ASSESSMENT OF CARDIOVASCULAR RISK FACTORS (CRP, INSULIN SENSITIVITY & LIPID PROFIL) IN RHEUMATOID AND OSTEOARTHRITIS

Mohammad Rushdy Al-Mesry*, Essam Tawfiq Attwa and Hisham Mohammad Omar**

Rheumatology & Rehabilitation and Clinical Pathology*, Departments, Zagazig University Faculty of Medicine and Internal Medicine Department**, Cairo University Faculty of Medicine

KEY WORDS: CARDIOVASCULAR RISK FACTORS IN RA, OA.

ABSTRACT

Hypothesis: The incidence of coronary heart diseases (CHD) in RA patients is nearly twice its incidence in OA patients. Also, RA patients experience four fold increases in cardiovascular events. Furthermore, the mortality rate from CHD increased by about two folds when compared to the general population. The exact interacting mechanisms of these findings are not yet clear especially that dyslipidemia and coronary vasculitis do not account for these respective findings. In fact, a chronic inflammatory state evidenced by elevated CRP levels can result in significant damages to the arterial system.

Aim of Work: This study was designed to evaluate the extent of cardiovascular risk factors in RA patients and the role of inflammatory activity in their incidence via its comparison comprehensively in OA patients as a control group.

Subjects and Methods: Sixty patients were included in this study. They were divided into two groups. The first group consisted of thirty patients (24 females and 6 males) fulfilling the criteria of the American College of Rheumatology for the classification of RA. The mean age and disease duration for these patients were 51.6 ± 3.5 and 8.2 ± 2.1 years respectively. The second group included thirty age-matched (mean 53.2 ± 2.8), sex-matched (25 women and 5 men) consecutive OA patients. All patients were selected from the Outpatient Clinics of Dr. Erfan General Hospitals, Kingdom of Saudi Arabia.
Venous blood samples were obtained after a 12 overnight fasting. Plasma was assayed for total cholesterol (TC), HDL-C, LDL-C, triglycerides and plasma glucose. Lipid profile was done using the enzymatic method. Also; determination of the ultra sensitive CRP (Tina'quant CRP latex enhanced immunoturbidimetric assay) was done. Fasting serum insulin was measured using radio-immuno-assay (RIA). Insulin sensitivity (IS) was estimated by the quantitative insulin sensitivity check index (QUICKI).

**Results:** The study showed some cardiovascular risk factors that displayed no significant differences between RA and OA patients with p value > 0.05. These factors included frequency of hypertension, family history for coronary heart disease, estrogen use, BMI and waist circumference. Also, both groups showed no significant differences in TC (216 ± 21 in RA & 222 ± 18 mg/dl in OA patients), LDL-C (133 ± 11 in RA & 136 ± 9 mg/dl in OA patients) and triglycerides (163 ± 28 in RA & 158 ±24.5 mg/dl in OA patients). There were no significant differences in the lipid profile values in glucocorticoid and non-glucocorticoid RA users with p value > 0.05. HDL-C levels decreased below normal in 13 RA patients while decreased values were detected in 5 OA patients (p< 0.001). The IS was below normal in 12 RA patients while it decreased in 8 OA patients (p> 0.05).

**Conclusion:** The prevalence of cardiovascular risk factors in RA patients as a part of the inflammatory arthritis is greater than that noticed in OA patients. These include the acute phase response evidenced by elevated CRP, decreased IS and HDL-C levels.

**INTRODUCTION**

Rheumatoid arthritis (RA) patients experience a markedly increased frequency of cardiovascular disease (CVD) as compared with osteoarthritis (OA) patients and the general population. This high incidence of arteriosclerotic CVD is considered one of the major causes of death in RA patients. The exact mechanisms of this high incidence are not clear especially that it is not explained by dyslipidemias and coronary vasculitis.

Metabolic syndrome is a cluster of cardiovascular risk factors that include obesity, high blood pressure, low high density lipoprotein-cholesterol (HDL-C), high triglycerides and insulin resistance which is considered the key defect in this syndrome. These features tend to appear in
some individuals (10-20%) and increase the risk for type II diabetes and CVD\(^3\). Searching for these metabolic defects together with determination of the low density lipoprotein-cholesterol (LDL-C) is considered the pivotal assessment of cardiovascular risk factors in the individual patient\(^4\).

C-reactive protein (CRP) is a 110 KDa non-specific acute phase protein produced by the liver in response to tissue injury, infection and inflammation and made up of five identical subunits\(^5\). CRP activates the classical pathway of complement and consequently affects a host defense function mediated at least in part through elimination of pathogens\(^6\). In addition, CRP promotes the clearance of apoptotic cells, an effect that likely contributes to homeostasis in systemic autoimmune diseases\(^7\).

