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Protective effects of simvastatin and/or telmisartan on cardiovascular system in patients with mild to moderate chronic obstructive pulmonary disease (COPD).

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الخلاصة:

إن مرض التهاب الرئتين ألانسدادي المزمن، تلك الحالة المرضية التي تتميز بقصور والتهاب المجرى الهوائي وهبوط وظيفة الرئتين لأمد طويل، هو أحد أهم الأسباب التي تنتهي بالوفاة في كل أنحاء العالم. لقد بينت العديد من الدراسات الوبائية بان الأشخاص المصابين بمرض التهاب الرئتين ألانسدادي المزمن تكون لديهم خطورة الإصابة بأمراض الجهاز القلبي الوعائي ثلاثة مرات أعلى من جمهور الأصحاء.

ان الهدف من هذه الدراسة هو لتقييم التأثيرات الوقائية لعقار السمفاستاتين و/أو التلميسارتان على الجهاز القلبي الوعائي لمرضى التهاب الرئتين ألانسدادي المزمن البسيط أو المتوسط.

تم مشاركة 80 مريضا مصابين بالتهاب الرئتين ألانسدادي المزمن في هذه الدراسة وتم توزيعهم على أربعة مجموعات تضمنت المجموعة الأولى 20 مريضا يستخدمون منشقة السالبيوتامول فقط (كمجموعة مقارنة)، المجموعة الثانية تضمنت 20 مريضا يستخدمون منشقة السالبيوتامول مع عقار السمفاستاتين 20ملغ يوميا، المجموعة الثالثة تضمنت 20 مريضا يستخدمون منشقة السالبيوتامول مع عقار التلميسارتان 40ملغ يوميا وتضمنت المجوعة الرابعة 20 مريضا يستخدمون منشقة السالبيوتامول مع خليط العقارين معا. تم اختيار 20 شخصا من الأصحاء ظاهريا كمجموعة طبيعية للمقارنة أيضا. لقد تم مراقبة المرضى عند بدء الدراسة، بعد 3 و6 أشهر من العلاج. تم قياس البروتين النشط عالي الحساسية، جزيئة الالتصاق الوعائية ومستوى الدهون في الدم.

لقد بينت النتائج أن هناك انخفاضا شديدا في المستويات الدموية للبروتين النشط عالي الحساسية، جزيئة الالتصاق الوعائية ومستوى الدهون في الدم بعد استخدام عقار السمفاستاتين أو التلميسارتان أو كليهما.

يمكن الاستنتاج بان استخدام عقار السمفاستاتين 20 ملغ يوميا أو التلميسارتان 40 ملغ يوميا أو كليهما لمدة 3 و6 أشهر له تأثير وقائي على الجهاز القلبي الوعائي لمرضى التهاب الرئتين ألانسدادي المزمن البسيط أو المتوسط.

Abstract:

The objective of this study is to evaluate the protective effects of simvastatin, telmisartan or their combination on cardiovascular system in patients with COPD.

Eighty patients with mild to moderate COPD were participated in this study. They were recruited into four groups where the first group includes 20 patients on an inhaled β2- agonist only (control), the second group includes 20 patients on an inhaled β2- agonist plus 20mg/d simvastatin, the third group includes 20 patients on an inhaled β2- agonist plus 40mg/d telmisartan and the fourth group includes 20 patients on an inhaled β2- agonist plus combination of both simvastatin and telmisartan. Twenty apparently healthy subjects were selected to be a normal group for comparison. Baseline, 3 and 6 months periods were used to monitor patients. Assessing the plasma levels of hs-CRP, VCAM-1 and lipid profile. ANOVA method for statistics were used to compare the results.

There was a great reduction in hs-CRP and VCAM-1 in addition to modulation of lipid profile after the use of simvastatin 20mg/d, telmisartan 40mg/d and their combination in COPD patients.

Simvastatin 20mg/d, telmisartan 40mg/d and their combination exerted a protective effect on the cardiovascular system in COPD patients after 3 and 6 months of therapy by reducing hs-CRP, VCAM-1 and lipid profile.

