DYSLIPIDEMIA IN SYSTEMIC LUPUS ERYTHEMATOSUS

Leong Keng Hong

MBBS, M,Med (Internal Medicine), MRCP (UK), FRCP (Edinburgh), FAMS (Rheumatology)

A THESIS SUBMITTED FOR THE DOCTORATE OF MEDICINE
DEPARTMENT OF MEDICINE
NATIONAL UNIVERSITY OF SINGAPORE
2004
Acknowledgement

The Candidate wishes to thank

Professor Chan Heng Leong for his invaluable advice and input.

A/Professor Fong Kok Yong for his insightful comments

In addition he wishes to express his gratitude to collaborators at the Royal Hospital for Rheumatic Diseases, Bath and the Department of Rheumatology and Immunology at Tan Tock Seng Hospital, Singapore
SUMMARY

Systemic Lupus Erythematosus (SLE) is an illness with a poor prognosis in the past. In recent years, treatment options have improved and patients often survive more than ten years from the time of diagnosis. This has given rise to new problems related to organ damage and long term side effects of medications. One of these problems which only recently has been recognised is dyslipidemia.

In a study of 100 Singaporean SLE patients with a mean age of 32, 35% had severe lipid abnormalities of high LDL, high TG, low HDL and abnormal TC/HDL ratios. The mean LDL was 233 mg/dl, HDL 51 mg/dl, total cholesterol 355 mg/dl, TG 354 mg/dl and ratio of 7.8. These abnormalities were found to be associated with the presence of lupus nephritis and high current daily doses of prednisolone. Lupus nephritis was defined as in the 1982 ARA criteria for SLE. 27 out of 35 with abnormal lipid profiles had nephritis compared to only 10 out of 27 with normal lipid profiles (p<0.001). The mean current dose of patients with normal lipid profiles was 9 mg and 23.5 mg for those with abnormal profiles (p<0.001). Lupus activity was assessed using Lupus Activity Criteria Count and although there was a trend towards lower HDL it did not reach significance after controlling for renal disease and other confounding factors.
In a different SLE cohort in Bath, abnormalities seem to be related to lipoprotein lipase suppression and this could be associated with lupus activity. In this cohort there were far fewer patients with lupus nephritis and many were not on systemic corticosteroids. Compared to age and gender matched control subjects these patients had low HDL 2 subfraction (17.5 mg/dl vs 21.8 mg/dl, p<0.023) and low apoprotein A I levels (120 mmol/l vs 142 mmol/l, p<0.0001). Therefore, hyperlipidemia in SLE is associated several different factors including the presence of nephrotic syndrome, active lupus and the use of systemic corticosteroids.

Many studies have shown premature atherosclerosis to be a significant problem in rheumatic diseases including SLE. Although a five year follow up study of the Singapore cohort did not reveal new atherosclerotic events in these young patients, the risk of premature atherosclerosis is a real one the older they get. To prevent the premature onset of atherosclerotic complications such as stroke and myocardial infarction, hyperlipidemia in SLE patients should be diagnosed early and treated accordingly.
Systemic Lupus Erythematosus (SLE) is an illness with a poor prognosis in the past. In recent years, treatment options have improved and patients often survive more than ten years from the time of diagnosis. This has given rise to new problems related to organ damage and long term side effects of medications. One of these problems which only recently has been recognised is dyslipidemia. In a study of Singaporean SLE patients with a mean age of 32, 35% had severe lipid abnormalities of high LDL, high TG, low HDL and abnormal TC/HDL ratios. Hyperlipidemia in SLE is associated with the presence of nephrotic syndrome, active lupus and the use of systemic corticosteroids. To prevent the onset of atherosclerotic complications hyperlipidemia in SLE patients should be diagnosed early and treated accordingly.

**Key words:** SLE, hyperlipidemia, premature atherosclerosis, corticosteroids, nephritic syndrome, active lupus
CONTENTS

1) INTRODUCTION

2) LIPIDS AND INFLAMMATION
   a. LIPID METABOLISM
   b. LIPIDS AND INFLAMMATION
   c. THE ROLE OF INFLAMMATION IN ATHEROSCLEROTIC DISEASE

3) LIPIDS AND SLE
   a) THE RELEVANCE OF LIPID ABNORMALITIES TO PATIENTS WITH SYSTEMIC LUPUS ERYTHEMATOSUS
   b) CONTRIBUTING FACTORS TO ABNORMAL LIPID PROFILES IN SLE

4) AIMS AND METHODS

5) HOW COMMON IS HYPERLIPIDEMIA IN SLE?
   LIPID ABNORMALITIES IN PATIENTS WITH SLE

6) WHAT ARE THE RISK FACTORS FOR HYPERLIPIDEMIA IN SLE?
   a) CORTICOSTEROIDS
   b) RENAL DISEASE
   c) ACTIVE SLE
7) WHAT ARE THE CLINICAL CONSEQUENCES OF DYSLIPIDEMIA IN SLE?

OUTCOME OF SLE PATIENTS WITH HYPERLIPIDEMIA AFTER FIVE YEARS

8) DISCUSSION

9) CONCLUSION
1 INTRODUCTION
This thesis explores the relationship between dyslipidemia and systemic lupus erythematosus.

Chapter Two entitled Lipids and Inflammation gives a background to the understanding of lipid metabolism, the relationship between lipid abnormalities and inflammation and the increasingly recognized importance of inflammation in the development of atherosclerosis.

Chapter Three – Lipids and SLE discusses the importance of hyperlipidemia in SLE patients in terms of causing premature atherosclerosis. It also presents some of the possible contributing factors to development of lipid abnormalities in SLE patients.

Chapter Four – Aims and Methods states the aims of the thesis and the methods used to test various hypotheses in the area of lipids and SLE.

Chapter Five - How Common is Hyperlididemia in SLE? presents data from two cohorts of SLE patients to show that the extent of hyperlipidemia varies in different patient subsets but are common in lupus cohorts with severe lupus, who have a high prevalence of renal disease and who are on oral corticosteroids.
Chapter Six – What are the Risk Factors for Hyperlipidemia in SLE? examines risk factors for hyperlipidemia in the SLE patients studied. Attention is paid in particular to corticosteroid use, presence of renal disease and active lupus.

Chapter Seven – What could be the clinical consequences of hyperlipidemia in SLE? presents data from the more severe lupus cohort after a period of five years.

Chapter Eight is a discussion on the whole thesis, including suggestions regarding the plan of management in SLE patients who have hyperlipidemia.

Chapter Nine is the concluding chapter.
I. LIPIDS AND INFLAMMATION
I a. LIPID METABOLISM

Lipid Composition

Lipoproteins are complex molecules which transport lipids through the plasma. Each lipoprotein molecule has a non-polar core of hydrophobic lipids such as triglycerides and cholesterol ester and a polar coat of phospholipids and free cholesterol, within which are various apoproteins. There are five main types of lipoprotein which differ in their composition of lipid and the type of apolipoprotein. Apolipoprotein A (apo A) is the major apolipoprotein in high density lipoprotein (HDL) and apolipoprotein B (apo B) is the major structural apolipoprotein of the other lipoproteins, chylomicrons, very low density lipoprotein (VLDL), intermediate density lipoprotein (IDL) and low density lipoprotein (LDL). The full apoB (apo B100) is found in VLDL, IDL and LDL but a truncated form, apo B48 is found in chylomicrons made by gut cells. The main cholesterol-carrying lipoproteins are LDL and HDL and the main triglyceride-carrying lipoproteins are chylomicrons and VLDL.

Major lipoproteins are heterogenous and the subclasses can be detected by precipitation or ultracentrifugation. HDL can be separated into HDL2 and HDL3 whereas LDL exists in three main subclasses, namely LDL1, LDL2, LDL3. LDL2 is the predominant subclass. VLDL can be separated into VLDL1, VLDL2, VLDL3. Changes in proportion of lipoprotein subclasses will not be apparent on basic lipid screening but may have an important bearing on risk of atherosclerosis.
Exogenous pathway

This pathway deals with the handling of dietary lipids. Chylomicrons carry triglycerides and cholesterol from the intestine to adipose tissue and skeletal muscle. Lipoprotein lipase then liberates free fatty acid and monoglycerides which cross the endothelium to peripheral tissue for further metabolism. The chylomicron remnant is removed by the liver.

Endogenous pathway

Triglycerides are synthesised in the liver and incorporated into VLDL which is a substrate for lipoprotein lipase in peripheral tissue where triglycerides are hydrolysed. VLDL becomes IDL which is either taken back up by the liver or loses more triglyceride and apolipoproteins and becomes cholesterol rich LDL. Both the liver and extrahepatic tissues that utilise cholesterol recognise LDL by receptor mediated pathways. A variable amount of LDL is scavenged by the reticuloendothelial system. HDL can accept cholesterol from cholesterol replete tissues. A HDL core cholesterol ester is formed when cholesterol is esterified on the surface of HDL by lecithin:cholesterol acyltransferase. This ester can then be exchanged with VLDL or IDL through the action of cholesterol ester transfer protein or the HDL can be returned to the liver.
I b. LIPIDS AND INFLAMMATION

Essential Fatty Acids

Fatty acids are core components of complex lipids, they are incorporated into cell membranes and serve as precursors for prostaglandins and leukotrienes. Omega 3 and omega 6 fatty acids have been investigated as therapeutic agents for reducing inflammation in conditions ranging from psoriasis to rheumatoid arthritis (1-3).

Lipid Peroxidation

Polyunsaturated fatty acids are the main target for lipoperoxidative injury by oxygen free radicals. They can be oxidised by endothelial cells and macrophages. Oxidised LDL may exert proinflammatory effects. LDL is modified by contact with endothelial cells and becomes more readily taken up by receptors on scavenger cells which become lipid-laden foam cells. This is an early event in atheroma formation. LDL3 is more likely to be oxidised, is more immunogenic and is more readily taken up by scavenger pathways. Oxidised LDL is thought to play a part in various forms of glomerulonephritis including lupus nephritis.
**Cytokines and lipoprotein lipase activity**

Lipoprotein lipase is a membrane bound enzyme responsible for liberation of fatty acids from VLDL resulting in formation of LDL. Reduction in activity of this enzyme would result in reduced clearance of VLDL-triglyceride and an associated rise in plasma triglycerides. Normal or slightly low LDL-cholesterol would be expected. HDL would also tend to fall.

Lipoprotein lipase is inhibited by several cytokines such as tumour necrosis factor alpha, interleukin 1 and gamma-interferon. These cytokines are upregulated in inflammation and have been shown to be increased in active SLE. Evidence of this relationship between cytokines and lipoprotein lipase exists in the demonstration that 24 hour infusion of human tumour necrosis factor alpha is associated with a decrease in serum cholesterol and HDL (4).
The role of cytokines and inflammation in atherosclerotic disease

Increasingly it is recognized that inflammation plays an important factor in the pathogenesis of atherosclerosis. High sensitivity C reactive protein (hsCRP) has been shown to be a reliable prognostic predictor in stroke and ischemic heart disease. Yamashita et al (5) analysed various inflammatory markers such as interleukins IL-6, IL-10, IL12, IL-28 and hsCRP in 40 patients with unstable angina, 39 patients with stable angina and 52 age and gender matched controls. HsCRP was significantly higher in the unstable angina patients, was positively correlated with the pro-inflammatory cytokines IL-6, IL-12 and IL-18 and negatively associated with the anti-inflammatory cytokine IL-10.

C-reactive protein predicts progression of atherosclerosis measured at various sites in the arterial tree. Van Der Meer at al (6) measured CRP levels in 773 subjects in the Rotterdam Study. Subclinical atherosclerosis was assessed at various sites at two points of time, with a mean duration between measurements of 6.5 years. After adjustment for age, sex and smoking, odds ratios (OR) associated with CRP levels in the highest versus lowest quartiles were increased for progression of atherosclerosis at carotid, aortic, iliac and lower extremity sites. The OR for generalized progression of atherosclerosis as indicated by a composite score was 4.5 (95%CI 2.3-8.5). This is as high as OR’s for traditional cardiovascular risk factors such as high cholesterol, hypertension and smoking.
The mechanisms by which inflammation and C-reactive protein contributes to atherosclerosis are not completely understood. Devaraj et al (7) showed recently that CRP induces plasminogen activator inhibitor-1 expression and activity in human aortic endothelial cells. More recent studies show that IL-18 plays a significant role in atherosclerosis. Elhage et al (8) showed that there was reduced atherosclerosis in IL-18 deficient apolipoprotein E-knockout mice. Mallat et al (9) found increased plasma concentrations of IL-18 in patients with acute coronary syndromes and this correlated with the severity of myocardial dysfunction. Yamaoka-Tojo et al (10) found that human recombinant C-reactive protein induced IL-18 in human endothelial cells providing a link between the two that may suggest a mechanism by which C-reactive protein is important to atherosclerotic events. Another interesting observation by Esposito et al (11) was that weight loss reduces circulating IL-18 levels in obese women.

Treatment of hyperlipidemia with statins has effects on hsCRP. This was shown by van Wissen et al (12) in a randomized double blind 2 year trial with 325 patients with familial hypercholesterolemia treated with atorvastatin 80 mg versus simvastatin 40 mg. The extent of hsCRP reduction was associated with improvement in progression of atherosclerosis as measured using intima media thickness of carotid artery segments.

