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AUTOMATED GRADING OF GALLBLADDER CONDITIONS: A PILOT STUDY

[1]Chinelo Emeka Okafor and [2]Ijeoma Nnamdi Eze

[1]Department of Anatomy, Ebonyi State University, Abakaliki, Ebonyi State, Nigeria [2]Department of Physics, Rivers State University of Science and Technology, Rivers State, Nigeria.

Abstract: *Milk ultrasonography (MU) emerges as a valuable diagnostic tool for evaluating gallbladder function by assessing its emptying or refilling dynamics following oral administration of milk. Employing milk as a cholecystokinetic agent, MU enables cholecystodynamic studies with implications for understanding gastrointestinal hormone-mediated processes. Early experiments elucidated the hormonal-mediated contraction of the gallbladder upon food, particularly fat, entering the duodenum, accompanied by increased secretion of enzyme-rich pancreatic juice. Initially attributed to gastrointestinal hormones cholecystokinin (CCK) and pancreozymin, it was later revealed that a single hormone, CCK-pancreozymin (CCK-PZ), governed both actions, characterized by a 33 amino-acid sequence.*

Furthermore, the discovery of caerulein, a polypeptide with properties resembling both gastrin and CCK, extracted from the skin of Australian frogs, offers insights into novel approaches for inducing gallbladder contraction in humans. Notably, the vagus nerve plays a pivotal role in mediating motor signals to facilitate gallbladder contraction.

This paper delves into the principles and applications of MU in cholecystodynamic assessment, shedding light on its utility in elucidating the complex interplay of gastrointestinal hormones and neural pathways governing gallbladder function. By synthesizing insights from experimental studies and clinical applications, it underscores the significance of MU in diagnosing gallbladder disorders and guiding therapeutic interventions.

Keywords: *Milk ultrasonography, Gallbladder function, Cholecystokinin, Cholecystokinetic agent, Gastrointestinal hormones.*

INTRODUCTION

Milk ultrasonography (MU) is the ultrasound examination of gallbladder emptying or refilling by oral administration of milk. In milk ultrasonography, which is a cholecystodynamic study, milk is used as a cholecystokinetic agent. Experiments have demonstrated that there was a hormonal mediated contraction of the gallbladder when food, particularly fat, was placed in the duodenum, as well as increase in the secretion of an enzyme-rich pancreatic juice produced by food in the duodenum (The New Encyclopedia Britannica in 30 volumes (15th edition), 1973 - 1974). It was initially thought that a gastrointestinal hormone, cholecystokinin was responsible for gallbladder contraction while another hormone called pancreozymin produced an increased pancreatic secretion. It has since been proven that a single gastrointestinal hormone is responsible for both actions and this hormone named cholecystokinin – pancreozymin (CCK) has a 33

amino-acid sequence (The New Encyclopedia Britannica in 30 volumes (15th edition), 1973 - 1974). It is interesting to note that a polypeptide with a structure and actions that resemble both gastrin and CCK has been isolated from the skin of an Australian frog. This material, caerulein, is being used to produce gallbladder contraction in humans. The motor mediation to gallbladder contraction is controlled by the vagus nerve.

Lack of response (normal emptying) of gallbladder to milk ingestion in some cases of gallbladder diseases have been noted (Ugwu, 2006). Literature reveals that gallbladder of postoperative patients (proven normal at surgery) also fail to respond to the administration of CCK (Raduns et al., 1990). Large gallbladder volume and gallbladder hypomotility, predictors of biliary stasis and sludge, have been recognized as precursors of acute *acalculous cholecystitis* and *idiopathic pancreatitis*, rare but very serious complications after cardiac surgery (Murray et al., 1992; Sahorafas and Tsiotos, 1999; Kalliafas et al., 1998; Lee et al., 1992).

Changes suggesting cholesterosis or cholelithiasis may show on plain radiographs and gallbladder ultrasound. However, a sonographic assessment of Gallbladder Emptying Rate (GBER) may indicate slight functional impairment thereby obviating the need for surgery, in favour of medical management. It could also provide a more objective way of assessing disability instead of making use of patients' subjective feeling.