Key words: Simvastatin, telmisartan, COPD**.**

Introduction:

Chronic obstructive pulmonary disease is an extremely important cause of morbidity and mortality. For example, the prevalence of COPD more than doubled between 1990 and 2002, making it the fourth leading cause of death in the United States. COPD is an independent risk factor for cardiovascular disease[1]. Arterial wall stiffness, which relates to cardiovascular risk, is increased in patients with COPD compared with control subjects who smoke [2, 3]. This suggests that COPD may result in systemic endothelial dysfunction, which may be a mechanism for the enhanced cardiovascular risk in COPD [1]. Systemic arterial wall stiffness is also independently related to emphysema as assessed by CT scanning [4, 5]. Statins are used primarily as lipid-lowering agents in the treatment of metabolic syndrome, but they also have potent anti-inflammatory properties that might explain their positive effect on frequent comorbidities of both metabolic syndrome, for example, CHF and vascular disease, and COPD [6, 7]. The interest in these agents was further enhanced by the discovery that statins may cause regression of atherosclerosis lesions [8, 9], an effect that has not previously been observed in COPD with any intervention, not even after successful smoking cessation [10]. Studies considering that statins' effects on mortality, even in subjects at risk of developing cardiovascular diseases, significantly reduces cardiovascular morbidity and mortality, the

results of these studies on cardiovascular diseases increase the hopes of reducing mortality from other chronic diseases, such as COPD [11].

There have been several recent pharmacoepidemiologic studies that have demonstrated that statin and/or ACE inhibitor use were associated with improved outcomes for patients hospitalized with acute COPD exacerbations or for those with pre-existing COPD [12, 13]. The possibility that these classes of drugs have dual cardiopulmonary protective properties has not been seriously considered in discussions of new therapies for COPD [14].

Materials and Methods:

This study was carried out at Al- Basra General Hospital from December 2009 until June 2011. Eighty patients aged 40-65 years old (Mean = 58.8 ± 9.1). They, 64 patients (80%) male and 16 patients (20%) female were participated in this study and where grouped into four groups. The first group involved (20) COPD patients on salbutamol inhaler only (control). The second group involved (20) COPD patients on salbutamol inhaler plus simvastatin 20mg/d. The third group involved (20) COPD patients on salbutamol inhaler plus telmisartan 40mg/d. The fourth group involved (20) COPD patients on salbutamol inhaler plus combination of both simvastatin and telmisartan. Twenty apparently healthy subjects were selected to participate as a normal group for comparison, they were 16 males (80%) and 4 females (20%) with a mean age of (59.09 ± 8.71).

A specialized physician in internal medicine made diagnosis for patients as having COPD depending on patient history, clinical examination, radiographic findings and spirometry. Data were assessed as baseline, 3months and 6 months intervals after treatment with the drugs used in the study and these data were represented as mean ± standard error of the mean (SE). Assessing the plasma levels of hs-CRP, VCAM-1 and lipid profile was performed. Hs-CRP and VCAM-1 plasma concentrations were measured by Enzyme Linked Immunosorbent Assay (ELISA) technique. Lipid profile plasma concentrations were measured and identified by spectrophotometric methods.

Results:

Table-1 shows the treatment by simvastatin 20mg/d, telmisartan 40mg/d or their combination for 3 and 6 months. Significant reduction at ($p<0.05$) in hs-CRP levels as compared to pretreatment values. After treatment with simvastatin, telmisartan or combination of both for 3 and 6 months, the values of hs-CRP were significantly lower as compared to that of control group of patients at the same time course. Patients treated with telmisartan and those treated with combination of both simvastatin and telmisartan showed a significant decline in hs-CRP values after 6 months treatment as compared to the 3 months period in the same groups.

Groups	Number of subjects	hs-CRP (mg/l) ± SD		
		pretreatment	3months	6months
Normal	20	1.78 ± 0.14	1.71 ± 0.14	1.74 ± 0.14
Control	20	13.16 ± 0.61*	14.67 ± 0.8 *	15.24 ± 0.69 *a
Simvastatin	20	15.7 ± 0.82 *b	10.26 ± 1.2 *ab	7.27 ± 0.98 *ab
Telmisartan	20	15.75 ± 0.59 *	8.54 ± 0.9 *ab	5.01± 0.67 *abc
Simvastatin + Telmisartan	20	16.6 ± 0.69 *b	7.57± 0.95 *ab	3.23 ± 0.35 *abcde

Table-1: Effect of treatment with Simvastatin 20mg/d, telmisartan 40mg/d and their combination on **hs-CRP** in patients with mild to moderate COPD, untreated group of COPD patients (control) after 3, 6 months of treatment, and normal healthy individuals.

