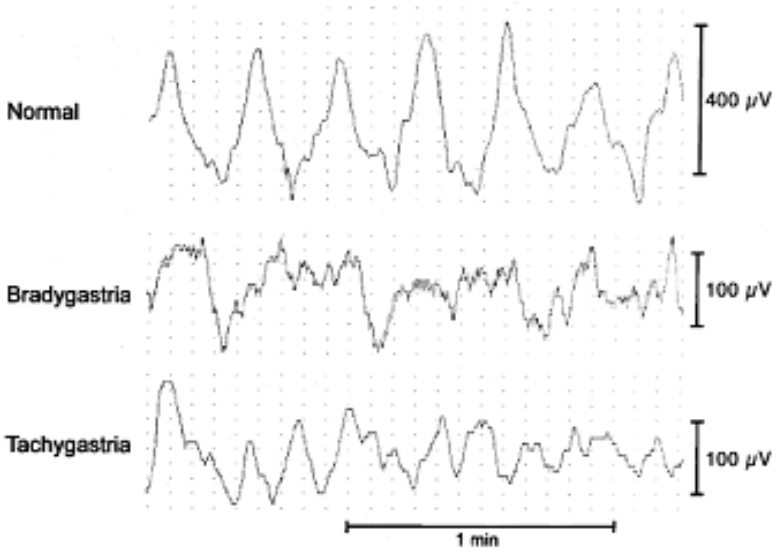

Figure 4.3 Raw EGG Tracings showing normal rhythm, bradygastria and tachygastria [1].

Table 4.1
Defined Ranges of Slow Wave Frequency in Various EGG Recordings [2]

Normal Range (c.p.m.)	**Bradygastria (c.p.m.)**	**Tachygastria (c.p.m.)**
2-4	0-2	3.6-9.9
2-4.5	0.5-2	3.6-10
2.4-3.6	1-2	$>$3.6
2.4-3.7	0.5-2.4	3.7-9
2.5-3.75	1-2.4	3.7-10
2.5-4	$<$2.4	3.7-11
	0.5-2.5	3.75-10
	1-2.5	3.9-9.9
	0-3	4-9
		4.5-9

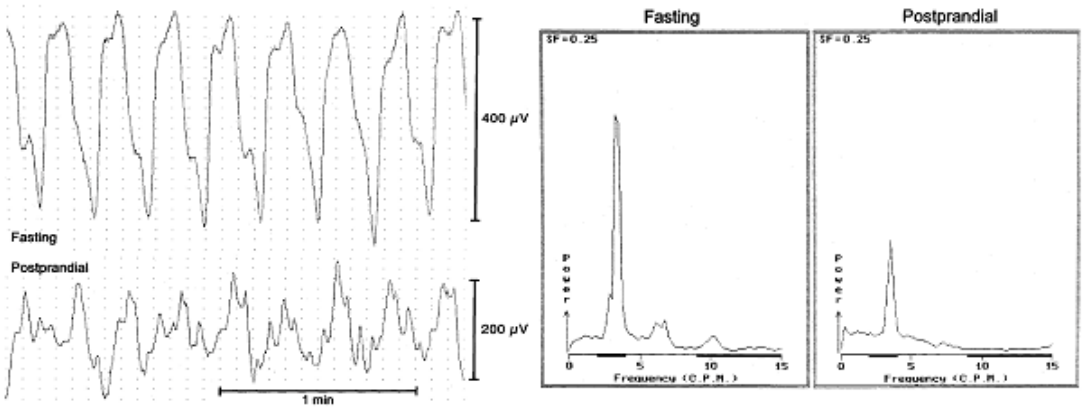

Figure 4.4 Raw EGG Tracings of a Patient with an impaired electrogastrography (EGG) power response to meal ingestion. (A) The raw signals show normal 3 cpm activity during the fasting and postprandial periods (B) but signal amplitude (power)is decreased after eating.

4.2.1 Dominant Frequency:

As EGG is a multi-component signal and in the time domain, these multiple components are superimposed on each other and make accurate quantitative analysis of the data impossible. However, in the frequency domain, the signal and noise are usually separated and if the EGG recording is correct, gastric signal is the main (dominant) component. The frequency, believed to be of gastric origin and at which the power has a peak value is called the dominant frequency [20].

4.2.2 Dominant Power:

Dominant power is the power at the dominant frequency. The dominant frequency and power are computed from the power spectrum analysis of the data. Power spectrum analysis of a data sequence is defined as the Fourier transform of the autocorrelation function of the data sequence or the squared magnitude of the Fourier transform of the infinite data sequence with appropriate statistical averaging [20].

4.3 Applications of Electrogastrography

EGG has been advocated as a diagnostic test for the clinical evaluation of patients with unexplained nausea, vomiting and other dyspeptic symptoms to gain insight into mechanisms of symptom generation. International Classification of Diseases (ICD-9) Ninth revision, diagnostic codes for which EGG might be considered an appropriate investigation include 787.01 for nausea with vomiting, 787.02 for nausea alone, 787.03 for vomiting alone, 536.3 for gastroparesis, 536.8 for dyspepsia and 536.9 for unspecified functional disorders of the stomach.

