Dyslipidaemic pancreatitis clinical assessment and analysis of disease severity and outcomes

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Declaration

The following represents my own original work conducted at the department of surgery in Addington hospital, Durban. This work has not been submitted to another institution for degree purposes.

Dedications

My family
They make countless sacrifices when I am engaged in research and running a surgical unit.

The patients who were part of this study for providing me the opportunity to research and understand a sometimes fatal disease process.

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Ethical Approval

This study was approved by the ethics committee of the Faculty of Health Sciences at the University of Kwa Zulu Natal

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Summary

Introduction: The relationship between pancreatitis and dyslipidaemia is unclear and has never been studied in a South African context.

Patients and methods: A prospective evaluation of all admissions with acute pancreatitis to a regional hospital general surgical service was performed to ascertain its relationship to dyslipidaemia. Aetiology was determined by history and ultrasound assessment. Disease severity was assessed using a modified Imrie score and an organ failure score. Body mass index was calculated. A lipid profile was obtained. Abnormal profiles were repeated. Secondary causes of dyslipidaemia were noted. A comparison of the demographic profile, aetiology, disease severity scores, complications and deaths were made in relationship to the lipid profiles.

Results: From June 2001 to May 2005, there were 230 admissions, of whom 31% were women and 69% men. The median age was 38 years(range 13-73). The pancreatitis was associated with alcohol in 146(63%), gallstones in 42(19%) and idiopathic in 27(12%). The amylase was significantly higher with a gallstone aetiology ($p< 0.001$) and significantly lower when dyslipidaemia was the aetiology($p< 0.001$). The ethnic distribution was: African 41.3%; Indian 41.3%; Coloured 12.2%; White 5.2%. Thirty five(15%) patients developed local complications of pancreatitis and 23(10%) died. Seventy eight(34%) of those admitted with acute pancreatitis had associated dyslipidaemia and 152(66%) were normolipaemic at admission. The average

body mass index was significantly higher in the dyslipidaemic group (27 vs 24,5:p = 0.004). Fourteen per cent of the admissions with dyslipidaemia had primary and 86% secondary lipid abnormalities.There was significant ethnic variation in the prevalence of the admissions with dyslipidaemia between the two predominant race groups Indian 50.5% and African 17.9% (p=<0.000017) Two patients with familial lipid abnormalities had 9 admissions despite supervised therapy. Of the dyslipidaemic admissions, 71% had hypertriglyceridaemia and 29% had hypercholesterolaemia. Seven of the primary dyslipidaemias had hypertriglyceridaemia and 4 hypercholesterolaemia.

The indices of disease severity were similar in the dyslipidaemic and normolipaemic groups and in those with hypercholesterolaemia and hypertriglyceridaemia. There was no difference in the mortality rate between the dyslipidaemic and normolipaemic patients (p=0.58).

In the dyslipidaemic admissions the majority of complications and all the deaths(n=9) occurred in those with hypertriglyceridaemia (p = 0.05) or with persistent lipid abnormalities(p = 0.003).

Conclusion:

The results showed a preponderance of the Indian ethnic group in those with pancreatitis associated with dyslipidaemia. The average body mass index was significantly higher in the dyslipidaemic group. Adverse outcomes in those with dyslipidaemia were predominantly associated with hypertriglyceridaemia.

CHAPTER 1

INTRODUCTION

Definition and prevalence

Acute pancreatitis, an inflammatory condition of the pancreas associated with elevated serum amylase and lipase is common among emergency hospital admissions.[1] In 1987 there were 108 000 admissions in the United States of America (excluding Veterans Administration affairs hospitals) with 2251 deaths. In the United Kingdom the incidence has risen by a factor of 10 from the 1960s to the 1980's.[1] In the 1980s the incidence in the Aberdeen area of Scotland was 242 per million.[2] There is only one hospital prevalence study in South Africa.[3] The authors assessed 133 admissions of acute pancreatitis over a period of 14 months.

Aetiology

In the assessment of pancreatitis, knowledge of the aetiology is important as it may alter the course of the disease and influence immediate management and long term outcome. Data from the USA, Western Europe and Asia show gallstones to be the cause in 45% of cases with alcohol responsible for 35%.[1] This does vary with the population studied. In a study reported from London [4] alcohol was found to be the causative factor in 30% and gallstones in 29% of patients. None were attributed to dyslipidaemia. In study from Glasgow 50.5% were associated with gallstones and 34.1% were alcohol.[5] In Aberdeen, gallstones were causative in 30% males and 53% females, whereas alcohol accounted for 26.5% of males but only 3% of females.[2] In Verona(Italy), gallstones were aetiologically implicated in 76% of cases, alcohol 12% and unspecified metabolic causes in 1.6% of the cases.[6]

The remainder, approximately 10% are due to a host of conditions. These causes are detailed in Appendix A Table 1. They include the following broad categories: metabolic abnormalities, drugs or toxins, obstruction pancreatic duct, trauma, infections, inherited conditions, vascular abnormalities and miscellaneous conditions. 10% of cases are considered idiopathic.[1] Metabolic abnormalities are usually the first to be excluded by a lipid profile and calcium estimation.

Prevalence of lipid abnormalities in pancreatitis

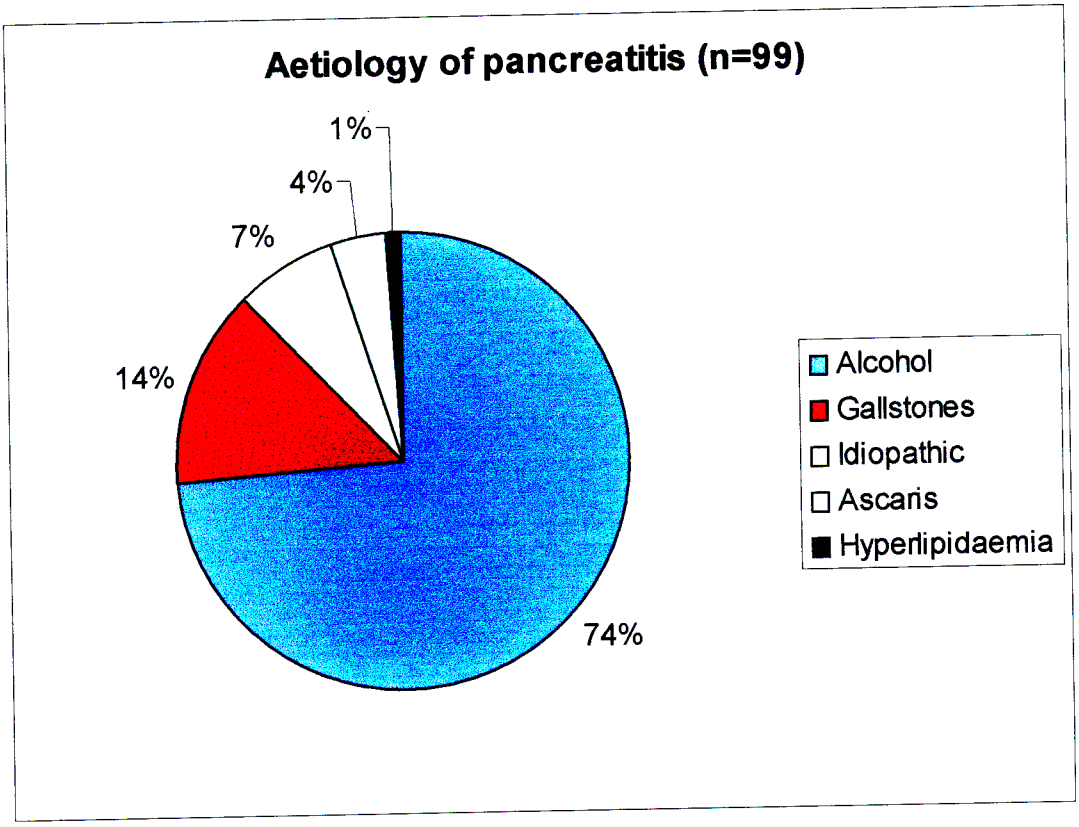
The reported prevalence of pancreatitis related to lipid abnormalities is variable and depends on how actively lipid abnormalities are pursued in patients admitted with a diagnosis of acute pancreatitis and what is considered an abnormal level. In the following studies it is not clear whether all patients were screened for lipid abnormalities and what levels were considered to be abnormal.

A prospective analysis by Athyros et al found a prevalence of 6.9% pancreatitis associated with dyslipidaemia. However, this study was restricted to those patients with hypertriglyceridaemia in excess of 10 mmol/l and lactescent serum.[7] In a retrospective review over a twelve year period, Fortson et al[8] found that only 1.3-3.8% had pancreatitis associated with dyslipidaemia. In a prospective analysis in Glasgow, 50.5% were associated with gallstones, 34.1% alcohol and 4.5% had lipid abnormalities on routine screening[5].

Farmer et al, in retrospective review, described a higher prevalence of 22% in their cohort of 45 patients with pancreatitis associated with lipid abnormalities[9], while Cameron et al found 39% of their cohort to have the combined abnormalities.[10]

There is a paucity of epidemiological information in the South African context. In a cohort from Cape Town, over 14 months, the predominant aetiology was alcohol (Figure 1) Only one patient had pancreatitis associated with dyslipidaemia.[3]

Figure 1: Aetiology in Cape Town cohort.



Diagnosis and Severity Grading

Pancreatitis is a clinical diagnosis based on the history and physical examination and commonly but not universally associated with an elevation in the serum amylase in excess of twice the upper limit of a normal reference range.[11] In dyslipidaemic pancreatitis the amylase levels have at times been found to be normal despite clinical and radiological evidence of pancreatitis.[12-15] Following a diagnosis of pancreatitis, severity grading is important in triaging patients for more intensive or specific therapies and in the comparison

of novel therapies and outcomes between centres. The Glasgow criteria and the presence of organ dysfunction as proposed by Banks are commonly used grading systems.[16,17]

Fortson et al found that the severity assessment of pancreatitis associated with dyslipidaemia by the Ranson, Apache 11, Banks and Balthazar CT scan methods to be no different from historical controls.[52,57]However only 18 of 70 patients is this series were assessed for severity in the dyslipidaemic group.[8] Whether dyslipidaemia influences disease severity is not addressed by previous investigators. The prevalence and outcomes of dyslipidaemia and pancreatitis in a South African cohort is unknown and is the focus of this study. Central to this study is a basic understanding of lipid metabolism and its abnormalities.

CHAPTER 2

LIPID METABOLISM

Introduction

Dyslipidaemia may result from a primary genetic disorder or as a consequence of secondary factors which may be other medical conditions, pharmaceutical agents or toxic substances. These may be found in combination where secondary factors reveal or exacerbate a primary disorder.[18-23]

Composition of lipoproteins and metabolism

Lipids are transported in plasma as components of lipoprotein complexes which enables the transport of these non-polar lipid compounds through the aqueous plasma.[18]

Triglycerides and cholesterol are the major lipid constituents of plasma. Being insoluble in water they are packaged with protein as lipoprotein particles for transport to tissues. The lipoprotein particle has a polar surface coat and a hydrophobic core which gives it solubility in plasma. The core contains cholesterol ester and triglyceride and the surface comprises phospholipids, apolipoproteins and free cholesterol.[19-23]

Every lipoprotein has a minimum of 1 apolipoptrotein. These are polypeptides serving a variety of functions in lipoprotein metabolism. They give identity to the class of lipoprotein, serve as receptor ligands, provide lipoprotein stability and may serve as co-factors in enzymatic processes involving lipoproteins.[19-23]

The principal apolipoproteins, their distribution and functions are enumerated and summarized in the following table.

