THE MUTUAL EFFECT OF HYPERLIPIDEMIA AND PROINFLAMMATORY CYTOKINES RELATED TO PERIODONTAL INFECTION

Presented By

MOHAMMAD MOHAMMAD AL BAHRAWY

(BDS. Ain Shams University)-(2002G)

Thesis submitted in partial fulfillment of Master Degree of Oral Medicine, Periodontology, Oral Diagnosis and Radiology

Faculty of Dentistry

Ain Shams University

2011

التأثير المتبادل للدم الدهني المفرط و روابط الخلايا سابقة الالتهاب الخاصه بعدوي السلخ السني

رساله بحثيه مقدمه الي كلية طب الاسنان –جامعة عين شمس كجزء من مقومات الحصول علي درجة الماجستير في طب الفم وأمراض اللثه و التشخيص و **الاشعه**

مقدمه من

الطبيب/محمد محمد عبد اللطيف البحراوي

بكلوريوس طب و جراحة الاسنان-٢٠٠٢ جامعة عين شمس

كلية طب الاسنان

جامعة عين شمس

٢٠١١

Introduction:

Coronary heart disease has become a public health problem and major cause of death both in developed and developing countries **(Murray et al 1997, Ross 1999)**. As a significant risk factor for the development of coronary heart disease, there is a great concern about the blood lipid levels. Lipoproteins such as HDL, LDL and Triglycerides have assumed considerable importance in the prediction of individual future risk for cardiovascular events **(Kannel et al 1992, Grover et al 2003)**. Alterations in concentrations of these lipoproteins have also been associated with acute and chronic infections, and in this respect bacterial infections have been implicated as a possible risk factor in the etiology of coronary heart disease **(Danesh et al 1998, Epstein et al 1999, Leinonen et al 2002, Losche et al 2005)**.

Inflammation plays an important role in atherothrombogenesis and its clinical complications **(Danesh et al 1997, Goran 2005)**. Acute

systemic or local chronic infections seem to induce changes in the plasma concentration of cytokines and hormones, which result in alteration of the lipid metabolism **(Alvarez et al 1986, Prabu et al 1996)**.

Periodontitis is often associated with endotoxemia and mild systemic inflammatory reactions, and periodontal pathogens have been identified in early atherosclerotic lesions **(Haraszthy et al 2000, Loos et al 2000, Noack et al 2000)**. It has also been shown to be associated with increased levels of proatherogenic plasma lipoproteins; in particular, low-density lipoprotein (LDL) cholesterol, and triglycerides **(Losche et al 2000, Noack et al 2001, Katz et al 2002, Craig et al 2003)**. Several case control and cohort studies have indicated that patients with periodontitis have an increased risk of cardiovascular disease (CVD) compared with subjects with a healthy periodontium, even after adjustment for established cardiovascular risk factors **(Mattila et al 1993, Beck et al 1996).** It is well known that there is a causal relationship between serum lipid levels and

cardiovascular disease and serum levels of proinflammatory cytokines. Periodontitis-induced changes in immune cell function may cause metabolic dysregulation of lipid metabolism through a mechanism involving proinflammatory cytokines **(Kinane 1998, Lacopino et al 2000)**.

Review of literature

Periodontitis is defined as an inflammatory disease of the supporting tissues of the teeth caused by specific microorganisms or groups of specific microorganisms resulting in progressive destruction of the periodontal ligament and alveolar bone with pocket formation, recession, or both **(AAP International Workshop on periodontology 1999)**.

Also Periodontitis is defined as an inflammatory disease of the supporting tissues of the teeth caused by specific microorganisms or groups of specific microorganisms resulting in progressive destruction of the periodontal ligament and alveolar bone with pocket formation, recession, or both **(Gary 1999)**. Studies indicated that periodontal disease may have profound effects on systemic health; subjects with periodontal disease may have higher risk for cardiovascular disease when compared to subjects with healthy periodontium, in Garlet review **(2010),** it was postulated that with the discovery of several T-cell subsets bearing distinct immunoregulatory properties, this proves anti-inflammatory scenario became more complex, and a series of studies has hypothesized protective or destructive roles for Th1, Th2, Th17, and Treg subpopulations of polarized lymphocytes. Interestingly, the "protective vs. destructive" archetype is usually considered in a

framework related to tissue destruction and disease progression. However, it is important to remember that periodontal diseases are infectious inflammatory conditions, and recent studies have demonstrated that cytokines (TNF-α and IFN-γ) considered harmful in the context of tissue destruction play important roles in the control of periodontal infection.

Hyperlipidemia (hyperlipoproteinemia): excessive amounts of fat and fatty substances in the blood.

Dyslipidemia: is the presence of abnormal concentrations of lipids and/or lipoproteins in the blood **(Fredrickson 1965).**

A- Lipids:

1-**Cholesterol**:

-Is an essential component of mammalian cell membranes and furnishes substrate for steroid hormones and bile acids.

-Most of the cholesterol in plasma circulates in the core of lipoprotein particles.

-The enzyme lecithin cholesterol acyltransferase (LCAT) forms cholesteryl esters in the blood compartment by transferring a fatty acyl chain from phosphatidylcholine to cholesterol.

2-Triglycerides:

-Consist of a three-carbon glycerol backbone covalently linked to three fatty acids. The fatty acid composition varies in terms of chain length and presence of double bonds (degree of saturation).

-Triglyceride molecules are nonpolar and hydrophobic; they are transported in the core of the lipoprotein.

-Hydrolysis of triglycerides by lipases generates free fatty acids (FFAs) used for energy.