In literature [4][2][1] there are numerous studies that have used EGG on clinical grounds. The main topics were:

1. gastric myoelectrical activity in diabetic gastroparetic patients
2. effects of gut hormones and pharmacological and prokinetic agents on gastric myoelectrical activity
3. gastric myoelectrical activity in pregnant women
4. gastric myoelectrical activity in patients with motion sickness
5. gastric myoelectrical activity with suspected gastroparesis
6. detection of slow wave propagation from the EGG
7. prediction of gastric emptying using the EGG
8. forms of gastric dysrhythmia
9. gastric myoelectrical activity in some systemic diseases like systemic sclerosis
10. recovery of gastrointestinal tract motility and myoelectrical activity change after abdominal surgery

5. EXPERIMENTAL PROCEDURE

The studies were performed in 12 diabetic patients admitted to FSM Training and Research Hospital and in 8 healthy volunteers with no gastrointestinal symptoms and documented gastrointestinal system disease. All the subjects were informed about the procedure and their inform consents were taken.

5.1 Subjects

The studies were performed in 12 diabetic patients admitted to FSM Training and Research Hospital and in 8 healthy volunteers with no gastrointestinal symptoms and documented gastrointestinal system disease. All the subjects were informed about the procedure and their inform consents were taken.

Inclusion Criteria:

Being diagnosed type1 or type 2 diabetes mellitus at least for ten years

HbA1c $\geq$ %7.5

Exclusion Criteria:

Hypothyroidism

Hyperthyroidism

Using drugs affecting gastrointestinal motility

5.2 Data Acquisition and Analyzing Procedure

Data acquisition and analyzing procedure steps are summarized in the given Figure 5.1.

Step 1: After an overnight fasting period, subjects were taken to the recording room and Ag/Ag-Cl ECG electrodes were placed as shown in Figure 4.1 A. After a 30 minutes pre-prandial recording, a standard diet (appropriate for diabetic patients) was given to the subjects and following the ingestion of the diet, an additional 30 minutes post-prandial recording was carried out. The recordings were taken non-invasively with an EGG instrument which uses Biopac MP30 hardware system.

Data were collected at a sapling rate of 100 Hz with 0-35 Hz low pass filter and then digitally downsampled in MATLAB environment down to 5 Hz. Power spectrum of each subject data were then calculated by periodogram method with a window of 1 minute long with overlap of 50 %. The power spectrum was further analyzed for its major two peaks in the slow wave (2-15 cpm) and spike activity (50-100 cpm) ranges. The dominant frequency within these bands and their power were computed for each subject.

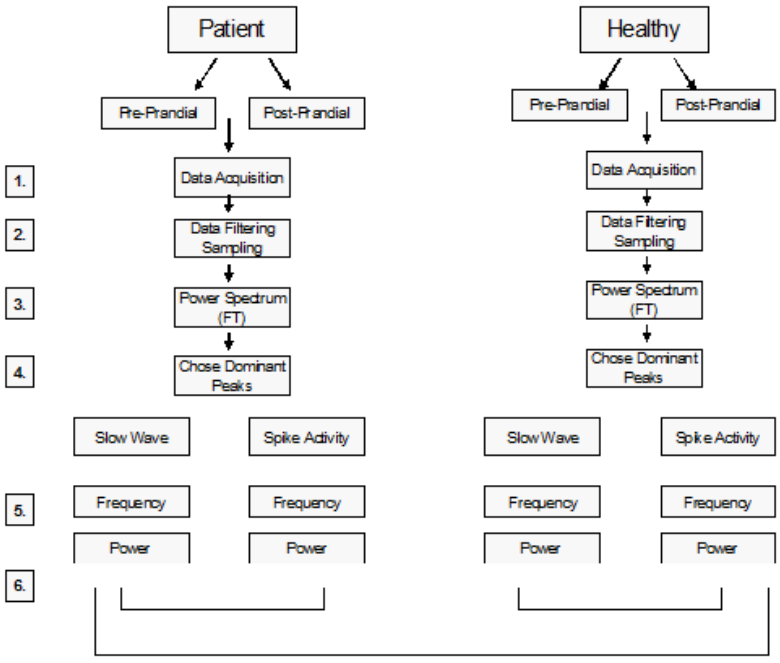

Figure 5.1 Steps of Experimental Procedure

Step 2: The Raw EGG Signal of a Subject is given in Figure 5.2

This raw signal is firstly down sampled to 5 samples / sec. Then, it is filtered

by a band-pass (0.01 - 1.5 Hz) IIR filter.

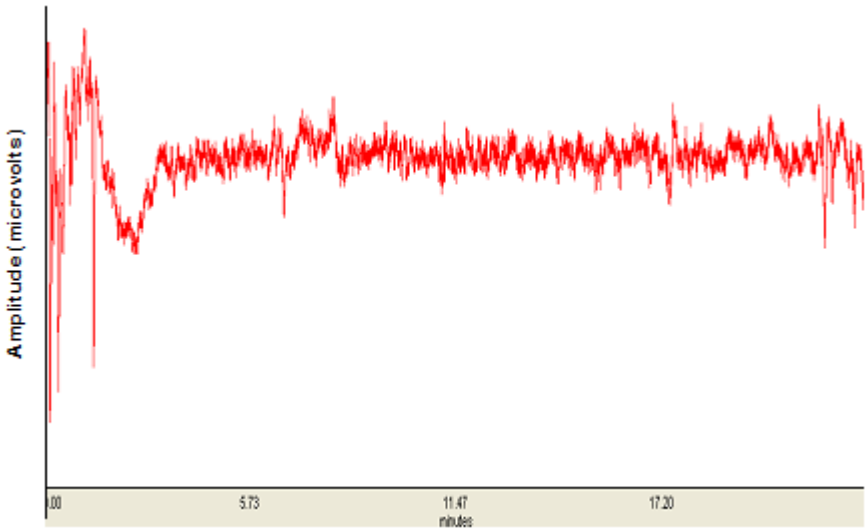

Figure 5.2 Raw EGG Signal of a Subject

Step 3: Then, data is transformed into frequency domain by Fast Fourier Transform by using matlab programme. The FFT of the EGG of a subject is given in Figure 5.3.

