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The Role of Adipose Tissue In Rheumatoid Arthritis

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الملخص

هدف الدراسة: تقييم معدل الإصابة بالسمنة في مجموعة من المرضى السعوديين المصابين بالتهاب المفاصل الروماتويدي المبكر (RA)، وتحديد تركيز الأديبوسيتوكينات (أديبونيكتين، ليبتين) وعلاقتها بمؤشرات نشاط RA.**منهجية البحث**. شملت الدراسة ٤٧ مريضًا مصابًا بالتهاب المفاصل الروماتويدي المبكر والذين استوفوا معايير ACR/EULAR (٢٠١٩) ولم يتلقوا أدوية مضادة للروماتيزم معدلة للمرض وجلوكوكورتيكويدات. **النتائج:** لم يختلف مرضى التهاب المفاصل الروماتويدي عن مجموعة المتبرعين من حيث متوسط مؤشر كتلة الجسم، ولكن كان لديهم محيط خصر أكبر ونسبة الخصر إلى الورك ($p = 0.003$ و $p = 0.04$). السمنة حسب معايير NCEP/ATPIII تم تشخيصها في ٦٣,٨% من مرضى التهاب المفاصل الروماتويدي وفي ٤٠% فقط من المتبرعين الأصحاء ($p = 0.04$)، لم يتم الكشف عن أي اختلافات في تواتر السمنة بين المجموعتين ($p = 0.9$). كان مستوى الأديبونيكتين في مرضى التهاب المفاصل الروماتويدي أعلى ($p = 0.04$)، وكان اللبتين ونسبة L/A أقل ($p = 0.02$ و٠,٠٠٣ على التوالي) من المجموعة الضابطة. الارتباط المباشر بين معدل ترسيب كرات الدم الحمراء وتركيز اللبتين

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ونسبة اللبتين إلى الدم والارتباط العكسي مع مستوى الأديبونيكتين (قيمة P < 0.05 لجميع المؤشرات). النتائج تشير البيانات التي تم الحصول عليها إلى ارتفاع معدل انتشار السمنة لدى مرضى التهاب المفاصل الروماتويدي المبكر وعلاقتها بالالتهاب. وعلى النقيض من عامة السكان، كانت السمنة في بداية التهاب المفاصل الروماتويدي مصحوبة بزيادة في تركيز الأديبونيكتين في المصل وانخفاض في مستويات اللبتين ومقاومة الأنسولين بشكل عام.

الكلمات المفتاحية: التهاب المفاصل الروماتويدي؛ السمنة؛ الأنسولين؛ الأديبونيكتين؛ اللبتين.

The Role of Adipose Tissue In Rheumatoid Arthritis

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Abstract

Objective: To assess the incidence of obesity in a group of Saudi patients with early rheumatoid arthritis (RA), and to determine the concentration of adipocytokines (adiponectin, leptin) and their relationship with RA activity indicators.

Methodology: The study included 47 patients with early RA who met the ACR/EULAR criteria (2019) and were not receiving disease-modifying antirheumatic drugs and glucocorticoids. **Results:** RA patients did not differ from the donor group in terms of mean BMI, but had a larger waist circumference and waist-to-hip ratio (p = 0.003 and p = 0.04). Obesity according to NCEP/ATPIII criteria was diagnosed in 63.8% of RA patients and only in 40% of healthy donors (p = 0.04), no differences in the frequency of obesity were detected between the two groups (p = 0.9). The level of adiponectin in RA patients was higher (p = 0.04), and leptin and L/A ratio were lower (p = 0.02 and 0.003, respectively) than in the control group.

Direct correlation between erythrocyte sedimentation rate and leptin concentration and leptin-to-blood ratio and inverse correlation with adiponectin level (P < 0.05 for all indicators).**Conclusion:** The obtained data indicate a high prevalence of obesity in early RA patients and its relationship with inflammation. In contrast to the general population, obesity at the onset of RA was accompanied by an increase in serum

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adiponectin concentration, a decrease in leptin levels and overall insulin resistance.
Keywords: Rheumatoid arthritis; obesity; insulin; adiponectin; leptin.