Table 2: Principal apolipoproteins and their associated Lipoproteins and their function [23]

Apolipoprotein	Lipoproteins	Function
Apo-B100	VLDL,IDL,LDL	Secretion of VLDL from liver, structural protein of VLDL,IDL,LDL. Ligand for LDL receptor
Apo-B48	Chylomicrons	Secretion of chylomicrons from intestine
Apo E	Chylomicrons,VLDL, IDL, HDL	Ligand for binding of IDL and remnants to LDL receptors and LRP
Apo-A1	HDL, Chylomicrons	Structural proteins of HDL.activator of LCAT
Apo-A11	HDL, Chylomicrons	unknown
Apo-C11	Chylomicrons,VLDL, IDL, HDL	Activator of LPL
Apo-c111	Chylomicrons,VLDL, IDL, HDL	Inhibitor of LPL activity

Apo=apolipoprotein. VLDL=very low density lipoprotein; IDL=intermediate density lipoprotein; LDL=low density lipoprotein; HDL=high density lipoprotein; LRP= LDL –Receptor Protein ; LCAT= Lecithin : cholesterol acyl transferase ; LPL=lipoprotein lipase

Major lipoprotein classes

All the major lipoprotein classes comprise cholesterol, triglycerides, phospholipids and apolipoproteins in differing concentrations and their origins and electrophoretic patterns are summarized in the following table.[19]

Table 3: Characteristics of lipoproteins[23]

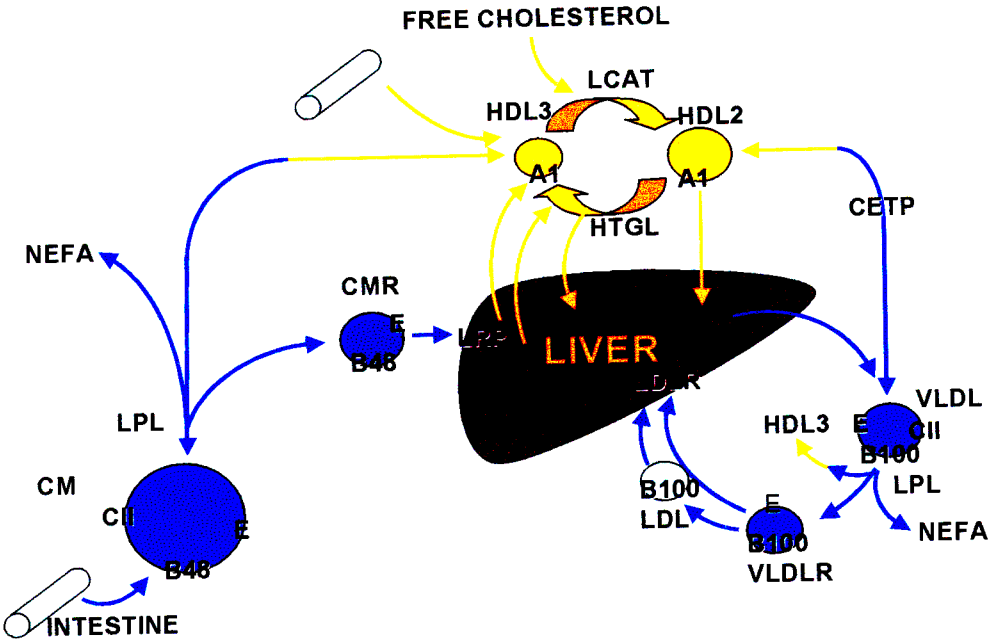
Lipoprotein	Density (g/ml)	Diameter (nm)	Major lipid	Electro-phoresis
Chylomicron	<< 1.006	500-80	Dietary triglycerides	Origin
VLDL	<1.006	80-30	Endogenous triglycerides	Pre-β
IDL	1.006 -1.019	35-25	Cholesterol esters, triglycerides	Slow pre- β
LDL	1.019 -1.063	25-18	Cholesterol esters	β
HDL	1.063 -1.210	5-12	Cholesterol esters, phospholipids	α
Lp(a)	1.055 -1.085	30	Cholesterol esters	Slow pre- β

VLDL= very low density lipoproteins
IDL= intermediate density lipoproteins
LDL= low density lipoproteins
HDL= high density lipoproteins; Lp(a)=lipoprotein a.

Major pathways of lipid metabolism

The major pathways of lipid metabolism are depicted in Figure 2 and discussed in subsections A, B and C[22].

Figure 2.



CM = chylomicrons; A1, B48, B100, B400, C11, E= apoproteins A1, B48, B100, B400, C11, E; NEFA = non esterified fatty acids; LPL= lipoprotein lipase; CMR= chylomicron remnants; LRP= LDL receptor-related protein ; HDL3/2 = high density lipoprotein 3/2; LDL = low density lipoproteins; VLDL = very low density lipoproteins; VLDLR = very low density lipoprotein receptors; LCAT = Lecithin:Cholesterol acyl transferase ; CETP = Cholesterol ester transfer protein

Synthesis and transport of exogenous lipids (Figure 2, section A)

Chylomicrons, large triglyceride-rich particles, are produced in the intestinal epithelial cells and packaged with apolipoprotein B-48 and other lipoproteins. These particles are released into the lymphatics and then the bloodstream. Lipoprotein lipase, located in the endothelial cells removes triglycerides, releasing fatty acids for tissue use. Apolipoprotein apo C-11 acts as a co-factor. This hydrolysis results in chylomicron remnants which are taken up by the liver. There is exchange of lipids and apolipoproteins with other classes of lipoproteins[19-22]

Synthesis and transport of endogenous lipids(Figure 2, section B)

In between meals, the liver produces very low density lipoprotein(VLDL). These triglyceride-rich particles are packaged with apolipoprotein apoB-100 along with other apolipoproteins. Hydrolysis of VLDL is also mediated by apo C-11 producing intermediate density lipoproteins which are smaller remnants relatively rich in cholesterol. Their predominant apolipoprotein is apo E which is a ligand for hepatocyte uptake by the Low density lipoprotein-receptor-related protein(LRP) and the Low density lipoprotein receptor(LDLR). Low density lipoprotein(LDL) is the ultimate product of VLDL hydrolysis and contains the apolipoprotein apo B-100 which is the ligand for hepatocyte uptake of of LDL. LDL delivers cholesterol to all nucleated cells by endocytosis through receptors that recognize apolipoprotein B-100[19-22]

Reverse cholesterol transport pathway (Figure 2, section C)

High density lipoprotein(HDL) which originates from the liver functions to circulate cholesterol from the peripheral tissues to the liver. This cholesterol is accumulated and esterified to cholesterol esters by lecithin-cholesterol

acyltransferase(LCAT). Apolipoprotein apo A-1 mediates this process. These cholesterol esters are removed in the liver by hepatocyte receptors, including the scavenger receptor(SR-B1). Transfer of cholesterol from HDL to IDL, LDL and VLDL occurs in the plasma in exchange for triglyceride. This is mediated by cholesterol ester transfer protein(CETP) and is dependent on the cholesterol ester and triglyceride load. This process results in depletion of HDL cholesterol esters in hypertriglyceridaemia and triglyceride- rich HDL which enhances lipolysis by hepatic lipase. This is independent of apo C-11 and produces small dense LDL particles.[21]

CHAPTER 3

DYSLIPIDAEMIA

Definitions

Dyslipidaemia refers to the disorders found in lipoprotein metabolism and can result in premature atherosclerosis or pancreatitis. Hyperlipidaemia emphasizes the importance of elevated lipids in the adverse consequences of the common dyslipidaemias[18,22]

Classifications

There are various classifications. The Frederickson classification, first presented in 1965, is shown in Table 4. In using the Frederickson classification problems may arise during the resolution of hyperlipoproteinaemia as type V abnormalities may regress to other types i.e IV, III and IIB before resolution.[24,25] Hence it is no longer commonly used as a management classification for the common dyslipidaemias.

The current trend is to classify dyslipidaemias according to their known or suspected aetiology. These are grouped as primary or secondary lipid disorders.[26] Table 5 enumerates the common primary dyslipidaemias and their estimated prevalence in a European setting. Table 6 enumerates the known lipoprotein disorders, associated Frederickson typing, the primary lipoprotein disorders and the possible secondary aetiologies.[17,18,20,23]

Table 4: Frederickson classification[21]

Pheno type	Elevated particle	Lipid disorder	Frequency	Etiology
I	Chylomicron	Triglcerides > 1000mg/dl	Rare	Lipoprotein lipase deficiency
IIA	LDL	LDL >130mg/dl	Common	Familial hypercholesterolaemia
IIB	LDL,VLDL	LDL >130mg/dl Triglcerides > 125mg/dl	Common	Familial combined hyperlipidaemia(diabetes, hypothyroidism, nephrosis
III	IDL	Cholesterol > 200mg/dl Triglycerides > 125mg/dl	Rare	Apolipoprotein E2 homozygosity(diabetes and kidney disease)
IV	VLDL	Triglycerides > 125mg/dl	Common	Familial hyperlipidaemia
V	VLDL, Chylomicron	Triglycerides > 1000 mg/dl	Uncommon	Familial hypertriglyceridaemia(diabetes, hypothyroidism, nephrosis,drugs

LDL = low density lipoprotein
VLDL = very low density lipoprotein
IDL = intermediate density lipoprotein.

Primary dyslipidaemia

Primary disorders refers to dyslipidaemia with a known familial or genetic cause. [19-23]

Table 5: Primary lipid disorders and estimated prevalence in European setting[23].

Dyslipidaemia	Diagnosis	Estimated prevalence (European adults)
Mainly Hypercholesterolaemia	Polygenic hypercholesterolaemia	20-80%
	familial hypercholesterolaemia	0.20%
	familial defective apolipoprotein B	0.20%
Combined hypercholesterolaemia		
and hypertriglyceridaemia		
a. Triglycerides 2.0-10.0 mmol/l	familial combined if relatives have	10%
	hyperlipoproteinaemia,otherwise	
	simply combined hyperlipidaemia	
b. Triglycerides 5.0-20.0 mmol/l	frequently called type 111	0.02%
(cholesterol typically	hyperlipoproteinaemia	
7.0-12.0 mmol/l)		
c. Triglycerides >10.0 mmol/l	Familial lipoprotein lipase	0.10%
	deficiency or heterozygous	
	lipoprotein lipase	
	mutation plus another cause for	
	hypertriglyceridaemia	
Raised Trigylerides alone	Familial or sporadic	1%
	hypertriglyceridaemia	
Hypoalphalipoproteinaemia	Most undiagnosed or associated	10-25%
	with hypertriglyceridaemia.	