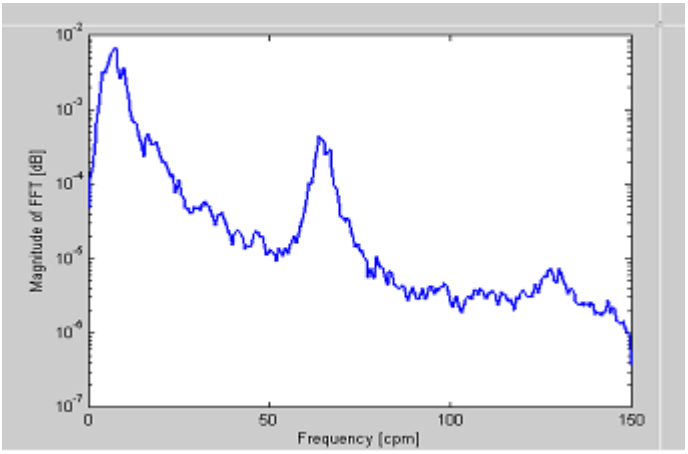

Figure 5.3 FFT of the EGG Signal of a Subject

These procedures are repeated for pre-prandial and post-prandial recordings of patients and healthy volunteers.

Step 4: The Dominant Peaks were Chosen as in Figure 5.4 and 5.5

Step 5: By choosing the dominant peaks on the left side of the frequency 50

cpm threshold (Figure 5.4) we determine frequency and power of the slow waves. In additionally we chose the second dominant peak located on the right side of 50 cpm threshold (Figure 5.5). We believe that this peak may be the recordings of spike activity of stomach.

This procedure is repeated for all transformed data in order to find frequency and power of each recording. The frequency and power of a recording is given in Figure 5.6

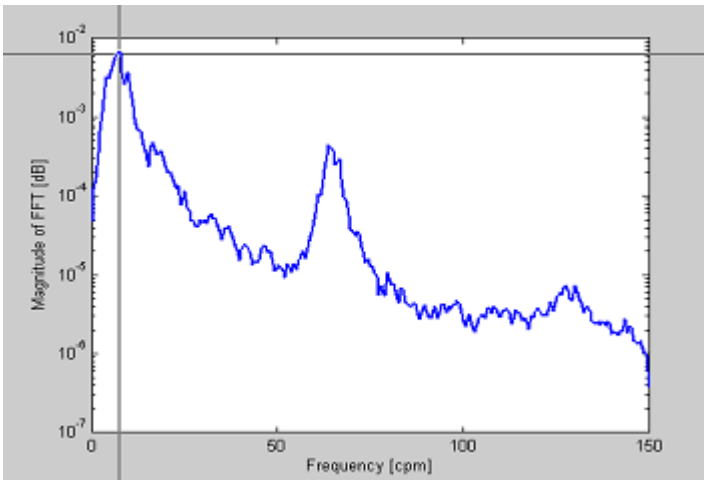

Figure 5.4 First Dominant Peak of FFT EGG Signal

Step 6: The statistical analysis is carried out on Excel statistical analysis programme and student t test is used to determine the statistical significance of the changes that occur between both pre-prandial and post-prandial recording data of all subjects and the differences between diabetic patients and healthy volunteers.

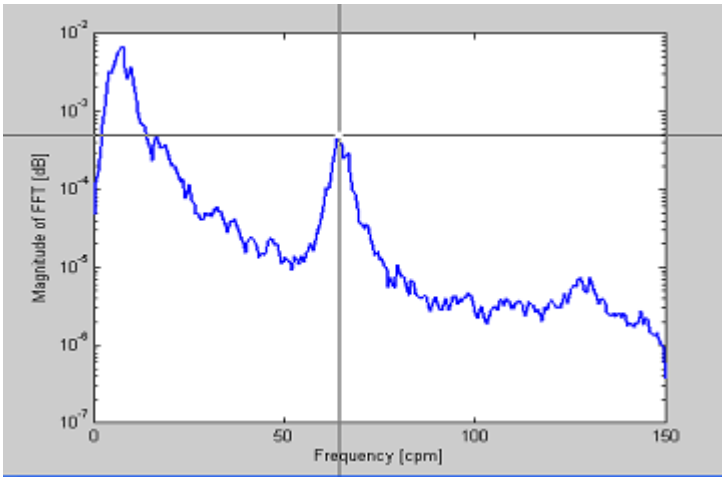

Figure 5.5 Second Dominant Peak of FFT EGG Signal

```
  Using Toolbox Path Cache.  Type "help toolbox_path_cache" for more info.

  To get started, select "MATLAB Help" from the Help menu.

>>
freq =

    5.3571
   54.5046


power =

    0.0064
    0.0000

>>
```