Ugwu et al. (2007) in a previous study established a grading model of gallbladder diseases using gallbladder contraction index. An alternative model is necessary to create a platform for comparisons in future studies.

The aim of this study was to use an established regression equation of GBER and gallbladder volume (GBV) to grade gallbladder diseases and thus determine severity, prognosis and possible treatment options.

SUBJECTS AND METHODS

Fifty normal adult Nigerians between the ages of 18 and 62 were studied. These subjects fulfilled the criteria for inclusion in this study thus:

- Negative history of hepatobiliary diseases.
- Negative history of other diseases known to affect gallbladder motility e.g. diabetes, and serve injury.
- Not pregnant.

Two regression equations: GBER = 0.0264GBV – 0.0065 and GBER = 0.0274GBV – 0.0901 were established for healthy men and women respectively (Ugwu 2006).

A pilot sample of five patients was selected for the present study. Informed consent was obtained from each subject. Approval for the study was given by Federal Medical Centre, Ebonyi State Research Board according to the declaration of Helsinki (1996) and Declaration of Tokyo (1975). Each of the patients was advised to fast overnight and report to the department in the morning. Two serial gallbladder ultrasound (cholecystosonography) scans were carried out on each subject before drinking a tin of milk (165 mls) and 20 min post prandial. These serial scanning protocols enabled the variation of gallbladder volume with bile emptying to be determined. Sonographic imaging was performed using sonoline SL-1 ultrasound machine (Siemens Medical Systems, USA Inc., Ultrasound Group, Issaquah WA) with a linear array transducer of 3.5 MHz frequency. The skin of the right upper quadrant was

covered with ultrasound gel and the probe adhibited to it. After visualization of the maximal gallbladder longitudinal outline, the length and maximal anteroposterior diameter (height) were measured on arrested respiration either in supine or oblique position with electronic calipers crossing each other at 90°. Subsequently, the probe was rotated through 90° to obtain the maximal transverse diameter. The same measurements were taken 20 min after milk ingestion. Gallbladder volumes were obtained using the volume calculation (approximation) for the prolate ellipsoid (length × width × Height × 0.523) (Ho et al., 1998). GBER was computed as change in volume per minute (cm^3/min) (Ugwu et al., 2007), the fasting volume is denoted as gallbladder volume (GBV).

Statistical (Cholecystodynamic) analysis

Cholecystodynamic analysis was done using Microsoft Excel. Both predicted and actual GBER was computed and compared, upon which grading was done.

RESULTS

Milk ingestion did not show any significant adverse effect
(intolerance) in any of the subjects. The minimum actual GBER was 37% of the predicted GBER equation (Ugwu, 2006); hence a 30% (compromise) value was chosen as a proposed benchmark for this model.

Table 1 is a comparison between actual and predicted GBER (from equation) in subjects with gallbladder disease. While some showed normal emptying, some showed poor emptying rate and indication of increase rather than decrease in volume. This gave a negative emptying rate and a suggestion of higher severity.

Model development

From observations made among the five subjects with gallbladder disease used in this pilot study, the severity of gallbladder disease could have a significant effect on gallbladder motility as depicted by the obvious and discrepant effects on the emptying rates. The emptying rates on the other hand are derivable from the changes in gallbladder volume (Ugwu et al., 2007).

These regression equations were used to propose a model for the assessment of the severity of gallbladder disease with grade 1 being the most severe and grade 3, the least severe.

Three variable namely GBER, Ultrasound signature of the gallbladder and clinical assessment of the patient were used for this model.

Grade 1: GBER < 30% of the predicted GBER (from equation) + clinical evidence of gallbladder disease (e.g. gall attack) + sonographic evidence of gallbladder disease (e.g. thickened wall (> 3.3 mm) or intracavitary mass.

Grade 2: GBER < 30% of the predicted GBER + Sonographic evidence of gallbladder disease + No Clinical evidence of gallbladder disease.