Secondary dyslipidaemias

Secondary dyslipidaemias are associated with an identifiable secondary cause which may be aetiological or exacerbate a primary lipid disorder and marked hyperlipoproteinaemia is frequently the result.[19-23] Some of the commoner secondary causes of dyslipidaemia are discussed further. Alcohol may be associated with mild to moderate hypertriglyceridaemia (high VLDL) or severe hypertriglyceridaemia when there is a genetic lipid disorder (chylomicronaemia syndrome).

In diabetes mellitus, triglycerides are predominantly elevated, whereas thyroid disease produces elevation of LDL cholesterol and less frequently triglycerides.

Obesity predominantly causes hypertriglyceridaemia but will exacerbate any primary disorder. Anorexia is paradoxical in that it may cause elevation of serum cholesterol. Because of improvements in long term management, renal disease is assuming a more important cause of secondary dyslipidaemia. In the nephrotic syndrome the abnormality is predominantly cholesterol, whereas chronic renal failure causes hypertriglyceridaemia which is from an increase in both VLDL and in LDL triglycerides.

β-Blockers without intrinsic sympathomimetic activity raise triglycerides and lower HDL cholesterol. Thiazides tend to increase both cholesterol and triglycerides. Oestrogens tend to raise serum triglycerides and HDL with androgens having the opposite effect.

Cholestatic liver disease produces hypercholesterolaemia. Later in the disease when cirrhosis and hepatocellular damage sets in, the lipid abnormality resolves[18,21,26]

Table 6: Dyslipidaemia: Elevated lipoprotein, Frederickson equivalent, Primary disorders and secondary causes.[23]

Elevated Lipoprotein	Primary Disorder	Secondary Disorder
Exogenous Hyperlipaemia	Familial lipoprotein lipase	Dysglobulinemias
(Chylomicrons)	deficiency	SLE
Type 1	C-11 apolipoprotein deficiency	
	Unclassified	
Endogenous Hyperlipaemia	Familial Hypertriglyceridaemia	Dysglobulinaemias
(VLDL)	(mild form)	SLE
Type 1V		Diabetic hyperliaemia
		Glycogenosis, type 1
Mixed Hyperlipaemia	Familial Hypertriglyceridaemia	Lipodystrophies
(VLDL + Chylomicrons)	(severe form)	Uremia
Type V	Familial lipiprotein lipase	Hypopituitarism
	deficiency	Nephrotic syndrome
	C-11 apolipoprotein deficiency	Alcoholism
		Oestrogen use
		Glucocorticoid use
		Stress-induced
Hypercholesterolaemia(LDL)	Familial hypercholesterolaemia	Nephrotic syndrome
Type 11-a	(LDL receptor defects)	Hypothyroidism
	Familial multiple lipoprotein-type	Dysglobulinaemias
	hyperlipaemia	Cushing syndrome
	Polygenic hypercholesterolaemia	Acute intermittent porphyria
	(includes exogenous hyper-	
	cholesterolaemia)	
Combined hyperlipidaemia	Familial multiple lipoprotein-type	Nephrotic syndrome
(LDL + VLDL)	hyperlipaemia	Hypothyroidism
Type 11-b	Unclassified	Dysglobulinaemias
		Cushing syndrome
Remnant hyperlipidaemia	Familial dysbetalipoproteinaemia	Hypothyroidism
(beta-VLDL)	Unclassified	SLE
Type 111		
Lamellar hyperlipoproteinaemia	Familial lecithin: cholesterol	Cholestasis(with LP-X)
(Vesicular and discoidal	acyltransferase deficiency	Hepatic failure(with lamellar
lipoproteins)		HDL)

Clinical Grading of Dyslipidaemia:

A simpler and more practical, management orientated classification of Dyslipidaemias is outlined in the Table 7. This refers to a grading system that is used in the assessment of cardiac risk and the targeting of the appropriate therapies. It notes the predominance of cholesterol or trigycerides in assessing dyslipidaemia. The mixed grade may be considered as mild hypertriglyceridaemia.

Therefore, in the appraisal of the dyslipidaemias, measurement of serum cholesterol, triglycerides, HDL-cholesterol and obtaining the LDL cholesterol by Friedewald equation is usually sufficient in the majority of patients.[18,22] Assessing the pattern of the dyslipidaemia by these assays determines the modes of dietary and drug therapy administered.

Table 7: Classification and Grading of dyslipidaemia[22]

	Hypercholesterolaemia			Mixed	Hypertriglyceridaemia	
	Severe	**Moderate**	**Mild**	**Hyperlipidaemia**	**Moderate**	**Severe**
TG		< 1.5		1.5 - 5	5 - 15	> 15
TC	> 7.5	> 5.0	> 5.0	variable	Variable	
LDLC	> 5.0	> 4.0	> 3.0	variable	Variable	little to none
				Small dense LDL in all hypertriglyceridaemias		
IDLC	Negligible	contribution		Dysbetalipoproteinaemia		
Lp(a)	Negligible	contribution				
HDLC		> 1.6			Low HDLC with	
					Hypertriglyceridaemia	
LpX	Cholestasis					

All Units are mmols/l
TG = Triglyceride; TC = total cholesterol; IDLC = intermediate density lipoprotein cholesterol; LDLC = low density lipoprotein cholesterol; HDLC = high density lipoprotein cholesterol; LpX = lipoprotein X .

Dyslipidaemia in a South African context

Primary Dyslipidaemia in the South African context has been studied in its effect on the incidence of coronary heart disease and has been found to be commonest in the Caucasian and Indian groups, intermediate in the Coloured

population and low in the indigenous African population.[18,27-30] In a cohort of Black patients with diabetes, the incidence of dyslipidaemia had not changed in 25 years in an urban environment and there appeared to be no differences according to socioeconomic position.[31] Familial hypercholesterolaemia is particularly common in Afrikaners, Jews and Indians. In most white populations this has an incidence of 1 in 500. In the Afrikaner population of South Africa the incidence is approximately 1 in 72. [27,29,30] In this context the most important and commonest dyslipidaemia is hypercholesterolaemia. The association between dyslipidaemia and pancreatitis has not been assessed in South Africa.

CHAPTER 4

DYSLIPIDEAMIC PANCREATITIS

Clinical manifestations of Acute Pancreatitis

In more than 90% of patients the predominant clinical feature is acute onset of mid-epigastric pain. When alcohol is the cause, the pain usually commences 12 to 48 hours after a binge episode. With gallstone pancreatitis, the pain may follow a large meal. Nausea and vomiting accompany the pain. This is caused by the paralytic ileus associated with retroperitoneal inflammation. Patients may present with a severe systemic illness without abdominal symptoms but this is rare. This is characterised by hypotension, hypoperfusion, and mental depression. There may be evidence of respiratory compromise and pleural collections. Fever, tachycardia, epigastric tenderness and distension are typical. In less than 3% of patients, severe pancreatitis may result in bluish discolouration of the left flank (Grey Turner's sign) or in the paraumbilical region (Cullen's sign).[1] Jaundice may be present as a consequence of common bile duct obstruction caused by a gallstone or oedema.[19,20,23,32-37] Laparotomy has generally been abandoned in the initial management of acute pancreatitis. In those with severe pain and hypotension, perforated ulcer or a ruptured aneurysm should be considered and an erect chest radiograph and an ultrasound may provide the necessary diagnostic information to instigate emergency surgery. Chest and abdominal radiographs are suggestive when they demonstrate pleural effusions basal atelectasis, a sentinel loop or the colon cut-off sign. Diagnostic contrast-enhanced CT scan is the most sensitive non-invasive diagnostic tool. CT scan can give conclusive evidence of the diagnosis. The amylase or the lipase serum levels are usually elevated

but more so in gallstone pancreatitis.[1,11] There are more false positives with the amylase and it must be remembered that 10% of patients with an amylase over 1000IU/litre will be harbouring another diagnosis which may include necrotic bowel.[38] If there is diagnostic doubt, a laparoscopy or laparotomy should be performed.

Dyslipidaemia and pancreatitis

It is generally accepted that triglycerides above 1000mg/dl(11.3 mmol/l) cause episodes of acute pancreatitis. This is the level at which serum becomes lactescent. [22] Clinical observation of patients with primary lipid abnormalities have noted onset of acute pancreatitis with the development of lactescent serum.[25,39-41]

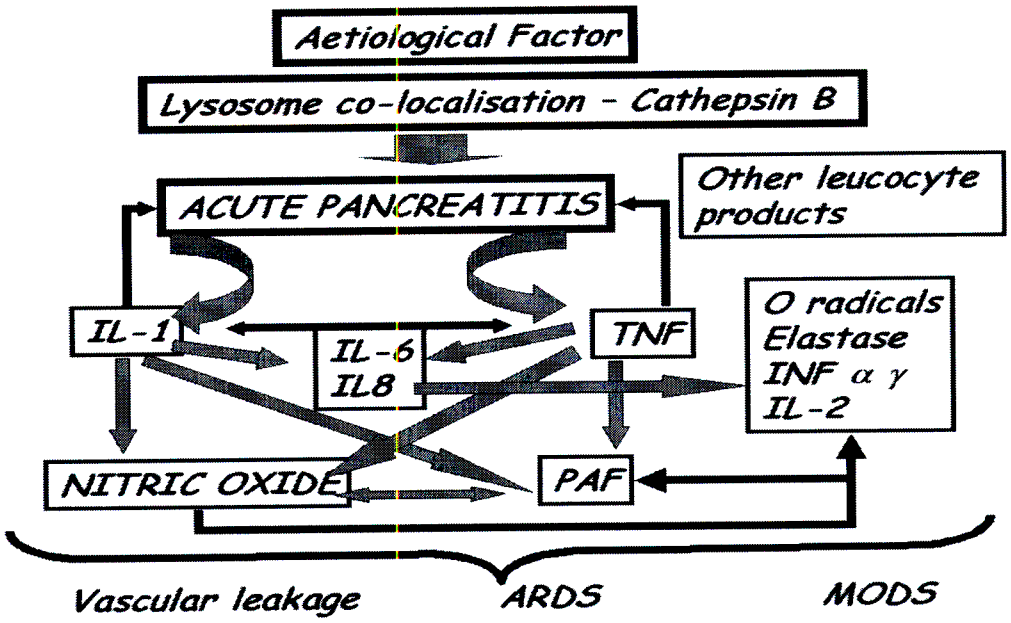
The association between abnormalities of lipid metabolism and pancreatitis was first documented by Speck in 1846[42]. The clinical associations vary and the pathogenesis is unclear.[25] They are found in association with alcohol consumption, diabetes, obesity, certain medications and pregnancy.[25,43-49] Furthermore the lipid abnormalities in this context have been found to be transient abnormalities which normalise with the resolution of the pancreatitis. However, Wilson Cox et al [50] described the relatives of a patient known to have apolipoprotein C-11 deficiency. The kindred originated from an isolated population on a Carribean island with significant inbreeding. The inheritance was found to be autosomal recessive with 5 of seven homozygotes having variable attacks of pancreatitis from the age of six years. It is not clear whether this population was tested for familial pancreatitis due to mutations affecting Trypsinogen activating protein.[50] The age of onset varies with the familial dyslipidaemias. The first episode is frequently in childhood or early adulthood. These variables make it difficult to establish a causal relationship.