In SLE, many patients suffer from multiorgan involvement and have a high degree of inflammation with elevated acute phase reactants. This may have a bearing on the increased frequency of coronary artery disease and stroke observed in SLE patients. Esdaile et al (13)
assessed retrospectively two SLE cohorts in relation to traditional Framingham risk factors and the presence of vascular events such as nonfatal myocardial infarction (MI), death due to coronary heart disease (CHD), stroke and overall CHD (nonfatal MI, death due to CHD, angina pectoris and congestive heart failure due to CHD). He found that the traditional risk factors cannot fully explain the increased risk of CHD and strokes in SLE.
3 LIPIDS AND SLE
2 a. THE RELEVANCE OF LIPID ABNORMALITIES TO PATIENTS WITH SYSTEMIC LUPUS ERYTHEMATOSUS

Systemic lupus erythematosus (SLE) is an autoimmune disease with protean manifestations affecting mainly young women (14). The age of onset is generally from 20 to 50 and female to male ratio is 9:1. It is a relatively new disease although reference was made to “lupus” since the early 20th century but it was not until 1982 before the international community agreed on classification criteria for SLE as put forth by the American Rheumatism Association (ARA) (15) which has now become the American College of Rheumatology. Up to the 1970’s, SLE had a poor prognosis and many medical textbooks in those days painted a bleak picture. Things have gradually improved and nowadays, the 10 year survival of most SLE populations is in the region of 80 or 90 percent. Many patients are able to lead fairly normal lives, holding on to full time jobs and bear children as well. Now that SLE patients can live longer, the impact of uncontrolled active lupus disease has lessened but then complications arising from chronic illness and prolonged therapy with potentially toxic drugs have increased. Many of the drugs used in lupus are immunosuppressive in nature and hence the SLE patient is more prone to getting infections some of which are serious and life-threatening. Corticosteroid therapy is unfortunately still the mainstay in the treatment of lupus. The onus is on the rheumatologist to use the lowest possible dose which will control the disease and yet have minimal side effects. This can be achieved with steroid sparing agents or second line agents. The best agent varies according to the clinical situation and include anti-malarial agents, cyclophosphamide, azathioprine,
methotrexate, intravenous immunoglobulin and newer drugs such as cyclosporin and mycophenolate mofetil.

In spite of this, many patients do suffer from side effects of corticosteroid therapy. They include steroid induced osteoporosis, premature cataracts, hypertension, hyperlipidemia, diabetes mellitus and features of Cushing’s syndrome. In the light of this, treatment of SLE should not only be directed at treatment of active lupus disease but also would involve close monitoring for side effects due to medication or chronicity of illness.

One of these side effects which has increasingly been recognised is hyperlipidemia and premature atherosclerosis. These problems would affect the long term outlook for these patients. Up to now, the research on SLE and hyperlipidemia has been fairly limited compared to that done regarding other side effects such as increased infections, avascular necrosis and steroid induced osteoporosis.

SLE in Singapore is a relatively common rheumatological problem. Outcomes have been poor in the past due to various factors including poor patient compliance. Prognosis has steadily improved and patients nowadays survive long enough to develop problems such as hyperlipidemia.

Abnormal lipid profiles have been described in SLE patients and premature atherosclerosis has been documented in lupus cohorts in the West. The risk of clinical thrombotic events increases in the presence of antiphospholipid syndrome and vasculitis.
2b. Contributing Factors to Abnormal Lipid Profiles in SLE

In SLE, there are many risk factors for vascular events. These include the presence of anti-phospholipid antibodies, abnormal lipid profiles produced by illness, treatment or renal disease and less commonly concomitant vasculitis. Broadly speaking, the causes of dyslipidemia in SLE can be grouped into three main categories: use of corticosteroids, lupus activity and renal disease.

Use of Corticosteroids

The use of corticosteroids contributes to a Type IIb hyperlipidemia as does the presence of a nephrotic syndrome which is common in lupus nephritis. Ettinger et al (16) compared 46 SLE patients and 30 controls and found that SLE patients who were on corticosteroids had higher levels of total cholesterol, total triglyceride and LDL-cholesterol. Those who were not on steroids had levels similar to controls except for a lower HDL cholesterol level.

Lupus Activity

Lupus sera has been found to be atherogenic. Kabakov et al (17) showed that in the presence of lupus sera, lipid accumulation in cultured smooth muscle cells is increased 1.5 to 6 fold compared with cells cultured with normal human sera from healthy donors. Incubation of the smooth muscle cells with circulating immune complexes isolated from lupus sera caused a 3 to 4 fold increase in intracellular cholesterol level. This atherogenic effect is generally due to LDL-containing immune complexes.
Lipoprotein(a) also has great atherogenic potential. Takegoshi et al (18) reported a case of an 18-year-old SLE patient who had severe elevations of Lp(a) resulting in myocardial infarction and cerebral infarction. Rantapaan-Dahlqvist et al (19) showed that 93 patients with classical RA of moderately active disease had significantly increased levels of Lp(a). In those with concentrations above 480 mg/l there was a significant correlation between Lp(a) levels and acute phase reactants such as the platelet count and the erythrocyte sedimentation rate. Mechanisms for elevated Lp(a) are not clear. Although corticosteroids have been known to cause elevated levels of LDL-cholesterol, Aoki and Kawai (20) in fact showed that corticosteroids reduced the Lp(a) levels in a dose-dependent manner in patients who did not have nephrotic syndrome. The nephrotic syndrome rather than corticosteroid use contributes to high levels of Lp(a).

The interplay between lipid abnormalities and the presence of antiphospholipid antibodies is likely to be complex. A plasma co-factor which is needed for thrombosis to occur in some patients harbouring anti-phospholipid antibodies has been identified as beta2-glycoprotein1 or apolipoprotein H. Whether lipoproteins other than beta2GP1 is involved in the pathogenesis of the anti-phospholipid syndrome is presently unknown. There would however be an additive risk of thrombotic clinical events if both the antiphospholipid syndrome and hyperlipidemia are present. This is shown by various studies. An increase in vascular disease in a set of SLE patients was found by MacGregor et al (21) in those with elevated triglyceride levels who also expressed anticardiolipin antibodies. In patients on prednisolone of more than 10 mg a day in the six months before
testing, there were increased levels of triglyceride and apoprotein B. Patients not on steroids did not have lipid abnormalities in this study.

Lahita et al (22) showed that there is an association between the presence of anticardiolipin antibodies and lowered levels of serum cholesterol, HDL and apoA-I levels in SLE patients. In the 72 patients not on corticosteroids, serum total cholesterol was lower compared with 72 healthy blood donors. The SLE patients not on steroids were divided in those with and those without IgG anticardiolipin antibodies. Anticardiolipin positive patients had lower levels of total cholesterol, HDL-cholesterol and apo-AI compared to patient without anticardiolipin antibodies.

Another potentially important mechanism is the effect of cytokines such as interleukin-1 (IL-1) and tumour necrosis factor-alpha on lipoprotein lipase activity. The pro-inflammatory cytokines are upregulated in active SLE and suppress lipoprotein lipase causing low HDL and high TG levels.
Renal Disease

It is well known that lipid abnormalities exist in the nephrotic syndrome. Proteinuria is a known stimulus for increased lipid synthesis. Urinary loss of HDL may also be significant. Animal studies reveal that hyperlipidemia may accelerate deterioration of renal function and control of hyperlipidemia has been shown in these models to retard development of glomerulosclerosis and renal failure.

In the nephrotic syndrome it is thought that there is overproduction of apolipoprotein B 100. The stimulus for this overproduction is the loss of albumin and other macromolecules in the urine. Hepatic synthesis of cholesterol is increased and the increased hepatic cholesterol content results in a down regulation of synthesis of LDL receptors. This retards the clearance of LDL from the circulation and together with increased production of lipoproteins, LDL-cholesterol concentration can become grossly elevated. Hypertriglycerideremia can occur in the nephrotic syndrome from an overproduction of very low density lipoproteins (VLDL) by the liver and defective lipolysis of triglyceride rich lipoproteins.
4 AIMS AND METHODS
AIMS

The candidate tries to explore in this thesis certain issues surrounding dyslipidemia and SLE:

1) How common is hyperlipidemia in SLE in Singapore?
2) What are the risk factors for hyperlipidemia in SLE?
3) What are the clinical consequences of hyperlipidemia in SLE?

SLE is a heterogeneous disease. For some time it is known that patient characteristics differ in different countries. For example, Oriental and Afro-Carribean patients are thought to have more severe lupus with higher prevalence of renal involvement than Caucasian patients (23, 24). The candidate wanted to establish the prevalence of hyperlipidemia in SLE patients in Singapore as there had been no data previously. Therefore a consecutive set of 100 SLE patients were studied at Tan Tock Seng Hospital which is one of the main referral centres for lupus in Singapore at the time of study. Findings from this study would give an idea of the prevalence of hyperlipidemia in SLE in Singapore.
To explore possible contributing factors to hyperlipidemia, the study of Singapore SLE patients can help to explore the role of corticosteroid use, presence of renal disease and the nephrotic syndrome and lupus activity. However it is difficult to separate the role of lupus activity from steroid use and renal disease. It would be preferable to study a set of lupus patients who may have active lupus from involvement other than renal, and who have a lesser usage of corticosteroids. A Western lupus cohort would fit these criteria. The author studied a group of SLE patients from Bath with the intention to study this possible relationship between lupus activity and lipid abnormalities. Lupus activity can be measured using validated tools such as BILAG but how this corresponds to cytokine activity especially as assessed by serum levels is complex. The author collected data regarding lipid profiles, BILAG assessment and serum IL-1 and TNF-alpha levels from these patients.

As for clinical consequences in SLE patients with hyperlipidemia, the outcomes of the 100 Singaporean patients were assessed at five years. These were young patients and any clinical atherosclerotic event at a young age would be significant, assuming there were no other contributing factors such as vasculitis or the anti-phospholipid syndrome.

As a result of clarifying these issues, a treatment strategy can be devised to lessen the impact of the problem on SLE patients in Singapore.
METHODS

The candidate performed a study (25) at Tan Tock Seng Hospital to determine the extent of
the problem of dyslipidemia in Singaporean patients with SLE. This hospital receives
nation wide referrals from general practitioners and other specialists. Fasting lipid profiles
were measured in 100 consecutive patients with SLE hospitalised or attending the
outpatient clinics over a two month period from September to November 1990. Informed
consent was given. Serum total cholesterol (TC), high density lipoprotein (HDL) and serum
triglyceride (TG) were assayed using the Kodak Ektachem analyser and Kodak Ektachem
clinical chemistry slides for TC, HDL and TG. This is an enzymatic method using
multilayered film elements for analysis. Low density lipoprotein (LDL) and TC/HDL ratios
were calculated. Biodata noted for each patient were age, gender, race, presence of diabetes
mellitus, hypertension, thyroid disease, familial hyperlipidemia, smoking history, renal
involvement as defined by the revised 1982 ARA criteria for SLE, ie proteinuria greater
than 0.5 g per day or the presence of cellular casts; active disease was defined by the Lupus
Activity Criteria Count (LACC) (26); the presence of nephrotic syndrome, previous and
current use of anti-hypertensive agents, duration of SLE to the nearest month, the
cumulative dose of steroids since diagnosis and current dose of steroids. History of any
previous clinical events related to atherosclerosis such as myocardial infarction and/or
stroke was also noted. Patients who fulfilled at least four criteria of the 1982 revised criteria
for SLE were recruited. The definition of a normal lipid profile followed guidelines of the National Cholesterol Education Programme (NCEP) published in 1988. Most of our patients had less than 2 of the following cardiac risk factors, ie hypertension, diabetes mellitus, smoking, familial hyperlipidemia and family history of coronary artery disease. Comparison of means was done using Student's t test and proportions were tested using the chi square or the chi square for trend. The effect of SLE activity, renal disease, age, current prednisolone dose and use of lipid interfering agents on lipid profiles were assessed using the multiple linear regression analysis (ANCOVA test).

The candidate also studied a cohort of SLE patients with age and gender matched controls from the same region in the UK with regards to lipid profiles (27). One hundred patients with SLE were recruited from the Royal National Hospital for Rheumatic Diseases, Bath, UK. They fulfilled at least 4 of the 11 criteria of the 1982 ARA Revised Criteria for SLE. Clinical data relevant to dyslipidemia were obtained: age, gender, history of smoking and alcohol intake, relevant family history, usage of corticosteroids, anti-malarial drugs and anti-hypertensive agents, past history of diabetes mellitus, hypertension, ischemic heart disease, stroke, peripheral vascular disease, body mass index, waist-hip ratio and diet questionnaire. Disease activity was assessed using the British Isles Lupus Assessment Group (BILAG) score. Laboratory markers of activity (serum C3, C4, anti-dsDNA, ESR, CRP) and serum cytokine levels (IL-1, IL-6, TNF alpha) were measured. Fasting blood
samples were taken for measurement of lipid profiles comprising VLDL, HDL, TG, Lp(a), apo-B100 and apo AI and postheparin lipolytic activity. The lipid profiles were obtained through ultracentrifugation and chromatography.

An attempt was made to measure lipoprotein lipase activity by doing a postheparin measurement of lipolytic activity. Heparin was given to the patient and blood samples were obtained at the time of heparin injection and thirty minutes later. Total lipolytic activity was measured using a chromatography procedure.

In the Bath cohort, the lipid profiles of SLE patients and their age and gender matched controls were compared. The patients with active lupus as assessed by BILAG were compared to their age and gender matched controls. Similarly those with inactive lupus were also compared to their own controls. This is to observe differences if any in the different lipid subfractions in active versus inactive lupus. Serial data involving lupus activity, cytokine levels and lipid profiles will also yield useful information.

