Real-Time Sonography for Screening of Gallbladder Motility in Diabetic Patients and Its Relation to Autonomic and Peripheral Neuropathy

Thesis

Submitted in Partial Fulfillment for M.Sc. Degree in
Internal Medicine

By
Mohamed Mohamed Ahmed Ibrahim
(M.B., B.Ch.)

Supervisors

Prof. **Rawia Khater**
Professor of Internal Medicine and Endocrinology
Faculty of Medicine, Cairo University

Prof. **Hebatallah Mustafa Kamal**
Professor of Internal Medicine
Faculty of Medicine, Cairo University

Assis. Prof. **Yasser Bakr Mohamed**
Assistant Professor of Internal Medicine
Faculty of Medicine, Cairo University

FACULTY OF MEDICINE
CAIRO UNIVERSITY
2007

ABSTRACT

Diabetes mellitus type 2 is known as one of the factors causing the cholesterol gallstones. The aim of the present study was to investigate gallbladder function (motility) in diabetic patients type 2 and determine its relation with peripheral and autonomic neuropathy. The study demonstrated that there is a significant increase in fasting gall bladder volume and a significant reduction of the ejection fraction in diabetic patients with peripheral neuropathy and patients with autonomic neuropathy, these changes is considered a risk factors for gall stone disease in those patients.

Keywords:

Gallbladder – ultrasound – diabetes mellitus – autonomic neuropathy – peripheral neuropathy

ACKNOWLEDGEMENT

First I thank **"GOD"** *for giving me the effort to complete this work*

I am profoundly indebted to Prof. ***Rawia Ahmed Khater****, Professor of Internal Medicine and Endocrinology, Faculty of Medicine, Cairo University, for her experience and kind supervision throughout the work. Her untiring effort and guidance were most supportive and extremely helpful.*

I am deeply grateful to Prof. ***Hebatallah Mustafa Kamal****, Professor of Internal Medicine, Faculty of Medicine, Cairo University, who offered much of her time, experience and guidance through the practical part and rest of the work.*

I also wish to express my great appreciation to Dr. ***Yasser Bakr Mohamed****, Assistant Professor of Internal Medicine, Faculty of Medicine, Cairo University, for his valuable suggestions, assistance and encouragement during my work in this study.*

LIST OF ABBREVIATIONS

ACE	: Angiotensin converting enzyme
Ach	: Acetylcholine
AGE	: Advanced glycation end product
ALA	: Alpha lipoic acid
ALT	: Alanine transaminase
ARI	: Aldose reductase inhibitor
AST	:Aspartate transaminase
BMI	: Body mass index
CAN	: Cardiovascular autonomic neuropathy
CCK	: Cholecystokinine
CGRP	: Calcitonin gene related polypeptide
DAN	: Diabetic autonomic neuropathy
DM	: Diabetes mellitus
EF	: Ejection fraction
EPSPs	: Excitatory postsynaptic pontentials
FBG	: Fasting blood glucose
GB	: Gallbladder
GD	: Gallstone disease
HbA1c	: Haemoglobin A1c, glycated haemoglobin
HIDA	: Hydroxy-imino-diacetic acid
HRV	: Heart rate variability
IGF	: Insulin like growth factor
IGT	: Impaired glucose tolerance
NAFLD	: Non-alcoholic fatty liver disease
NASH	: Non-alcoholic steatohepatitis
NDS	: Neuropathy deficit score
NGF	: Nerve growth factor
NOS	: Nitric oxide synthase
NSS	: Neuropathy symptom score

NT-3 : Neurotrophin-3
OGTT : Oral glucose tolerance test
PGE_2 : Prostaglandin E_2
PP : Pancreatic polypeptide
PPBG : Postprandial blood glucose
SD : Standard deviation
SP : Substance P
SSRI : Selective serotonin reuptake inhibitor
TCA : Tricyclic antidepressants
TNF-α : Tumour necrosis factor-α
TNF-β : Tumour necrosis factor-β
V_1 : Fasting gallbladder volume
V_2 : Postprandial gallbladder volume
VIP : Vasoactive intestinal peptide

LIST OF TABLES

LIST OF FIGURES

CONTENTS

INTRODUCTION AND AIM OF THE WORK

Hypertriglyceridemia and obesity together with impaired gallbladder motility in diabetics are risk factors for gallstone formation. Neurologic control of gallbladder emptying is under parasympathetic and sympathetic nervous systems where parasympathetic system controls contractility, sympathetic system controls relaxation. The reduced motility of gallbladder can be caused by autonomic nervous system dysfunction and defective response to gastrointestinal hormones such as cholecystokinin, motilin and secretin. There are limited data concerning peripheral neuropathy and gallstone relation.