The attacks of pancreatitis in this setting are no different from pancreatitis due to other aetiological agents. There is no gender or ethnic preponderance and obesity has not been a consistent feature.[8,50] Fortson et al found dyslipidaemic pancreatitis in both Caucasian and Black subjects and 44% of this cohort had recurrent episodes of pancreatitis.[8]

Pathophysiology

The triggers of the inflammation in all forms of pancreatitis are poorly understood and the complexity of the process once intiated is shown in the Figure 3. Premature activation of the digestive enzyme trypsinogen to trypsin is the earliest detectable event in the pathogensis of acinar cell injury in pancreatitis. An as yet ill-defined sequence of events results in the failure of orderly segregation of newly synthesized zymogen granules within acinar cells. Consequently, the lysosomal hydrolase cathepsin B co-localises with zymogen granules and activates trypsinogen, which in turn activates other enzymes. Extracellular/interstitial activation , perhaps by macrophages may be the initiating event. Acinar cell injury recruits leukocytes and subsequent cytokine production. The result is local and systemic production of inflammatory mediators, including cytokines, complements, bradykinin, nitrous oxide and Platelet activating factor, which have been linked to shock and organ failure.

Figure 3: Inflammatory cascade in acute pancreatitis



IL-1,2,6,8: Interleukins 1,2,6,8. TNF: Tumor necrosis factor. PAF: Platelet activating factor. INFα, γ: Interferons α, γ. O radicals: Oygen derived radicals. ARDS: Adult respiratory distress syndrome. MODS: Multiple organ dysfunction syndrome.

The mechanism by which lipid abnormalities cause pancreatitis remains unclear. A postulation is that hydrolysis of triglycerides and phospholipids results in excess lysolecithin and free fatty acids in the pancreatic microvasculature. This is proposed to be the noxious agent to the acinar cells that initiates the inflammation.[51] Alternatively, trypsinogen could be activated by the disturbance of the microcirculation caused by damage to the vessel endothelium of the pancreatic microcirculation as a result of the acid milieu created by the fatty acids.[51]

Diagnosis and Severity grading

Following a diagnosis of pancreatitis, severity grading is important in triaging patients for more intensive or specific therapies, transfer to specialist centres, in the comparison of novel therapies and outcomes between centres ,and, in selecting patients for inclusion within trials. Trials evaluating clinical assessment for predicting outcome have shown sensitivities of 38-64% and a positive predictive value of 49-100%. The Atlanta symposium definition of severe acute pancreatitis includes the development of organ failure detected clinically.[52,53]. The criteria for the assessment of organ failure are listed.

Shock: Systolic blood pressure less than 90mm Hg

Pulmonary insufficiency: PaO_2, 60 mm Hg or less

Renal failure: creatinine greater than 177μmol/l after rehydration

Gastrointestinal bleeding: greater than 500ml/ 24 hours

A multifactorial scoring system for acute pancreatitis was initially proposed by Ranson et al.[54,55] They used 11 factors at admission and after 48 hours. This system was modified by Imrie et al to 9 factors within 48hours of admission. These Glasgow criteria were further modified by Osborne et al. They excluded age > 55years to arrive at 8 factors.[56] The presence of 3 or more factors in the Ranson and Glasgow criteria denotes severe disease. These have not been evaluated for predicting disease severity beyond 48hours of admission. The Glasgow criteria are detailed in Table 8.

Table 8: GLASGOW CRITERIA

Variable	Cut off Level
Age	> 55 years
White Blood Cell count	> 15 x 10^9/litre
Glucose	> !0 mmol/litre
Urea	> 16 mmol/litre
Arterial partial pressure of oxygen	< 60 mmHg
Calcium	< 2 mmol/litre
Albumin	< 32 g/litre
Lactate dehydrogenase	> 600 IU/litre
Aspartate or alanine aminotransferase	> 100 units/litre

The Apache II scoring system is used for initial prognostication at admission and subsequent daily assessment of recovery, disease progression or the onset of sepsis. Multifactorial scoring systemns provide accuracy of prognostication in the region of 70-80%. A comparison of the Apache II, Ransons, Imrie and clinical assessment revealed the following sensitivity and specificity at 48 hours after admission.[57] The Apache-O attempts to factor in obesity as a body mass index of more than 30 is associated with an increase risk of a severe clinical outcome.[3]

Table 9: Sensitivity and specificity of scoring systems[57]

	Sensitivity	Specificity
Clinical	66%	95%
Ranson >2	75%	68%
Imrie >2	61%	89%
Apache-II >9	75%	92%

Disease severity in dyslipidaemic pancreatitis

An animal experiment has suggested that dyslipidaemia is associated with a more intensive course of pancreatitis.[58] Fortson et al found that the disease severity of pancreatitis associated with dyslipidaemia to be no different from historical controls when using the Ranson, Apache, Banks and Balthazar CT scan methods. However only 18 of 70(26%) patients is this series were assessed for disease severity in the dyslipidaemic group.[8] Whether dyslipidaemia influences disease severity has not been previously investigated. The prevalence and outcomes of dyslipidaemia and pancreatitis in a South African cohort is unknown and is the focus of this study.

Summary

Pancreatitis is a common cause for acute emergency admissions to surgical wards. The commonest causes are alcohol and gallstones. Various scoring systems are used to predict outcome in pancreatitis. The efficacy of these scoring systems is similar. Two of the commonly used are the Glasgow criteria and Organ failure.

The metabolism of lipids is a complex pathway which largely deals with the transport and degradation of cholesterol and triglycerides. Dyslipidaemia refers to the abnormalities in these metabolic pathways which are classified as either primary or secondary.

Dyslipidaemia and pancreatitis have a variable association. The prevalence of pancreatitis in a particular series depends on whether these are routinely sought on admission. Patients with familial dyslipidaemia in particular those with elevated chylomicrons and triglycerides are prone to attacks of

pancreatitis which tend to recur if the dyslipidaemia is not adequately managed.

The diagnosis of pancreatitis in the setting of lipaemic serum may be difficult as the serum and urine amylase may be within normal levels. However a classical clinical presentatiton with lipaemic serum is diagnostic of pancreatitis. If the presentation is doubtful, imaging may be helpful in arriving at a diagnosis. At times the diagnoses have been established at laparotomy.

The treatment of dyslipidaemic pancreatitis, as with other causes of pancreatitis, is in the main supportive with more intense monitoring reserved for those identified with severe disease.

It is unclear as to whether the currently available predictors of outcome are universally applicable to patients with dylipidaemic pancreatitis and whether pancreatitis in this setting has a similar outcome to other more common aetiologies such as alcohol and gallstones.

Chapter 5

HYPOTHESIS:

Dyslipidaemia is associated with a more severe disease and a higher incidence of complications and deaths.

AIM:

In a mixed ethnic South African cohort with pancreatitis to:

- Determine frequency of the aetiological factors.
- Determine the frequency, type, severity and persistence of dyslipidaemia.
- Assess for all aetiologies of dyslipidaemias
- Compare the severity and outcome variables relationship to the type, severity and persistence of dyslipidaemias.
- Compare the clinical course of dyslipidaemic patients with pancreatitis in relation to other aetiological causes.

Chapter 7

METHODOLOGY

Patients:

Data was prospectively collected on all admissions to Addington hospital with a diagnosis of pancreatitis . Demographic data were initially collected and the aetiology was ascertained.

Diagnostic tools:

Clinical presentation and serum or urine amylase were the primary diagnostic tools. A serum amylase level of twice the upper limit of normal or an elevated urine amylase was considered significant (normal serum amylase 25-125 u/l and urine amylase 50-760 u/l). Imaging by ultrasound or CT scan was used as a confirmatory or primary diagnostic investigation where indicated. Laparotomy, when performed for diagnostic doubt in critically ill patients was also a source of the diagnosis.

Severity assessment:

All patients were staged by a modified Glasgow criteria (less LDH) and/or the presence of organ dysfunction(Clinical criteria) as evidenced by shock(blood pressure less than 90 mmHg), pulmonary dysfunction (PaO^2 less than 60 mmHg), renal failure (creatinine greater than 177 μmol/l) and gastrointestinal bleeding (greater than 500ml/hour).

Lipid assessment:

Patients were assessed for lipid abnormalities within 48-72 hours of admission and those with lipid abnormalities were assessed for persistence or resolution during the index admission. If at discharge, the lipid abnormalities persisted, the patients were referred to an endocrine unit for further assessment and therapy.

Lipids were measured after a 14 hour fast. Cholesterol and triglycerides were measured by a timed endpoint method using the Beckman CX7 analyser. Both cholesterol and triglyceride are enzymatically converted to a quinoneimine dye. The system monitors the change in absorbance at 520 nanometers which is directly related to the concentration of the compounds in the sample and is used to calculate and express their concentrations. HDL is measured by a homogenous assay in which a detergent releases HDL and this is enzymatically converted to a colour product. VLDL, LDL and chylomicrons are inhibited by this detergent. Cholesterol is then measured by a timed-endpoint reaction read at 560nm. LDL is calculated by the HIS (meditech) using the following formula:

Total cholesterol only – ((Triglyceride/2.2) + HDL)

This formula is not valid when triglycerides exceed 4.00 mmol/l.

The reference ranges were as in Table 10.

Table 10: lipoproteins and reference ranges

Lipoprotein	Normal Ranges
Triglyceride	0.39-1.84 mmol/l
Total cholesterol	3.60-5.1 mmol/l
Low density lipoprotein	> 4.9 mmol/l elevated
High density lipoprotein	0.90-1.68 mmol/l

All data were entered prospectively into an excel data base.

Clinical outcomes assessment:

The patients with lipid abnormalities were compared to the patients without lipid abnormalties with respect to the following variables: Body mass index, Glasgow score ≥3, the development of organ dysfunction, local complications (Pseudocyst formation, gastric outlet obstruction, jaundice, abscess formation), ICU admission and death. These same outcomes were used in comparing the different grades of dyslipidaemia as well as the admissions with persistent or transient lipid abnormalities.

Body mass index:

Where feasible the height in meters and the body mass in kilograms was determined within 48hours of admission. The body mass index was determined by the following formula:

Body mass index = Mass(kg)/ Height(m)^2

Obesity was considered to be a body mass index of greater than 30.

Statistical analysis

Statistical significance was determined by the use of the Fisher exact test (two tailed) and a value of $p < 0.05$ was considered significant. Where sample size was small and zero values present, the measures of exposure effect were calculated using confidence intervals of 95%. Risk and odds ratios were calculated to assess trends.

Chapter 7

RESULTS

Overview

In the period June 2001 to May 2005, there were 230 admissions with acute pancreatitis. The majority were male with an equal number in the Indian and African groups. Thirty four percent had associated dyslipidaemia. The majority had alcohol as an aetiology (Table11).

Table 11: Descriptive summary of the cohort

Female: Male	71(31%): 159(69%)
African	95(41.3%)
Coloured	28(12.2%)
Indian	95(41.3%)
White	12(5.2%)
Median age(range)	38.5(13-73)
Alcohol	146(63%)
Gallstones	42(18%)
Other	42(18%)
Dyslipidaemia	78(34%)
Normolipaemia	152(66%)
Imrie > 3	32(14%)
Clinical criteria	30(13%)
ICU admission	25(11%)
Local complications	35(15%)
Deaths	23(10%)

Demographics

The sex and age distributions in the dyslipidaemiac and normolipaemiac groups of admissions are summarized in table 12.