Values expressed as mean ± standard error of mean.

***** Significantly different ($p<0.05$) as compared with normal values.

a Significantly different ($p<0.05$) as compared with pretreatment values.

b Significantly different ($p<0.05$) as compared with control values.

c Significantly different ($p<0.05$) as compared between 3 and 6 months values.

d Significantly different ($p<0.05$) as compared with simvastatin group of values.

e Significantly different ($p<0.05$) as compared telmisartan and the combination group of values.

Table-2 shows the VCAM-1 levels in patients treated with simvastatin 20mg/d, telmisartan 40mg/d and those treated with combination of both. Significant reduction ($p<0.05$) in VCAM-1 values after 3 and 6 months treatment as compared to that of pretreatment values**.** Meanwhile, after 3 and 6 months treatment with simvastatin, telmisartan and combination of both, there was a significant decrease in VCAM-1 values from that of control group of patients at the same time course.

Groups	Number of subjects	VCAM-1 (ng/ml) ± SD		
		pretreatment	3months	6months
Normal	20	1.13 ± 0.06	1.08 ± 0.05	1.11 ± 0.06
Control	20	5.47 ± 0.44 *	5.99 ± 0.33 *	5.95 ± 0.33 *
Simvastatin	20	4.89 ± 0.15 *	3.43 ± 0.3 *ab	3.0 ± 0.25 *ab
Telmisartan	20	4.51 ± 0.15 *	3.19 ± 0.19 *ab	2.87 ± 0.17 *ab
Simvastatin + Telmisartan	20	4.68 ± 0.16 *	3.12 ± 0.32 *ab	2.54 ± 0.18 *ab

Table-2: Effect of treatment with Simvastatin 20mg/d, telmisartan 40mg/d and their combination on **VCAM-1** in patients with mild to moderate COPD, untreated group of COPD patients (control) after 3, 6 months of treatment, and normal healthy individuals.

Values expressed as mean ± standard error of mean.

***** Significantly different ($p<0.05$) as compared with normal values.

a Significantly different ($p<0.05$) as compared with pretreatment values.

b Significantly different ($p<0.05$) as compared with control values.

Table-3, represents Total Serum Cholesterol, the data showed that pretreatment values of total serum cholesterol in all patients of the study groups were significantly higher ($p<0.05$) as compared to those of normal group of healthy individuals. However, after 3 and 6 months of treatment with simvastatin 20mg/d, the data showed a significant decrease in total serum cholesterol as compared to the pretreatment values. The same was true for patients treated with telmisartan 40mg/d and those treated with combination of both simvastatin and telmisartan where, in these patients, there was a significant decrease in total serum cholesterol values after 3 and 6 months treatment as compared to that of pretreatment values and as compared to that of control group of patients at the same time courses.

Groups	Number of subjects	Total serum cholesterol (mg/dl) ± SD		
		pretreatment	3months	6months
Normal	20	169.87 ± 3.37	162.37 ± 3.17	165.7 ± 3.12
Control	20	197.49 ± 2.89 *	196.75 ± 2.23 *	196 ± 2.41 *
Simvastatin	20	195.9 ± 2.38 *	172.71 ± 3.31 ab	165.06 ± 3.23 ab
Telmisartan	20	194.14 ± 3.48 *	186.49 ± 3.2 *ad	182.96 ± 3.44*abd
Simvastatin + Telmisartan	20	192.91 ± 2.61 *	176.02 ± 3.08*abe	160.19 ± 2.6 abce

Table-3: Effect of treatment with Simvastatin 20mg/d, telmisartan 40mg/d and their combination on **total serum cholesterol** in patients with mild to moderate COPD, untreated group of COPD patients (control) after 3, 6 months of treatment, and normal healthy individuals.

Values expressed as mean ± standard error of mean.

***** Significantly different ($p<0.05$) as compared with normal values.

a Significantly different ($p<0.05$) as compared with pretreatment values.

b Significantly different ($p<0.05$) as compared with control values.

d Significantly different ($p<0.05$) as compared with simvastatin group of values.

e Significantly different ($p<0.05$) as compared telmisartan and the combination group of values.