3-Phospholipids:

-Constituents of all cellular membranes.

-Consist of a glycerol molecule linked to two fatty acids.

-The third carbon of the glycerol moiety carries a phosphate group to which one of four molecules is linked: choline (phosphatidylcholine,lecithin),ethanolamine(phosphatidylethanolamine), serine (phosphatidylserine), or inositol (phosphatidylinositol).

-Phospholipids participate in signal transduction pathways: Hydrolysis by membrane-associated phospholipases generates second messengers such as diacyl glycerols, lysophospholipids, phosphatidic acids, and FFAs such as arachidonate that can regulate many cell functions **(Fredrickson 1965).**

B-Lipoproteins:

Structure: Phospholipids are oriented with their polar group toward the aqueous environment of plasma. Free cholesterol is inserted

within the phospholipid bilayer. The core of the lipoprotein is made up of cholesteryl esters and triglycerides **(Fredrickson 1965).**

Classification:

	Origin	Major apo
Chylomicrons	Intestine	B48
VLDL	Liver	B100
IDL	VLDL	B100, E
LDL	IDL	B100
HDL	Liver, intestine	AI, AII
Lipoprotein(a)	Liver	B100, (a)

(Braunwald's Heart Disease 2008)

C-Apolipoproteins:

Roles:

1-Assembly and secretion of the lipoprotein (apo B_{100} and B_{48}).

2-Structural integrity of the lipoprotein (apo B, apo E, apo AI, apo AII).

3-Co activators or inhibitors of enzymes (apo AI, CI, CII, CIII); and

binding or docking to specific receptors and proteins for cellular uptake of the entire particle or selective uptake of a lipid component (apo AI, B_{100}, E)

Classification of lipoprotein disorders:

Type I: Elevations of chylomicrons.

Type II: Beta lipoproteins (LDL).

Type III: "broad beta"disease .

Type IV: VLDL or pre–beta lipoproteins.

Type V: Elevations of both chylomicrons and VLDL.

In addition, the combined elevations of pre–beta lipoproteins (VLDL) and beta (LDL) lipoproteins was recognized as type IIb Hyperlipoproteinemia **(Choluj et al 1991).**

Etiology of Dyslipidemia:

A-<u>Genetic Lipoprotein Disorders</u>

e.g. Familial hypercholesterolemia due to Genetic disorder of Gene LDL-R

B- Secondary Causes of Dyslipoproteinemias

Metabolic	Lipodystrophy
	Glycogen storage disorders
	D.M
Renal	Chronic renal failure
	Glomerulonephritis
Hepatic	Cirrhosis
Hormonal	Estrogens increase
	Progesterones increase
Hormonal	Growth hormone
	Thyroid disorders (hypothyroidism)
	Corticosteroids
Lifestyle	Physical inactivity
	Obesity
	Diet rich in fats, saturated fats
	Alcohol intake
Medications	Retinoic acid derivatives
	Glucocorticoids
	Exogenous estrogens

	Thiazide diuretics
	Beta-adrenergic blockers (selective)
	Testosterone (hormonal supply)
	Immunosuppressive medications (cyclosporine)
	Antiviral medications (human immunodeficiency virus protease inhibitors)

(Braunwald's Heart Disease 2008)

Diagnosis of Hyperlipidemia

Diagnosis is typically based on medical history, physical examination, and blood tests (done after overnight fasting) in order to determine the specific levels of LDL cholesterol, HDL cholesterol, and triglycerides.

Treatment of Hyperlipidemia

It is necessary to first identify and treat any potential underlying medical problems, such as diabetes or hypothyroidism that may contribute to hyperlipidemia. Treatment of hyperlipidemia itself includes dietary changes, the ATP III and the American Heart Association recommend a diet in which protein intake represents 15 to 20 percent of calories, fats represent less than 35 percent, with only 7 percent from saturated fats, and the remaining calories derive

from carbohydrates. Cholesterol intake should be less than 300 mg/day, weight reduction and exercise. If lifestyle modifications cannot bring about optimal lipid levels, then medications may be necessary.

American guidelines suggest a LDL cholesterol goal of <100 mg/dl for individuals already with heart disease or diabetes, <130 mg/dl for those with moderate risk of heart disease, and <160 mg/dl for everyone else.

Most experts agree that optimal HDL cholesterol and triglyceride levels are >40 mg/dl and <200 mg/dl, respectively.

DRUGS THAT AFFECT LIPID METABOLISM:

Current Lipid-Lowering Medications

Generic Name	Trade Name	Recommended Dose Range
Statins		
Atorvastatin	Lipitor	10-80 mg
Fluvastatin	Lescol	20-80 mg
Lovastatin	Mevacor	20-80 mg
Pravastatin	Pravachol	10-40 mg

Generic Name	Trade Name	Recommended Dose Range
Rosuvastatin	Crestor	5-40 mg
Simvastatin	Zocor	10-80 mg
Bile Acid Absorption Inhibitors		
Cholestyramine	Questran	4-24 gm
Colestipol	Colestid	5-30 gm
Colesevelam	WelChol	3.8-4.5 gm
Cholesterol Absorption Inhibitors		
Ezetimibe	Zetia (Ezetrol)	10 mg
Fibrates		
Bezafibrate	Bezalip	400 mg
Fenofibrate	Tricor	67-200 mg (Lipidil Micro, EZ)
Gemfibrozil	Lopid	600-1200 mg
Niacin	Niacin	1-3 gm
Nicotinic acid	Niaspan	1-2 gm

(Braunwald's Heart Disease 2008)