Volume : 5 | Issue : 8 | August 2016 • ISSN No 2277 - 8179 | IF : 3.508 | IC Value : 69.48

Original Research Paper

Assessment of Dyslipidemia and Other Cardiovacular Risk Factors in Patients With Mycosis Fungoides and Lichin Planus

Medical Science

KEYWORDS : Dyslipidemia; Cardiovascular risks; Mycosis fungoides; Lichen planus

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ABSTRACT

Background: *Coronary heart disease has been the leading cause of death in developed and developing nations .Study the association between mycosis fungoides (MF)and lichen planus(LP)as cardiovascular risk factors can decrease the mortality from cardiovascular disease. We aimed to assess the dyslipidemia and other cardiologic risk factors in patients suffering from mycosis fungoides and lichen planus.* ***Subjects and methods****: 30 patients with mycosis fungoides, 30 patients with lichen planus(they did not start treatment)and 20 age and gender matched healthy subjects were included in the study. The diagnosis was made through clinical picture and was confirmed by skin biopsy. Weight, height and body mass index (BMI) were measured, also we assessed routine laboratory tests, serum total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, triglyceride, fasting blood glucose, homocysteine and high sensitivity C- reactive protein .****Results:*** *There was no significant difference in age, gender ,weight, height and BMI between studied subjects . Serum total cholesterol , LDL levels and LDL-C/HDL-C ratio, homocysteine and high sensitivity C- reactive protein were significantly elevated in patients with MF &LP compared to control. Fasting blood glucose ,HDL and triglycerides did not differ between patients and control . Percentage of dyslipidemia in MF and LP patients were significantly elevated.* ***Conclusions****: Mycosis fungoides and LP are association with dyslipidemia and risks of cardiovascular disease, which should be investigated and followed up for earlier diagnosis and proper managements to decrease the cardiovascular comorbidities, and improve patients' long-term outcome.*

INTRODUCTION:

Coronary heart disease (CHD), also known as atherosclerotic heart disease, usually caused by atherosclerosis, atheroma plaques reducing blood supply to myocardium resulting in angina or infarction with complete coronary artery occlusion . The majority of the burden is tilted towards low and middle income countries (1). The most common risk factors of CHD include, age, gender, smoking, family history, hypertension, obesity, diabetes, high alcohol consumption, sedentary life, stress, and hyperlipidemia(2). Homocysteine(Hcy) is a sulphur-containing amino acid in the body produced by conversion of methionine, it is essential amino acid present in foods regularly consumed within the diet(3). Hyperhomocysteinemia has been regarded as a new modifiable risk factor for atherosclerosis and vascular disease. Hcy increases the damage to the cardiovascular system in different ways; one of them is the formation of reactive oxygen species resulting from the auto-oxidation of Hcy. It is widely seen now as an independent risk factor of cardiovascular disease in adults (4). C-reactive protein (CRP) is an acute-phase protein of hepatic origin, its levels rise in response to a wide range of acute and chronic inflammatory conditions. These conditions cause release of interleukin-6 and other cytokines that trigger the synthesis of CRP and fibrinogen by the liver (5).CRP is a moderate risk factor for cardiovascular disease (6)

Some dermatologic diseases are associated with increased cardiovascular risk , psoriasis is associated with metabolic syndrome and increased cardiovascular risk(7,8). Also, lichen planus (LP), androgenetic alopecia and acne rosacea are associated with abnormal lipid status(9,10,11).

Mycosis fungoides(MF) is the most common presentation of cutaneous T-cell lymphomas, affecting lymph nodes and internal organs in late stages. Old patients usually exposed to it, but children and adolescents also can be affected. MFhas indolent course, from skin patch to tumor stage(12).

Lichen planus is a chronic inflammatory disease that affects the skin, mucous membranes and appendages. LP occurs in 0.4–1.9 % of the population, and is more common in women and in patients over 45 years old (13,14). Epidermal cells in LP have shown abnormalities in enzymatic activity. Increased prevalence of diabetes and carbohydrate intolerance were noted in patients with LP, oral LP also associated with diabetes (15). Romero MA, et al (16) and Eisen D(17)reported that ,the incidence of hypertension (21%), arthritis (14%) and diabetes (5%) was not higher than general population. Some drugs used for dyslipidemia producing lichen planus-like eruption and treatment of LP by retinoid acid, methotrexate or systemic corticosteroids are also associated with dyslipidemia.