The data in table-4 represents LDL-c values, in patients treated with simvastatin 20mg/d, telmisartan 40mg/d and those treated with combination of both, showed a significant decrease ($p<0.05$) in LDL-c values as compared to that of pretreatment values and to that of control group of patients at the same time periods.

Groups	Number of subjects	LDL-c (mg/dl) ± SD		
		pretreatment	3months	6months
Normal	20	89.5 ± 0,83	85.83 ± 0,68	87.55 ± 0,75
Control	20	118.09 ± 1.84 *	117.61 ± 1.82 *	116.63 ± 1.57 *
Simvastatin	20	116.92 ± 1.5 *	93.56 ± 1.6 *ab	85.91 ± 1.43 abc
Telmisartan	20	115.47 ± 1.39 *	107.47 ± 1.71 *abd	103.08 ± 1.3 *abd
Simvastatin + Telmisartan	20	114.31 ± 1.78 *	97.45 ± 2.00*abe	82.58 ± 1.24*abce

Table-4: Effect of treatment with Simvastatin 20mg/d, telmisartan 40mg/d and their combination on **LDL-c** in patients with mild to moderate COPD, untreated group of COPD patients (control) after 3, 6 months of treatment, and normal healthy individuals.

Values expressed as mean ± standard error of mean.

***** Significantly different ($p<0.05$) as compared with normal values.

a Significantly different ($p<0.05$) as compared with pretreatment values.

b Significantly different ($p<0.05$) as compared with control values.

c Significantly different ($p<0.05$) as compared between 3 and 6 months values.

d Significantly different ($p<0.05$) as compared with simvastatin group of values.

e Significantly different ($p<0.05$) as compared telmisartan and the combination group of values.

Table-5, the data showed HDL-c level that after 6 months treatment with simvastatin 20mg/d, there was a significant increase ($p<0.05$) in HDL-c values as compared to that of pretreatment values. Meanwhile, patients treated with combination of both simvastatin 20mg/d and telmisartan 40mg/d for 6 months showed a significant increase in HDL-c values as compared to pretreatment values and to that of control group of patients at the same time course.

Groups	Number of subjects	HDL-c (mg/dl) ± SD		
		pretreatment	3months	6months
Normal	20	47.67 ± 0,44	46.13 ± 0,33	47.09 ± 0,37
Control	20	46.47 ± 0.44	46.37 ± 0,49	46.49 ± 0.5
Simvastatin	20	46.36 ± 0.48	47.31 ± 0.54	47.86 ± 0.46 a
Telmisartan	20	46.96 ± 0.64	46.84 ± 0.59	47.51 ± 0.53
Simvastatin + Telmisartan	20	46.67 ± 0.46	47.63 ± 0.47	48.21 ± 0.41 ab

Table-5: Effect of treatment with Simvastatin 20mg/d, telmisartan 40mg/d and their combination on **HDL-c** in patients with mild to moderate COPD, untreated group of COPD patients (control) after 3, 6 months of treatment, and normal healthy individuals.

Values expressed as mean ± standard error of mean.

a Significantly different ($p<0.05$) as compared with pretreatment values.

b Significantly different ($p<0.05$) as compared with control values.

Table-6, shows LDL/HDL Ratio, in patients treated with simvastatin 20mg/d, telmisartan 40mg/d and those treated with combination of both for 3 and 6 months showed a significant reduction ($p<0.05$) in LDL/HDL Ratio from that of pretreatment values and from that of control group of patients at the same time periods. In the group of patients treated with telmisartan 40mg/d for 3 and 6 months, there was a significant change in LDL/HDL Ratio as compared to that of simvastatin group.

Groups	Number of subjects	LDL/HDL Ratio ± SD		
		pretreatment	3months	6months
Normal	20	1.87 ± 0,03	1.84 ± 0,05	1.89 ± 0,04
Control	20	2.55 ± 0.05 *	2.54 ± 0,04 *	2.51 ± 0.04 *
Simvastatin	20	2.53 ± 0.04 *	1.98 ± 0.04 *ab	1.8 ± 0.04 abc
Telmisartan	20	2.48 ± 0.05 *	2.3 ± 0.05 *abd	2.17 ± 0.04 *abd
Simvastatin + Telmisartan	20	2.45 ± 0.04 *	2.05 ± 0.04 *abe	1.7 ± 0.03*abcde

Table-6: Effect of treatment with Simvastatin 20mg/d, telmisartan 40mg/d and their combination on **LDL/HDL Ratio** in patients with mild to moderate COPD, untreated group of COPD patients (control) after 3, 6 months of treatment, and normal healthy individuals.