Until recently, CRP is only routinely measured as a marker of inflammation in a variety of diseases as systemic autoimmune diseases like RA and ankylosing spondylitis, its level usually correlates with that of interleukin-6\(^8\). However, it has been a growing interest as regard the value of serum CRP determination in other medical illnesses where the inflammation is more subtle as in patients with circulatory problems. It has been found that, the higher the serum CRP levels, the greater the mortality risk in patients with stable or unstable angina\(^9\).

Research on CRP indicates that cholesterol-filled plaques in the blood vessels may not pose any real changes unless they are affected by inflammation, which weakens the plaques, making them more vulnerable to bursting or pinching off a clot that can block coronary vessels\(^10\). This means that, a chronic inflammatory state as evidenced by elevated CRP levels results in significant damage to the arterial system\(^11\).

In inflammatory arthritis (IA), LDL-C concentrations were found to be similar to its levels in age-matched, sex-matched and race-matched controls\(^12\). Moreover, insulin resistance has been previously reported in IA where it is associated with inflammation, obesity, low HDL-C and high triglycerides, which all reflect pathophysiological interactions\(^13\).

**Aim of Study:**

So, the aim of this study was to assess cardiovascular risk factors in RA patients (*as a part of inflammatory arthritis*) comprehensively with osteoarthritis (OA) patients, aiming to document the previous reports about increased incidence of cardiovascular risk factors in RA patients. Furthermore, it aims to study the clustering of cardiovascular risk factors in RA as described in the metabolic syndrome.
SUBJECTS AND METHODS

Sixty patients were included in this study. They were divided into two groups. The first group consisted of thirty patients (24 women and 6 men) meeting the criteria of the American College of Rheumatology for the classification of RA\textsuperscript{14}. The mean age and disease duration for these patients were $51.6 \pm 3.5$ and $8.2 \pm 2.1$ years respectively. The second group had included thirty age-matched (mean $53.2 \pm 2.8$), sex-matched (25 women and 5 men) consecutive OA patients\textsuperscript{15}. All patients were selected from the Outpatient Clinics of Dr. Erfan General Hospitals, Jeddah, Kingdom of Saudi Arabia.

Clinical assessment of the study patients included proper history taking particularly detailed family history of premature coronary heart disease in addition to history of full medications taken by the included patients at the time of the study.

Exclusion criteria included; intake of lipid lowering agents, cigarette smoking and alcohol consumption. Also, none of the patients were following any dietary advice at the time of the study. All the patients included showed no history of previous diagnosis of diabetes mellitus or intake of hypoglycemic medications. The patients were considered hypertensive with a blood pressure $> 140/90$ mmHg or were on antihypertensive agents (blood pressure measured on three separate occasions). Moreover, all patients were subjected to calculation of body mass index (BMI; kg/m$^2$) and measurement of the waist circumference (cm) at the umbilical level.

Venous blood samples were obtained after a 12 hour overnight fasting. Plasma was assayed for total cholesterol (TC), HDL-C, LDL-C, triglycerides and plasma glucose. Lipid profile was done using the enzymatic method. Also; determination of the ultra sensitive CRP (Tina'quant CRP latex enhanced immunoturbidimetric assay) was done. Fasting serum insulin was measured using radio-immuno-assay (RIA). Insulin sensitivity (IS) was estimated by the quantitative insulin sensitivity check index (QUICKI) through using the following formula $1/log$ insulin ($\mu$U/ml) x log glucose (mg/dl)$^{16}$. A threshold QUICKI value of 0.337 was used for determination of decreased IS$^{12}$.

RESULTS

The clustering of metabolic syndrome features was evaluated in this study using the paradigm proposed by Timar et al. (2000)$^3$ in which decreased IS was associated with obesity, inflammation, low HDL-C and
high triglycerides. The medications taken by the study patients are presented in table (1) & Fig. (1). All results were expressed as a mean ± SD.

Table (1): Medications taken by RA and OA patients.

<table>
<thead>
<tr>
<th>Medication</th>
<th>RA (n=30)</th>
<th>OA (n=30)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antihypertensive</td>
<td>15 (50%)</td>
<td>12 (40%)</td>
</tr>
<tr>
<td>Estrogen</td>
<td>3 (10%)</td>
<td>6 (20%)</td>
</tr>
<tr>
<td>Prednisone</td>
<td>6 (20%)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>DMARDs</td>
<td>15 (50%)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>NSAIDs</td>
<td>18 (60%)</td>
<td>21 (70%)</td>
</tr>
<tr>
<td>Glucosamine</td>
<td>0 (0)</td>
<td>3 (10%)</td>
</tr>
</tbody>
</table>

- Data were presented as n (%)
- DMARDs, disease modifying agents, including methotrexate (10), sulfasalazine (2), chloroquine (2), azathioprine (2), all given in combination or as monotherapy.