Or

GBER < 30% of the predicted GBER + Clinical evidence of gallbladder disease + No Sonographic evidence of gallbladder disease.

Or

GBER > 30% of the predicted GBER + clinical evidence of gallbladder disease + Sonographic evidence of gallbladder disease.

Grade 3: GBER > 30% of the predicted value + Sonograpgic evidence of gallbladder disease + No clinical of gallbladder disease.

Or

GBER > 30% of the predicted GBER + clinical evidence of gallbladder disease + No Sonographic evidence of gallbladder disease.

Or

GBER < 30% of the predicted GBER + Sonographically normal gallbladder + clinically normal gallbladder in diabetics, AIDS, pregnancy, pancreatitis, severe injury or post surgery, hormonal disorder that affect CCK balance or neurological disorder which affects the vagus nerve, or other conditions which affect gallbladder motility, otherwise normal variant.

Table 1. Actual and predicted GBER in cholecystopathy patients.

S/No	Sex	Clinical history	ıctual GBER (CM^3/ min)	ɐedicted GBER (CM^3/ min)	ɜ0% of predicted GBER(Cm^3/ min	Remark
1	M	Hepatomegaly, lymphadenopathy, mild ascites, cholecystitis (4.0 mm) wall thickness), cholelithiasis (Solitary 9.6 mm cholelith, gall attack.	-0.036	0.158	0.0474	Grade 1
2	M	Acalculous cholecystitis, six months of treatment, no gall attack, wall thickness = 2.4 mm, patient still on drugs.	1.18	0.89	0.2670	Improved from graded disease status to normality
3	M	Cholecystitis, six months post diagnosis, patient still on drugs, reduced gall attack, no cholelith seen.	1.36	1.14	0.3420	Recorded improvement Grade 3
4	F	Chronic Cholecystitis (7.4 mm wall thickness), Cholelithiasis	-1.9	1.41	0.4230	Grade 1
5	M	(Multiple stones averaging 7.4 mm) six weeks post partum, Gall attack. 2.2 mm asymptomatic gallstone. No gall attack. Incidental finding.	1	0.48	0.1440	Grade 3

DISCUSSION

Currently and to the best of our knowledge (using relevant search engines), there is no standard empirical method of grading the severity of gallbladder disease objectively using emptying rate. Physical examination has been shown to be of limited value. Some researchers adopted the use of cholecystokinin infusion in studying gallbladder motility but this present study, which adopted milk ultrasonography, could be justifiable on account of the non-invasive nature of its use.

In the present pilot study, we have proposed a new linear regression model for predicting the severity of gallbladder disease. This model similar to the previous model has been developed with few cases and on three variables: GBER (Cholecystodynamic parameter), Sonographic appearance and clinical assessment. Future validation studies may require a larger population to obtain a better model. It would seem reasonable that the combined and simultaneous use of several different parameters (like contraction index as a cholecystodynamic variable), all of which are independent predictors of disease severity, would offer better diagnostic performance than a single technique. The prolate ellipsoid approximation method of measuring volume is an accepted mathematical formula but to the best of

our knowledge remains inferior to dynamic cholecystodynamic (DCS) assessment of gallbladder volume in view of the different gallbladder shapes/contour. Measurements were taken by one person with a consistent measurement protocol adopted to avoid inter ob-server variation. Further studies on intra observer variation or consistency are hereby advised. Studies on inter observer variation would be necessary so that multiple researchers could be employed in future studies to enable the generation of more data from various clinical environments.

This is a preliminary study in which a method of predicting gallbladder diseases is presented. The small sample size makes it difficult to gauge the potential utility (validity) of this proposed grading scheme. Further studies validating this model against longer-term clinical outcome, preferably using a Receiver Operating Characteristic (ROC) type analysis is recommended. In such study, benchmark can be varied over a wide range instead of being fixed at 30%. Volume sonography has become the most current procedure in the ultrasound laboratory and hence its use in future studies is highly advised, while still bearing in mind that DCS is a gold standard.

In conclusion, the authors believe that model needs to be prospectively evaluated in various populations (races) and in a large series of patients to determine its actual value.

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