As for assessing consequences of hyperlipidemia in SLE, the records of the original 100 Singaporean SLE patients were traced after five years. Contact tracing was attempted for those who had defaulted. In the review of casenotes, attention was paid to capturing causes of death, new lupus manifestations, complications of treatment or illness, occurrence of other autoimmune disease and relationship between events and duration of illness.
5 HOW COMMON IS HYPERLIPIDEMIA IN SLE?
4 a. LIPID ABNORMALITIES IN PATIENTS WITH SLE

The Singaporean patients were divided into three groups according to their lipid profiles (Table 1). Group 1 comprised patients with a normal profile based on three variables (normal TC, TG and TC/HDL). Group 2 had abnormalities in 1 or 2 of the 3 variables. Patients in Group 3 had abnormalities in all 3 variables. LDL was not used as a criterion in this study because it was calculated by the Friedewald formula which becomes inaccurate in the presence of marked hypertriglyceridemia, which was found in a substantial number of our patients. There were 27 patients in Group 1, 38 in Group 2 and 35 in Group 3.

Compared to Group 1, after adjustment for age, use of beta-blockers, diuretics and current prednisolone dose, Group 3 had higher mean TC (355 mg/dl, SE 18.1 vs 190 mg/dl, SE 20.3), LDL (233 mg/dl, SE 13.6 vs 95 mg/dl, SE 15.6), TG (354 mg/dl, SE 32.9 vs 127 mg/dl, SE 37), TC/HDL (7.8, SE 0.7 vs 3.1, SE 0.8) and lower HDL (51 mg/dl, SE 3.6 vs 68 mg/dl, SE 4.1). Less prominent but statistically significant differences were also found in the same parameters when Group 2 was compared to Group 3.
Table 2 shows the characteristics of these patients. Although there were more men in Group 3, the difference was not statistically significant. The mean age was similar as was the racial distribution. The majority were Chinese. The number of patients receiving hydroxychloroquine, having diabetes mellitus, hypothyroidism, coronary heart disease and familial hyperlipiemia did not differ significantly among the 3 groups. Sixteen patients in the study population received diuretics and/or beta-blockers for hypertension.
### Table 1. Lipid Indices of 100 SLE Patients in Singapore

<table>
<thead>
<tr>
<th>Lipid Indices</th>
<th>Group 1 (n=27)</th>
<th>Group 2 (n=38)</th>
<th>Group 3 (n=35)</th>
<th>p value 1 vs 2</th>
<th>p value 1 vs 3</th>
<th>p value 2 vs 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>TC (U)</td>
<td>184.7 (30.9)</td>
<td>225.5 (64.9)</td>
<td>361.6 (156.3)</td>
<td>NS</td>
<td>p&lt;0.001</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td>(A)</td>
<td>190.8 (20.3)</td>
<td>227.1 (16.7)</td>
<td>355.3 (18.1)</td>
<td>NS</td>
<td>p&lt;0.001</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td>LDL (U)</td>
<td>93.4 (27.8)</td>
<td>127.2 (46.6)</td>
<td>236 (17.4)</td>
<td>NS</td>
<td>p&lt;0.001</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td>(A)</td>
<td>95.8 (15.6)</td>
<td>127.9 (12.7)</td>
<td>233.4 (13.6)</td>
<td>NS</td>
<td>p&lt;0.001</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td>HDL (U)</td>
<td>69.6 (14.9)</td>
<td>61.1 (26.7)</td>
<td>50.4 (14.9)</td>
<td>NS</td>
<td>p&lt;0.002</td>
<td>p&lt;0.05</td>
</tr>
<tr>
<td>(A)</td>
<td>68.7 (4.1)</td>
<td>61.1 (3.3)</td>
<td>51.0 (3.6)</td>
<td>NS</td>
<td>p&lt;0.002</td>
<td>p&lt;0.05</td>
</tr>
<tr>
<td>TG (U)</td>
<td>107.5 (31.1)</td>
<td>200.1 (88.1)</td>
<td>374.9 (305.6)</td>
<td>NS</td>
<td>p&lt;0.001</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td>(A)</td>
<td>127.6 (37)</td>
<td>204.4 (30.5)</td>
<td>354.7 (32.9)</td>
<td>NS</td>
<td>p&lt;0.001</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td>TC/HDL</td>
<td>2.7 (0.6)</td>
<td>4.1 (1.9)</td>
<td>8.2 (6.1)</td>
<td>NS</td>
<td>p&lt;0.001</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td>(A)</td>
<td>3.1 (0.8)</td>
<td>4.2 (0.6)</td>
<td>7.8 (0.7)</td>
<td>NS</td>
<td>p&lt;0.001</td>
<td>p&lt;0.001</td>
</tr>
</tbody>
</table>
(U): unadjusted mean lipid indices

(A): adjusted mean lipid indices for age, use of betablockers/diuretics and current prednisolone dose

All units in mg/dl
Table 2. Characteristics of the Singaporean cohort of SLE Patients

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Group 1 (n=27)</th>
<th>Group 2 (n=38)</th>
<th>Group 3 (n=35)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male:Female</td>
<td>1:26</td>
<td>2:36</td>
<td>7:28</td>
</tr>
<tr>
<td>Age (mean and SD)</td>
<td>33.7 (7.7)</td>
<td>31.2 (9.7)</td>
<td>32.2 (11.7)</td>
</tr>
<tr>
<td>Median</td>
<td>32</td>
<td>32</td>
<td>33</td>
</tr>
<tr>
<td>Race (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chinese</td>
<td>25 (92)</td>
<td>32 (84)</td>
<td>28 (80)</td>
</tr>
<tr>
<td>Malay</td>
<td>1 (4)</td>
<td>4 (10)</td>
<td>5 (14)</td>
</tr>
<tr>
<td>Indian</td>
<td>1 (4)</td>
<td>1 (3)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Others</td>
<td>0 (0)</td>
<td>1 (3)</td>
<td>2 (6)</td>
</tr>
<tr>
<td>History of</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>0</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>Smoking</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Familial hyperlipidemia</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Hypertension*</td>
<td>5</td>
<td>9</td>
<td>12</td>
</tr>
<tr>
<td>Family history of CAD**</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>0</td>
<td>2</td>
<td>0</td>
</tr>
</tbody>
</table>
* Only 2, 4 and 10 patients in Group 1, 2 and 3 respectively were taking diuretics or beta blockers. The remainder were taking calcium channel blockers or methyldopa.

** coronary artery disease
This study showed that dyslipidemia is common in a fairly severe cohort of Singaporean SLE patients. There was no attempt made to compare differences in dietary intake and this may have been a confounding factor. Nonetheless, the degree of the hyperlipidemia in the 35 patients were of the extent that they were unequivocally high compared to population norms. The mean total cholesterol was 361 mg/dl, LDL-C was 236 mg/dl, HDL-C was 50.4 mg/dl, TG was 374 mg/dl and TC/HDL ratio was 8.2. These patients have a mean age of 32 and the risk of premature atherosclerosis is a real one.

Although 100 patients were recruited for the study in Bath, only 64 patients and 64 matched controls had complete lipid profiles. The data is presented in Table 3.
Table 3

Lipid Profiles of 64 British SLE patients versus age and gender matched controls

<table>
<thead>
<tr>
<th></th>
<th>SLE</th>
<th>Control</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>n=64</td>
<td>n=64</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Cholesterol</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TC mean (SD)</td>
<td>197.3 (45.6)</td>
<td>207.5 (50.3)</td>
<td>NS</td>
</tr>
<tr>
<td>VLDL</td>
<td>17.9 (10.1)</td>
<td>18.7 (12.1)</td>
<td>NS</td>
</tr>
<tr>
<td>LDL</td>
<td>134.9 (37.4)</td>
<td>140.8 (47.2)</td>
<td>NS</td>
</tr>
<tr>
<td>Total HDL</td>
<td>44.5 (13.7)</td>
<td>47.9 (15.2)</td>
<td>NS</td>
</tr>
<tr>
<td>HDL 2</td>
<td>17.5 (10.1)</td>
<td>21.8 (10.1)</td>
<td>0.023</td>
</tr>
<tr>
<td>HDL 3</td>
<td>26.1 (8.2)</td>
<td>25.7 (10.9)</td>
<td>NS</td>
</tr>
<tr>
<td><strong>Triglycerides</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total TG</td>
<td>107.1 (47.8)</td>
<td>108.8 (53.9)</td>
<td>NS</td>
</tr>
<tr>
<td>VLDL</td>
<td>33.6 (26.5)</td>
<td>34.5 (31.9)</td>
<td>NS</td>
</tr>
<tr>
<td>LDL</td>
<td>49.6 (25.7)</td>
<td>58.4 (30.1)</td>
<td>NS</td>
</tr>
<tr>
<td>HDL</td>
<td>19.5 (18.6)</td>
<td>19.5 (21.2)</td>
<td>NS</td>
</tr>
<tr>
<td>Apo A1</td>
<td>120.23 (27.4)</td>
<td>142.84 (28.9)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Apo B</td>
<td>64.15 (21.04)</td>
<td>69.74 (22.32)</td>
<td>NS</td>
</tr>
</tbody>
</table>

Units in mg/dl
The Bath and Singapore cohorts were not studied at the same time and were not designed for direct comparison. Nonetheless there were interesting differences in the two cohorts

In the earlier predominantly Oriental population of 100 SLE patients, the candidate found that 35 had a Type IIb hyperlipidemia with a raised mean total cholesterol level of 361 mg/dl, LDL of 236 mg/dl, HDL of 50.4 mg/dl and triglyceride level of 354 mg/dl. These levels are very grossly abnormal compared to the mean values of the Singaporean Chinese population.

In contrast, in this cohort of Caucasian SLE patients at Bath, UK, it was found that compared to age and gender matched controls, the patients did not have grossly different lipid abnormalities except for a significantly lower HDL 2 subfraction and also lower apoprotein A I. Interestingly, HDL2 was lower but not HDL3. One possible explanation of this differing pattern of lipid abnormalities may be explained by the fact that the Bath cohort generally represented a milder subset of lupus. Only 6% of the Bath patients had renal involvement and only 46% were on corticosteroids. In contrast, 60% of the Singapore patients had renal involvement and 97% were on oral corticosteroids.

The nephrotic syndrome and corticosteroid usage both tend to produce a Type IIb pattern and hence in the Singapore cohort this was the more obvious abnormality. In the Bath cohort, the effects on LDL and triglycerides were negligible. This is despite the fact that the
cohort was older than the Singaporean cohort in which case one would have expected more lipid abnormalities.

Therefore hyperlipidemia is common in the subset of SLE patients in whom renal involvement is common and steroid usage is relatively high. The pattern of hyperlipidemia is a Type IIb whereas in a cohort of milder patients with little renal involvement and low usage of steroids, the pattern is that of low HDL.
6 What are the risk factors for hyperlipidemia in SLE?
5 a) Corticosteroids

As mentioned earlier, possible mechanisms of hyperlipidemia are many but three mechanisms are explored in this thesis, namely the use of corticosteroids, the presence of renal disease and the extent of lupus activity.

With regards to corticosteroid use, there were no differences in the mean duration of illness and mean cumulative dose of prednisolone in the three groups of Singaporean patients with differing lipid profiles (Table 4). However, the mean current daily prednisolone dose in Group 1 and Group 3 were 9 and 23.5 mg respectively (p<0.001). Patients taking more than 30 mg of prednisolone a day had higher mean TC, LDL, TG and TC/HDL but lower HDL compared to those taking less than 30 mg a day. This data is presented in Table 5.

In the Bath cohort, steroid usage was very low as only 46% of the patients were ever on steroids. Compared to age and gender matched controls there were no differences in TC, LDL and TG levels. This provides indirect evidence that corticosteroid usage gives rise to elevated LDL and TG levels.
Table 4. Clinical variables of 100 Singaporean SLE patients

<table>
<thead>
<tr>
<th></th>
<th>Group 1</th>
<th>Group 2</th>
<th>Group 3</th>
<th>chi-sq for trend</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n=27)</td>
<td>(N=38)</td>
<td>(N=35)</td>
<td></td>
</tr>
<tr>
<td>Duration of illness (months)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>68 (60.9)</td>
<td>90 (35.6)</td>
<td>68.1 (65.7)</td>
<td>NS</td>
</tr>
<tr>
<td>Median</td>
<td>48</td>
<td>40</td>
<td>50</td>
<td></td>
</tr>
<tr>
<td>Renal disease</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Renal/Total</td>
<td>10/27</td>
<td>23/38</td>
<td>27/35</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td>Nephrotic/Total</td>
<td>0/27</td>
<td>4/38</td>
<td>12/35</td>
<td>ND*</td>
</tr>
<tr>
<td>Nephrotic/Renal</td>
<td>0/10</td>
<td>4/23</td>
<td>12/27</td>
<td>ND*</td>
</tr>
<tr>
<td>Active SLE</td>
<td>4/27</td>
<td>3/38</td>
<td>19/35</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td>Drugs</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diuretics/betablockers</td>
<td>2/27</td>
<td>9/38</td>
<td>10/35</td>
<td>NS</td>
</tr>
<tr>
<td>Prednisolone</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nil</td>
<td>1/27</td>
<td>1/38</td>
<td>1/35</td>
<td>NS</td>
</tr>
<tr>
<td>Mean current dose (mg)</td>
<td>9 (11.8)</td>
<td>15 (16.4)</td>
<td>23.5 (18.7)</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td>Cumulative dose (g)</td>
<td>20.5 (25.5)</td>
<td>19.7 (18.2)</td>
<td>23.8 (21.6)</td>
<td>NS</td>
</tr>
<tr>
<td>Hydroxychloroquine</td>
<td>1/27</td>
<td>1/38</td>
<td>0/35</td>
<td>ND*</td>
</tr>
</tbody>
</table>