Figure 5.6 Frequencies and Power of Dominant Peaks

6. RESULTS

6.1 Demographic Features

12 diabetic patients (5 females and 7 males) and 8 healthy controls (5 females and 3 males) participated in this study. Among diabetic patients 10 of them are type 2 diabetes mellitus and eight of them are on insuline therapy and the remain two patients are type 1 diabetes mellitus. The mean age of diabetic patients and controls are 53.75 and 33.12, respectively. The mean disease duration of patients is 11.41 with an average 10.26 HbA1c which reflects non-regulated blood glucose levels. The demographic features of the subjects are given on Table 6.1

Table 6.1
Demographic Features of Subjects

Patient	**Gender**	**Age**	**D. Duration (year)**	**HbA1c %**	**Tx**
1	F	51	15	11,1	INS
2	M	52	12	12,4	INS
3	F	38	10	11,4	INS
4	M	63	10	11,1	INS
5	M	74	12	6,9	OAD
6	F	66	10	9,5	INS
7	M	24	15	9,6	INS
8	F	47	10	10,8	INS
9	F	60	10	7,2	OAD
10	M	67	12	13,2	INS
11	M	43	11	10	INS
12	M	60	10	10	INS
Mean		**53.75**	**11.41**	**10.26**	
Control	**Gender**	**Age**			
1	F	43			
2	F	29			
3	M	32			
4	M	45			
5	F	30			
6	F	26			
7	F	20			
8	M	40			
Mean		**33.12**			

Ten of twelve patients have one or more documented complications of diabetes mellitus. Four patients have neuropathy documented with electromyography, two patients have both nephropathy and retinopathy, three patients have nephropathy and one patient has retinopathy.

6.2 Dominant Frequency

The average post- prandial dominant frequencies of diabetic patients are 7,13 while it is 10,54 cpm in healthy controls. This difference confirms correctness of recordings as it reflects the expected slow gastric electrical activity in diabetic patients due to gastroporesis. However the dominant frequencies for both pre-prandial and post-prandial recordings are not compatible with gastric electrical activity, which is between 2 to 4 cpm. Since the electrodes were replaced along with antral axis in single channel technique, these frequencies may reflect duodenum activity which is between 11-12 cpm.

Pre-prandial and post-prandial dominant frequencies for each patient are given on Table 6.2 and for controls given on Table 6.3

After sorting the values, Table 6.4 and Table6.5 are formed up by removing the highest different values in order to carry out statistical evaluation. For example pre-prandial slow power of 6th patient on the Table 2 is extremely higher than other values and removed before analysis.

While the mean post-prandial frequency (11,78 cpm) increases according to mean pre-prandial frequency (8,81 cpm) in healthy controls (not statistically significant), it contrarily decreases in diabetic patients and it is marginally significant ($p = 0.06$). The mean pre-prandial and post-prandial frequencies of diabetic patients are 6,87 and 6,79, respectively. Post-prandial frequency of diabetic patients is significantly smaller than post-prandial frequency of healthy controls ($p = 0.024$), (Fig 6.1).

Table 6.2
Dominant Frequencies of Diabetic Patients

	FREQ Slow	FREQ Spike		POWER Slow	POWER Spike
Patient Pre-prandial					
1	5,70	85,89		0,0303	0,0002
2	6,39	85,20		0,2021	0,0018
3	5,36	84,16		0,0061	0,0000
4	9,85	82,43		0,0103	0,0009
5	10,54	71,37		0,0286	0,0008
6	6,39	118,03		5,9346	0,0008
7	10,54	69,30		0,0068	0,0009
8	12,96	97,29		0,1827	0,0003
Mean	**8,47**	**86,71**		**0,8002**	**0,0007**
Patient Post-prandial					
1	6,39	80,70		0,0216	0,0030
2	6,05	86,23		0,0657	0,0013
3	6,39	83,47		0,0335	0,0001
4	7,09	84,85		0,0171	0,0006
5	7,09	78,28		0,0502	0,0009
6	9,50	56,51		0,0635	0,0020
7	9,16	72,06		0,0037	0,0011
8	5,366	76,90		0,0043	0,0005
Mean	**7,13**	**77,38**		**0,0325**	**0,0012**

