

Psoriasis: Tumor Necrosis Factor $-\alpha$, Interleukin 18, C Reactive Protein Polymorphism , and Osteopontin Role.

Ibrahim Mohamed Abed

Ph D Theses conducted in Tikrit University College of Medicine [TUCOM], Iraq in 2012.

Background: Psoriasis is a common chronic skin disorder with prevalence of 2.7% in Iraqi community. Many factors affect the prevalence of psoriasis which include genetic, environmental, infectious, immunological, biochemical, endocrinological and psychological. Psoriasis is a chronic inflammatory disease with unknown exact pathogenesis, which may be started as skin condition that subsequently associated with systemic complications. The recurrent proliferative inflammatory processes in subject with psoriasis may lead to abnormal lipid metabolism and associated with cardiovascular diseases. Gene polymorphisms represent either a protective or risk factors for development of psoriasis and cardiovascular disease.

Aim of the Study: The aim of the present study is to provide a picture about the association between psoriasis and atherosclerosis.

Objectives: To:

1. Estimate the prevalence of impending atherosclerosis in patients with psoriasis.
2. Identify the pattern of association among inflammatory markers in one hand and lipoproteins as traditional markers in another.
3. Clarify the risk assessment of atherosclerosis in patients with psoriasis using multi- biomarkers score.
4. Appraise the inter – traditional and new markers.
5. Evaluate the role of IL-18, TNF $-\alpha$, osteopontin in the pathogenesis of psoriasis and atherosclerosis.
6. Illustrate the association between disease susceptibility and different gene polymorphism such as IL-18, TNF- α and CRP.

Methodology:

Settings: Tikrit Teaching Hospital, Primary Health Care Centers in Salahuldean Governorate..

Study Design: Descriptive Case Control Study.

Study Population: The study population included individual with psoriasis with age range of 18- 50 years. Patients and controls were recruited from outpatient dermatology clinic in Tikrit Teaching Hospital and Primary Health Care Centers in Tikrit and Shergat.

Study population groups are:

Group 1: Psoriatic patients , minimum number of patients is 53 as determined by sample size equation.

Group 2: Control Non psoriatic normal individuals, age and sex matched, equal in number to patients group.

Group 3: Patients with atherosclerosis [Myocardial infarction] with age range same that of psoriasis, age and sex matched .

Results:

Serum TNF- α mean level was markedly elevated in patients with psoriasis and MI than in control subjects. The significant increase in TNF- α , IL-18 and osteopontin in psoriasis and MI patients as compared to control confirmed that there was a link between the two diseases and these markers play a role in pathogenesis of psoriasis and MI. In addition, all lipid profile and CRP serum levels mean values, and lipid profile rates values were significantly higher in patients with psoriasis and MI compared to controls. Furthermore, mean serum level of HDL was lower in patients with psoriasis and MI than in controls.

Gender influence the serum levels of IL-18 in patients with psoriasis, MI and controls. However, the higher mean serum level was demonstrated in female with MI, followed by female with psoriasis and then by male controls. This results suggest that in our study population, female are more prone for increase of serum IL-18 in both MI and psoriasis patients. CRP was significantly higher in male psoriatic patients than in female psoriatic patients. However, there was no significant differences in CRP between male and female in patients with MI and control.

CRP levels were significantly correlated with BMI, PASI, LDL, NHDL, disease duration, LDL/HDL, NHDL/HDL and TC/HDL. These findings suggest that high sensitivity CRP serum levels were correlate to disease duration, obesity and lipid profile rates of LDL/HDL NHDL/HDL and TC/HDL, the indices with the high predictivity of risk for development of CVD in psoriasis. ROC analysis indicated that AUC for CRP demonstrated a significant prediction at BMI of ≥ 26 , PASI of ≥ 11 , duration of ≥ 8 years, and age of ≥ 25 years.

An interesting findings for this study are the early biomarkers that are with significant predictive value include circulating IL-18, OPN, and TG/HDL which with AUC of >0.5 at 2 years of psoriasis disease duration. This finding is of value in preventing psoriasis disease comorbidities such as CVD. In relation to obesity, TNF- α , IL-18, CRP, LDL, HDL, NHDL, LDL/HDL, NHDL/HDL, TG/HDL and TC/HDL were the earlier risk factor that can be used for monitoring of patients with psoriasis to prevent development of CVD. However, from these TNF- α and TC/HDL are with high predictivity (≥ 5) than others. While in relation to disease severity, IL-18, Triglycerides, and TG/HDL were the earliest risk factors for disease monitoring as they are with significant predictive value at PASI of 10. At 2 years psoriasis disease duration, the risk factors with significant predictive values were IL-18, OPN, and TG/HDL. While in relation to age, TNF- α , IL-18, OPN, Triglycerides, and HDL were the earlier risk factors with significant predictivity.