Table 12: Gender and age distribution

	Female	Male	Age(median:range)
Dyslipidaemia	30(38%)	48(62%)	40(15-73)
Normolipaemia	41(27%)	111(73%)	37(13-69)
Entire cohort	71(31%)	159(69%)	38.5(13-73)

Table 13: Ethnic mix of Dyslipidaemic and Non dyslipidaemic admissions

	Entire cohort	Dyslipidaemia	Normolipaemia
African	95(41.3%)	17(17.9%)	78(82.1%)
Indian	95(41.3%)	48(50.5%)	47(49.5%)
Coloured	28(12.2%)	8(28.6%)	20(71.4%)
White	12(5.2%)	5(41.7%)	7(58.3%)
Total	230(100%)		

Column 1: Total ethnic groups

Column 2 and 3: percentage of the ethnic group with dyslipidaemia and normolipaemia

A comparison was made into the number of admissions with dyslipidaemia in a particular ethnic group and the rest of the admissions with dyslipidaemia. The greatest prevalence was found in the Indian ethnic group with a p-value of 0.000008. Dyslipidaemia was the lowest in the African group with a p-value of 0.000017. The values in the Coloured and White groups were intermediate and not statistically significant with p-values 0.41 and 0.34 respectively (Table 13).

Diagnosis

In the dyslipidaemic group, the serum and/or urine amylase were above diagnostic cut off level in 72(92%) of the patients and in 147(97%) of the normolipaemic group.

The mean amylase levels by aetiology are illustrated by Table 14.

Table 14: Amylase and aetiology

	Amylase: mean(range)
Alcohol	1155.85(107-24061)
Gallstones	1931.24(201-6278)
Idiopathic	1064(102-3169)
Lipids	634.5(0-3040)

The amylase level in the gallstones was significantly higher than the other groups, $p<0.001$ and significantly lower in the lipids group $p<0.001$.

In 6(8%) of the dyslipidaemic group the amylase levels were within normal range and a lipaemic serum and a typical clinical presentation was used in making the diagnosis. In the normolipaemic group of admissions the diagnosis was made at laparotomy in 3(2%) patients who had normal amylase assays. In another 2(1%) patients the diagnosis was also made at laparotomy despite raised amylase levels because of a suspicion of other causes of an acute abdomen.

Aetiology

The variation in the aetiologies of the dyslipidaemic and the normolipaemic groups are illustrated in Table 15.

There was no significant difference between alcohol in the dyslipidaemic group and the normolipaemic group(p = 0.47). Gallstones were less common in the dyslipidaemic group as opposed to the normolipaemic group(p=0.058).

Table 15: Dyslipidaemia and aetiology

	Overall	Dyslipidaemia	Normolipaemia
Alcohol	146(63%)	47(32.2%)	99(67.8%)
Gallstones	42(18%)	9(21.4%)	33(78.6%)
Idiopathic	20(9%)	0(0%)	20(100%)
Hyperlipidaemia	22(10%)	22(100%)	0(0%)
Total	230(100%)		

Column 1: Total aetiological groups

Column 2 and 3: percentage of aetiological group with dyslipidaemia and normolipaemia

Familial dyslipidaemia

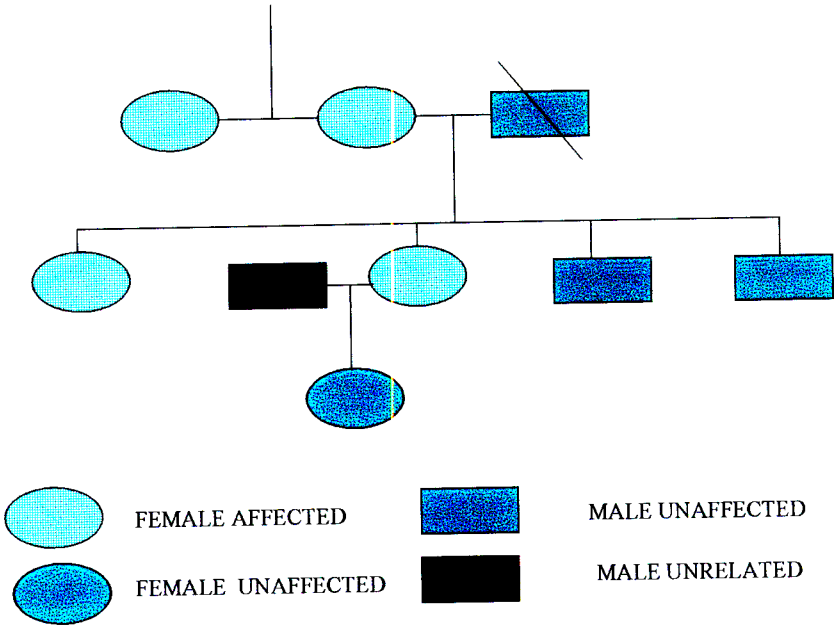
Of the 78 admissions with dyslipidaemia, 9(12%) were of 2 patients with familial dyslipidaemia, representing 2 families. Both families were of Indian origin. The family tree illustrates 2 generations of affected females in one of the families associated with seven of these admissions (Figure 4)

Both affected generations had severe hypertriglyceridaemia and had experienced episodes of pancreatitis.

The other patient had 3 members of the same generation affected with hypertriglyceridaemia, She was the only one to present with recurrent pancreatitis.

Figure 4:

Family tree of 2 generations of affected females



Clinical Grading of the Dyslipidaemias

Fifty five (71%) of the dyslipidaemic group had hypertriglyceridaemia and 23(29%) had hypercholesterolaemia. Sixty one percent of the hypercholesterolaemia and 51% of the hypertriglyceridaemia were mild elevations.

Table 16. Clinical Grading of the dyslipidaemias

	Mild	Moderate	Severe	Total
Hypercholesterolaemia	14	3	6	**23**
Hypertriglyceridaemia	28	14	13	**55**

Primary Dyslipidaemia

Eleven (14%) of the admissions with dyslipidaemia had primary lipid abnormalities.

Table 17: Lipid grading of 1° dyslipidaemia

Hypercholesterolaemia			Mixed	Hypertriglyceridaemia	
mild	moderate	severe	mild	moderate	severe
3	0	0	5	0	3

Secondary Dyslipidaemia

Sixty seven(86%) of the admissions with dyslipidaemia had secondary lipid abnormalities. In 42 of these admissions there was a single secondary cause for the dyslipidaemia and in 25 admissions there was a combination of secondary aetiologies (Table 18).

Table 18: Secondary Dyslipidaemia.

Isolated secondary aetiologies of dyslipidaemia	**Number**
Alcohol	32
Diabetes	7
Obesity	3
Total	**42**

Combined secondary aetiologies of dyslipidaemia	**Number**
Diabetes/Drugs	7
Alcohol/Obesity	3
Alcohol/Drugs	5
Alcohol/Diabetes	4
Alcohol/Diabetes/Obesity	3
Diabetes/Obesity	1
Alcohol/Diabetes/Obesity/Drugs	1
Obesity/pregnancy	1
Total	**25**

Dyslipidaemia in Alcohol,Diabetes and Obesity

Twenty three (29%) of the admissions with dyslipidaemia and pancreatitis were diabetic as opposed to 10(7%) in the normolipaemic group($p = 0.000003$). Ten(43%) of these admissions had poor sugar control on admission with ketoacidosis.

In this cohort, 47(60%) of the patients with dyslipidaemia and pancreatitis consumed alcohol as opposed to 99(65%) of patients who had normolipaemia and pancreatitis (p = 0.467).

The clinical grading of the dyslipidaemias associated with alcohol, diabetes and obesity are illustrated in Table 19. The majority are hypertriglyceridaemia and associated with alcohol consumption.

The mean body mass index was significantly higher at 27 (±6) in the dyslipidaemic group than in the non dyslipidaemic group at 24,5 (±6.20) with p = 0.004. The assessment for differences in the number of obese admissions (BMI>30), revealed this to be significantly higher in the dyslipidaemic group(p = 0.031).

Table 19: Secondary dyslipidaemias and clinical grading

	Hypercholesterolaemia			Hypertriglyceridaemia		
	Mild	**Moderate**	**Severe**	**Mild**	**Moderate**	**Severe**
Alcohol	5	1	1	17	4	4
Diabetes	1	0			3	3
Obesity	2				1	
Alcohol, Diabetes, Obesity				1	1	1
Diabetes, Drugs			2		2	3
Alcohol, Obesity	1			2		
Alcohol, Drugs	1	1	1	1	1	
Alcohol, Diabetes		1		2	1	
Diabetes, Obesity				1		
Obesity, Drugs			1			
Pregnancy, Obesity	1					
Total	**11**	**3**	**5**	**24**	**13**	**11**

Other secondary dyslipidaemias

Pregnancy, thiazide diuretics, oestrogens, hypothyroidism, renal disease: Two admissions (3%) were also of pancreatitis associated with first trimester pregnancies. One had transient mild hypercholesterolaemia with gallstone related pancreatitis. The other had persistent lipid abnormalities of a mixed nature despite spontaneous termination of the pregnancy in the first trimester. This was considered to be a primary lipid abnormality. Six(8%) of the dyslipidaemics used thiazide diuretics. Four of them had alcohol as an aetiology, 1 gallstones and the other idiopathic. Five had transient abnormalities of mild, moderate and severe hypercholesterolaemia and mixed and moderate hypertriglyceridaemia respectively. One had persistent hypercholesterolaemia.

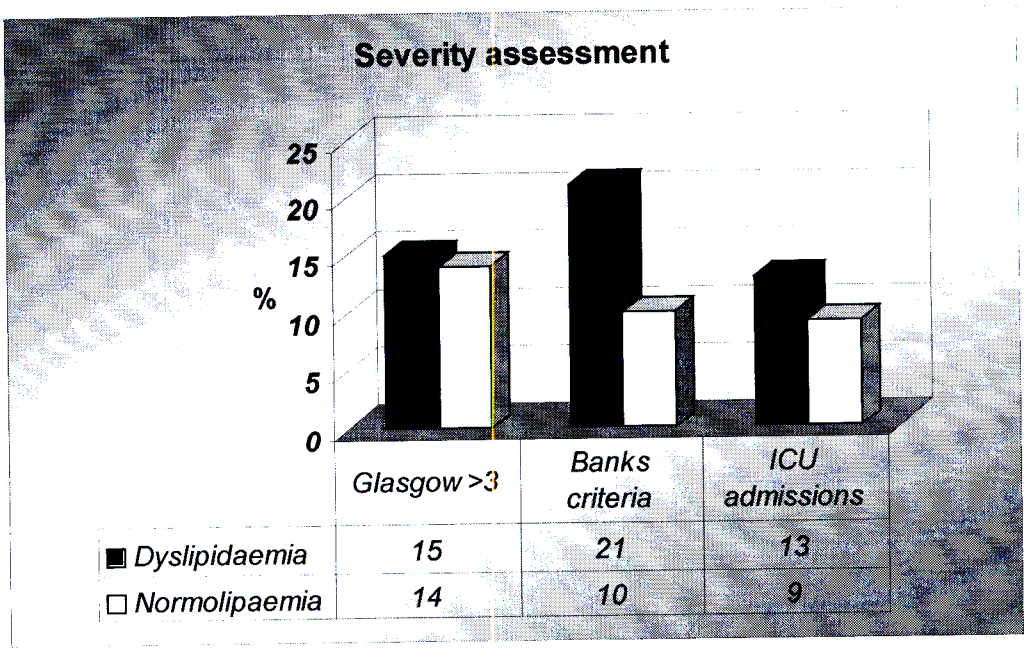
There were 8(10%) admissions associated with oestrogen use. Two had moderate hypertriglyceridaemia and 6 severe hypertriglyceridaemia. Seven of these admissions were of the same patient with familial dyslipidaemia associated with diabetes.