ND: not done, as each group has a cell where there are no patients
U: Unadjusted mean lipid indices
A: Adjusted mean lipid indices for age, current prednisolone dose and use of betablockers and diuretics
Table 5. Effect of corticosteroids on lipid profiles

<table>
<thead>
<tr>
<th>Mean Lipid</th>
<th>Prednisolone &lt;30 mg/day</th>
<th>Prednisolone &gt;30 mg/day</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Indices</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>(n=81)</td>
<td>(n=19)</td>
<td></td>
</tr>
<tr>
<td>TC (U)</td>
<td>247.9(95.6)</td>
<td>322.6(204.6)</td>
<td></td>
</tr>
<tr>
<td>(A)</td>
<td>247.9</td>
<td>322.9</td>
<td>p&lt;0.05</td>
</tr>
<tr>
<td>LDL (U)</td>
<td>146.9(81.7)</td>
<td>198.5(140.8)</td>
<td></td>
</tr>
<tr>
<td>(A)</td>
<td>146.9</td>
<td>198.4</td>
<td>p&lt;0.05</td>
</tr>
<tr>
<td>HDL (U)</td>
<td>62.1(20.5)</td>
<td>49.0(22.7)</td>
<td></td>
</tr>
<tr>
<td>(A)</td>
<td>62.2</td>
<td>48.3</td>
<td>p&lt;0.05</td>
</tr>
<tr>
<td>TG (U)</td>
<td>204.7(133.5)</td>
<td>370.8(394.9)</td>
<td></td>
</tr>
<tr>
<td>(A)</td>
<td>202.6</td>
<td>380</td>
<td>p&lt;0.05</td>
</tr>
<tr>
<td>TC/HDL (U)</td>
<td>4.5(2.8)</td>
<td>8.2(7.9)</td>
<td></td>
</tr>
<tr>
<td>(A)</td>
<td>4.4</td>
<td>8.4</td>
<td>p&lt;0.05</td>
</tr>
</tbody>
</table>

U: Unadjusted mean lipid indices
A: Adjusted mean lipid indices for age and hypertension
NB: No adjustment was made for activity of SLE and renal status because majority of patients with active SLE and renal disease took >30 mg prednisolone per day
We found that the use of corticosteroids was associated with the abnormal lipid profiles. Patients taking more than 30 mg of prednisolone a day had higher mean TC, LDL, TG and TC/HDL but lower HDL compared to those taking less than 30 mg a day. Most of these patients were on corticosteroid therapy as they generally had more severe lupus disease. The mean current daily dose of those with normal lipid profiles was 9 mg whereas it was 23.5 mg in those with abnormal lipid profiles (p<0.001). These findings are consistent with several previous studies which show that the use of systemic corticosteroids is associated with lipid abnormalities. Corticosteroid therapy has been shown to produce abnormal lipid profiles including high serum triglycerides, high LDL cholesterol and decreased HDL cholesterol. Ettinger and Hazzard (28) confirmed this in a study on 28 women with SLE treated with corticosteroids, comparing them with 10 women with SLE not taking steroids and 15 normal women. He found that the prednisone treated group had higher mean plasma triglyceride levels, higher LDL cholesterol and higher apolipoprotein B levels than the other two groups.

In this Singaporean cohort of patients with fairly severe lupus disease, the use of corticosteroids contributed significantly to hyperlipidemia. Therefore, in such patients, this potential side effect has to be taken into consideration when monitoring these patients.
5 b) Renal Disease

In the Singapore study, we found that there were 27 out of 35 patients with the most abnormal lipid profiles had renal involvement (ie high TC, low HDL, high LDL, high TG) versus 10 out of 27 in the group with normal lipid profiles ($p<0.001$). Therefore it seems that the presence of renal involvement is associated with abnormal lipid profiles. This was renal involvement as defined by the 1982 ARA Criteria for the diagnosis of systemic lupus erythematosus rather than the presence of the nephrotic syndrome. Out of the 27 with renal involvement in the abnormal lipid group, 12 had the nephrotic syndrome but none of the 10 in the normal lipid group were nephrotic. This however did not reach statistical significance on analysis, perhaps because of small numbers. Nonetheless, the trend suggests the importance of the nephrotic syndrome in contributing to abnormal lipid profiles in this group of patients. The impact of nephrotic syndrome on lipid profiles has been well documented in other renal diseases such as primary glomerulonephritis.

In this Singaporean SLE cohort, renal involvement is common and occurs in 60% of our patients. Many of these patients have the nephrotic syndrome. This contributes significantly to their risk of persistent hyperlipidemia and premature atherosclerosis. When Group I and Group 3 were compared, significant differences were found in the proportion of patients with renal involvement ($p<0.001$). Two patients in Group 3 had clinical events related to hyperlipidemia. One had myocardial infarction at age 29 and the other had renal
infarction at age 30. There was no evidence of vasculitis or antiphospholipid syndrome in these 2 patients. Their anticardiolipin antibody and lupus anticoagulant were negative.

Among the 64 patients with inactive SLE (LACC score of <2), those with renal involvement had higher mean TC, LDL, TG and TC/HDL but no difference in HDL compared to those without renal involvement (Table 6).

In the Bath study, only 6% had renal involvement and therefore the patients did not have abnormal LDL or TG levels.
Table 6. Lipid Profiles in Different Clinical States

<table>
<thead>
<tr>
<th>Lipid Indices</th>
<th>Non-renal (n=42)</th>
<th>Inactive disease (n=64)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Active (n=11)</td>
<td>Inactive (n=31)</td>
</tr>
<tr>
<td>TC (U)</td>
<td>244.7(98.3)</td>
<td>209.5(51.5)</td>
</tr>
<tr>
<td>(A)</td>
<td>197.8</td>
<td>226.2</td>
</tr>
<tr>
<td>LDL (U)</td>
<td>141.2(91.9)</td>
<td>116.5(43.9)</td>
</tr>
<tr>
<td>(A)</td>
<td>93.8</td>
<td>133.3</td>
</tr>
<tr>
<td>HDL (U)</td>
<td>49.8(18.6)</td>
<td>64.1(16.3)</td>
</tr>
<tr>
<td>(A)</td>
<td>53.1</td>
<td>62.9</td>
</tr>
<tr>
<td>TG (U)</td>
<td>266.9(133.5)</td>
<td>142.9(77.6)</td>
</tr>
<tr>
<td>(A)</td>
<td>246.8</td>
<td>150</td>
</tr>
<tr>
<td>TC/HDL (U)</td>
<td>5.6(4.1)</td>
<td>3.4(1.1)</td>
</tr>
<tr>
<td>(A)</td>
<td>4.3</td>
<td>3.9</td>
</tr>
</tbody>
</table>
5 c) Active SLE

In SLE patients, dyslipidemia is linked to the presence of renal disease and high doses of corticosteroids. Lipid abnormalities may also be linked to the presence of active SLE.

In the Singapore study, when Group I and Group 3 were compared, significant differences were found in the proportion of patients with active SLE (p<0.001) (Table 4).

In the subgroup of 42 patients without renal involvement, those with active SLE had lower mean HDL-C, higher mean TC, LDL-C, TG and TC/HDL when compared to those with inactive SLE (Table 6). However, the differences did not reach statistical significance after adjusting for age, use of beta blockers, diuretics and prednisolone. Nonetheless, this suggests that active SLE per se may have an influence on lipid profiles. In this study, the Lupus Activity Criteria Count was used as a measure of lupus activity. At the time of the study, the newer assessment tools such as BILAG (British Isles Lupus Activity Assessment Group) (32), SLAM (Systemic Lupus Activity Measurement) (33) and SLEDAI (Systemic Lupus Erythematosus Disease Activity Index) (34) were not in use yet.

This pattern of lipid abnormalities could be due to the effect of cytokines on lipid metabolism. Cytokines, in particular IL-1 and TNF-alpha have been shown to suppress lipoprotein lipase synthesis and activity in-vitro. This would lead to a Type IV dyslipidemia similar to that which is found in some diabetic patients. This form of dyslipidaemia is not
likely to be innocuous although the data supporting its clinical role is not as substantial as that which is available for LDL and Lp(a). Pathogenicity may reside with an abnormal VLDL particle and this can be tested for by lipoprotein subfractionation and analysis.

It is possible that active SLE causes a Type IV dyslipidemia via the suppression of lipoprotein lipase as cytokines such as IL-1 (Interleukin-1) and TNF-alpha (Tumour necrosis factor alpha) are upregulated. Studies in active rheumatoid arthritis show a Type IV dyslipidemia compared to inactive RA but few studies have tried to establish a link between active rheumatic disease, upregulation of cytokines, suppression of lipoprotein lipase and a Type IV dyslipidemia.

In the Bath cohort, because of the low rate of renal disease and the infrequent use of systemic corticosteroids, it was a good opportunity to study the effects of active lupus activity per se on hyperlipidemia.

There were logistic difficulties with the post heparin lipolytic challenge and also the availability of serial data. Therefore data involving cytokine profiles, serial BILAG and lipoprotein lipase activity both cross sectionally and longitudinally were incomplete and may not be subject to stringent analysis. Nonetheless, the trends may give some idea of the complexity of the problem.
There was however complete data collection with regards to detailed lipid profiles in sixty four patients versus their age and gender matched controls, as presented in Table 3. Forty six patient had complete lipid profiles with matched controls as well as BILAG assessment done. Of these 33 were inactive and 13 were active. When the active patients were compared to controls, the patients had lower total HDL, lower HDL2, lower apoA and higher TC/HDL ratio. When compared to matched controls, the patients who did not have active disease showed a different pattern. These patients had lower TC, lower LDL, lower total HDL, lower HDL2, lower apoA and lower apoB. (Table 7)

In nine patients there was complete data on serial BILAG assessment, serum lipid levels and cytokine profiles (TNF alpha and soluble IL2 receptor). This is presented in Tables 8 and 9. Serial assessments were done 6 months apart. Of the nine patients, four had inactive SLE as measured by BILAG in both visits and five patients went from active to inactive SLE.

In these patients followed up serially, soluble IL2-R and BILAG generally correlated as markers of lupus activity. Out of the nine patients, serial sIL2R decreased in seven. Of these seven, four progressed from active to inactive lupus on BILAG and the other three remained inactive at both visits. In all of the seven patients in whom sIL2R decreased, there was an increase in apoprotein A I.
There were no differences in serum levels of IL-1 and TNF-alpha between patients with active and inactive SLE. The numbers are really too small to make any definite conclusions. However a possible reason for the lack of correlation is that serum cytokine levels do not reflect perfectly changes in cytokine regulation at the cellular level. Hence the use of serum cytokines to monitor lupus activity may not be useful and may not add significant information that is useful clinically.

Another reason may have to do with BILAG score (British Isles Lupus Activity Group) being applied to a patient population where the change in lupus activity is small. The BILAG is a validated tool for assessing lupus activity and comprises clinical as well as laboratory parameters. It is thought to be more sensitive change compared to other tools such as SLAM (Systemic Lupus Activity Measurement) and SLEDAI (SLE Disease Activity Index). However in the British cohort, the patients had generally mild lupus and low lupus activity. Therefore the changes in their lupus activity over time was also not very significant and could not be detected with serial use of BILAG.

We measured lipoprotein lipase by a post-heparin lipolytic activity (PHLA) assay and also levels of hepatic lipase. In cross-sectional analysis, we were unable to detect differences in either PHLA or hepatic lipase between patients with active and inactive SLE. This could be due to PHLA being an imperfect measure of lipoprotein lipase. The numbers of patients in the two groups may have been too small to pick up significant differences and some were on corticosteroid therapy.
Other evidence to support this hypothesis was difficult to obtain in the Bath study because of incomplete data collection from logistic difficulties. As a result, we failed to establish a link between active SLE, upregulation of cytokines, suppression of lipoprotein lipase and the resulting lipid abnormalities.