HDL was with highly predictive value risk factor in both psoriasis and control as it was with highly significant RR in psoriasis (RR=63.42) and MI (RR=56.67). Other biomarkers (cholesterol, LDL, TG, NHDL) were with significant relative risk, with the exception of total cholesterol in MI. In the present study lipid profile rates and CRP were highly significant risk factors in individuals with psoriasis and MI. CRP and all lipid profile rates calculated in this study was with significant relative risk in both psoriasis and MI. However, the highest relative risk was achieved by calculating the rates of NHDL/HDL in both psoriasis and MI. TC/HDL was with highly significant relative risk indicating that the rate is better than total or LDL cholesterol in determining risk of CVD development in patients with psoriasis. In MI total cholesterol serum concentration was with non significant RR, while the ratio of TC/HDL was with

highly significant RR, indicating higher predictivity of ratio than the using of absolute total cholesterol concentration. The same pattern this study demonstrated for LDL/HDL ratio.

In the present study, the RR of serum HDL was 63.42 for psoriasis and 56.67 for MI; triglycerides 4.6 for psoriasis and 3.9 for MI; LDL cholesterol 2.2 for psoriasis and 2.08 for MI; NHDL cholesterol 2.7 for psoriasis and 3.24 for MI. In addition, the RR of 2.64 in psoriasis and 3.11 in MI subjects for LDL/HDL; 12.4 in psoriasis and 14.44 in MI for TG/HDL; 21.6 in psoriasis and 43.3 in MI for TC/HDL; 39.6 in psoriasis and 53.33 MI for NHDL/HDL. From the present study data we can suggest that NHDL/HDL was the excellent predictor of CVD in patients with psoriasis.

From the findings of this study and recommended guidelines we developed a cut-off values for CRP, TNF- α , IL-18, OPN, cholesterol, HDL, LDL, NHDL, triglyceride, and lipid profile rates. These cut-off was used for calculation of relative risk for each biomarkers. The cardiovascular risk index in patients with psoriasis in Iraqi population was calculated as described in results section. The present study data indicated that the values for LDL/HDL, NHDL/HDL, TG/HDL, and TC/HDL were with low values as compared to NCEP, while it was higher for CRP. Thus use of NCEP values for the determination of predictivity may result into underestimation of lipid profile risk state and overestimation of CRP risk state. To overcome this problem we determine a mean values for lipid profile rates and CRP from the findings of this study and NCEP values. These calculated values of overall index were with significant predictive value as risk factor in individual with psoriasis and those with MI. Inclusion of serum TNF- α , IL-18, OPN will increase the risk predictivity value of the index. In the present study we developed a new index for monitoring cardiovascular risk in patients with psoriasis. This approach identifies different biomarkers to select people being at a high risk of development of CVD. Future follow up research for application of this index is warranted.

A significant decrease of IL-18 GG genotype was also observed in psoriasis patients compared to control individuals. In MI patients, GC genotype was significantly lower than in control, while CC genotype was significantly higher than in controls. Both psoriasis and MI patients demonstrated a lower frequencies for GG genotype as compared to controls and this may suggest that GG genotype may be of clinical importance in psoriasis and MI. The IL-18 CC genotype not detected in control individuals, while it was detected in psoriasis and MI patients. In addition, C allele of the IL-18 gene was significantly predominant in patients with psoriasis and MI, while G allele was the predominant in control individuals. Thus C allele of the IL-18 is significantly associated with psoriasis and MI. The higher IL-18 circulating levels were associated with CC and GC genotype in psoriasis, while in MI patients the higher IL-18 serum levels were associated with GG and CC genotype. The IL-18 CC genotype found to have risk association (OR=30.81, P=0.0174) with psoriasis, in contrast, GG (OR=0.41, P=0.037) and GC (OR=0.71, P=0.71) were associated with decreased risk of psoriasis. In addition, IL-18 C allele was found to have increased risk of psoriasis (OR=1.96, P=0.0045), while G allele was with decreased risk OR=0.51, P>0.05) of psoriasis. The same pattern for IL-18 genotypes and alleles was demonstrated in patients with MI indicating that both MI and psoriasis sharing a common Pathogenicity processes. In patients with psoriasis, comparison of IL-18 G versus C indicated that G allele was protective for psoriasis, while C allele was

risk factor (OR=0.73, 95%CI=0.49-1.07,P=0.11). In addition, comparison of CC genotype versus GG genotype shows that CC genotype was a risk factor while GG not (OR=2.78, 95% CI=1.01-7.64, P=0.0479). The same pattern was demonstrated in patients with MI.