None of the admissions were of patients with renal disease or hypothyroidism.

Severity assessment

The number of admissions with a Glasgow score >2, organ dysfunction and Intensive care unit admission did not reach statistical significance between the dyslipidaemic and normolipaemic groups($p = 0.74$, $p=0.3$ and $p=0.3$ respectively). Assessment of trends showed odds ratios of **1.13**; 95% confidence interval, 0.53, 2.45; **2.36**; 95% confidence interval, 1.1, 5.07 and **1.57**; 95% confidence interval, 0.66, 3.77 respectively, for the admissions with dyslipidaemia. This trend is most marked with the organ dysfunction.

Figure 5: Severity assessment



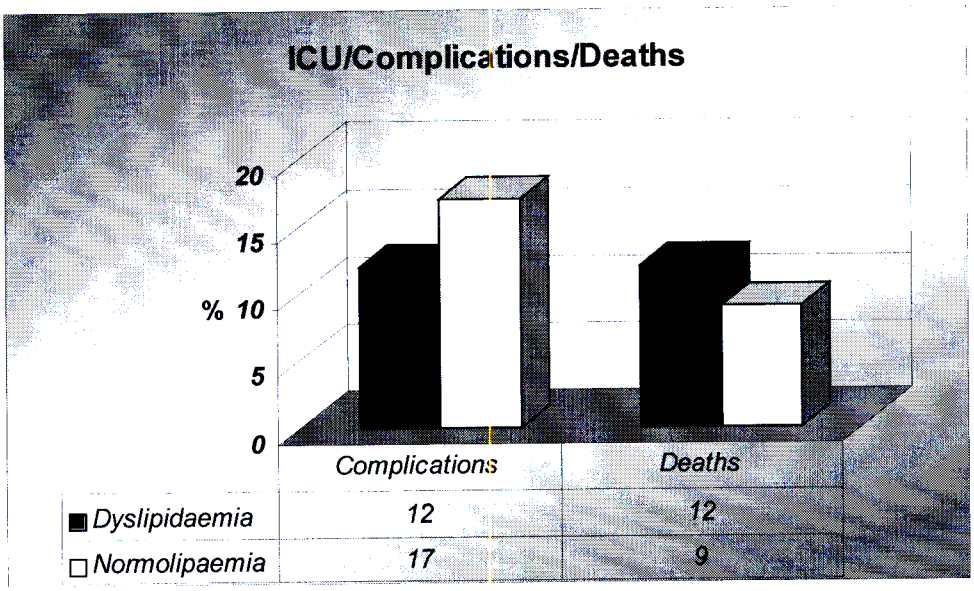
Complications

In dyslipidaemic group 9(12%) developed complications and 26(17%) in the non dyslipidaemic group with a p-value 0.27 and an odds ratio of 0.63; 95% confidence interval, 0.28, 1.43. The trend is for dyslipidaemia to be protective for the development of complications.

Deaths

The comparison of deaths in the 2 groups revealed a p-value of 0.58 and a odds ratio of 1.29; 95% confidence interval, 0.53, 3.12. There is a trend towards more deaths in the dyslipidaemic group.

Figure 6: Outcomes



Transient and Persistent dyslipidaemia

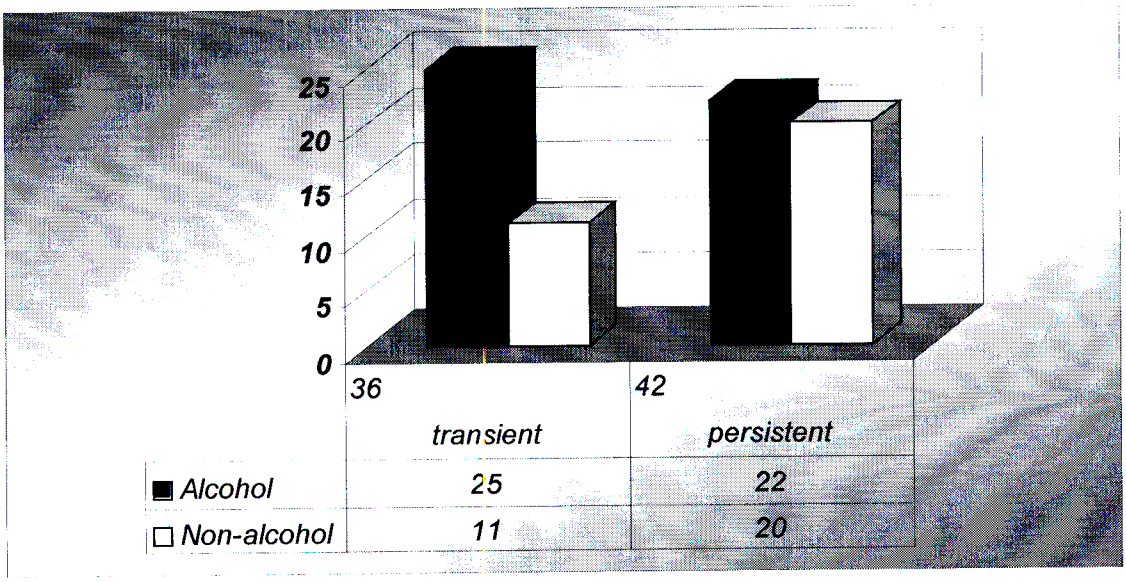
Some patients with dyslipidaemia were observed to have abnormalities which resolved on discharge or at 1 month review (n= 36), and, a second group which had persistent abnormalities (n= 31). A third group was undefined due to death or absconding prior to complete evaluation (n=11). Lipid measurements in this group were similar to the admissions with persistent lipid abnormalities and were grouped as such (Table 20).

Table 20: Initial lipid measurements in dyslipidaemic patients expressed in transient or persistent lipid abnormalities

Variables expressed as median and range.

Lipid abnormality	Triglycerides	Cholesterol	HDLC	LDLC
Persistent	5.5(0.7-108)	7.5(2.2-24.7)	0.98(0.2-2.1)	4.33(0.7-18.2)
Transient	1.7(0.54-14.4)	5.6(3.5-8.4)	1.3(0.7-2.2)	3.6(1.3-6.1)

Figure 7: Alcohol and transient or persistent lipid abnormalities



Alcohol is associated with a greater proportion of transient lipid abnormalities (69.4%) as opposed to persistent lipid abnormalities(52.4%)

Disease severity: Transient and Persistent Dyslipidaemia

The proportion of admissions with a Glasgow score of ≥ 3 and positive clinical criteria was insignificantly greater in the group with persistent lipid abnormalities (p = 0.33) and (p = 0.82) respectively. There were no admissions to the intensive care unit with transient lipid abnormalities whereas 24% of those with persistent lipid abnormalities were admitted to the intensive care (p = 0.002), suggesting a trend towards more severe disease in those admissions with persistent lipid abnormalities.

Figure 8: Disease severity transient and persistent lipid abnormalities

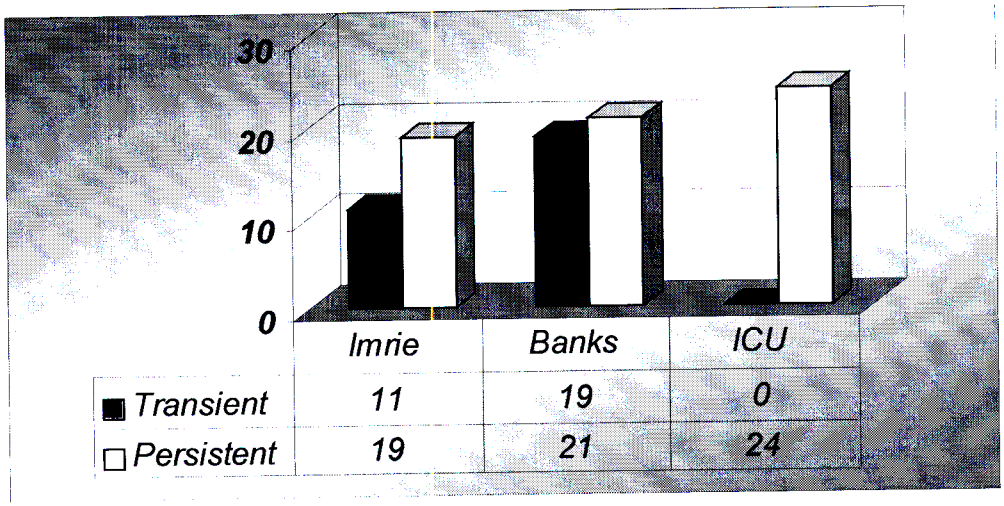
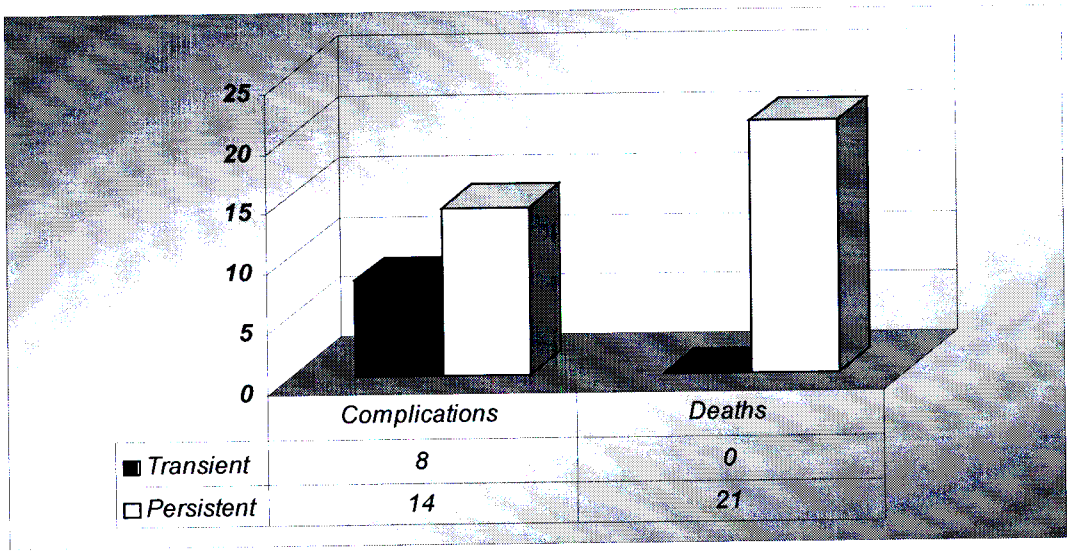


Figure 9: Disease outcomes in transient and persistent lipid abnormalities



The difference in the development of complications between the 2 groups was insignificant(p = 0.41). There were no deaths among those with transient lipid disorders and 21% among those with persistent lipid disorders(p = 0.003).