The **aim** of this work is to investigate gallbladder motility in diabetic patients and determine its relation to autonomic and peripheral neuropathy.

ANATOMICAL OVERVIEW

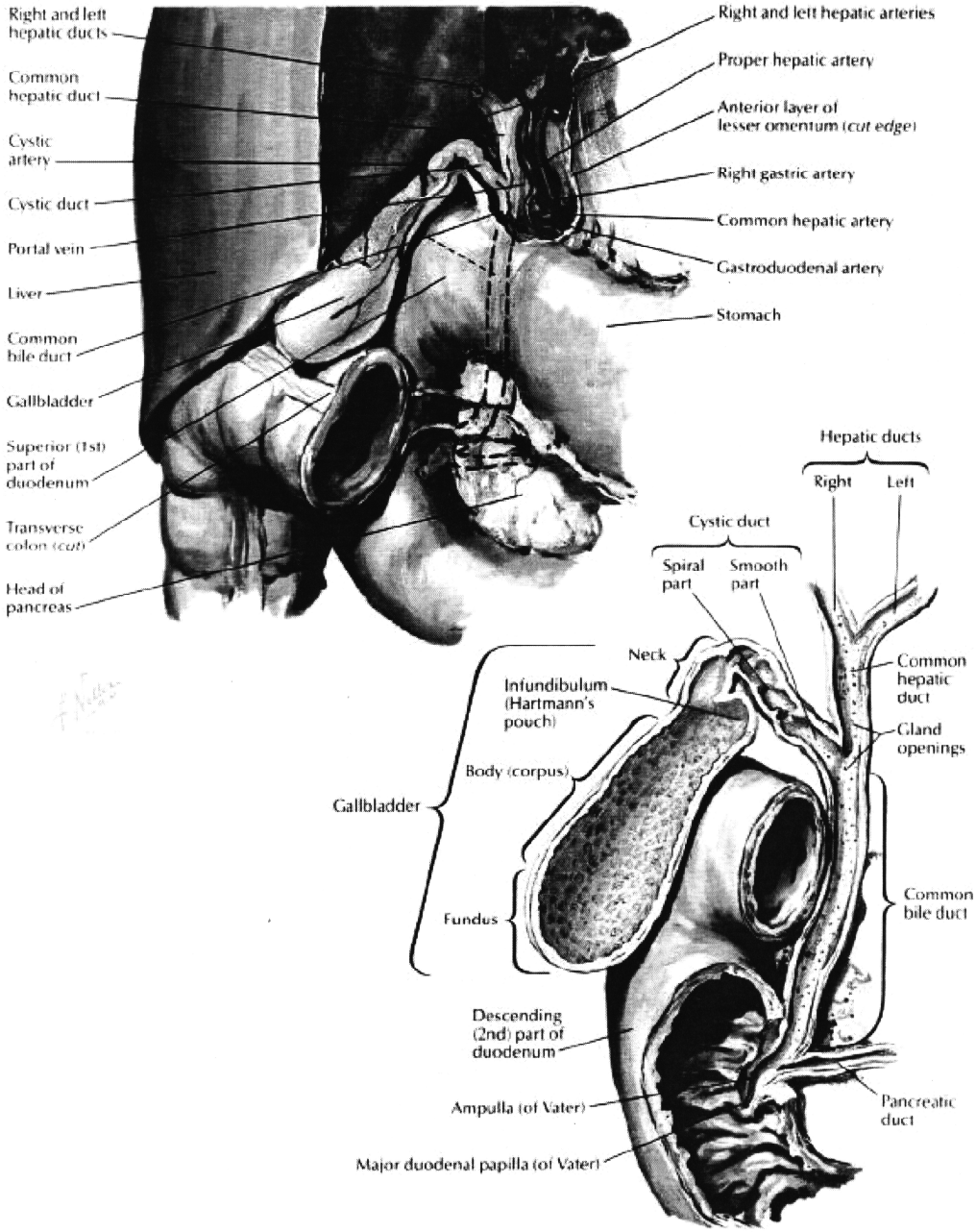