The study showed some cardiovascular risk factors that displayed no significant differences between RA and OA patients with p value > 0.05. These factors included frequency of hypertension, family history for coronary heart disease, estrogen use, BMI and waist circumference. Also, both groups showed no significant differences in TC (216 ± 21 in RA & 222
Cardiovascular Risk Factors in RA & OA

± 18 mg/dl in OA patients), LDL-C (133 ± 11 in RA & 136 ± 9 mg/dl in OA patients) and triglycerides (163 ± 28 in RA & 158 ± 24.5 mg/dl in OA patients). There were no significant differences in the lipid profile values in glucocorticoid and non-glucocorticoid RA users with p value > 0.05. All similar risk factors were summarized in table (2) & Fig. (2).

Table (2): Cardiovascular risk factors that was insignificantly different between RA and OA patients (p > 0.05):

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>RA (n=30)</th>
<th>OA ( n=30)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incidence of hypertension</td>
<td>15 (50%)</td>
<td>12 (40%)</td>
</tr>
<tr>
<td>Family history of CHD</td>
<td>6 (20%)</td>
<td>5 (17%)</td>
</tr>
<tr>
<td>Estrogen use</td>
<td>3 (10%)</td>
<td>2 (7%)</td>
</tr>
<tr>
<td>Body mass index(kg/m²)</td>
<td>24.9 (23.8-26.6)</td>
<td>26 (24.9-27.6)</td>
</tr>
<tr>
<td>Waist circumference(cm)</td>
<td>94.1 (88.2-97.9)</td>
<td>92.1 (88.2-96.4)</td>
</tr>
<tr>
<td>Total cholesterol (mg/dl)</td>
<td>216 ± 21</td>
<td>222 ± 18</td>
</tr>
<tr>
<td>LDL-C ( mg/dl)</td>
<td>133 ± 11</td>
<td>136 ± 9</td>
</tr>
<tr>
<td>Triglycerides (mg/dl)</td>
<td>163 ± 28</td>
<td>158 ± 24.5</td>
</tr>
</tbody>
</table>

- Data were presented as n (%) or mean ± SD.
- CHD, Coronary heart disease.
- LDL-C, low density lipoprotein cholesterol.
HDL-C was 44.5 ± 4.8 mg/dl in RA patients and 51.8 ± 2.3 mg/dl in OA patients. HDL-C levels decreased below normal in 13 RA patients while decreased values were detected in 5 OA patients \((p< 0.001)\). The insulin sensitivity detected by QUICKI was 0.342 ± 0.023 in RA patients, while its value in OA patients was 0.357 ± 0.027. The IS was below normal in 12 RA patients while it decreased in 8 OA patients \((p> 0.05)\).

The acute phase response was evaluated by measurement of the ultrasensitive CRP. Its level in RA patients was 16.5 ± 4.8 mg/L and was 2.2 ± 0.5 mg/L in OA patients.16 RA patients had CRP values ≥ 8mg/L, among them 12 were hypertensive as compared with only 3 hypertensive RA patients with a CRP levels < 8 mg/L \((p<0.05)\). These findings suggest that a high CRP levels was associated with the presence of hypertension. Only 2 OA patients had CRP levels ≥ 8 mg/L.

The acute phase response evidenced by increased CRP levels in RA patients was associated with decrease IS \((p = 0.015)\) and low HDL-C \((p = 0.033)\). After controlling CRP, the QUICKI values were insignificantly different \((p= 0.06)\) but HDL-C remained lower in RA patients when compared to OA patients \((p = 0.03)\). On the other hand, QUICKI was not significantly associated with HDL-C and triglycerides in OA patients.

Table (3): Correlation analysis between CRP and cardiovascular risk factors (HDL-C, IS) in RA patients.

<table>
<thead>
<tr>
<th>Variable</th>
<th>C-reactive protein</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>During disease activity</td>
<td></td>
<td>After activity control</td>
</tr>
<tr>
<td></td>
<td>p value</td>
<td>Significance</td>
<td>p value</td>
</tr>
<tr>
<td>Insulin sensitivity</td>
<td>0.015</td>
<td>S</td>
<td>0.06</td>
</tr>
<tr>
<td>HDL-C</td>
<td>0.033</td>
<td>S</td>
<td>0.03</td>
</tr>
</tbody>
</table>

- HDL-C high density lipoprotein –cholesterol
- S, significant
- NS, non-significant.