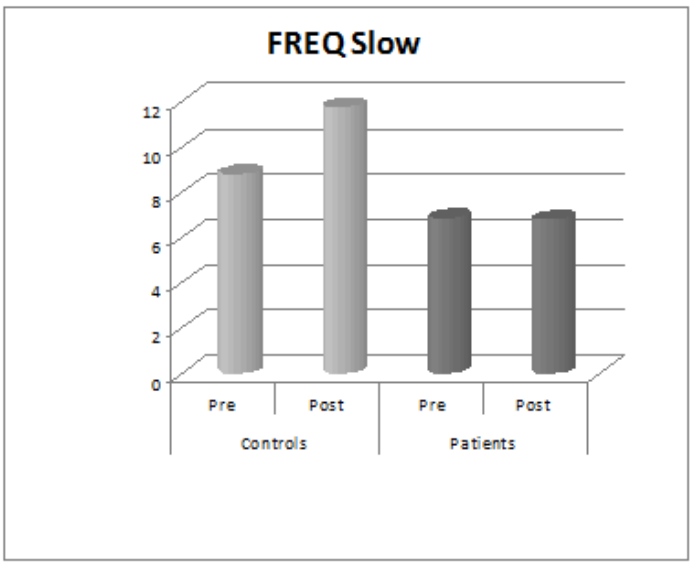

Figure 6.1 Comparison of Pre-prandial and Post-prandial Slow Wave Frequencies

Table 6.3
Dominant Frequencies of Controls

	FREQ Slow	**FREQ Spike**		**POWER Slow**	**POWER Spike**
Control Pre-prandial					
1	7,78	86,58		0,0077	0,0002
2	7,43	64,11		0,0068	0,0005
3	10,54	67,22		0,0428	0,0072
4	9,85	62,38		0,0037	0,0022
5	10,20	69,64		0,0118	0,0004
Mean	**9,16**	**69,99**		**0,0146**	**0,0021**
Control Post-prandial					
1	7,43	90,38		0,0130	0,0001
2	6,74	82,09		0,0070	0,0006
3	20,56	60,66		0,0264	0,0081
4	9,50	64,80		0,0177	0,0015
5	8,47	91,07		0,1062	0,0002
6	29,38	67,91		0,0293	0,0014
7	9,85	77,94		0,0239	0,0001
8	19,87	71,72		0,3027	0,0033
Mean	**10,54**	**77,80**		**0,0341**	**0,0021**

Table 6.4
Dominant Frequencies of Controls

	FREQ Slow	**FREQ Spike**		**POWER Slow**	**POWER Spike**
Patient Pre-prandial	5,36	69,30		0,0061	0,0000
	5,70	71,37		0,0068	0,0002
	6,39	82,43		0,0103	0,0003
	6,39	84,15		0,0286	0,0008
	9,85	85,20		0,0303	0,0008
	10,54	85,89		0,1827	0,0009
	10,54	97,29		0,2021	0,0009
Mean	**6,87**	**82,23**		**0,0667**	**0,0006**
STD	**2,36**	**9,47**		**0,0866**	**0,0004**
Patient Post-Pre-prandial	5,35	56,51		0,0037	0,0001
	6,05	72,06		0,0043	0,0005
	6,39	76,90		0,0171	0,0006
	6,39	78,28		0,0216	0,0009
	7,09	80,70		0,0335	0,0011
	7,09	83,47		0,0502	0,0013
	9,16	84,85		0,0635	0,0020
Mean	**6,79**	**76,11**		**0,0277**	**0,0009**
STD	**1,20**	**9,64**		**0,0227**	**0,0006**

Table 6.5
Analyzed Dominant Frequencies of Controls

	FREQ Slow	**FREQ Spike**		**POWER Slow**	**POWER Spike**
Control Pre-prandial	7,43	62,38		0,0037	0,0002
	7,78	64,11		0,0068	0,0004
	9,85	67,22		0,0077	0,0005
	10,20	69,64		0,0118	0,0022
Mean	**8,81**	**65,84**		**0,0075**	**0,0008**
STD	**1,41**	**3,23**		**0,0033**	**0,0009**
Control Post-Pre-prandial	6,74	60,66		0,0070	0,0001
	7,43	64,80		0,0130	0,0001
	8,47	67,91		0,0177	0,0002
	9,50	71,72		0,0239	0,0006
	9,85	77,94		0,0264	0,0014
	19,87	82,09		0,0293	0,0015
	20,56	90,38		0,1062	0,0033
Mean	**11,78**	**73,64**		**0,0319**	**0,0010**
STD	**5,87**	**10,43**		**0,0337**	**0,0012**

6.3 Power of Dominant Frequency (PDF)

Power of Dominant Frequency is power at the dominant frequency. PDF values for each subject are given on Table 6.2 and Table 6.3

According to mean PDF values on Table 6.4 and Table 6.5, power of pre-prandial slow waves decreases 3-fold in diabetic patients at post-prandial period. The mean values for PDF are 0,0667 $\mu\ V^2$ and 0,0277 $\mu\ V^2$ for pre-prandial and postprandial recordings of diabetic patients, respectively ($p = 0.08$).

Contrarily power of pre-prandial slow waves 4-fold increases in healthy subjects at post-prandial period. The mean values for PDF are 0,0075 $\mu\ V^2$ and 0,0319 $\mu\ V^2$ for pre-prandial and post-prandial recordings of healthy controls, respectively. The increase is statistically significant ($p = 0.002$).

However, it is not statistically significant when we compare the power of dominant frequencies between patients and controls for pre-prandial and post-prandial recordings ($p > 0.05$), (Fig 6.2).