Fig. (1): Anatomical overview of the gallbladder **(Netter, 1997)**

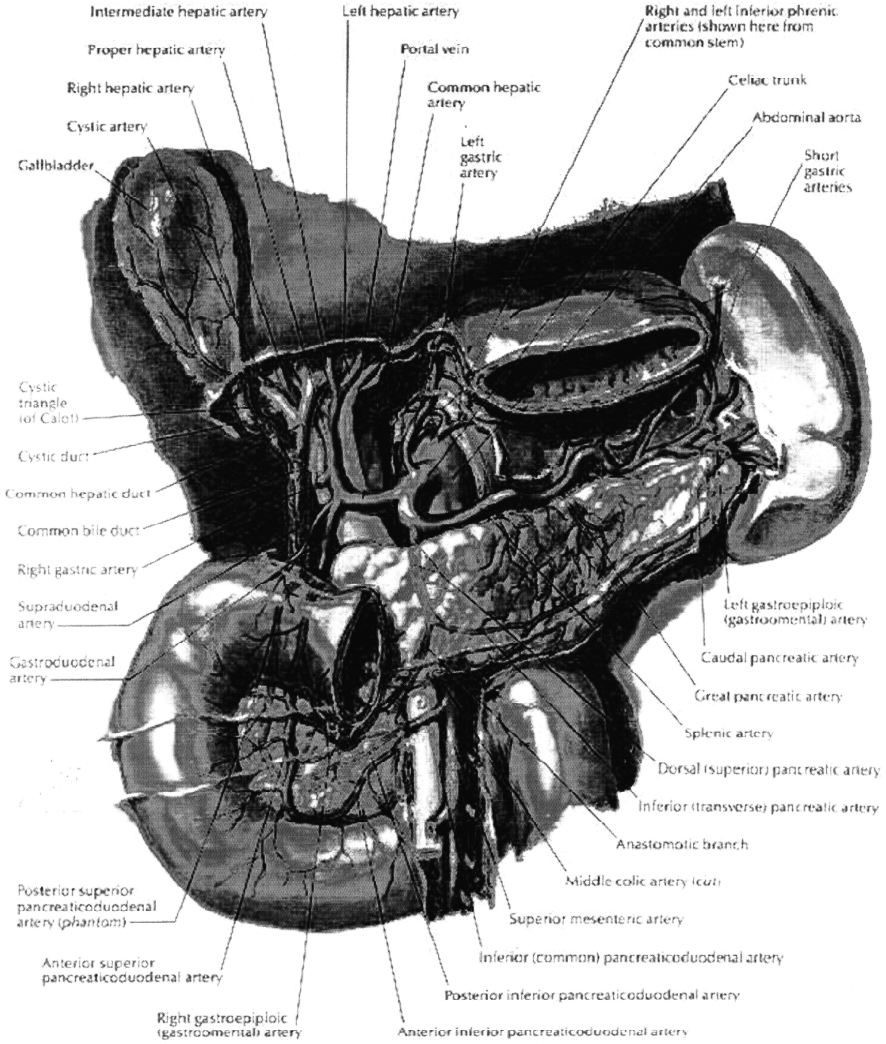

Fig. (2): Anatomical overview of the blood supply of the gallbladder **(Netter, 1997)**.