Nonetheless, we found a pattern of low HDL2 and apoprotein AI compared to age and gender matched controls. This is consistent with a suppression of lipoprotein lipase. As mentioned earlier, lipoprotein lipase is suppressed by pro-inflammatory cytokines such as IL-1 and TNF alpha which should be elevated in active lupus.
Table 7

<table>
<thead>
<tr>
<th></th>
<th>Patient</th>
<th>Control</th>
<th>p</th>
<th>Patient</th>
<th>Control</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>TC</td>
<td>214.1</td>
<td>211.4</td>
<td>NS</td>
<td>195.8</td>
<td>241.0</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>VLDL</td>
<td>20.9</td>
<td>18.3</td>
<td>NS</td>
<td>18.3</td>
<td>19.9</td>
<td>NS</td>
</tr>
<tr>
<td>LDL</td>
<td>150.9</td>
<td>140.8</td>
<td>NS</td>
<td>130.3</td>
<td>165.8</td>
<td>0.0003</td>
</tr>
<tr>
<td>HDL-T</td>
<td>43.3</td>
<td>53.4</td>
<td>0.03</td>
<td>46.4</td>
<td>52.7</td>
<td>0.05</td>
</tr>
<tr>
<td>HDL-2</td>
<td>14.0</td>
<td>23.8</td>
<td>0.009</td>
<td>19.9</td>
<td>24.9</td>
<td>0.05</td>
</tr>
<tr>
<td>HDL-3</td>
<td>28.9</td>
<td>30.0</td>
<td>NS</td>
<td>26.5</td>
<td>27.7</td>
<td>NS</td>
</tr>
<tr>
<td>TC/HDL</td>
<td>5.12</td>
<td>4.15</td>
<td>0.05</td>
<td>4.62</td>
<td>4.95</td>
<td>NS</td>
</tr>
<tr>
<td>Apo A</td>
<td>117.8</td>
<td>137.4</td>
<td>0.02</td>
<td>120.4</td>
<td>153.7</td>
<td>0.0003</td>
</tr>
<tr>
<td>Apo B</td>
<td>69.5</td>
<td>73.0</td>
<td>NS</td>
<td>63.6</td>
<td>80.8</td>
<td>0.002</td>
</tr>
<tr>
<td>TG</td>
<td>112.4</td>
<td>119.5</td>
<td>NS</td>
<td>104.4</td>
<td>121.2</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>Patient 1</td>
<td>Patient 2</td>
<td>Patient 3</td>
<td>Patient 4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>--------------------------------------</td>
<td>-----------</td>
<td>-----------</td>
<td>-----------</td>
<td>-----------</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1\textsuperscript{st} Total HDL</td>
<td>67.1</td>
<td>60.1</td>
<td>25.7</td>
<td>35.9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2\textsuperscript{nd} Total HDL</td>
<td>54.9</td>
<td>28.5</td>
<td>32.8</td>
<td>37.8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1\textsuperscript{st} HDL2</td>
<td>37.1</td>
<td>21.5</td>
<td>8.9</td>
<td>10.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2\textsuperscript{nd} HDL 2</td>
<td>38.2</td>
<td>9.8</td>
<td>14.8</td>
<td>19.1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1\textsuperscript{st} ApoA I</td>
<td>138</td>
<td>141</td>
<td>77</td>
<td>101</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2\textsuperscript{nd} ApoA I</td>
<td>143</td>
<td>161</td>
<td>88</td>
<td>100</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1\textsuperscript{st} TC</td>
<td>198.9</td>
<td>295.2</td>
<td>134.5</td>
<td>147.8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2\textsuperscript{nd} TC</td>
<td>167.3</td>
<td>283.1</td>
<td>105.3</td>
<td>132.6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1\textsuperscript{st} LDL</td>
<td>173.2</td>
<td>219.9</td>
<td>91.7</td>
<td>95.9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2\textsuperscript{nd} LDL</td>
<td>106.5</td>
<td>239.1</td>
<td>62.8</td>
<td>95.9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1\textsuperscript{st} TG</td>
<td>61.1</td>
<td>59.3</td>
<td>74.3</td>
<td>76.1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2\textsuperscript{nd} TG</td>
<td>66.4</td>
<td>82.3</td>
<td>27.4</td>
<td>68.1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1\textsuperscript{st} VLDL</td>
<td>16.8</td>
<td>15.2</td>
<td>17.2</td>
<td>15.9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2\textsuperscript{nd} VLDL</td>
<td>5.8</td>
<td>15.6</td>
<td>9.8</td>
<td>4.3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1\textsuperscript{st} TNF alpha</td>
<td>21</td>
<td>12</td>
<td>15</td>
<td>3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2\textsuperscript{nd} TNF alpha</td>
<td>19</td>
<td>6</td>
<td>12</td>
<td>12</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1\textsuperscript{st} sILR</td>
<td>2800</td>
<td>1550</td>
<td>1170</td>
<td>2280</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2\textsuperscript{nd} sIL.2R</td>
<td>1310</td>
<td>730</td>
<td>2620</td>
<td>2000</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Table 9

Serial data on five patients who had active disease on the first visit and inactive disease on the second

<table>
<thead>
<tr>
<th></th>
<th>Patient 1</th>
<th>Patient 2</th>
<th>Patient 3</th>
<th>Patient 4</th>
<th>Patient 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>1&lt;sup&gt;st&lt;/sup&gt; Total HDL</td>
<td>45.6</td>
<td>50.7</td>
<td>33.5</td>
<td>30.8</td>
<td>34.3</td>
</tr>
<tr>
<td>2&lt;sup&gt;nd&lt;/sup&gt; Total HDL</td>
<td>38.6</td>
<td>57.3</td>
<td>37.8</td>
<td>35.9</td>
<td>40.2</td>
</tr>
<tr>
<td>1&lt;sup&gt;st&lt;/sup&gt; HDL2</td>
<td>16.4</td>
<td>33.5</td>
<td>10.9</td>
<td>8.2</td>
<td>8.9</td>
</tr>
<tr>
<td>2&lt;sup&gt;nd&lt;/sup&gt; HDL2</td>
<td>23.4</td>
<td>10.1</td>
<td>17.2</td>
<td>7.4</td>
<td>6.2</td>
</tr>
<tr>
<td>1&lt;sup&gt;st&lt;/sup&gt; ApoA I</td>
<td>107</td>
<td>125</td>
<td>89</td>
<td>94</td>
<td>104</td>
</tr>
<tr>
<td>2&lt;sup&gt;nd&lt;/sup&gt; ApoA I</td>
<td>116</td>
<td>151</td>
<td>114</td>
<td>112</td>
<td>122</td>
</tr>
<tr>
<td>1&lt;sup&gt;st&lt;/sup&gt; TC</td>
<td>141.9</td>
<td>242.6</td>
<td>165.8</td>
<td>190.7</td>
<td>229.7</td>
</tr>
<tr>
<td>2&lt;sup&gt;nd&lt;/sup&gt; TC</td>
<td>136.9</td>
<td>235.6</td>
<td>143.1</td>
<td>205.5</td>
<td>257.0</td>
</tr>
<tr>
<td>1&lt;sup&gt;st&lt;/sup&gt; LDL</td>
<td>88.9</td>
<td>173.6</td>
<td>118.6</td>
<td>131.4</td>
<td>161.5</td>
</tr>
<tr>
<td>2&lt;sup&gt;nd&lt;/sup&gt; LDL</td>
<td>90.9</td>
<td>157.2</td>
<td>93.6</td>
<td>135.7</td>
<td>180.2</td>
</tr>
<tr>
<td>1&lt;sup&gt;st&lt;/sup&gt; TG</td>
<td>49.6</td>
<td>113.3</td>
<td>71.7</td>
<td>115.1</td>
<td>140.7</td>
</tr>
<tr>
<td>2&lt;sup&gt;nd&lt;/sup&gt; TG</td>
<td>53.9</td>
<td>139.8</td>
<td>48.5</td>
<td>146.0</td>
<td>150.5</td>
</tr>
<tr>
<td>1&lt;sup&gt;st&lt;/sup&gt; VLDL</td>
<td>7.4</td>
<td>18.3</td>
<td>11.3</td>
<td>24.9</td>
<td>33.9</td>
</tr>
<tr>
<td>2&lt;sup&gt;nd&lt;/sup&gt; VLDL</td>
<td>7.4</td>
<td>21.1</td>
<td>15.9</td>
<td>33.9</td>
<td>36.7</td>
</tr>
<tr>
<td>1&lt;sup&gt;st&lt;/sup&gt; TNF alpha</td>
<td>20</td>
<td>11</td>
<td>10</td>
<td>15</td>
<td>13</td>
</tr>
<tr>
<td>2&lt;sup&gt;nd&lt;/sup&gt; TNF alpha</td>
<td>19</td>
<td>11</td>
<td>15</td>
<td>14</td>
<td>13</td>
</tr>
<tr>
<td>1&lt;sup&gt;st&lt;/sup&gt; sIL2R</td>
<td>1150</td>
<td>480</td>
<td>1330</td>
<td>1220</td>
<td>3200</td>
</tr>
<tr>
<td>2&lt;sup&gt;nd&lt;/sup&gt; sIL2R</td>
<td>700</td>
<td>930</td>
<td>750</td>
<td>920</td>
<td>2560</td>
</tr>
</tbody>
</table>
7 What could be the clinical consequences of dyslipidemia in SLE?
6 a) OUTCOME OF SLE PATIENTS WITH HYPERLIPIDEMIA AFTER FIVE YEARS

In the earlier study referred to where 100 SLE patients had lipid profiles measured, the candidate did a chart review of these same patients after five years (35). At that time, only notes from 94 patients were available. Of these 94, 7 had emigrated or defaulted follow up. Therefore, we were only able to analyse casenotes from 87 of the original 100 patients, a dropout rate of only 13 % over 5 years. Contact tracing was attempted for the missing 13 patients but was unfruitful

When they were first recruited in 1990, the mean age was 32 years, mean duration of illness was 60 months and mean cumulative dose of corticosteroids was 20 g. Sixty percent had renal involvement. This then represents a cohort of moderate to severe SLE.
RESULTS

Of the 87 patients, 13 perished. This gives a five year survival rate of 85%. However data was not available for 13 out of the original 100 patients. Hence the true figure for five year survival ranges from 74% to 87%.

Six deaths were lupus related, five were due to infection and two were due to neither. Of the lupus related deaths, two deaths were from CNS lupus, one from end stage renal failure, one from lupus gut, one from pulmonary haemorrhage and one from pulmonary hypertension. Duration of illness before death ranged from 3 to 15 years. Three deaths occurred within the first five years of diagnosis. All six patients had Class IV lupus nephritis.

Of the infection related deaths, two had pyogenic infection, one had pneumocystis carinii pneumonia, one had disseminated atypical mycobacterial infection and one had fulminant septicemia. Duration of illness before death ranged from 3 to 13 years.

Two deaths occurred due to malignancy, one a carcinoma of the ovary and the other a teratocarcinoma.
Of the 87 patients, 19 had new lupus manifestations in the five years of study. Seven developed lupus nephritis while on follow up, six of which were biopsy proven. Three of these were Class IV. Other new lupus manifestations included myositis, vasculitis, seizures, subacute cutaneous lupus, autoimmune hemolytic anemia, lupus panniculitis, thrombocytopenia, the antiphospholipid syndrome, transverse myelitis and pulmonary hypertension.

Six patients developed end stage renal failure requiring dialysis as a result of worsening lupus nephritis. Twenty-two patients had complications judged to be related to treatment of lupus rather than the illness. Seven had avascular necrosis of the hip, three had cataracts, infections occurred in ten and two patients, aged 35 and 45 developed ischemic heart disease. Duration of lupus at the time of detection of ischemic heart disease was ten years in one and twenty years in the other. Both had persistent hyperlipidemia contributed by recurrent nephrotic syndrome and prolonged use of systemic corticosteroids. Neither had vasculitis or the antiphospholipid syndrome.
IMPLICATIONS

In this study on morbidity and mortality of SLE in a severe subset, there was a five year survival of 85%. Of the 13 deaths, six were lupus related, five were from infections and two were due to malignancy, one a carcinoma of the ovary and the other a teratocarcinoma. The lupus related deaths were in a younger age group (mean age of 20) compared to the mean age of 32 in the whole cohort. All 6 had Class IV lupus nephritis. The infections tended to occur later in the illness, most of them after the fifth year of illness.

Hence lupus related deaths tend to occur early on in the illness particularly in those with poor prognostic factors such as the presence of Class IV nephritis and a young age of onset. Infections usually occur as a complication of immunosuppressive treatment and hence occurs a little later on in the course of the illness. Presumably deaths could also occur as a result of premature atherosclerosis but this may only occur perhaps even later on in the illness and hence did not show up in this study which looked at a five year outcome. Our cohort was also generally young with a mean age of 32 and this again makes it more difficult to pick up mortality from premature atherosclerosis if the duration of follow up is too short.

However, there were two patients who suffered myocardial infarction at the ages of 35 and 45 respectively. Both had hypertension and hyperlipidemia and were negative for
anticardiolipin antibody and lupus anticoagulant. There was no clinical evidence of systemic vasculitis. The presence of these events in two out of 100 such young patients confirm the need for vigilance in addressing the potential problem of hyperlipidemia and premature atherosclerosis in SLE patients.
8 DISCUSSION
THE IMPORTANCE OF HYPERLIPIDEMIA IN SLE

SLE is a potentially devastating illness that afflicts young women in their most productive years and thankfully, outcomes of treatment have been improving over the years (36). The consequence of this however is that, although patients with SLE now live longer, they are more likely to develop complications related to treatment side effects. These include many of the evils of prolonged corticosteroid therapy as well as side effects from some manifestations such as recurrent, persistent nephrotic syndrome and vasculitis. Corticosteroid induced osteoporosis can lead to fragility fractures in a subset of women and avascular necrosis of the hips and rarely other bones. Arthroplasty may be necessary at an early age. Premature cataracts can occur with chronic corticosteroid use. Infertility and early amenorrhoea is associated with the use of certain immunosuppressive agents and life threatening infections can be a problem.

One of the more potentially life threatening complications in SLE patients is premature atherosclerosis. In 1976, Urowitz et al (37) recognized a bimodal pattern in the morbidity and mortality of SLE with early events due to active disease or infections and late events related to atherosclerotic complications. From that study it was unclear whether this was linked to hyperlipidemia or to other factors. Petri et al (38) studied prospectively the risk factors for coronary artery disease in 229 SLE patients. Nineteen patients (8.3%) had coronary artery disease and accounted for 3 out of 10 deaths in this cohort. The most significant factors using a best multiple logistic regression model were age at diagnosis,
duration of prednisone use, requirement for anti-hypertensive treatment, maximum cholesterol level and obesity.

Many studies including some involving autopsies have shown premature coronary atherosclerosis and myocardial infarction in relatively young patients with SLE. Bulkley and Roberts (39) compared necropsy findings of 36 SLE patients with findings in patients who were not on corticosteroids. Subepicardial and myocardial fat was increased in all 36 patients. In 42% of the 18 patients who received corticosteroids for more than one year, the lumen of at least one of the three major coronary arteries was narrowed by more than 50% by atherosclerotic plaques. In contrast, none of the 17 patients who received corticosteroids for less than one year had such findings.