Study of the association between MF, LP and cardiovascular risk factors can decrease the possibility of cardiovascular comorbidities, and improve patients' long-term outcome. In this study, we aimed to assess the dyslipidemia and other cardiologic risk factors in patients suffering from mycosis fungoides and lichen planus.

MATERIALS AND METHODS

This study was performed at the Department of Dermatology and Internal Medicine, outpatient clinics, Faculty of Medicine, Zagazig University,Egypt, from April 2014 to March 2015. Newly-diagnosed patients with MF and LP in addition to healthy control subjects were selected to participate to fulfill the criteria of our work. They consented to be included in the study. Approval from the Institutional Review Board of Zagazig University Hospitals was obtained.

Patients group: They were newly diagnosed, patients with mycosis fungoides and lichen planus, the study included patients before starting treatment to avoid the effect of the treatment on dyslipidemia. Physical and laboratory assessment were performed to exclude smokers, alcohol consumers , receiving lipid lowering drugs, corticosteroids or immunosuppressive drugs and patients of thyroid disorders , diabetes mellitus, hypertension, cardiac, respiratory and renal diseases.

MF group: 30 patients with MF, their mean age was 42.9 ± 10.64, 16/30 (53.3%) of them were males and 14/30 (46.6%) were females. Diagnosis was accomplished through a skin biopsy.

Volume : 5 | Issue : 8 | August 2016 • ISSN No 2277 - 8179 | IF : 3.508 | IC Value : 69.48

Several biopsies were taken, to be more certain of the diagnosis. The diagnosis was made through a combination of the clinical picture and histopathology &immunohistochemistry of skin biopsy , several biopsies were taken for good diagnosis. The disease was limited to skin without internal organ involvement.

LP group: 30 patients with LP, mean age was 38.0± 9.21, 50% were males, and 50% were females. LP was diagnosed by clinical picture and examinations of tissue biopsy. The lesion was affecting skin and/ or mucous membranes. Lichen planus like drug eruption cases were excluded.

Control group: 20 age and gender matched healthy subjects were selected. Their mean age was 39.5± 8.44 years, 50 % of them were males and 50% were females.

In addition to full history, physical examination was performed with stress on weight, height and body mass index (BMI) was calculated by dividing weight (kg) by height in squared meters (m^2). Also we assessed routine laboratory tests, serum total cholesterol, high-density lipoprotein cholesterol(HDL), low-density lipoprotein cholesterol(LDL), triglyceride(TG), fasting blood glucose, homocysteine and Hs CRP.

Sample preparation: Morning samples of blood for fasting glucose were obtained after 8 hours fasting while blood samples for total cholesterol, low-density lipoprotein cholesterol (LDLc), high-density lipoprotein cholesterol (HDLc), triglyceride (TG), homocysteine, high sensitivity CRP (HsCRP) were obtained in the morning after 12 hours of fasting . Blood was collected to measure homocysteine in EDTA containing tubes and kept on ice to be centrifuged (3500 rpm/min for 15 min).

Biochemical analysis: All biochemical analysis was performed on c702 module of cobas 8000 modular series (Ro diagnostics). We measured serum glucose, total cholesterol, low-density lipoprotein cholesterol (LDL-c),high-density lipoprotein cholesterol (HDL-c), triglyceride (TG), homocysteine and high sensitivity CRP(HsCRP), as cardiac risk factors. Serum concentrations of glucose determined by hexokinase method.Triglyceride, total cholesterol, HDL-c, LDL-c and homocysteine were determined by enzymatic procedures. Glucose, total cholesterol, HDL-c, LDL-c and triglyceride levels were expressed in mg/dL and homocysteine was expressed in µmol/L. Serum high sensitivity CRP (HsCRP) was measured by immunoturbidimetric assay,levels were expressed in mg/L.

Statistical Analysis: The data were tabulated and statistically analyzed using Microsoft Office Excel 2010,and Statistical Package for Social Sciences version 20 (SPSS: An IBM Company). Data were represented as Mean ± SD, and were analyzed statistically by using analysis of variance(ANOVA),Chi-squared test($\chi 2$), paired T test and correlation coefficient(r).Values were considered significant if $p < 0.05$.

RESULTS: Clinical cardiovascular risk factors were assessed in patients and control ,there was no significant difference in male/ female ratio between the studied groups ,males were 53.3%, 50%,50%of MF,LP and control respectively, females were 46.7%,50%,50% of MF,LP and control respectively ($x^2 = 0.08$, p= 0.96). There was no significant difference regarding, age ,weight, height and BMI between all subjects of the study **(Table1)** .