**DISCUSSION**

The incidence of CHD in RA patients is nearly twice its incidence in OA patients. Also, RA patients experience four fold increases in cardiovascular events when compared to the general population\(^1^7\). Furthermore, the mortality rate from CHD increased by about two folds when compared to the general population\(^1^8\). The exact interacting mechanisms of these findings are not yet clear especially that dyslipidemia and coronary vasculitis do not account for these respective findings\(^2\).

The production of CRP is considered an essential component of the inflammatory process and its measurement correlates with the degree of
inflammatory activities. In fact, a chronic inflammatory state evidenced by elevated CRP levels can result in significant damage to the arterial system. So, this study was designed to evaluate the extent of cardiovascular risk factors in RA patients and the role of inflammatory activity in their incidence via its comparison comprehensively in OA patients as a control group.

This study showed as expected that CRP levels were higher in RA patients as compared to OA patients. Now it is known that CRP contributes to atherosclerosis through its localization in the atheromatous plaques and stimulation of macrophages to produce tissue factor, an important procoagulant found in atheromatous plaques. So, this finding confirms the previous suggestion that inflammatory acute phase response evidenced by elevated CRP is implicated in the pathogenesis of CHD in RA patients. Also, it can explain the increased incidence of hypertension encountered in RA patients included in this study.

Furthermore, IS and HDL-C concentrations were lower in RA patients in comparison to OA patients. This lower level was significantly associated with the higher CRP levels elicited in RA patients. These data which are concomitant to previous findings reported by Dessein et al. (2002), confirm the suggestion that RA may selects for subjects with low HDL-C and that RA and CHD may share a common predisposition. So, genetic linkage studies may be indicated to confirm whether HDL-C concentrations are intrinsically low in RA patients.

Although OA can be associated with insulin resistance and dyslipidemia, both IS and HDL-C were still significantly lower in RA patients as compared with OA patients. It is well known that psychosocial stresses and other environmental factors related abnormalities in cortisol, sex steroids and growth hormone secretion can be related to the predisposition of insulin resistance and other metabolic features, so, the role of these stressors in decreased IS which is a pivotal mechanism in the metabolic syndrome should be considered. Also, it was interesting that patients on glucocorticoids and/or DMARDs experienced no significant differences in IS and HDL-C when compared to the non-users. For that reason, exclusion of patients on these agents may be indicated in further studies especially that, both glucocorticoids and DMARDs were shown to attenuate insulin resistance in inflammatory arthritis, an effect which was related to acute phase response suppression.

Conclusion

The prevalence of cardiovascular risk factors in RA patients as a part of inflammatory arthritis is greater than that noticed in OA patients. These
include the acute phase response evidenced by elevated CRP, decreased IS and HDL-C levels. The interaction of these risk factors in the pathogenesis of enhanced atherosclerosis in RA patients requires further evaluation. Meanwhile, control of inflammatory activity in these patients will significantly decrease the damage of arterial system so reduces the incidence of this fatal risk.

REFERENCES


331
Cardiovascular Risk Factors in RA & OA


دراسة لتقييم عوامل الخطورة المحتملة لأمراض القلب والأوعية الدموية (البروتين النشط، حساسية الأنسولين - معدل وجود الدهون بالدم) في مجموعه من المرضى المصابين بالرئيسيين المفصلي أو الفص الامعائي

محمد رشدي المصري

**عصب توفيق عطوة هشام محمد عمر**

قسم الروماتيزم والتهابات والكيمياء الاكسيميكية - كلية الطب جامعة الزقازيق وقسم الأمراض الداخلية - كلية الطب جامعة القاهرة

المقدمة:

إن معدل وقوع أمراض الشريان التاجي لدى المرضى المصابون بالرئيسيين المفصلي يعانون من اضطرابات القلب يمكن تقريباً ضعيف ما يحدث لدى المرضى الذين يعانون من اضطرابات القلب، وفي معدل حديث أمراض الشريان التاجي يكون العامل المحتمل يتعرضون لحوالي أربعة أضعاف زيادة في معدل حديث أمراض الشريان التاجي والوعائي الدموي، وأيضاً يجب أن يتسنى حالات اسكتة أمراض الشريان التاجي تزيد بقدر كبير من الوفيات مقارنة بما يحدث لدى الناس العاديين. وحتى الآن لم يتم تعرف على كيفية حدوث هذه الملاحظات و خاصة أن أسباب أمراض الشريان التاجي لم تكن هي المسألة الرئيسية عن هذه الأحداث، في المقابلة وجد أن حالات الالتهاب المزمن تؤدي إلى زيادة في معدل ارتفاع نسبة البروتين النشط بالدم، وقد تؤدي إلى تدمير الجهاز الشرياني.