Clinical Grading of the Dyslipidaemias, aetiology, disease severity indices, disease outcomes and mortality

Table 21: Grading of the dyslipidaemia

	Mild	Moderate	Severe	Total
Hypercholesterolaemia	14	3	6	23
Hypertriglyceridaemia	28	14	13	55

Table 21 denotes that there were 13 admissions with Triglycerides above 15mmol/l and there were 2 admissions in the moderate group with a Triglyceride level above 10 mmol/l(19%). This is the level at which

triglycerides are considered to be a cause of the pancreatitis. Six of these were associated with alcohol consumption, 7 were diabetic and 2 primary abnormalities.

Clinical grading of dyslipidaemia by aetiology

Table 22: Grading of dyslipidaemia by aetiology

		Hypercholesterolaemia			Mixed	Hypertriglyceridaemia	
	Total	mild	moderate	severe	mild	moderate	severe
Dyslipidaemia	22	2	0	2	5	5	8
Gallstones	9	5	0	2	1	1	0
Alcohol	47	7	3	2	23	7	5

In those with gallstones as an aetiology 7(78%) had hypercholesterolaemia and 2(22%) had hypertriglyceridaemia. In those associated with alcohol 12(26%) had hypercholesterolaemia and 35(74%) had hypertriglyceridaemia

Table 23: Grading of dyslipidaemia and disease severity indices

	Cholesterol	Imrie>3	Clinical	ICU	Triglyceride	Imrie>3	Clinical	ICU
Mild	14	1	0	1	28	3	2	1
Moderate	3	0	2	1	14	4	2	2
Severe	6	1	0	1	13	3	5	4
Total	**23**	**2***	**2#**	**3****	**55**	**10***	**9#**	**7****

*p= 0.49
#p= 0.49
**p= 1.00

In Table 23 the indices of severe disease are predominantly found in the hypertriglyceridaemia group irrespective of the grade. The differences in the indices between the grades of dyslipidaemia did not reach statistical significance with the p-values illustrated above.

Table 24: Disease outcome and clinical grading

	Cholesterol	Complications	Deaths	TG	Complications	Deaths
Mild	14	1	0	28	0	5
Moderate	3	0	0	14	2	2
Severe	6	0	0	13	4	2
Total	23	1*	0**	55	6*	9**

* p= 0.66
****p= 0.05**

Table 24 denotes that the complications and deaths were predominantly in the group with hypertriglyceridaemia.

There were 9 deaths(12%). The deaths were among admissions who had dyslipidaemia were located as follows: 6 deaths in patients with hypertriglyceridaemia and alcohol as a secondary association and 3 deaths in patients with primary hypertriglyceridaemia. The majority of the deaths(56%) were in admissions with mild hypertriglyceridaemia. The majority of mortalities were in the first week of admission(Table 25)

Table 25: Patterns of mortality

	Time to death		
	< 1 week	**1-2 weeks**	**> 2 weeks**
Dyslipidaemia	7(78%)	1(11%)	1(11%)
Normolipaemia	8(57%)	2(14%)	4(29%)

Summary

Seventy eight (34%) of the admissions had dyslipidaemia associated with the pancreatitis.

The dyslipidaemic admissions were significantly higher among Indian people and lowest in the African group. The coloured and the White groups were intermediate.

The amylase levels were significantly higher in the admissions with gallstones and lowest in those with dyslipidaemia.

Differences in alcohol and gallstones aetiologies was not significant between the dyslipidaemic and normolipaemic admissions.

The body mass index was significantly higher in the dyslipidaemic admissions.

Familial dyslipidaemia may be associated with repeat admissions. One patient having 8 admissions in the study period.

Alcohol was the most frequent of the secondary causes of dyslipidaemia. The majority had hypertriglyceridaemia. In the admissions with dyslipidaemia mortalities were located in those with hypertrigylceridaemia irrespective of the levels.

Diabetes was significantly more common in patients with dyslipidaemia.

Obesity was a factor in 15.4% admissions with dyslipidaemia.

The transient lipid abnormalities numbered 32(41%) and the persistent abnormalities 46(59%). The cholesterol and triglyceride levels were significantly higher in the admissions with persistent lipid abnormalities.

The group with persistent lipid abnormalities showed a trend towards more severe disease by intensive care unit admission. Transient dyslipidaemia appeared to be protective for the development of complications, and all deaths occurred in patients with persistent dyslipidaemia.

Markers of disease severity were predominantly located in those with hypertriglyceridaemia. All the mortalities were in admissions with hypertriglyceridaemia. The majority of deaths were in those with mild hypertriglyceridaemia.

The majority of the mortalities occurred within the first week of admission.

Chapter 9

DISCUSSION

Prevalence

This study is the first report on dyslipidaemia and pancreatitis in South Africa within a mixed ethnic background.

In this cohort, 34% of the admissions had dyslipidaemia associated with pancreatitis over a four year period. Six(8%) had severe hypercholesterolaemia and 13(17%) severe hypertriglyceridaemia.

Dickson et al in a prospective trial identified 14(4.5%) of 311 adissions over a seven year period who had dyslipidaemia on routine screening.[5] Half of them had major lipid abnormalities (triglycerides > 10 mmol/l). Cameron et al found 39% of their cohort to have the combined abnormalities over a five year period[10]. Half of them had major triglyceride abnormalities. Buch et al found 32.5% had dyslipidaemia in a prospective evaluation over an unspecified period with 29(24.8%) with varying degrees of hyperlipidaemia(transient elevations) and 9(7.7%) had constant hyperlipidaemia. [39] Fortson et al on the other hand found that only 1.3-3.8% had pancreatitis associated with dyslipidaemia in a retrospective review[8] These were patients with hypertriglyceridaemia above 500mg/dl(5.6 mmol/l) composed of 70 patients from 4 institutions over a twelve year period.[39] In a cohort from Cape Town, 1% had pancreatitis associated with dyslipidaemia.[3] The focus of their study however was on the influence of obesity on the outcomes of acute pancreatitis over a 6 month period. In a prospective evaluation of 246 admissions with acute pancreatits, Athyros et al found 17(6.9%) of admissions associated with hypertriglyceridaemia of more than 1000 mg/dl(11.3 mmol/l)[7]

The prevalence in this study is in keeping with one of the prospective evaluations cited. The cut-off values in the other studies may be the cause of the lower prevalence figures and this makes comparison difficult.

Whether alcohol consumption as a predominant cause of pancreatitis in a cohort influences the prevalence of dyslipidaemia and pancreatitis is unclear as Toskes found that 75% in their series had hyperlipaemia unrelated to alcohol ingestion.[25] Whereas Buch et al found that 73.6% and Cameron et al. 95.45% in their series had hyperlipidaemia associated with alcohol consumption.[24,39] In this study there was no difference in alcohol or gallstones as an aetiology between the dyslipidaemic and the normolipaemic admissions. Alcohol consumption does not appear to be a causative factor of dyslipidaemia.

Sex, Age, Ethnic distribution and Obesity

The average age of 42 in patients with dyslipidaemia and pancreatitis in this study is similar to the median age of 38 and 41 reported by Athyros[7] et al and Fortson et al[8] respectively.

There was a females(62%) bias in the admissions with dyslipidaemia and a male(73%) bias in those with normolipaemia.

The dyslipidaemic group is predominated by the Indian ethnic group (62%) whereas Africans are the majority in the normolipaemic group.

In the studies cited in Table 26 Caucasians and males are the majority in admissions with dyslipidaemia.

Table 26 : sex, alcohol and ethnic distribution dyslipidaemic pancreatitis. [5,8,24]

	Sex		% alcohol		Ethnicity	
Author	**Male**	**Female**	**Dyslipidaemia**	**Normolipaemia**	**Caucasian**	**Black**
Dickson	92.90%	7.10%	85.70%	ns	ns	ns
Cameron	77.30%	12.70%	94.50%	ns	63.60%	36.40%
Fortson	51.40%	48.60%	23%	ns	71.40%	28.60%

ns: the respective values were not stated

Obesity and dyslipidaemic pancreatitis

The average body mass index was significantly higher in the dyslipidaemic group of admissions(p=0.031).

Obesity has not been a consistent feature in previous studies of dyslipidaemia and pancreatitis.[50,59] and it has not been actively sought. However, obesity has been described as a marker of severe outcome in pancreatitis[3] and the Apache-II score was modified to the Apache-O scoring system to factor in obesity in severity assessment.[60]

Diagnosis

The serum amylase levels was normal in 6(8%) of the admissions of patients with dyslipidaemia and pancreatitis and 3(2%) of admissions with normolipaemia and pancreatitis which is insignificant.

In the 6 admissions with dyslipidaemia and normal lipids the diagnosis was achieved by the clinical presentation and lipaemic serum. Imaging was not used to confirm the diagnosis and none were diagnosed at surgery.

In those with normolipaemia the diagnosis was established at surgery performed because of clinical suspicion of other causes of an acute abdomen. In previous studies the experience with amylase as a confirmatory test varies. Buch et al found a tendency to lower serum amylase levels in the dyslipidaemic group. Amylase assays confirmed the diagnosis in all instances.[39]

Athyros et al found amylase levels increased less than 3-fold normal in 47% and above 3-fold normal in the rest of patients in their series. Acute pancreatitis was confirmed by ultrasound or CT scan in those with less than 3-fold normal amylase levels which was their cut-off point in confirming a diagnosis of pancreatitis.[7]

Warshaw et al found that serum dilution produced an increase in amylase activity in those patients with pancreatitis associated with hypertriglyceridaemia. Serum dilution resulted in amylase levels which confirmed the diagnosis when the initial undiluted serum assays were within normal limits. This rise in serum activity was found in 5 patients with pancreatitis and a mean triglyceride level of 6100mg/dl(68.8 mmol/l) and not in controls without pancreatitis with a mean level of 2200mg/dl(24.8 mmol/l)[13] This increase in amylase activity was also found in urine dilution. They proposed the use of dilution of serum and urine to assess for increased amylase activity. Since urine does not contain triglycerides, the inhibition of amylase activity was thought to be another unknown factor.[13]

The number of admissions with a diagnostic dilemma in this series have been limited and the clinical picture with lipaemia was used for arriving at a diagnosis. Serum dilution was not used to unravel amylase levels below the cut-off level as suggested by Warshaw et al.

The serum amylase levels were significantly higher and lower in the gallstone pancreatitis and dyslipidaemic groups respectively when comparing amylase levels associated with gallstones, alcohol and dyslipidaemia. The comparison between amylase levels in pancreatitis with these three associations has not been reported before.