Laboratory cardiovascular risk factors were assessed in patients and control, no significant difference was found in fasting blood glucose levels between patients with MF, LP and control. Serum total cholesterol, LDL-C,LDL-C/HDL-C were significantly elevated in patients with MF &LP when compared to control, but no significant difference between MF and LP patients. HDL and triglycerides did not differ between patients and control (Table 2).There was significantly elevated homocysteine, high sensitivity C- reactive protein (HsCRP) in patients with MF &LP when compared to control but no significant difference between MF and LP patients **(Table 2).**

As regard dyslipidemia, the prevalence of abnormally elevated total cholesterol (>200mgldl) was significantly elevated in MF and LP patients vs. healthy controls (50% of MF and 53%of LP and 15% of control)(x^2=8.32, p<0.05)and the prevalence of abnormally elevated LDL-C(>130mgldl) was highly significantly elevated in MF and LP patients vs. healthy controls (90% of MF and 86.7%of LP and 10% of control) ($x^2 = 42.92$, p= <0.001) . There was no significant difference in the prevalence of dyslipidemia between MF and. LP **Table(3).**

There was significant positive correlation between CRP and total cholesterol in MF and LP cases, p=0.02, p=0.005 respectively. There was no correlation between CRP & homocysteine and age, BMI ,FBS, LDL-C,HDL-C and TG in the studied MF and LP cases **Table (4)**

Table (1) : Study of Mean ± SD(Range) of some clinical parameters of the subjects

	MF group (No.30)	LP group (No.30)	Control (No.20)	F	P
Age	42.9 ± 10.64 (22-60)	38.06±9.21 (20-59)	39.5 ± 8.44 (28-59)	1.98	0.15
Weight	65.5±6.78 (55-79)	65.7±7.46 (53-76)	63.9±7.75 (50-77)	0.41	0.66
Height	162.11±5.66 (150-170)	160.4±4.48 (152-170)	163.6±4.71 (154-171)	2.60	0.08
BMI(Kg/m^2)	24.8±2.17 (21.2-28.3)	25.8±2.7 (20.7-30)	24.06±2.66 (19.7-28.9)	2.98	0.06

Table (2) : Study of mean±SD (range) of some cardiovascular risk factors of the subjects

	MF group	LP group	Control	F	P
Fasting blood glucose (FBG) (mg/dl)	100.2 ± 8.34 (87-120)	99.4 ±7.43 (87-114)	97.7 ± 6.87 (88-109)	0.68	0.51

Total cholesterol(TC)(mg/dl)	223.7 ± 40.6 (177-290)	220 ± 40.4 (169-283)	165.7 ± 36.3 (130-255)	5.36	<0.001*
HDL (mg/dl)	45.9 ± 3.9 (40-53)	44.8 ± 4.5 (32-53)	46.2 ± 2.4 (44-53)	0.98	0.38
LDL(mg/dl)	152.2 ± 8.6 (136-169)	152.8 ±7.8 (140-170)	93.7 ± 6.8 (84-107)	409	<0.001*
LDL-C/HDL-C	3.31 ± 0.31 (2.7-4.1)	3.4 ± 0.36 (2.9-4.6)	1.9 ± 0.14 (1.6-2.1)	167.5	<0.001*
Triglycerides(TG) (mg/dl)	100.3 ± 8.6 (87-120)	103.9 ± 10.6 (87-123)	100.5 ± 10.1 (86-117)	1.22	0.30
Homocysteine (μmol/L)	11.2 ± 2.95 (7.1-16.5)	10.5 ± 2.35 (6.9-14.8)	5.3 ± 0.58 (4.4-6.2)	3.02	<0.001*
High sensitivity C reactive protein (HsCRP) (mg/L)	6.8±1.27 (4.4-8.9)	7.5 ± 1.5 (4.3-9.6)	2.4 ± 0.4 (1.9-3.1)	110.5	<0.001*

*=significant difference between control and patients (MF&LP)

Table (3) : Study of the percentage of dyslipidemia between the studied groups

	MF (30 cases)	LP (30 cases)	Control (20 cases)	X^2	P
Total cholesterol>200	15/30 50%	16/30 53.3%	3/20 15%	8.32	0.02*
LDL>130	27/30 90%	26/30 86.7%	2/20 10%	42.92	<0.001*