Besides causing atherosclerotic clinical events, hyperlipidemia has increasingly been recognized to worsen renal prognosis in patients with various forms of glomerulonephritis (40). The nephrotic syndrome causes hyperlipidemia which in turn causes a degree of damage to the mesangium. A stark example of the impact of the combination of steroids and the nephrotic syndrome was the case report of the death of a five year girl two years after onset of nephrotic syndrome which was refractory to corticosteroid and cyclophosphamide therapy. Severe atherosclerotic changes were noted in her coronary arteries (41).

In SLE patients, the traditional risk factors for atherosclerosis such as hyperlipidemia, hypertension and age are important. However, there are also some non traditional risk
factors that have been shown to be important as well and these are linked to the illness itself. Roman et al (42) studied 197 SLE patients with 197 matched controls. Carotid ultrasonography and echocardiography were used in the evaluation. Atherosclerosis (carotid plaque) was more prevalent among patients (37.1% vs 15.2 %, p<0.01). In multivariate analysis, only older age, higher serum cholesterol and presence of SLE (odds ratio 4.8, confidence interval 2.6 to 8.7) were independent risk factors for the presence of plaque. Among SLE patients, independent predictors of plaque were a longer duration of illness, a higher damage-index score, a lower incidence of the use of cyclophosphamide and the absence of anti-Smith antibodies. This study shows that atherosclerosis in SLE patients are related not just to traditional risk factors for cardiovascular disease. Disease related factors play an important role too.

If significant hyperlipidemia exists in SLE patients, it has to be treated as it would be a tragedy for a lupus patient for whom life threatening lupus disease is averted, to die from an atherosclerotic clinical event linked to hyperlipidemia.

Therefore, some important questions need to be answered:

1) How common is hyperlipidemia among SLE patients?

2) What are the risk factors for hyperlipidemia in SLE patients?

3) What are the consequences of hyperlipidemia in these patients?

This thesis tries to address these three questions. As a result of these questions being clarified, the next step would be to explore treatment options in these patients with regards
to hyperlipidemia. Proof of whether earlier detection and treatment of hyperlipidemia would lead to improved outcomes would only be available through subsequent large prospective randomised controlled trials.
HOW COMMON IS HYPERLIPIDEMIA AMONG SLE PATIENTS?

In the study published in Journal of Rheumatology, the candidate recruited 100 Singaporean SLE patients in a cross-sectional study. These patients were typical of the severe spectrum seen in the Dept of Rheumatology and Immunology which is a tertiary centre for management of such patients in Singapore. This is reflected by the fact that 60% had renal involvement and cumulative dose of prednisolone at the time of recruitment was 20 g.

It turns out that 35% had the worst possible lipid profiles with raised TC, LDL, TG, TC/HDL ratio and low HDL. Although there were no age and gender matched controls in this study, the mean values in this group are grossly abnormal compared with values in the general population. The mean TC was 355 mg/dl, LDL-C 233 mg/dl, HDL-C 51 mg/dl, TG 354 mg/dl, TC/HDL ratio 7.8. One must remember that these were all females with a mean age of only 32. In the 1998 Singapore Health Survey out of 1558 Chinese women with a mean age of 37.8, the mean total cholesterol was 214 mg/dl LDL 130, HDL 62, TG 104 mg/dl. (43) This pattern of hyperlipidemia can be more of a problem in those who have more severe lupus disease as they are exposed to more corticosteroids, more likely to have nephritis and the nephrotic syndrome and have more active lupus disease.

The SLE studies in Singapore and Bath cannot be used in direct comparison because they were not conducted at the same time and had different methodology and aims. Nonetheless
some interesting differences between these two cohorts can be observed. The cohort of patients in the Bath study did not show the same pattern of lipid abnormalities. In this cohort they had a much lower prevalence of renal lupus and they were on much lower doses of corticosteroids. Although they were older patients they did not have abnormal LDL or TG. They instead had low HDL and apoprotein A1 compared to age and gender matched controls. This could be possibly explained by the fact that pro-inflammatory cytokines are upregulated in SLE and these in turn depress lipoprotein lipase giving rise to low HDL.

Similar abnormalities have been found in other autoimmune diseases. It is well known that tumour necrosis factor, IL1 and IL6 decrease lipoprotein lipase mRNA levels, synthesis and activity (44-6). In a study of patients with cystic fibrosis (47), plasma TNF alpha was increased when compared with controls. The patients had lower total cholesterol, LDL and HDL but higher TG. ApoA1 and postheparin lipolytic activity were lower.

There is ample evidence that prolonged lipid abnormalities lead to premature atherosclerosis and the subsequent clinical events of stroke and coronary heart disease. The study showed that hyperlipidemia is a common phenomenon in Singaporean patients with moderate to severe SLE increasing the potential for atherosclerotic events to occur. These young patients had very high levels of LDL-cholesterol, low HDL and high TG, all of which is likely to predispose them to significant atherosclerotic clinical events if left untreated. It is important to think of hyperlipidemia in any SLE patient regardless of age, especially if they have active lupus, renal disease or are taking high doses of corticosteroids.
Although the Bath cohort was older, the patients did not have abnormal lipid profiles compared to their younger counterparts in Singapore. However, their pattern of abnormal lipids may not be all that harmless. HDL protects against cardiovascular disease. It removes and transports excess cholesterol from peripheral cells to the liver for removal from the body and also protects LDL from oxidation and inhibits expression of adhesion molecules in endothelial cells, preventing monocyte movement into the vessel wall. A low HDL is also associated with clinical events although to a lesser extent than with LDL or lipoprotein (a) abnormalities. Evidence of this exists for SLE patients as well. Sella et al (48) studied 82 female SLE patients with myocardial perfusion scintigraphy and found abnormalities in 23 patients (23%). Their mean age was 37 and the main factors having a significant influence on abnormal perfusion results were lower HDL cholesterol levels, presence of diabetes mellitus and vasculitis.
WHAT ARE THE POSSIBLE RISK FACTORS FOR HYPERLIPIDEMIA IN SLE PATIENTS?

Various patterns of hyperlipidemia may be present in a patient with rheumatic disease (49). Contributing factors are likely to be nephrotic syndrome when present and the prolonged use of corticosteroids. Some contribution could be related to active inflammatory disease mediated by the effect of cytokines on lipid enzymes such as lipoprotein lipase, presence of anti-lipoprotein antibodies, C reactive protein and other cytokines such as IL 18.

In SLE patients, there are many mechanisms which can give rise to hyperlipidemia. The main ones are corticosteroid therapy, presence of renal disease and lupus activity.

Corticosteroids

The role of corticosteroids in causing hyperlipidemia is well known (50). The pattern that arises from this is usually a Type IIb hyperlipidemia. This has been shown to be true in different types of patients. In heart transplant patients cumulative prednisone dose was the strongest predictor for a high total cholesterol and LDL (51). In renal transplant patients a strong etiologic relationship between hypercholesterolemia and corticosteroid dose was found. As steroid doses were decreased, the hypercholesterolemia improved. There was a reduction of 13% by three years when steroid doses were less than 10 mg daily.
Formiga et al (52) studied 53 premenopausal SLE patients and 45 controls. An increase in TC, HDL3, apo A1, and apoB with decrease in HDL2 were found in the patients versus controls. Increased total cholesterol, LDL and triglyceride correlated well with higher doses of prednisolone.

Doria et al (53) followed up a prospective cohort of 78 SLE patients without overt atherosclerotic disease for five years. At 5 years, intima thickness was measured using duplex carotid sonography. Patients with carotid abnormalities were significantly older, had higher blood pressure, higher prednisone cumulative dose and total serum cholesterol. In multivariate analysis, age and cumulative prednisone dose were associated with carotid abnormalities.

It would be helpful to know if there is a threshold dose above which side effects and problems start to arise. For example, it is generally thought that a daily dose of prednisolone greater than 7.5 mg a day for more than six months would give rise to significant corticosteroid induced osteoporosis. For lipid abnormalities, Petri et al (54) performed a cohort longitudinal study involving 264 patients with SLE. In a regression model for steroid use, a change in prednisone dose of 10 mg was associated with a change in cholesterol level of 7.5 +/- 1.46 mg% and a weight gain of 5.5 +/- 1.23 pounds. In the Singaporean cohort of patients, we did find a correlation between daily prednisolone dose and lipid abnormalities. Patients taking more than 30 mg of prednisolone a day had higher mean TC, LDL, TG and TC/HDL but lower HDL compared to those taking less than 30 mg a day. The mean current
daily dose of those with normal lipid profiles was 9 mg whereas it was 23.5 mg in those with abnormal lipid profiles (p<0.001).

The pattern of lipid abnormalities induced by corticosteroid use is strongly associated with the risk of clinical atherosclerotic events and it suggests to us that patients taking high daily doses of prednisolone should have their lipid profiles checked regularly to detect lipid problems early. Treatment should be started appropriately to prevent adverse outcomes. Other contributing factors to hyperlipidemia and atherosclerosis should also be addressed such as dietary adjustment, weight control, cessation of smoking and control of hypertension. Non-traditional factors should be considered. These include homocysteine, nephrotic syndrome and the presence of antiphospholipid antibodies. Martinez-Berriotxoa et al (55) found that plasma homocysteine concentrations are higher in SLE patients than in healthy controls.

This underlies the fact that the use of corticosteroids in SLE is a two edged sword. Besides the protean side effects including osteoporosis, early cataract formation, increased tendency to infection, hypertension, diabetes mellitus and cosmetic problems when used in high doses, hyperlipidemia too has to be taken into account. Therefore the onus is on the rheumatologist to carefully balance the risks and benefits of using corticosteroids in each individual patient. Steroid sparing agents should be used if a maintenance dose of steroids is unacceptably high.
The Bath cohort on the other hand had less lipid abnormalities and were on lower doses of steroids. Many of the patients were not on corticosteroid therapy at all. Only 6% of the patients had renal involvement and only 46% were on corticosteroids. The differences seen in the Bath cohort could be due to the milder spectrum of lupus disease and hence the reduced usage of oral corticosteroid therapy. The only differences when compared to healthy age and gender matched controls were in a lower HDL2 subfraction and lower apoprotein AI. This may be linked to disease activity and release of pro-inflammatory cytokines which depress lipoprotein lipase.

**Renal Disease**

Another factor which causes hyperlipidemia in SLE is the presence of renal disease. This is important because besides causing clinical events related to vascular thrombosis, dyslipidemia can accelerate the progression of renal disease. The obese Zucker rat is an animal model that illustrates this point (56). These animals develop hyperlipidemia by the age of two weeks and renal injury by 16-18 weeks especially if they are fed a high-cholesterol diet. The use of lipid lowering therapy prevents this injury. The mechanism of injury is possibly through the presence of cholesterol or triglyceride rich VLDL particles. These particles bind to receptors on macrophages resulting in the formation of the foam cells which are often found in atheromatous plaques and glomeruli. Lipoproteins in the mesangium undergo oxidative modification and are taken up by scavenger receptors on macrophages and mesangial cells.
Furthermore, oxidized LDL is thought to play an important role in the pathogenesis of inflammatory disease. For example, oxidised LDL may be an important part of the pathogenesis of inflammation in rheumatoid arthritis. Winyard et al (57) showed that oxidised LDL is present in the synovial fluid of RA but not osteoarthritic patients and suggests a proinflammatory role for oxidised LDL in patients with rheumatoid arthritis. In renal disease hyperlipidemia is thought to adversely affect renal prognosis as oxidised LDL may worsen inflammation within glomeruli in the patients. The situation is likely to be the same in lupus nephritis. Luzar and Ferluga (58) reported on histological features of two cases of SLE patients showing that lipids cause tissue damage in the nephron via mechanisms similar to the pathogenesis of systemic atherosclerosis. Hyperlipidemia was causally related to prominent tubulo-interstitial lipid deposits. In a larger study by Font et al (59), 70 patients with lupus nephritis and 70 age and matched control SLE patients without nephritis were prospectively followed up for 10 years. The mean age was 35. At entry the lupus nephritis patients had higher prevalence of hyperlipidemia (44% vs 2%, p<0.001) and positive anti-phospholipid antibodies (45% vs 22%, p=0.01). At the end of the study, hyperlipidemia (78% vs 27%, p<0.001) and hypertension (67% vs 32%, p=0.01) at study onset were found to be associated with the development of renal failure. Nine lupus nephritis patients and one control patient died, mainly of cardiovascular or cerebrovascular events and sepsis. Patients who died were more likely to have positive anti-phospholipid antibodies (56% vs 17%, p=0.03) and hyperlipidemia (78% vs 37%, p=0.03) at study onset. Therefore hyperlipidemia not only causes premature atherosclerosis leading to well known clinical events such as stroke and myocardial infarction, it can also worsen renal prognosis.
The pattern of hyperlipidemia in the nephrotic syndrome is a Type II b pattern which is that of elevated TC, LDL-C, TG and reduced HDL-C (29). The hyperlipidemia is generally thought to be reversible when the nephrotic state resolves. However, many SLE patients remain fairly nephrotic for much of their lives in spite of treatment for lupus nephritis. Many patients with Class IV continue to have active nephritis even after IV cyclophosphamide therapy. Gunnarson et al (30) found that albuminuria and serum C1q predicts for findings of persistent active lupus histology at serial renal biopsy. In his study, 6 out of 18 patients continued to have active lupus nephritis on a second biopsy. Bajaj et al (31) found that second renal biopsies in the Toronto Lupus clinic were done mainly because of increasing proteinuria. Twenty three out of fifty seven repeat biopsies showed a change in histology. There was significant increase in the chronicity index but decrease in the activity index. It cannot be assumed therefore that treatment of lupus nephritis will decrease proteinuria and the hyperlipidemia associated with it. Although more long term studies are needed to determine whether treatment of persistent hyperlipidemia in the nephrotic syndrome would be of benefit in lowering the risk of atherosclerotic clinical events, it would seem reasonable that patients with renal disease should as far as possible be rendered normolipidemic. This will not only prevent atherosclerotic clinical events but will also to prevent a vicious cycle from perpetuating in the kidney where the nephrotic syndrome leads to hyperlipidemia which then leads to renal injury which in turn exacerbates the nephrotic syndrome.