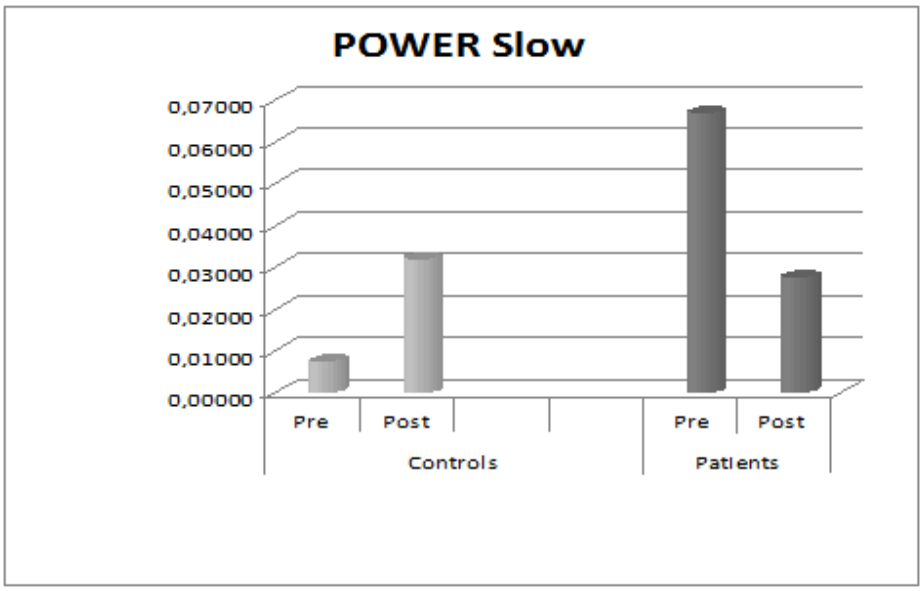

Figure 6.2 Comparison of Pre-prandial and Post-prandial Slow Wave Power

6.4 Spike Activity

The dominant frequency and power of dominant frequency found for possible spike activities are shown on Table 6.4 and Table 6.5 for patients and controls respectively.

Similarly with slow waves, the mean value of dominant frequency of spikes increases at post-prandial period in healthy controls and decreases in diabetic patients. Differences between pre-prandial and post-prandial frequencies are statistically significant for controls and diabetic patients with quietly low significance values $p = 0.016$ and $p = 0.008$, respectively.

While pre-prandial frequency between controls and patients are significantly different, post- prandial frequencies do not statistically differ ($p = 0.004$, $p = 0.326$ respectively). Comparisons of spike frequencies are shown in Figure 6.3

Power of spikes increases in post-prandial period for both controls and diabetic patients. However the difference is significant in diabetic patients ($p = 0.014$) but not in healthy controls ($p = 0.14$). Pre-prandial and post-prandial powers of spike are not

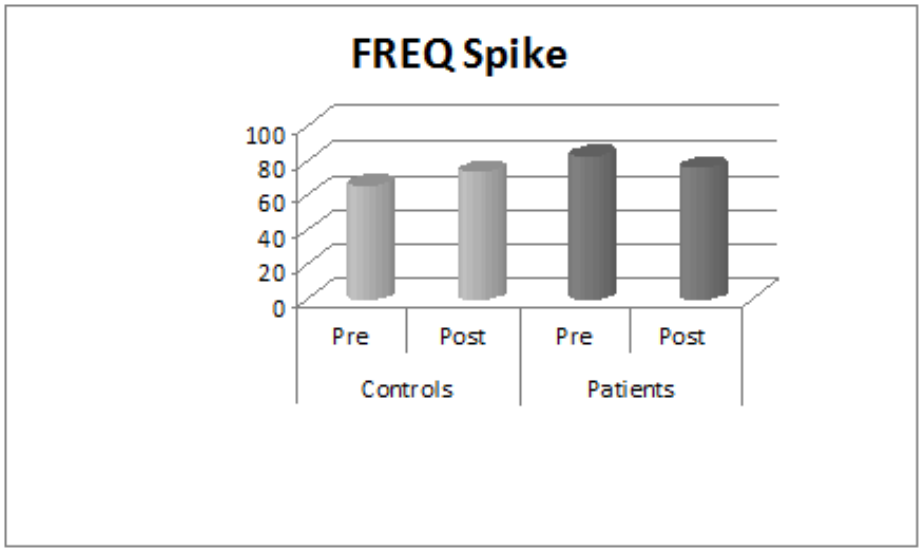

Figure 6.3 Comparisons of Pre-prandial and Post-prandial Spike Frequencies

statistically different between controls and diabetic patients (Fig 6.4).

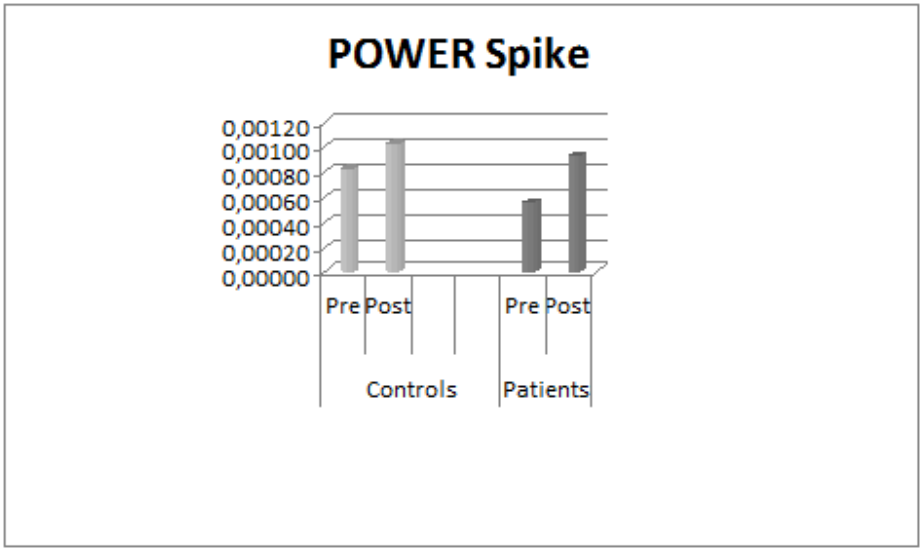

Figure 6.4 Comparisons of Pre-prandial and Post-prandial Spike Power

The statistical evaluation and significance of the examined EGG data are summurrized in Table 6.6 and Table 6.7.