Introduction

One of the most common autoimmune diseases rheumatic diseases - rheumatoid arthritis (RA) is characterized by chronic erosive arthritis (synovitis) and systemic inflammatory lesions of internal organs [1].

Along with the study pathogenesis, search for new diagnostic possibilities and pharmacotherapy of RA is currently becoming more and more a number of studies are devoted to the study of cardiovascular diseases (CVD), the risk of developing which in RA is similar to that in diabetes mellitus [2].

Atherosclerotic vascular disease and its complications in patients with RA are associated with the interaction three components: traditional risk factors for development of cardiovascular disease, inflammation and the drugs used to suppress it. Most patients with RA do not have one traditional risk factor, but a combination of them, which can be considered within the framework of metabolic syndrome (MS).

In recent years, among the classical components of MS, much attention from rheumatologists has been attracted by obesity. There are several main reasons for this prerequisites. Firstly, the idea of the typical RA patient as a person with a body mass deficit.

According to the Norfolk Registry [3], among patients with early RA (damage to two or more joints 25% of patients already had obesity (for 4 weeks or more). Secondly, the concept of rheumatoid arthritis appeared. hexia - a condition in which the mass decreases body is caused by hypo- and atrophy of muscle mass on against the background of stable or even increased content fat [4]. In this case, the body mass index (BMI) may not change or deviate slightly from the norm in any direction. Finally, adipose tissue, previously perceived used only as an energy depot and shock absorber for internal organs, began to be positioned as an important endocrine organ capable of producing not only a huge number of different pro- and anti-inflammatory cytokines, but also more than 50 hormonal factors, also called adipocytokines (ACC) [5]. The influence of two of them - adiponectin and leptin has been relatively well studied in patients with cardiovascular diseases, type 2 diabetes type and obesity,

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however, information about these ACCs at RAs are extremely limited and contradictory.

Objectives

The aim of our study is to assess the incidence of obesity in a saudi cohort of patients with early RA, to determine the concentration of ACC (adiponectin, leptin) and their relationship with RA activity indicators. According to the National Cholesterol Education Program's Adult Treatment Panel III (NCEP/ATP III), obesity was diagnosed as WC greater than 102 cm in men and greater than 88 cm in women [7], according to the criteria Scientific Society of Cardiologists - with WC more than 94 cm in men and more than 80 cm in women [8], according to the criteria WHO - with WC/OB more than 0.9 in men and more than 0.85 in women and/or BMI of 30 kg/m2 or more [9].

In addition, BMI was assessed according to the WHO classification: underweight was considered to be a BMI of less than 1,8.5 kg/m2 normal body weight - BMI from 18.5 to 24.9 kg/m2 , overweight - BMI from 25 to 29.9 kg/m2 , obesity - BMI 30 kg/m2 or more.

Statistical processing of the material was carried out using the SPSS26 program. The results are presented as median and interquartile range (Me [25%; 75%]. When comparing The Mann-Whitney test was used to compare two independent groups according to a quantitative characteristic, and qualitative indicators were compared in a contingency table with using the ÿ2 criterion . Correlation analysis was performed using the Spearman method. Differences were considered statistically significant at $p < 0.05$.

Methodology

The study included 47 patients (35 women and 12 men) with early RA who met the criteria. American College of Rheumatology (ACR) / European League Against Rheumatism (EULAR) 2010 [6], observed at the Some Specialist hospitals in Riyadh City Saudi Arabia kingdom. Average the age of the patients was 57 [47; 62] years, the duration disease - 7 [4; 8] months. All patients were positive for both antibodies to rheumatoid factor and blood serum, as well as antibodies to cyclic citrullinated peptide, had high RA activity (median DAS28 5.9 [5.3; 6.9] points), radiographic stage II and

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functional class II. The patients had not previously received disease-modifying anti-inflammatory drugs (DMARDs) or glucocorticoids.