TNF- α GG genotype was presented in a significant high frequency (f=0.52,OR=0.46,P=0.0264) among psoriatic patients, followed by GA genotype (f=0.44,OR=3.14,P=0.0026) as compared to control. However, TNF- α GG genotype was also the predominant genotype in control, indicated that this is a protective gene. TNF- α G allele was the predominant frequent in both psoriasis and MI patients. However, there was significant difference in G allele frequency between MI and control, but not between psoriasis and control. TNF- α GG genotype was significantly associated with high serum levels of triglyceride, LDL, NHDL, Cholesterol, in addition, TNF- α , IL-18, CRP, LDL/HDL, NHDL/HDL and TC/HDL high circulating levels were associated with GG genotype. This finding suggest that TNF- α GG genotype was with increased risk, while AA genotype was with decrease risk in psoriasis. In addition, G allele was associated with high mean values of all evaluated biomarkers in this study and disease severity. In cases of MI, TNF- α GA genotype was significantly the predominant, followed by GG, while A allele was the significant predominant in MI compared to control. However, TNF- α G allele was with frequency of 0,56 with an association to circulating high levels of TNF- α , IL-18, OPN, LDL, and CRP, LDL/HDL, NHDL/HDL and TC/HDL, but not significant. Thus it may be suggested that TNF- α A allele seems to be a risk factor for MI while G allele may be protective against development of CVD, however, this need to be evaluated in a large scale study. The comparison of distribution of TNF- α GA versus TNF- α GG indicated a significant difference (OR=4, 95%CI=1.87-8.55, P=0.0003). In addition, comparison of AA/GA versus GG shows significant difference in distribution (OR=6.76, 95% CI= 3.26-14.02,P<0.0001). These significant differences suggesting that TNF- α A allele was a risk for development of MI.

CRP +1444 C/T CT genotype was the predominant distribution in patients with psoriasis, followed by CC and then TT genotype. While in controls, the predominant genotype was CC and CT with distribution of 0.50 for each, and TT genotype not detected in any. There was a significant difference in distribution between psoriasis patients and control for CC, CT and TT genotypes. In addition, CRP C allele was the common one forming 0.55 and T allele form 0.45. However, in controls CRP C allele was the common one demonstrated in 0.75 while T allele presented in 0.25. There was highly significant differences in frequency of both T and C CRP alleles between psoriasis patients and controls. CRP C allele seems to be a protective, while T allele was a risk for development of psoriasis. Since to our knowledge this the first study that evaluated the CRP +1444 C/T polymorphism in psoriasis and thus there are no data available for comparison. High circulating IL-18, CRP, triglyceride, and high TG/HDL ratio were associated with T allele, indicating that this allele may be a risk for development of psoriasis. This suggestion strengthened by the present study findings that demonstrated a TNF- α , triglyceride, LDL, NHDL, cholesterol and LDL/HDL, NHDL/HDL and TC/HDL. The low T allele frequency in control and high frequency in MI patients suggest that T allele was a risk for development of MI.

CRP polymorphism not demonstrated an association with circulating CRP mean serum value in patients with psoriasis and control group subjects. However,

high serum mean value was associated with CRP CT genotype, followed by CRP TT genotype, while a lower value associated with CC genotype. Comparison of CRP genotypes indicated that CC genotype was protective, while CT and TT were risk factor for development of CVD. CRP C allele was a protective development of MI, while T allele was a risk for MI development.

Conclusion:

Inflammatory and dyslipidemia biomarkers used in this study confirmed that psoriasis are at risk factor for development of cardiovascular disease and the earliest significant biomarker with significant predictivity was IL-18 as it was with significant AUC values for duration (2 years), age (20 years), disease severity (PASI =10) and BMI (25 kg/m²). However, TNF- α was early significant risk factor for age and obesity, while HDL was early significant risk factor for obesity and age. In addition, OPN serum level was with early risk factor with significant predictivity was disease duration and age, while CRP with early predictive value in obesity. Furthermore, LDL and NHDL were with early risk factor significant predictivity was obesity, while for lipid profile rates, TG/HDL was disease severity, obesity, and disease duration; NHDL/HDL, LDL/HDL and TC/HDL was obesity. Serum TNF α , IL-18, Osteopontin, and lipid profile were increased in psoriasis may reflect risk factor for development of CVD in such population. IL-18, TNF- α , and CRP polymorphism play a role in Pathogenicity and susceptibility to psoriasis and MI.

Aalborg Academy of Science

College of Medicine

Master Program in Dermatology

Program Category: Medicine

College: Medicine

Program Level: M Sci.

Teaching Methods: Full- time or Part- time.

Program Starting Date:

Teaching Language: English.

Program Duration: Full-time 2 years; Part –time: 3 years.

Application Date:

Credit Hours: 36

Program Code: AAS-COM-DERMSC

Program Degree: M Sc Dermatology

Entry Requirement:

Candidates for the M Sc dermatology must hold a Bachelor degree in medicine.

Overview

The Clinical Dermatology MSc is an advanced study programme aimed at medical graduates wishing to specialise in the field of dermatology. You will gain advanced practical training in laboratory sciences relevant to skin disease, and enhance your skills and knowledge of the scientific basis of clinical dermatology. The study pathway also includes a critical evaluation of dermatological literature on a specialist subject.