In our study of Singaporean patients, the presence of renal disease as defined by the 1982 ARA criteria for SLE was associated with a risk for having hyperlipidemia. Twenty seven
out of 35 patients with the most abnormal lipid profiles had renal involvement (ie high TC, low HDL, high LDL, high TG) versus 10 out of 27 in the group with normal lipid profiles (p<0.001). There was a tendency for the presence of the nephrotic syndrome to have a bearing on hyperlipidemia although the number of patients in the study were too small to be conclusive. Given that 60% of the Singaporean lupus patients had renal disease, the hyperlipidemia that develops is likely to have a great impact of this cohort of patients. In the Bath cohort, only 6% had renal involvement. Nonetheless, the treatment of individuals with renal disease if they are found to have hyperlipidemia is still of importance.

**Active Lupus**

Active disease can have a bearing on lipid abnormalities via the upregulation of certain cytokines such as IL-1, IL-6 and TNF-alpha which in turn suppress lipoprotein lipase and cause a Type IV abnormality. This can be seen from studies done on a variety of rheumatic diseases.

Active rheumatic disease has been shown to be associated with low HDL levels. As mentioned earlier lipid profiles of patients with rheumatoid arthritis, psoriatic arthritis and ankylosing spondylitis when compared to age and gender matched controls show lower HDL values.

Svenson et al (60) studied 48 patients with untreated rheumatoid arthritis and 21 with seronegative spondyloarthropathy. Compared to healthy controls, these patients with active
rheumatic disease had lower levels of VLDL-cholesterol, VLDL-triglyceride, HDL-triglyceride and HDL-cholesterol.

Lazarevic et al (61) studied 60 patients with active rheumatoid arthritis, 40 patients with psoriatic arthritis, 21 with osteoarthritis and 65 healthy blood donors. Patients with severe rheumatoid activity had lower levels of LDL cholesterol and HDL cholesterol. When their illness became less active, the serum lipids normalized. This was also the case for psoriatic arthritis patients but not for osteoarthritis. Magaro et al (62) has shown like many others that patients with rheumatoid arthritis have lower levels of apoprotein A-I and apoprotein B compared with controls. Patients with type IIb hyperlipidemia undoubtedly have a higher risk of atherosclerotic clinical events but patients with low levels of HDL and high triglyceride levels are also at risk. This is increasingly clear from studies done mainly in diabetic patients (63).

The candidate co-authored a study done in Singaporean patients with ankylosing spondylitis to determine if active disease was associated with dyslipidemia (64). In these patients, there was again a tendency for active disease to be associated with low HDL levels. Fasting lipid profiles were obtained from 50 men with ankylosing spondylitis and 50 age and gender matched controls. Mean age was 31.5 years and none of the patients were on corticosteroids.

Presence of risk factors for coronary artery disease, including hypertension, diabetes mellitus, familial hyperlipidemia were assessed. Disease activity of ankylosing spondylitis
was assessed using erythrocyte sedimentation rate, C-reactive protein and clinical scoring methods namely the Bath Ankylosing Spondylitis Disease Activity, Functional and Metrological Indices (BASDAI, BASFI and BASMI). We found that seventy percent had abnormal lipid profiles and compared to controls, the patients had lower total cholesterol (mean 176.8 mg/dl vs 196 mg/dl, p<0.007) and lower HDL-cholesterol (mean 36.4 mg/dl vs 47.6 mg/dl, p <0.001 and higher TC/HDL ratios (5.04 vs 4.32). In this study, the HDL was negatively correlated with BASFI (Bath Ankylosing Spondylitis Functional Index) with a r of 0.32, p=0.03. There was no correlation with BASDAI and BASMI.

This pattern again suggests that active rheumatic disease is associated with lower HDL which supports the hypothesis that there is something which causes it to fall. One possibility is the upregulation of cytokines which suppress lipoprotein lipase activity. This is difficult to prove conclusively as disease activity is a difficult parameter to measure and established scoring methods do not correlate well with serum cytokine levels. This is illustrated by another study (65) which the candidate was involved in, looking at the relationship between disease activity in ankylosing spondylitis, sex hormone status and cytokine levels in relationship to bone mineral density. No correlation was found between disease activity as measured by BASDAI, BASFI, BASMI and serum levels of IL-1, IL-6 and TNF alpha. This could be because tissue levels of cytokines are better measures of disease activity than plasma levels but they would be far more difficult to measure and more complicated in interpretation.
Similiar profiles have been found in active RA, psoariatic arthritis and ankylosing spondylitis. Jones et al (66) studied 50 psoriatic patients and compared their detailed lipid profiles with controls in Bath, UK. The psoriatic patients have significantly lower levels of total HDL and HDL3 subfraction. The LDL3 seemed to be elevated in the patients. There was also a tendency for higher levels of Lp(a). This combination of low total HDL, HDL3, elevated LDL3 and Lp(a) has atherogenic potential (67). This is similar to findings in rheumatoid arthritis.

Therefore from all these various studies done in rheumatic disease, it appears that compared to controls, such patients had lipid abnormalities comprising low HDL, low LDL, low apoprotein A1 and apoprotein B. These abnormalities can be brought on when there is suppression of lipoprotein lipase activity. It turns out that one possible mechanism includes the suppression of lipoprotein lipase activity by cytokines upregulated in active rheumatic disease. It was found as early as 1989 by Fried et al (4) that a single infusion of tumour necrosis decreases human adipose tissue lipoprotein lipase mRNA levels, synthesis and activity. With the advent of anti-cytokine therapy, there arises the possibility that suppression of cytokine activity can favourably alter lipid profiles. This is especially relevant in the light of the rapidly growing body of evidence that there may be some key cytokines such as IL 18 involved in atherosclerosis. Wallberg-Jonsson et al (68) studied the relationship between lipoprotein lipase activity and mass, blood lipid profiles and inflammatory variables in rheumatoid arthritis patients. Lipoprotein lipase activity was lower in the patients versus controls. This was inversely related to inflammatory markers such as C reactive protein and IL6 but not for lipid levels. This could be because of the
small numbers as there were only 17 patients versus 16 controls. Ilowite et al (69) identified dynamic changes in lipid profiles in a set of paediatric SLE patients studied longitudinally. The mean HDL-cholesterol and apo-AI was markedly lower in untreated and clinically active SLE patients compared with controls. When the illness was treated and SLE became inactive, HDL-cholesterol and apo-AI rose.

Other possible mechanisms include the effect of anti-lipoprotein antibodies and the role of acute phase reactants such as serum amyloid A protein in modifying HDL metabolism. Lazarevic et al (57) found that anti-lipoprotein antibodies against VLDL and LDL were present in 26 of 69 (38%) of patients with active rheumatoid arthritis but not in patients with osteoarthritis, psoriatic arthritis or healthy blood donors. Patients with these antibodies had lower cholesterol levels in all subfractions and elevated serum triglycerides.

Another mechanism could be mediated via acute phase reactants such as serum amyloid A protein. Kumon et al (70) showed that in patients with rheumatic disease, total HDL cholesterol, apoprotein A-I and apoprotein A-II were lower than in normal subjects and were inversely correlated with plasma concentrations of serum amyloid A protein (SAA). SAA displaces apo A-I and apo A-II which results in increased catabolism of HDL.

Measurement of lupus activity is not easy. In the Singaporean study we used the LACC (Lupus Activity Criteria Count) which is an earlier tool and we found a tendency for active SLE to be associated with a low HDL. This pattern was also seen in the cohort of paediatric lupus patients studied by Ilowite et al and is consistent with the other studies done on
rheumatoid arthritis and psoriatic arthritis. In 1990 when the Singapore study was done, newer indices of lupus activity were not yet routinely in use.

In the Bath cohort, we used BILAG (British Isles Lupus Activity Group) score, which is a more accurate measure of lupus activity. This index is also sensitive to change. We directly measured cytokine profiles namely, IL-1, soluble IL-2 receptor and TNF-alpha. Lipid metabolism was studied at length via the subfractionation of cholesterol and also measurement of hepatic lipase and lipoprotein lipase activity by a post-heparin challenge.

In the Bath cross-sectional study we found that SLE patients have low HDL2, low apoprotein I when compared to age and gender matched controls from the same region in the UK. This is in stark contrast to the Singaporean cohort who have elevated TC and LDL, high TG and low total HDL. The differences could possibly be attributed to the differences in the severity of lupus particularly the presence of renal disease and the nephrotic syndrome, degree of lupus activity and the usage of corticosteroids.

In this cohort, we unfortunately did not have complete data collection in all respects except for nine patients. These patients never had renal disease and were not on corticosteroids. They had serial measurements of a full cytokine profiles (soluble IL-2 receptor, TNF-alpha, IL6, and IL 1-beta), and measurements of serum total cholesterol, LDL-chol, total HDL-chol, HDL 2 and HDL 3 subfractions, TG, apoprotein A1 and apoprotein B.

In these patients studied serially, sIL2R and apoprotein A1 generally correlated and this could be indirect evidence that our hypothesis holds true. Among the various serum
cytokines, the only one that correlated with the BILAG was sIL2R. In the patients who had increase in sIL2R, the activity status was also higher when assessed by BILAG and the apoprotein AI was lower.

It turns out that of the seven patients who had a fall in sIL-2R levels, all had a concomitant rise in apoprotein A1. This seems to support the hypothesis that lupus activity causes a fall in HDL through suppression of lipoprotein lipase activity. However, the number of study subjects was small and this finding has to be confirmed by larger studies. Also in this study, the BILAG, a clinical scoring method did not correlate well with dynamic changes in serum cytokines.

Assessment of lupus activity, measuring upregulation of cytokines and measurement of lipoprotein lipase directly are extremely difficult and probably accounts for the failure of our study to establish a firm link between these disease mechanisms. We did find however that in this cohort of SLE patients with relatively low frequency of renal disease and corticosteroid usage, lipid profiles suggest suppression of lipoprotein lipase activity. This supports the hypothesis that a Type IV dyslipidemia is found in active rheumatic disease. We were able to show this probably because this particular cohort of patients had a low frequency of renal disease and steroid use which would have been major confounding factors. We were however unable to show differences in serum levels of apoproteins A, B. Nonetheless our study suggests that active disease itself is a contributor to the problem through a mechanism mediated through the upregulation of cytokines in active rheumatic disease. This may present opportunities for novel therapeutic interventions.
The role of active SLE causing changes in cytokine profiles which in turn lead to lipid abnormalities is further supported by research done on other cohorts. Svenungsson et al (71) further documents this phenomenon in a study involving two hundred and eight SLE patients. Disease activity was assessed using SLAM and fasting blood was analysed for lipid profiles and serum TNF alpha, soluble TNF Type 1 (sTNFR1) and Type 2 (sTNFR2) receptors. Serum TG was found to be associated with SLAM score (r=0.48, p<0.0001), TNF alpha (r=0.29, p=0.0001), sTNFR1 (r=0.38, p<0.0001), sTNFR2 (r=0.40, p<0.0001). HDL levels on the other hand were negatively associated with SLAM score (r= -0.27, p=0.0003), TNF alpha (r= -0.15, p=0.04) and sTNFR2 (r= -0.19, p=0.01). In multiple logistic regression models, TNF alpha and serum TG were independent determinants of active disease as assessed by SLAM (p=0.003 for both). Therefore active SLE was shown to increase TNF alpha and its soluble receptors which then caused a rise in TG and a fall in HDL. This study then strongly supports the explanation for low HDL in the Bath cohort and also the Singapore cohort as being related to active SLE causing upregulation of cytokines like anti-TNF alpha which then suppresses lipoprotein lipase leading to low HDL and high TG.
What could be the clinical consequences of hyperlipidemia in SLE?

Hyperlipidemia carries with it several clinical consequences many of which are related to thrombotic events such as myocardial infarction and cerebrovascular thrombosis (72). Hence it would be interesting to know the extent to which this is a problem for SLE patients with persistent hyperlipidemia. In the previous section, it was pointed out that SLE patients as well as patients with other rheumatic diseases such as rheumatoid arthritis have been shown to have excess mortality from ischemic events.

The candidate performed a follow up study of the initial cohort of 100 Singaporean SLE patients after a period of five years to determine their outcomes. This study demonstrated that there was a significant number who developed complications from treatment including infections, cataracts and avascular necrosis. A number of patients had new manifestations of lupus while on follow up. Mortality was associated with a young age of onset of lupus and the presence of severe lupus nephritis. However, there were no new atherosclerotic events during these five years. Two of the patients already had a history of thrombotic events probably due to hyperlipidemia when they were first recruited in 1990 but they were no other new patients similarly affected. There were 13 patients who were lost to follow up and it is not known if any of them had atherosclerotic complications. It must be remembered that this was a young cohort of patients with a mean age of 32. It is likely that a five year follow up period is too short to be able to detect significant mortality and morbidity from atherosclerotic events.
MANAGEMENT

RATIONALE FOR TREATMENT

As has been discussed, rheumatic diseases carry an increased risk of morbidity and mortality from premature atherosclerosis. Rheumatoid arthritis is associated with increased mortality. Prior et al (73) studied 489 consecutive patients with classical rheumatoid arthritis followed up for a mean of 11.2 years and found a three fold increase in overall mortality compared with age and sex-specific rates in the general population. Cardiovascular deaths were 2.5 times higher than expected. Rasker and Cosh (74) followed up a cohort of 100 RA patients for 18 years. Of the 43 who died, 16 were related to RA and 27 were unrelated. In the latter group, 14 were cardiac deaths and 8 were cerebrovascular events.