The control group consisted of 30 healthy patients (23 women and 7 men) without rheumatic diseases, comparable in age to the main group.The concentration of C-reactive protein (CRP) and rheumatoid factor in the blood serum was measured by a highly sensitive immunonephelometric method on a BN Pro Spec analyzer (Siemens, Germany), antibodies to cyclic citrullinated According to the National Cholesterol Education Program's Adult Treatment Panel III (NCEP/ATP III), obesity was diagnosed as WC greater than 102 cm in men and greater than 88 cm in women [7], according to the criteria of the All Scientific Society of Cardiologists - with WC more than 94 cm in men and more than 80 cm in women [8], according to the criteria WHO - with WC/OB more than 0.9 in men and more than 0.85 in women and/or BMI of 30 kg/m2 or more [9].

In addition, BMI was assessed according to the WHO classification: underweight was considered to be a BMI of less than 1,8.5 kg/m2 peptide - by enzyme immunoassay using commercial kits Axis Shield Diagnostics (United Kingdom). The concentration of adiponectin and leptin was determined by ELISA (Human Adiponectin, Bio Vendor, Czech Republic). To assess the leptin/adiponectin (L/A) ratio was calculated to assess insulin resistance (IR).

The following anthropometric indicators were used in the work: waist circumference (WC), circumference hips (HB) and their ratio (HR/HB), BMI. According to the criteria normal body weight - BMI from 18.5 to 24.9 kg/m2,

overweight - BMI from 25 to 29.9 kg/m2 , obesity - BMI 30 kg/m2 or more.

Statistical processing of the material was carried out

using the SPSS26 program . The results are presented as median and interquartile range (Me [25%; 75%]. When comparing The Mann-Whitney test was used to compare two independent groups according to a quantitative characteristic, and qualitative indicators were compared in a contingency table with using the ÿ2 criterion . Correlation analysis was performed using the Spearman method. Differences were considered statistically significant at $p < 0.05$.

Results and discussion

RA patients did not differ from healthy donors in average BMI (26.4 [22.8; 31.5] and

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27.9 [25; 30.3] kg/m2 , p = 0.6), by the frequency of occurrence of excess body weight (31.9 and 46.7%, p = 0.2) and obesity (29.8 and 30%, p = 0.9), determined by this anthropometric indicator. At the same time, WC and the WC/OB ratio were higher in patients with RA than in healthy donors (102 [97; 111] and 88.6 [83; 96] cm, p = 0.003; 0.9 [0.8; 1.0] and 0.84 [0.8; 0.9], p = 0.04, respectively; (Table 1).

Table 1. Anthropometric indicators and the frequency of obesity in RA patients and healthy donors.

Indicator	RA patients (*n* = 47)	Healthy donors (*n* = 30)
Gender, female/male, *n* BMI,	35/12	23/7
kg/m2 (Me [25%; 75%]) BMI	26.4 [22.8; 31.5]	27.9 [25.0; 30.3]
gradations according to WHO, n (%):		
underweight (BMI < 18.5) normal weight	0	0
(BMI 18.5-24.9) overweight (BMI 25-29.9)	18 (38.3)	7 (23.3)
obesity (BMI ÿ 30)	15 (31.9)	14 (46.7)
	14 (29.8)	9 (30.0)
OT, cm (Me [25%; 75%]	102 [97; 111]*	88.6 [83; 96]
OT/OB (Me [25%;75%])	0.9 [0.8; 1.0]*	0.84 [0.8; 0.9]
Obesity, n (%):		
according to NCEP/ATPIII criteria	30 (63.8)*	12 (40.0)
according to VNOK criteria	35 (74.5)	22 (73.3)
according to WHO	31 (65.9)*	12 (40.0)

p = 0.005), and the inverse relationship with adiponectin levels (r = -0.30, p = 0.04). In different cohorts, the incidence of MS in RA varies from 19 to 55% [10]. According to our previously published [11], MS was found in 17.3% of patients with RA. Obesity is an integral part of MS, according to its The formation of RA is influenced by a sedentary lifestyle caused by functional disorders due to pain, inflammation and deformation of the joints, taking certain medications, and concomitant diseases. According to C. Crowson et al. [12] and D. Symmons et al. [13], obesity is a risk factor for the development of RA, however, in the work of T. Bartfai et al.