Table 6.6
Ferquency and Power Analysis of Pre-prandial and Post-prandail Recordings

		FREQ Slow	**FREQ Spike**			**POWER Slow**	**POWER Spike**
Controls	**Pre**	8,81	65,84	**Controls**	**Pre**	0,00750	0,00083
	Post	11,78	73,64		**Post**	0,03193	0,00103
p Value		**0,50**	**0,02**			**0,002**	**0,14**
Patients	**Pre**	6,87	82,23	**Patients**	Pre	0,06670	0,00056
	Post	6,79	76,11		**Post**	0,02770	0,00093
p Value		**0,06**	**0,01**			**0,08**	**0,01**

Table 6.7
Ferquency and Power Analysis of Diabetic Patients and Controls

	FREQ Slow	**FREQ Spike**		**POWER Slow**	**POWER Spike**
Pre-C	8,81	65,84		0,00750	0,00083
Pre-P	6,87	82,23		0,06670	0,00056
p value	**0,24**	**0,005**		**0,107**	**0,253**
Post-C	11,78	73,64		0,03193	0,00103
Post-P	6,79	76,11		0,02770	0,00093
p value	**0,02**	**0,33**		**0,394**	**0,422**

7. DISCUSSION

Diabetes mellitus is frequently associated with symptoms and disturbances of gastrointestinal motility and sensation [5]. Patients with diabetes mellitus have reduced frequency of antral contractions, antroduodenal incoordination, and pyloric spasm [12].

Increased compliance of the proximal stomach and abnormal postprandial proximal gastric accommodation and contraction may contribute to the development of delayed gastric emptying. The main pathogenetic factors in diabetic gastroparesis are vagal autonomic neuropathy and, based on data acquired in animal models and in humans, interstitial cells of cajal pathology [12][2][1].

The reported prevalence of delayed gastric emptying in patients with longstanding diabetes has ranged from 28-65% [5]; however, the relationship between symptoms and delayed emptying is variable [5][21]. Some studies have shown that the prevalence of symptoms was not generally higher in patients with diabetes compared to volunteers without diabetes [22] and some patients with delayed gastric emptying are asymptomatic [5]. Gastric emptying rates in the type 2 DM population have been reported to be slowed, unchanged or accelerated [8]. Samsom and colleagues reported that hyperglycaemia significantly delays gastric emptying of a solid meal in type 1 DM patients with autonomic neuropathy [5].

Patients with diabetes with a history of microvascular and macrovascular complications such as retinopathy, nephropathy, and neuropathy frequently have diabetic gastroparesis, a syndrome characterized by delayed gastric emptying that often develops after suffering from diabetes for at least 10 years [8].

Diagnostic tests that measure gastric myoelectrical activity and gastric emptying are indicated when the results of standard diagnostic tests are negative and symptoms persist. Electrogastrography is one of the many tests of gastrointestinal

function which were proposed to evaluate patients with unexplained nausea, vomiting and other dyspeptic symptoms.

Gastric emptying of a solid-phase meal by scintigraphy is considered the gold standard for the diagnosis of gastroparesis because this test quantifies the emptying of a physiologic, caloric meal that can assess the motor function of the stomach. When data from several studies are considered [1], the positive predictive value of an abnormal EGG to predict gastroparesis ranges from 50 to 81% (average of 65%), whereas the accuracy of a normal EGG to predict normal gastric emptying in a symptomatic population ranges from 65 to 100% (average of 76%) [23]. Gastric scintigraphy and EGG could be considered complementary examinations [23].

In this study we aimed to evaluate the effect of diabetes mellitus on gastric motility by using noninvasive electrogastrography measurements. We have chosen our patients among diabetic patients with at least 10 years of disease duration and HbA1c higher than 7% in order to be able to evaluate the differences of EGG signals between diabetic patients with likely gastroparesis and healthy controls.

In literature the number of articles after a Pubmed search with key words EGG and diabetic gastroparesis s actually very limited. However EGG was only approved by FDA as a test for patients with gastrointestinal motility disorders in 2000 [1].

EGG records gastric myoelectrical activity, or the gastric electrical slow wave, which is responsible for controlling the maximal frequency and the propagation of distal gastric contractions. A normal EGG is characterized by a waveform with a frequency of approximately 3 cpm wave activity that increases in amplitude (or power) after meal ingestion [1].

Rhythm abnormalities observed with EGG include tachygastria, bradygastria, and a non-specific dysrhythmia or lack of a single dominant frequency. Tachygastria and bradygastria are found in many patients with diabetic gastroparesis [1]. In addition to disturbances of EGG rhythm, some diabetics exhibit a concurrent loss of the signal

amplitude increase with meal ingestion [24].

In our study, the pre-prandial and post-prandial dominant frequencies (9 and, 10 cpm) for healthy controls were not compatible with gastric electrical activity, which changes between 2 to 4 cpm acquired from serosal or mucosal electrodes in various EGG recordings [2]. But the dominant frequency of diabetic patients in our study was lower than controls. Moreover the expected amplitude increases after meal ingestion was shown in healthy controls while it decreased in diabetic patients. This difference may confirm correctness of recordings as it reflects the stated slow gastric electrical activity and concurrent loss of the signal amplitude increase with meal ingestion in diabetic patients due to gastroporesis.