In patients on long term corticosteroid therapy, the main abnormalities are in the LDL subfraction. There have been many studies which clearly show the relationship between hypercholesterolemia and the risk of coronary artery disease. The Framingham study (75) showed that this risk is positively associated with levels of LDL cholesterol and inversely associated with HDL levels. This is particularly interesting as active rheumatic diseases have been found to be associated with low HDL and in some instances, high triglyceride levels.
There is good evidence that the treatment of lipid abnormalities result in improved outcomes. The US Lipid Research Clinics Coronary Primary Prevention Trial (76) randomized 3,806 men in a double blind study lasting 7 to 10 years. The treatment group received cholestyramine and showed a reduction in the total and LDL cholesterol levels. This was associated with a reduction in primary end points of deaths related to coronary artery disease and non-fatal myocardial infarctions. There was also a reduction in angina, positive exercise ECG and requirement for coronary bypass surgery. The Helsinki Heart Study (77) showed that lowering of serum triglyceride and raising of HDL levels led to a reduction in fatal and non-fatal myocardial infarction.

There have also been studies which use angiographic evidence of regression of coronary atherosclerosis as endpoints. The Cholesterol-Lowering Atherosclerosis Study (78) showed that colestipol combined with niacin can lead to regression in coronary atherosclerosis as assessed by coronary angiography.

Besides causing clinical events related to vascular thrombosis, dyslipidemia can accelerate the progression of renal disease. Type IIb hyperlipidemia is well known to be associated with the presence of a nephrotic syndrome which is common in lupus nephritis. In the past, it was thought that hyperlipidemia from the nephrotic syndrome did not require pharmacological therapy as it will resolve when the nephrotic syndrome improves. However, there are many patients in whom there is persistent renal involvement and hence persistent hyperlipidemia and they too then become at risk for atherosclerotic disease.
complications. Therefore, SLE patients who are persistently nephrotic need to be assessed for hyperlipidemia and they should be treated if appropriate.

Gheith et al (79) randomized 43 idiopathic nephrotic syndrome patients into a treatment group with fluvastatin and a control group. In the treated group there was a reduction in TC, LDL and TG but also improvement in proteinuria, creatinine clearance and serum albumin. Renal biopsy revealed reduction in interstitial fibrosis and renal fat deposits in the treated group. The Simvastatin in Nephrotic Syndrome Study Group (80) conducted a two year, prospective double blind trial involving 56 patients with primary glomerulonephritis and nephrotic syndrome. The patients were randomized into a treatment group with simvastatin and a placebo group. Achieving target levels of LDL HDL and TC were possible and safe.

The role of active disease and pro-inflammatory cytokines in the development of hyperlipidemia and atherosclerosis is increasingly recognized. Mizia-Stec et al (81) found that coronary artery disease is associated with increased serum levels of TNF alpha. TNF alpha is negatively associated with HDL and positively associated with TG. However, in the obese Zucker rat, anti-TNF treatment did not reverse any of the lipid abnormalities (82). However, in patients with active RA who were treated with adalimumab, an anti-TNF therapy, Popa et al (83) showed that there was an increase in HDL and reduction in CRP and IL 6 levels after two weeks. Whether this translates into a lower cardiovascular risk would require further study. Therefore it seems attractive to treat the inflammatory process with cytokine therapy to reduce the risk of atherosclerotic events. However the best
therapeutic target has yet to be determined although some cytokines like IL18 seem promising.

**TREATMENT**

Risk factors for hyperlipidemia and premature atherosclerosis have to be assessed for the individual patient. Some of these factors are amenable to modification. Smoking cessation, a sensible exercise program and weight control are important. Diabetes mellitus, steroid induced or otherwise has to be adequately treated. The role of hyperhomocysteinemia and folate supplementation should be considered.

The level of serum lipids to be attained would be based on studies in the indigenous population. An example is the US National Cholesterol Education Programme guidelines (84). The Ministry of Health, Singapore together with National Medical Research Council, Singapore Cardiac Society and National Committee on Cardiac Care published Clinical Practice Guidelines in July 2001 concerning Lipids (85). Lipid goal levels and levels for initiating drug therapy depends on the number of risk factors present and whether there is coronary heart disease (CHD) or CHD risk equivalents. This is summarised in Table 9. CHD equivalents are cerebrovascular or peripheral artery disease, diabetes mellitus. Risk factors are cigarette smoking, hypertension greater or equal to 140/90 or on anti-hypertensive medication, family history of premature CHD (CHD in male first degree relative younger or at age 55; or in female first degree relative younger or at age 65), age 45 or older in men and 55 or older in women.
<table>
<thead>
<tr>
<th>Lipid Levels</th>
<th>CHD or CHD</th>
<th>&gt; or = 2 Risk</th>
<th>0-1 Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>TC</td>
<td>&gt;160 (200)</td>
<td>&gt;200 (240)</td>
<td>&gt;240 (280)</td>
</tr>
<tr>
<td>LDL</td>
<td>&gt;100 (130)</td>
<td>&gt;130 (160)</td>
<td>&gt;160 (190)</td>
</tr>
<tr>
<td>TG</td>
<td>&gt;200 (250)</td>
<td>&gt;200 (400)</td>
<td>&gt;200 (400)</td>
</tr>
<tr>
<td>HDL</td>
<td>&lt;40 (35)</td>
<td>&lt;40 (40)</td>
<td>&lt;40 (40)</td>
</tr>
</tbody>
</table>
Dietary intervention plays a major role as a baseline measure in the treatment of hyperlipidemia. In mild cases, this may be all that is necessary to achieve the therapeutic target. An ideal weight should be maintained with a Body mass index between 18.5 and 23 kg/sq metres. Out of total calories per day, saturated fat should make up no more than 7%, total fat 25-30%, polyunsaturated fat up to 10%, monounsaturated fat up to 10%, carbohydrates as mainly complex carbohydrates 60%, protein 15%, fibre 10g/1000kcal per day and cholesterol <200 mg a day. However a study of dietary intervention in SLE patients (86) showed that after 6 months there was a reduction in only one parameter, namely total cholesterol. Therefore it is important to institute drug therapy if the therapeutic targets cannot be achieved by diet alone.

Cigarette smoking should be stopped. Aerobic exercise three or four times a week is recommended with each session lasting 30-40 minutes. Beneficial exercises include brisk walking, jogging, swimming and cycling. For lupus patients, sun protection must be remembered and if there is concomitant osteoporosis, weight bearing exercise is important as well. Alcohol intake should be restricted in patients with hypertriglyceridemia.

In some patients, dietary measures alone are inadequate and pharmacological agents have to be used. These include statins, fibrates, niacin, cholestyramine and probucol. Efficacy of these agents have been well proven, in particular statins such as simvastatin, pravastatin, atorvastatin and rosuvastatin. Their role in primary as well as secondary prevention of coronary events and stroke have been demonstrated in large randomised controlled trials.
The drug of choice depends on the lipid profile. In patients with high TG and low HDL, a fibrate would be a better initial choice whereas high LDL responds well to statins. In selected patients, combination therapy may be indicated.

With regards to factors related to SLE, the rheumatologist should control active disease, minimise the steroid dose where possible and consider the use of steroid sparing drugs especially antimalarial agents which seem to have a beneficial effect on lipid profiles in these patients. In future it may be possible to use anti-cytokine therapy in improving lipid profiles through regulation of cytokines involved in lipid metabolism. If there were certain key cytokines involved in atherosclerosis, then blocking these cytokines should have greater efficacy with fewer side effects and would be an advance in the treatment of atherosclerosis. The same concept has now been proven to be true for anti-TNF therapy in the treatment of rheumatoid arthritis.

**THE ROLE OF HYDROXYCHLOROQUINE**

Hydroxychloroquine is often used in the treatment of mild SLE and RA. Besides its immune-modulating effects, it has a protective role with regards to hyperlipidemia induced by corticosteroids. Hodi et al (92) performed a case-control study comparing patients with SLE who were on hydroxychloroquine versus those who were not. The treatment group had 35-45% lower levels of total triglyceride, VLDL-triglyceride, LDL-triglyceride, HDL-triglyceride, VLDL-cholesterol and apoprotein CIII. Wallace et al (93) studied 155 women with RA or SLE and divided them into four groups, namely
hydroxychloroquine without steroids, steroids without hydroxychloroquine, both steroids and hydroxychloroquine and neither. He found that hydroxychloroquine was strongly associated with low serum levels of cholesterol, triglycerides and LDL-cholesterol regardless of concomitant steroid use. Petri et al (94) performed a cohort longitudinal study involving 264 patients with SLE. In a regression model for steroid use, a change in prednisone dose of 10 mg was associated with a change in cholesterol level of 7.5 +/- 1.46 mg% and a weight gain of 5.5 +/- 1.23 pounds. On the other hand, hydroxychloroquine at 200 mg or 400 mg per day were both associated with lower serum cholesterol. Tam et al (95) also found that TC, VLDL, LDL were significantly lower in patients taking antimalarial drugs, including patient who are on concomitant prednisolone.

AWARENESS OF HYPERLIPIDEMIA IN SLE

Current data therefore suggests that there is a tendency for premature death in patients with rheumatic diseases. One significant contributor is the presence of cardiovascular or cerebrovascular disease. As our ability to manage such patients improves with time and new knowledge, survival of patients can now be significantly prolonged. This makes it important for rheumatologists to be aware of potential problems related to premature atherosclerosis in their patients.

The prevalence of premature atherosclerosis among SLE patients is increasingly recognised. In three large SLE cohorts namely the Toronto cohort (96), the Baltimore cohort (97) and the Pittsburgh cohort (98), factors associated with clinical coronary artery
disease were identified. Older age at onset of diagnosis and hyperlipidemia were found to be important in all three cohorts. Longer duration of steroid therapy and hypertension were present in two of the three. Other risk factors were related to active SLE such as pericarditis and others were non lupus related such as postmenopausal status, diabetes mellitus, antihypertensive treatment and congestive heart failure.

In this thesis, SLE patients from Bath and Singapore were studied. The Bath cohort is a more typical Western lupus cohort with generally milder disease, older age of onset and less usage of steroids. The Singapore cohort has more severe lupus disease, younger age of onset and generally need higher doses of steroids. Despite the use of steroid sparing agents, such patients often do develop complications of steroid therapy. Therefore, it is all the more important for the rheumatologist managing such patients to be extra vigilant with regards to monitoring and treating such complications early. In the Toronto study it was found that there was variability in the management of risk factors for coronary artery disease among rheumatologists. They did consistently well in trying to minimise steroid doses used, control disease activity and manage hypertension. There was less consistency in approaching modification of hyperlipidemia, obesity and smoking. In the Hopkins cohort (69), there was poor patient awareness that they were at increased risk of coronary artery disease and extremely low use of preventive practices.

Therefore, hyperlipidemia should always be considered when managing a patient with SLE (99). Early detection and treatment will lead to improved outcomes and lower the risk of clinical events due to premature atherosclerosis.
9 CONCLUSION
This thesis has explored the issue of hyperlipidemia in patients with systemic lupus erythematosus and the following conclusions can be drawn:

1) Hyperlipidemia is a common phenomenon in systemic lupus erythematosus in Singapore, particularly in those who have moderate to severe disease. The pattern of abnormalities are a high TC, LDL, TG and a low HDL. In the Bath SLE cohort, the only abnormality seen is low HDL.

2) Hyperlipidemia in SLE is associated with the presence of nephrotic syndrome the use of systemic corticosteroids and possibly active lupus disease.

3) The clinical consequences of persistent hyperlipidemia in SLE has to be better documented but it would seem sensible to treat this to prevent premature atherosclerosis in these relatively young patients.
REFERENCES


17) Kabakov AE, Tertov VV, Saenko VA, Poverenny AM, Orekhov AN: The atherogenic


64) Leong KH, Koh WH, Seah R, Lim SH, Fong KY. Dyslipidemia in patients with ankylosing spondylitis. ankylosing spondylitis. Proceedings of ILAR Scientific
Meeting 1997; pp74.


71) Svenungsson E, Gunnarsson I, Fei GZ et al: Elevated triglycerides and low levels of high density lipoprotein as markers of disease activity in association with up-regulation of the tumour necrosis factor alpha/TNF receptor system in SLE.


77) Frick MH, Elo O, Haapa K et al: Helsinki Heart Study: primary prevention trial with

78) Blankenhorn DH, Nessim SA, Johnson RL et al: Beneficial effects of combined
colestipol-niacin therapy on coronary atherosclerosis and coronary venous bypass
grafts. JAMA 1987; 257:3233.

79) Gheith OA, Sobh MA, Mohamed Kel-S et al: Impact of treatment of dyslipidemia on
renal function, fat deposits and scarring in patients with persistent nephrotic syndrome.


82) Lopez-Soriano J, Lopez-Soriano FJ, Bagby GJ et al: Anti-TNF treatment does not
reverse the abnormalities in lipid metabolism of the obese Zucker rat. Am J Physiol 1997,
272: E656-60.


92) Hodis HN, Quismorio FP, Wickham E, Blankenhorn DH: The lipid, lipoprotein and apolipoprotein effects of hydroxychloroquine in patients with SLE. J Rheumatol 1993; 20:661-5.