Values expressed as mean ± standard error of mean.

***** Significantly different ($p<0.05$) as compared with normal values.

a Significantly different ($p<0.05$) as compared with pretreatment values.

b Significantly different ($p<0.05$) as compared with control values.

c Significantly different ($p<0.05$) as compared between 3 and 6 months values.

d Significantly different ($p<0.05$) as compared with simvastatin group of values.

e Significantly different ($p<0.05$) as compared telmisartan and the combination group of values.

Discussion:

In this study, simvastatin 20mg/d showed a powerful effect on reducing cardiovascular risk in patients with COPD. Table-1, where simvastatin treatment for 3 and 6 months was accompanied by significant lowering of serum hs-CRP levels from their baseline values. So such effect could reduce the opportunity and the probability of atherosclerotic plaques formation, the major pathology that end with ischemic heart diseases, like myocardial infarction and stroke. In humans, serum levels of C-reactive protein predict vascular disease, implying that low-level inflammation accelerates atherosclerosis. The anti-inflammatory properties of statins may thus contribute to the observed effects on coronary heart disease [15]. Recent studies suggest that hs-CRP is both a marker of inflammation and a factor in the pathogenesis of atherosclerosis, in part by activating endothelial cells and coronary artery smooth muscle cells. Statins decrease hs-CRP levels, suggesting that statin treatment potentially could be an

anti-inflammatory in addition. This decrease in hs-CRP by statins has in some studies been reported to be independent of their effects on LDL cholesterol [16,17].

In fact, a recent study demonstrated that replacement of valsartan with telmisartan reduced serum highly sensitive C-reactive protein and increased serum adiponectin [18]. In addition to their beneficial effects on lowering blood pressure, angiotensin receptor blockers (ARBs) have anti-atherogenic effects by blocking angiotensin II, which promotes oxidative stress, inflammation, vasoconstriction, and thrombosis [19, 20]. After 3 and 6 months treatment with simvastatin, telmisartan and their combination, there was a significant decrease in VCAM-1 values from that of control group of patients at the same time course. Vascular cell adhesion molecule (VCAM-1) was related strongly to vascular comorbidities in COPD patients like atherosclerosis as shown in some recent studies. Therefore, the ability of simvastatin and telmisartan used in this study to reduce significantly this CV risk marker indicates the cardioprotective properties of these drugs (table-2). Upregulation of VCAM1 may indicate the importance of vascular co morbidities in COPD [21]. Telmisartan modulates pleiotropically TNF-α induced VCAM-1 expression and oxidative damage in vascular endothelium, possibly by acting as a hydroxyl radical scavenger. Those anti-inflammatory and antioxidant properties may contribute to the therapeutic effect, although the applicability of these data to the clinical situations has to be verified [22].

In TNFα-stimulated human umbilical vein endothelial cells (HUVEC), simvastatin decreased VCAM-1 and intercellular adhesion molecule-1 (ICAM-1). These effects were associated with reduction of adherence of monocytes and lymphocytes to HUVEC [23].

Lipid profile plays an important role in cardiovascular risk assessment. One of the major risk factors for the development of cardiovascular disease is dyslipidemia, which may be primary or associated with hypertension, diabetes mellitus and obesity [24]. Therefore, any amelioration of these risk factors can reduce the CV risk in COPD patients (which is high in the group of patients studied). This was demonstrated in this work which indicate the significant reduction in these markers as shown in tables (3, 4, 5, 6). It has been demonstrated that, with particular regard to subjects at high risk, the lower LDL-cholesterol levels, the lower the incidence of cardiovascular outcomes [25, 26]. Evidence indicates that the beneficial effects of statins can be attributed to their lipid-lowering ability as well as to additional benefits. The so-called pleiotropic effects on low grade inflammation status have been described in subsets of subjects with different cardiovascular profiles [27]. Telmisartan has been shown to improve plasma total cholesterol and low-density lipoprotein (LDL) cholesterol compared with nifedipine gastrointestinal therapeutic system in patients with type 2 diabetes and mild hypertension [28].

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