co-authors [14] did not observe such a dependence.To clarify the distribution of adipose tissue in the patient with RA not only instrumental methods are possible (computer or magnetic resonance tomography, ultrasound, densitometry), but

and simple anthropometric indicators (WC, WC/OB, BMI), the measurement of which

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does not require large logistical and time costs [4]. These indicators are included in all modifications of the MS criteria, in including the WHO, NCEP/ATPIII and GFCF criteria. In RA, the proportion of patients with overweight
and obesity reaches 63-68%, while underweight is much less common - only
1-13% of patients [3, 10]. In our study, BMI.

Abdominal obesity according to NCEP criteria/ATPIII was diagnosed in 30 (63.8%) patients with RA and only in 12 (40%) healthy donors (p = 0.04), according to WHO criteria in 31 (65.9%) and 12 (40%), respectively (p = 0.02). According to the criteria of the All-Saudi Society of Obesity, there were no statistically significant differences in the frequency of obesity between the groups. not detected (p = 0.9).

When assessing the impact of obesity on RA activity It turned out that the WC indicator correlated with the ESR (r = 0.36, p = 0.02) and CRP (r = 0.31, p = 0.04) indicators . An increase in BMI was associated not only with an increase in laboratory parameters: ESR (r = 0.46, p = 0.001), CRP (r = 0.38, p = 0.007), but also the DAS28 index (r = 0.40, p = 0.005).

Adiponectin levels were higher in RA patients (p = 0.04), and the leptin level and L/A ratio were lower (p = 0.02 and 0.003, respectively) than in healthy donors (Table 2). In RA, there was a dependence of leptin concentration and L/A ratio on BMI (r = 0.60, p = 0.0001 and r = 0.56, p = 0.0001) and WC (r = 0.51, p = 0.0003 and r = 0.44, p = 0.002, respectively). The level of adipocytes ponectin anthropometric parameters did not affect. A direct correlation of ESR with the concentration was noted leptin (r = 0.37, p = 0.01), L/A ratio (r = 0.4, 61.7% of patients had a BMI of 25 kg/m2 or
more, while the rest had a BMI of normal values. The distribution by BMI in healthy people turned out to be similar. Donors, which indicates that high prevalence of obesity in the population. When using different criteria for MS, abdominal obesity
Diagnosed in 63.8-74.5% of patients with RA and in 40-73.3% of those examined without rheumatic diseases. Frequency of obesity according to NCEP criteria/ ATPIII and WHO were in our work higher in RA, and according to the criteria of the All-Saudi Society of Cardiology did not differ from the group indicators
healthy donors.

Using instrumental methods, it was shown that in RA, there is a redistribution of fat mass in the body [15, 16]. Observed- its predominant accumulation is in

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Table 2. ACC levels in RA patients and healthy controls.

Indicator	RA patients (*n* = 47)	Healthy donors (*n* = 30)
Adiponectin, ng/ml (Me [25%; 75%])	21 [13; 52.3]*	9.2 [5.6; 12.2]
Leptin, ng/ml (Me [25%; 75%])	18 [7.8; 32]*	30.5 [19; 46.2]
L/A (Me [25%; 75%])	0.92 [0.1; 1.9]*	4.2 [2.7; 6.8]

areas of the body (abdominal obesity), and in women - in the subcutaneous fat tissue, and in men - in the abdominal cavity and retroperitoneal space. Similar data were obtained in our study: patients with RA had higher values of WC and WC/OB than healthy donors with comparable BMI values.

Adipocytes of white adipose tissue and macrophages infiltrating it synthesize up to 30% of proinflammatory cytokines: tumor necrosis factor ÿ (TNFÿ), interleukins (IL) 6, 1 [5]. In the work, S. Ajeganova et al. [17] obesity (BMI 28 kg/m2 and more) was associated with high RA activity DAS28, rare achievement of remission, worse indicators of pain severity and health status in overall on a visual analogue scale. In our patients, with an increase in BMI, the DAS28 index increased; OT and BMI correlated with acute phase indices inflammation (ESR and CRP).