*=significant difference between control and patients (MF&LP)

Table (4): Correlation between CRP and homocysteine and patients parameters

		MF		LP
	(HsCRP)	Homocysteine	(HsCRP)	Homocysteine
	r (P)	r (P)	r (P)	r (P)
(HsCRP)	-	0.37 (0.74)	-	0.01 (0.93)
Homocysteine	0.37 (0.07)	-	0.01 (0.93)	-
Age	0.21 (0.25)	0.05 (0.75)	0.20 (0.27)	-0.13 (0.48)
BMI	-0.21 (0.32)	-0.33 (0.06)	0.04 (0.81)	-0.05 (0.75)
FBS	0.04 (0.85)	0.05 (0.76)	0.25 (0.16)	0.11 (0.56)
T-C	0.44 (0.02) *	0.03 (0.84)	0.49 (0.005) *	0.08 (0.64)
LDL	0.10 (0.63)	0.29 (0.11)	0.11 (0.55)	0.12 (0.50)
HDL	0.28 (0.18)	-0.14 (0.43)	-0.03 (0.87)	0.17 (0.34)
TG	0.35 (0.08)	0.28 (0.12)	0.14 (0.45)	-0.08 (0.65)

DISCUSSION:

Over the past decade, coronary heart disease (CHD), has been the leading cause of death in developed and developing nations with persistently the incidence is rising(18). CHD is caused by coronary arteries plaque accumulation, reducing blood flow. Heart failure , an end result of CHD, treatment of CHD is, expensive, chronic with frequent hospitalization(19).There are several factors that have been determined as risk factors for CHD, such as, age, gender, diabetes, hypertension, obesity, and cholesterol level(2). Framingham Heart Study and other similar epidemiological studies reported long ago the association between dyslipidemia and CHD(20). Accumulation of LDL which isthe principal lipoprotein transporting cholesterol in blood, results in their subsequent oxidation, followed by engulfment by macrophages, forming plaque and atherosclerosis(21). Low density lipoprotein cholesterol (LDL-C) levels, in young adulthood predict development of CHD later in life indicating a continuous process beginning from early adulthood(22).

Mycosis fungoides (MF) or Alibert-Bazin syndrome or granuloma fungoides is the most common type of cutaneous T-cell lymphomas. The cause of mycosis fungoides is unknown, but it is not believed to be hereditary or genetic in the vast majority of cases. Diagnosis is sometimes difficult because the early phases of the disease often resemble eczema or even psoriasis. MF presented as patch (flat spots), plaque (slightly raised or 'wrinkled' spots) and tumor phases, and is incurable in most patients with the exception of those with stage IA of the disease(23,24).

Volume : 5 | Issue : 8 | August 2016 • ISSN No 2277 - 8179 | IF : 3.508 | IC Value : 69.48

Lichen planus (LP) is a disease of the skin and/or mucous membranes. The cause is unknown, but it is thought to be the result of an autoimmune process with an unknown initial trigger. There is no cure, but many different medications and procedures have been used to control the symptoms, the most common presentation of LP is a well-defined area of purple-coloured, itchy, flat-topped papules with interspersed lacy white lines (Wickham's striae) (25).

In this article we aimed to investigate dyslipidemia and other cardiovascular risk factors in skin diseases such as MF and LP. In this study, there was no significant difference regarding age, gender ,weight, height and BMI between patients with MF, LP and control. Also we noticed no significant difference was found in fasting blood glucose levels between patients with MF, LP and control, but Romero MA et al(16) reported that LP was associated with hyperglycemia and diabetes.

The association between diabetes and lichen planus especially oral lichen planus, has been the subject of much research. However, most studies have examined the prevalence of diabetes mellitus in patients with lichen planus. Petrou-Amerikanou et al(26) reported a significantly higher prevalence of oral lichen planus in type 1 diabetic patients, but not in type 2 diabetic patients.