الهدف من البحث:

و على هذا كان هدف هذه الدراسة هو تقييم مدى تأثير عوامل الخطورة التي قد تؤدي إلى زيادة معدل حديث أمراض القلب والأوعية الدموية، وكذلك دور الذين قد يلعبه الالتهاب المزمن لدى المرضى المصابون بالرئيسيين المفصلي، مقارنة بما قد يحدث لدى مجموعة مصابا بمرض الفص الامعائي.

مواد و طرق البحث:

اشتملت هذه الدراسة على ستون مريضاً تم تقسيمهم إلى مجموعتين:

المجموعة الأولى: و كانت مكونة من ثلاثين مريضا مصابا بالرئيسيين المفصلي (24 أفراد) كان توزع متوسط عمرهم 51.6 عاماً ومتوسط وجود المريض لديه هو 8.2 أعوام. وقد تم اختيارهم بعد استيفائهم الشروط الموضوعة من قبل الكلية الأمريكية لأمراض الروماتيزم عام 1988.

المجموعة الثانية: وقد اشتملت على ثلاثين مريضاً مصاباً بمرض الفص الامعائي (25 أفراد) كان توزع متوسط عمرهم 53.2 عاماً، و كذلك تم اختيارهم بعد استيفائهم الشروط الموضوعة من قبل الكلية الأمريكية لأمراض الروماتيزم منشور عام 1997م. والخاصة بالتقييس والتشخيص حالات الفص الامعائي.

قد تم حصر جميع الحالات التي شملت هذه الدراسة فحسباً كيميائياً، وكذلك تم جمع عينات دم ورئيسي بعد 12 ساعة صيام، ثم تم عمل الفحوصات المعملية على جميع المرضى الذين شملتهم الدراسة:

- قياس معدل الكوليسترول الكلي.

333
- قياس معدل الكوليسترول عالي الكثافة.
- قياس معدل الكوليسترول منخفض الكثافة.
- قياس معدل الدهون الثلاثية.
- قياس معدل الجلوكوز بالبلازما.
- قياس معدل وجود البروتينات النشط بالبلازما.
- قياس معدل الانسولين الصائم.
- حساب درجة حساسية الانسولين.

نتائج البحث:

أظهرت هذه الدراسة أن بعض عوامل الخطورة المسببة لأمراض القلب والأوعية الدموية لم تظهر فروق ذات دلاله إحصائية بين مرضى المجموعة، وهذه العوامل تشمل:
- معدل ارتفاع ضغط الدم الشرياني.
- التاريخ العائلي لوجود انتشار أمراض الشريان التاجي.
- استخدام الاستروجين كعلاج.
- معدل وزن الجسم.
- مقياس الوسط عند مستوى السرط.
- وأيضاً لم يوجد أي فرق ذات دلالة إحصائية بين أفراد المجموعة فيما يتعلق بمعدل الكوليسترول الكلي ومعدل الكوليسترول منخفض الكثافة وكذلك معدل الدهون الثلاثية. بالنسبة للمريض الرئيسي المعطى لم يتضح وجود أي فروق ذات دلاله إحصائية فيما يتعلق بمعدل وجود الدهون بالدم بين الذين يستخدمون أي من مثبتات الكورتيزون في العلاج أو لا يستخدمونه.
- وقد وجد تندي وجود الكوليسترول عالي الكثافة في 13 مريضاً من المجموعة الأولى و 5 مرضى من المجموعة الثانية وكان هذا التندي ذات دلاله إحصائية. و كانت درجة حساسية الانسولين أقل من الطبيعي في 12 مريضاً من المجموعة الأولى و 8 مرضى من المجموعة الثانية وهذا الانخفاض كانت له دلالات إحصائية.

الاستنتاج:

استنتجت هذه الدراسة وجود زيادة في عوامل الخطورة المؤدية إلى زيادة أمراض القلب والأوعية الدموية لدى المرضى المصابين الرئيسي المعطى أكثر مما وجدت هذه الدراسات السابقة. و أن تضح أن أهم عوامل الخطورة كان زيادة معدل الدهون النشط والقدرة حساسية الانسولين و تدفق معدل الكوليسترول عالي الكثافة.