Familial Dyslipidaemia

Nine of the 78(12%) admissions with dyslipidaemia were of 2 patients with familial dyslipidaemia, suggesting that these patients are prone to recurrent attacks of pancreatitis. These were of Indian descent and none of them traced onset of symptoms to childhood. In between attacks the lipid abnormalities remained abnormal and there was difficulty in controlling the dyslipidaemia despite supervised dietary and optimal medical management.

In other reports, patients with familial lipid abnormalities have been noted to develop episodes of pancreatitis in childhood or early adult life[40] The pancreatitis also tended to be relapsing with persistent lipid abnormalities between attacks. Dietary control of lipids has been reported to alter this cycle[40]. However there are no studies which assess the efficacy of medical therapy and dietary manipulation in preventing further attacks of pancreatitis. Management of dyslipidaemia entails control of any reversible secondary factors (eg. Alcohol excess, diabetes). Dietary measures are aimed at restricting fat intake and maintaining an ideal body weight (BMI< 27 kg/m2. Drug therapy depends on the predominace of triglycerides or cholesterol in the lipid profile. Fibrates in hypertriglyceridaemia, statins in hypercholesterolaemia or a combination when there is a mixed picture being the the mainstay of drug therapy[21,26]

Wilson Cox et al described a cohort with familial dyslipidaemia due to apolipoprotein C-11 deficiency. Some had attacks of pancreatitis from the age of six years.[50] There was no report on the success of dietary and medical therapy in preventing relapses or on the long-term outcome.

None of the patients in this series dated the first onset of symptoms to childhood and the testing of a third generation 13 year old revealed normal lipids.

Athyros et al described 8 of 17(47%) of patients with familial hypertriglyceridaemia and pancreatitis. One(6%) with familial hypercholesterolaemia and another(6%) familial combined hyperlipidaemia. One had relapses in the longterm due to neglect of dietary and medical therapy.[7]

There remains insufficient evidence from the previous reports of the efficacy of supervised dietary and medical therapy in preventing relapses. This aspect of the management of pancreatitis associated with dyslipidaemia has been scantily reported and has not been the focus of previous reports of dyslipidaemia and pancreatitis.

Secondary Dyslipidaemia and Pancreatitis

Alcohol, dyslipidaemia and pancreatitis

The relationship between alcohol consumption, dyslipidaemia and pancreatitis is controversial. Hypertriglyceridaemia which is composed of endogenous triglycerides is kwown to develop after acute alocohol intake in both alcoholics and non-alcoholics and hypertriglyceridaemia is also known to trigger attacks of pancreatitis. In assessing whether alcohol consumption was associated

with an increased prevalence of dyslipidaemia, Lifton and Scheig found that 26% of alcoholics had elevated triglycerides as opposed to 15% of controls[61] In this study there was no significant difference in alcohol consumption between the dyslipidaemic and the normolipaemic admissions.

Alcohol was a secondary consideration in 60% of the admissions with dyslipidaemia. The majority of dyslipidaemic admissions associated with alcohol consumption were transient hypertriglyceridaemias.

The study by Buch et al noted that alcohol played a role in more than 75% of their patients with pancreatitis, but there was no difference in the prevalence of alcohol between the dyslipidaemic and normolipaemic patients.[39]

Fortson et al found that a lower number, 23% of dyslipidaemic pancreatitis patients consumed alcohol in their series. No contrast was made with normolipaemic pancreatitis.[8] Toskes reported that 75% of their series had hyperlipidaemia and pancreatitis not asspciated with alcohol consumption.

In a contrasting finding, Dickson et al found only 4.5% to have lipid abnormalities when presenting with acute pancreatitis, of whom 86% consumed excessive alcohol. Continuous monitoring of this group found that resolution of the dyslipidaemia in association with alcohol abstinence in 43% and persistent dyslipidaemia in 36% associated with persistent alcohol consumption. This was presented as evidence that alcohol consumption was responsible for elevated lipids in acute pancreatitis in their series[5]

Buch et al found insignificant changes in the triglycerides on continuous monitoring of their group. These patients had persistent lipid abnormalities irrespective of abstainance from alcohol.[39] The evidence in this series was for a pre-existing dyslipidaemia.

This study has not examined the outcome of the dyslipidaemia after discharge from hospital, but the majority of dyslipidaemias associated with alcohol consumption resolved prior to discharge and may well have been secondary to alcohol consumption or the pancreatitis in this transient group.

Diabetes, dyslipidaemia and pancreatitis

In this study and in contrast with dyslipidaemic pancreatitis associated with alcohol the majority of admissions associated with diabetes (70%) had persistent lipid abnormalities at discharge. In this cohort 26% of the patients presented with poor diabetic control in diabetic ketoacidosis and 80% had persistent dyslipidaemia.

Gianfrate and Ferraris reported a different outcome. They described a diabetic, non-alcoholic who presented with ketoacidosis, pancreatitis and moderate hyperlipaemia (347 mg/dl)(3.9 mmol/l). Since the lipids were moderately elevated, and unlikely to be the cause of the pancreatitis, they propose that diabetic ketoacidosis may be a cause of pancreatitis with secondary dyslipidaemia.[62]

In another study with a similar finding, 90 patients of 100 admissions with diabetic Ketoacidosis were examined. Of these 11 patients were found to have pancreatitis, confirmed by CT Scan. Four of these patients were found to have hypertriglyceridaemia(11.3 mmol/l) on admission. The lipid abnormality resolved with the resolution of the pancreatitis and the diabetic ketoacidosis.[59]

In another study diabetes was found in 7 of 13 patients who presented with dyslipidaemia and pancreatitis. It was not clear whether these patients had diabetic ketoacidosis at the time and whether the dyslipidaemia resolved after the resolution of the pancreatitis.[63]

In the series by Buch et al., 7% of those with dyslipidaemic pancreatitis eventually required therapy for diabetes[39]. Athyros et al found 5 of 17(29%) of admissions with hypertriglyceridaemia(>11.3 mmol/l) and pancreatitis to be associated with uncontrolled diabetes[7] whereas

Fortson et al. found 72% of their group to have diabetes[8].

Persistent and Transient lipid abnormalities

In the dyslipidaemic group, 42(54%) had persistent lipid abnormalities and 36(46%) had transient lipid abnormalities.

Alcohol was associated with 69.4% of those with transient lipid abnormalities as opposed to 52.4% of those with persistent lipid abnormalities.

In contrast Cameron et al reported persistent lipid abnormalities in 77.3% of 22 patients. Twenty one (94.45%) of these were associated with alcohol consumption[24].

Biliary pancreatitis and dyslipidaemia

In this cohort, 10% of the dyslipidaemic pancreatitis was associated with biliary disease.

Fortson et al. found 22% of their group had dylipidaemic pancreatitis associated with biliary disease[8] . In other studies there is scant information on the association between biliary pancreatitis and dyslipidaemia.

Disease severity in Dyslipidaemic Pancreastitis

Severity scoring using the Glasgow criteria, Banks clinical assessment and ICU admission showed a trend toward more severe disease in patients with dyslipidaemia although this did not reach statistical significance.

Normolipaemia appeared to be protective for the development of complications.

Fortson et al found that the severity assessment by Ranson, Apache, Banks and Balthazar CT scan methods to be no different from historical controls. However only 18 of 70(26%) patients were assessed for severity in the dyslipidaemic group, making the assessment inconclusive.[8]

The use of scoring systems in pancreatitis associated with dyslipidaemia has not been previously reported and comparison between different studies is difficult.

Mortality in dyslipidaemic pancreatitis

In this cohort deaths in patients with dyslipidaemia and pancreatitis were found in those who had primary dyslipidaemia(3)and those with secondary dyslipidaemia associated with alcohol(6) with a cumulative death rate of 12%. All the deaths were in patients with hypertriglyceridaemia with the majority, 56% in patients with mild hypertriglyceridaemia.

Athyros et al had 1 death(6%) in 17 admissions with hypertriglyceridaemia(1000mg/dl)(11.3 mmol/L) and pancreatitis, and Fortson et al had a mortality of 6% in their patients with dyslipidaemia and pancreatitis[7,8]. Mortality in patients with < 1000mg/dl(11.3 mmol/l) of hypertriglyceridaemia and patients with hypercholesterolaemia was not alluded to in these findings[7]

Conclusion

This is the first study to assess dyslipidaemia associated with pancreatitis in a South African population composed mostly of Indians and Africans. The hospital prevalence of 34% in this study is comparable with the cited literature in which lipid abnormalities were routinely assessed. The mortality of 12% is similar to previously reported mortality rates.

The prevalence of dyslipidaemia was highest within the Indian group and lowest in the Africans These findings have not been corroborated in other studies which have predominantly been conducted in Caucasian populations.

Contrary to other reports, significantly elevated amylase levels, as a confirmatory test was sufficient to arrive at a diagnosis of pancreatitis in most of our cases.

Patients with familial dyslipidaemia had recurrent episodes of pancreatitis despite supervised medical therapy and remain problematic to manage.

There was a trend towards more severe disease in patients with dyslipidaemia and pancreatitis.

A greater proportion of patients with diabetes had triglyceride levels above 10 mmol/l when compared to the levels with alcohol or drugs. However, all fatalities were associated with dyslipidaemia and alcohol consumption. All the deaths in the dyslipidaemics had hypertriglyceridaemia and this was independent of the level. The lack of correlation between the level of hypertriglyceridaemia and mortality has not been previously reported.

Clinical implications

Indian patients with an alcohol aetiology have a high prevalence of dyslipidaemia and if this is hypertriglycaridaemia it carries a mortality risk hence it seems reasonable strategy to measure the lipids in this clinical category and if associated with severe disease should be actively monitored for organ dysfunction on a daily basis daily, and the level of support escalated accordingly.

Better managememt strategies need to be devised for the familial dyslipidaemias as thease are recurrent despite supervised medical therapy

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APPENDIX

Table 1: Potential causes in non alcohol/ non gallstone related pancreatitis

Aetiology

Obstruction
Ampullary or pancreatic cancers
Worms or foreign bodies obstructing the ampulla
Pancreas divisum with accessory duct obstruction
Choledochocele
Periampullary duodenal diverticulum
Hypertensive sphincter of Oddi

Toxins or drugs
Scorpion venom, organophosphorous insecticide
Drugs: azathioprine and mercaptopurine, valproic acid
oestrogens, tetracycline, metronidazole,
nitrofurantoin, pentamidine,furosemide, methyldopa
sulfonamides, cimetidine, ranitidine, sulindac,
didanosine, acetaminophen, erythromicin,
salicylates

Trauma
Accidental blunt abdominal trauma
Iatrogenic- postoperative, ERCP, manometry of sphincter
of ODDI,endoscopic sphincterotomy

Metabolic abnormalities
Hypertriglyceridaemia
Hypercalcaemia

Inherited Pancreatitis

Infections
Parasites- Ascariasis, Clonorchis
Viral-Mumps,Rubella, Human immunodeficiency virus
Bacterial- Mycoplasma,Leptospirosis, Campylobacter

Vascular abnormalities
Ischaemia- hypoperfusion
Atherosclerotic emboli
Vasculitis- Systemic Lupus erythematosus,
Polyarteritis nodosa

Miscellaneous conditions
Penetrating peptic ulcer
Crohn's disease
Reye's syndrome

Idiopathic causes