Increased LDL-C/HDL-C ratio and recently total cholesterol/ HDL-C ratio are considered as sensitive predictor metabolic index for cardiovascular risk (27). In the present study, patients with LP and MF demonstrated significantly elevated levels of total-Cholesterol, LDL-C and LDL-C/HDL-C ratio compared to healthy subjects. But HDL and triglycerides did not differ between patients and control. Most of the current anti-hypertensive regimens mainly focus on lowering LDL-C levels in plasma and the efficacy of the lipid lowering agents in reducing CHD related mortality have been discussed in clinical trials(28,29). On the contrary, high-density lipoprotein cholesterol (HDL-C) opposes atherosclerosis by removing cholesterol from foam cells, by inhibiting the oxidation of LDL, and by limiting the inflammatory processes underling atherosclerosis(21). An approximate 1 mg/dL increase in HDL level decreases coronary risk by 2 % in men and 3% in women. As a result, increasing blood HDL-C levels has been employed as a strategy to reduce CHD mortality(30). Sharrett et al (31) reported higher values of triglycerides and low levels of HDL-C were associated with the transition from atheroma to atherothrombosis and therefore control of these two cardiovascular risk factors is essential . Secreted adipocytokines by intra-abdominal fat, have many effects on inflammation, glucose metabolism and vascular endothelial biology(32). Visceral adipose tissue reveals cytokines, such as tumor necrosis factor alpha (TNF-α) and interleukin-6 (IL-6),these cytokines were also found to be elevated in skin lesion of MF patients. The pathogenesis of MF remains unclear, though it may be related to oxidative stress. As a result of oxidative stress and chronic inflammation, these cytokines are secreted (33).

The current trend is to consider LP as an autoimmune process, in which the released cytokines by activated T cells attracts inflammatory cells and leads to the destruction of keratinocytes, resulting in generation of reactive oxygen species. Various cytokines including IL (2, 4, 6,10), TNF-α, interferon (IFN)-α, IFN-γ and transforming growth factor-β1 are involved in LP(34). These inflammatory processes could potentially explain the link between LP and dyslipidemia, and possibly metabolic syndrome. TNF-α inhibitors were shown to be associated with a beneficial increase in HDL cholesterol(35).

In our study, the prevalence of dyslipidemia in the form of elevated total cholesterol was significantly elevated in MF and LP patients vs. control, and no difference was found between MF and LP (50% of MF and 53% of LP vs. 15% of control) , and the prevalence of dyslipidemia was 90% of MF and 86.7% of LP vs.10% of control as regarding elevated LDL-C ,but no significant difference between MF and LP. Santiago SA et al. (36) studied 80 cases suffering from LP, they reported that 61.3% of LP patients have dyslipidemia vs. 32.5% of controls. The presence of dyslipidemia in our patients of both MF and LP could be explained by the fact that they sharing the same pathogenesis and oxidative stress, where the previous studies found that cytokines such as TNF- α and interleukins were elevated in both diseases (33,36).

In the present study, homocysteine and HsCRP levels were noticed to be significantly elevated in patients with LP and MF, compared to healthy subjects and there was significant correlation between CRP and total cholesterol in MF and LP cases .These results are cosistant with Saleh et al(37) where they studied Homocysteine and other cardiovascular risk factors in patients with LP. Cengiz and Emiroglu (38) noticed that , MF patients had significantly increased HsCRP and homocysteine values vs. control group. CRP is used mainly as a marker of inflammation. Measuring CRP can be useful in determining disease progress or the effectiveness of treatments. Patients with elevated CRP are at increased risk of diabetes, hypertension and cardiovascular disease (39).To proof that CRP is a bystander or active participant in atherogenesis, Zacho J, et al 2008(40) studied people with genetic CRP variants, elevated CRP due to genetic variation did not increase cardiovascular risk compared to those with a normal or low CRP. In our study, we found that there was significant positive correlation between CRP and total cholesterol in MF and LP cases. Inflammatory processes , arterial damage are associated with coronary atherosclerosis, HsCRP estimation has been used as a cardiac risk assessment. HsCRP is a risk factor of vascular events in adults did not have history of cardiovascular disease (CVD). Assessment of HsCRP can improving the therapeutic outcomes in primary CVD prevention, particularly in patients with LDL levels of <160 mg/dL(41) . HsCRP levels of > 3 mg/L predict a high risk of CHD (42). Elevated homocysteine is associated with vascular inflammation, endothelial damage, resulting to atherogenesis. The amino acid homocysteine is synthesized normally by body, but hyperhomocysteinemia is a risk factor for CHD (43).

CONCLUSIONS: Mycosis fungoides and lichen planus are association with dyslipidemia and risks of cardiovascular disease, as there was significant elevation of total cholesterol ,low density lipoprotein cholesterol (LDL-C) , homocysteine and high sensitivity C- reactive protein in patients with MF &LP which should be investigated and followed up for earlier diagnosis and proper managements in order to decreasing the possibility of cardiovascular comorbidities, and improve patients long-term outcome.

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