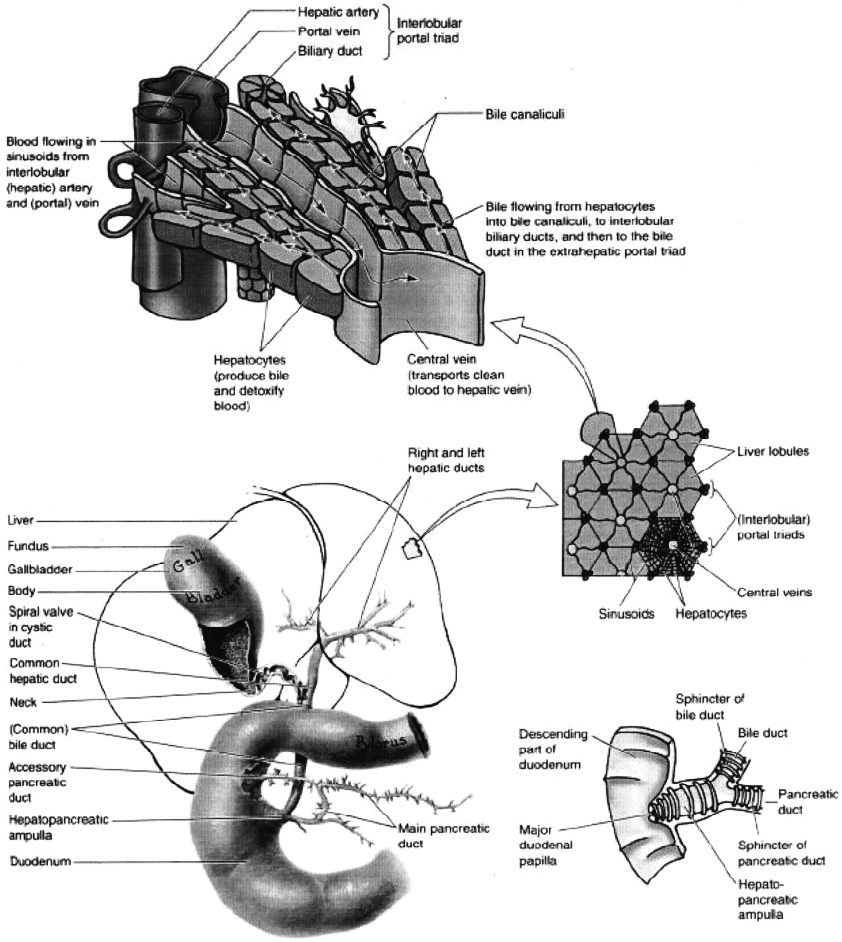

Fig. (3): Anatomical overview of the biliary system **(Moore and Dalley, 1999)**.

GALLBLADDER INNERVATION

Intrinsic gallbladder nerves are regarded as an extension of the enteric nervous system and named as the ganglionated plexus of gallbladder, found between serosa and submucosa and arranged into two irregular, anastomosing and interweaving net works **(Mawe et al., 1989)**.

Extrinsic supply of the gallbladder consists of sympathetic and parasympathetic branches of the autonomic nervous system and also afferent sensory and efferent motor neurones from and to the gallbladder that have been demonstrated by retrograde tracing to the dorsal root (T5 to T11) and nodose ganglia and to the celiac ganglion and dorsal vagal nucleus **(Mawe et al., 1997)**.

Vagal neurones liberates acetylcholine that acts on nicotinic receptors and stimulates postsynaptic parasympathetic neurones that release acetylcholine that causes gallbladder contractions by binding to cholinergic muscarinic receptors on smooth muscle membranes and this event can be inhibited by noradrenaline from postganglionic sympathetic fibers acting presynaptically on vagal α2 adrenergic receptors **(Mawe et al., 1997)**.

It was noticed also that vasoactive intestinal peptide (VIP) is also released as a result of vagal activity, with no evidence of any endocrinal cells in the gallbladder that might have been a source of VIP **(Bjorck et al., 1986)**.

VIP causes elongation of the gallbladder and also promotes secretion of epithelial cells **(Jansson et al., 1978)**.

Hepatic Bile and Gallbladder Bile

Bile is a complex variable mixture of organic and inorganic solutes elaborated by both the hepatocytes and biliary duct epithelia **(Nathanson et al., 1991)**.

Approximately 600 mL are secreted daily, the hepatocyte produces both bile salt dependent and independent fractions **(Sherlock et al., 1997)**.

These two fractions constitutes about 75% of the total bile production and the remainder is a bicaronate-rich fluid that is produced by biliary ductules and stimulated by secretin **(Muller et al., 1997)**.

Secretin is remembered as the first hormone, reported in **1902** when **Bayliss and Starling** were studying alimentary tract reflexes in dogs **(Bayliss et al., 1902)**.

About 75% of bile produced in the liver is conducted towards, stored and concentrated in the gallbladder **(Lanzini et al., 1987)**.

Hepatic bile is an isotonic fluid with an electrolyte composition resembling blood plasma. The electrolyte composition of gallbladder bile differs from that of hepatic bile because most of the inorganic anions, chloride and bicarbonate have been removed by reabsorption across the gallbladder epithelium **(Harrison, 2001)**.

Major components of bile by weight include water 82%, bile acids (12%), lecithin and other phospholipids (4%), and unesterified cholesterol (0.7%). Other constituents include conjugated bilirubin, proteins (IgA, metabolites of hormones and other proteins metabolized in the liver, electrolytes, mucus, drugs and their metabolites **(Harrison, 2001)**.

Hormones Acting on Gallbladder

*** Cholecystokinine (CCK)**:

Cholecystokinine, its name is coined by Ivy and Oldberg to describe the factor released from the proximal small intestine in response to fat that controls postprandial gallbladder contractions. Fifteen years after the Ivy and Oldberg report, Harper and Raper discovered that the introductions of polypeptides into the duodenal lumen elicited a secretion of pancreatic enzymes, they named the factor mediating the response pancreozymin **(Harper et al., 1943)**.

Subsequent purification of CCK and pancreozymin showed they were the same substance **(Walsh, 1987)**.

CCK has numerous effects other than controlling postprandial GB contractions as:

- Stimulating pancreatic growth **(Walsh, 1987)**.
- Potentiating the pancreatic bicarbonate secretion stimulated by secretin **(You et al., 1983)**.
- Delaying gastric emptying **(Debas et al., 1975)**.
- Modulating satiety **(Morley, 1995)**.