Absolute values of EGG power during fasting and the postprandial period are affected by a number of variables including body habitus, electrode placement, and body position [25]. However, these variables do not influence the relative increase in EGG power which is observed with ingestion of a caloric meal in healthy subjects [1]. Depending on the meal consumed, 90-95% of healthy volunteers exhibit increased postprandial signal power of dominant frequency [1]. In one study, all 24 normal subjects had a postprandial increase in the power of the dominant frequency [25]. In another study, 90% of 110 normal subjects had a postprandial increase in the power of the dominant frequency [13].

In patients with diabetic gastroparesis gastric dysrhythmias, including both tachygastria and bradygastria can be defined. But decrease in amplitude ("power") responses to meal ingestion is characteristic finding which our results are consistent with [1]. Interestingly, one investigation noted no increase in slow wave rhythm disturbances in diabetic patients in whom euglycaemia was maintained, although defects in meal-related amplitude responses persisted [1].

Other gastrointestinal organs also produce physiological myoelectricities. For instance, the small intestine has its own SW frequency, beginning at 11-12 cpm in the duodenum with decreasing gradient to distal ileum [2]. It is also found that even total

gastrectomy subjects display a 3-cpm rhythm, which is believed to be colonic in origin [2][26].

We could not find any data regarding to electrogastrographic analysis of duodenum in literature. Since our results are not in the range of reported SW frequencies but consistent for ingestion reactions both in healthy controls and diabetics, we may speculate that our findings may reflect duodenum activity which is between 11-12 cpm. On the other hand when we processed the collected data it was down sampled to 5 Hz (300 cpm) in order to analyze power spectrum of slow wave in the range 2-15 cpm which may encompass duodenum activity.

In this study the power spectrum was further analyzed for its major two peaks in the slow wave (2-15 cpm) and spike activity (50-100 cpm) ranges. As it was stated electrical activity of the stomach is composed of mainly two complementary rhythms: the slow wave activity around 3 cycles per minute (cpm), which physiologically triggers the onset of spike, and the electrical response activity (or the spike activity) with a higher frequency content which is responsible for triggering the peristaltic contractions [2][16][17].

According to Chang's review the spikes occurring in SW depolarization are not readily recorded using surface electrodes [2]. Also Chang notices that it should be noted that whenever the sine wave configuration recordings were seen by EGG, this does not mean the true occurrence of stomach contraction.

However Akin and Sun proposed that higher frequency signals of the antrum observed during peristaltic contractions can be detected and quantified from surface EGG recordings. Akin and Sun have presented the possibility of detecting the spike activity of the serosa in dogs from surface electrodes and the spike activity signals from the abdominal surface recordings in dogs detected with an accuracy of 96% using a new detection algorithm based on a continuous wavelet transform [16][17].

Ozcan aimed to apply a similar approach based on spectral estimation to the

recordings from the abdominal surface electrodes in the healthy human subjects and try to determine whether any discernable changes are observed in spectral bands for the EGG recordings in human objects. But he did not see any statistically significant rise in power of signal for higher frequencies [13].

Therefore this study in some extend is a continuation of the studies of Akin and Sun, and Özcan. In our study the frequencies of likely spike activity for healthy controls were 65.84 cpm pre-prandial and 73.64 cpm post prandial. In diabetic patients spike frequencies were 82.23 cpm for pre-prandial period and 76.11 cpm for post-prandial period.

Similarly with slow waves, the mean value of dominant frequency of spikes increases at post-prandial period in healthy controls and decreases in diabetic patients. Power of spikes increases in post-prandial period for both controls and diabetic patients.

The frequencies of likely spike we detected ranges from 65.84 to 82.23 cpm. These frequencies may be considered that the activity belongs to heart which ranges from 70 to 90 cpm for the patients in this study. However we expect a decrease in heart beats after meal ingestion in healthy person due to the parasympathetic activity. Our results in healthy controls mimic expected gastric activity and it is deteriorated in diabetic patients.

Understanding of the gastric neuromuscular function in diabetic patients may be an important component to consider in therapy, selecting appropriate drugs to regulate gastric emptying, and designing therapy for individual patients.

Although this was a preliminary study and the experimental group was small the results were consistent with previously reported ones in other studies in terms of discriminate possible myoelectrical changes in diabetic patients. Appropriate application of non-invasive EGG may provide more information and insight when planning the therapy. Also the results regarding to detection of spike activity is promising for further investigation in large groups.

8. FURTHER WORK

Our study confirms that longstanding diabetes mellitus effects gastric myoelectrical activity and cutaneous EGG can discriminate impaired gastric myoelectrical activity in diabetic patients. Further investigations may be planned for early stages of diabetes mellitus since it is believed that complications of diabetes mellitus settle down before diabetes is being manifest. In our study the results regarding to detection of spike activity is promising for further investigation in large groups. However for a proper interpretation more clinical data are needed such as actual medications, smoking history and concomitant diseases. But the most important data will be simultaneous heart beat recordings in order to differentiate spike activities from heart beats which is in the range of 60 to 90 in healthy individuals.

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