Proinflammatory cytokines play a major role not only in the pathogenesis of RA, but also in the production ACC - hormonal factors that are synthesized by adipose tissue, with paracrine, autocrine and endocrine mechanisms of action involved in

lipid metabolism, glucose homeostasis, processes inflammation, coagulation, immunity, angiogenesis and etc. [18]. The most studied ACCs include adiponectin and leptin, which are largely antagonists. Thus, adiponectin has antiatherogenic properties, and leptin has proatherogenic properties.

obesity and type 2 diabetes mellitus concentration leptin increases, and the level of adiponectin decreases. Currently, the L/ A ratio is considered as a reliable marker of IR, which plays a key role role in the development of MS [19].

Data on the importance of ACC in RA are scarce and contradictory. On the one hand, adiponectin suppresses the production of TNFÿ and stimulates the expression of IL-10

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by macrophages, thus determining its anti-inflammatory properties [20]. On the other hand, an increase in its concentration is associated with radiographic progression (destruction joints) in RA [21, 22]. Leptin in turn induces the production of IL-8 in cartilage and synovial membrane cells, which leads to migration into the inflamed joint neutrophils, T cells, basophils, macrophages and chronic joint inflammation [23]. D. Xibille-Friedmann et al. [24] found a relationship between leptin levels and DAS28, as well as IL-17. At the same time, time, according to H. Anders et al. [25], correlations high leptin levels with RA activity are not revealed. A number of studies indicate an increase in the concentration of adiponectin and leptin in the blood serum and synovial fluid of patients with RA [26, 27]. In the work of P. Dessein et al. [28], the level of ACC in rheumatic disease was lower or comparable to the indicators in healthy donors. Our results are consistent with a situation opposite to the classical picture of obesity: in patients with RA, the concentration of adiponectin was higher, and leptin is lower than that of healthy donors. At the same time, anthropometric indicators characterizing obesity, did not affect adiponectin levels. At that at the same time as in the general population, BMI and OT correlated with leptin and insulin resistance, represented by the L/A ratio. Insulin resistance is a decrease in response usually insulin-sensitive tissues (muscle, adipose tissue, hepatocytes) to insulin at its sufficient concentration, leading to chronic compensatory basal hyperinsulinemia. Insulin resistance is the earliest sign of carbohydrate metabolism disorder, an early stage of prediabetes associated with subclinical manifestations atherosclerosis, an increased risk of developing cardiovascular diseases and an increase in mortality from cardiovascular causes [29].

Assessing insulin resistance is complex and in most cases cases, its presence is judged indirectly, based on the calculation of the HOMA-IR index, which takes into account the levels of immunoreactive insulin and glucose. The dependence of HOMA-IR and MS in patients with RA was previously demonstrated from the activity of the disease, ESR, CRP, IL-6, TNFÿ and functional disorders [30, 31]. In our In a study using another known marker of insulin resistance, a direct correlation of the L/A ratio was observed with only one of the acute-phase reactants (ESR), but not with DAS28. An increase ESR was accompanied by an increase in leptin concentration and a decrease, probably compensatory, in adiponectin content, while the group of patients as a whole

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RA was characterized by low insulin resistance, despite the high frequency of obesity.

Conclusion

Thus, the results of our work indicate a high prevalence of obesity in patients with early rheumatoid arthritis and its relationship with inflammation. In contrast to the general population, obesity at the onset of rheumatoid arthritis was accompanied by an increase in serum concentrations adiponectin, decreased levels of leptin and insulin-resistance in general.

On the one hand, the present study has small sample size. At the same time, all patients with rheumatoid arthritis had high activity diseases and did not take glucocorticoids and basic anti-inflammatory drugs, which excludes the influence of these drugs on the data obtained.

Further study of this problem requires prospective observations, primarily concerning the association of insulin resistance indicators, expected

with the progression of rheumatoid arthritis, the relationship with destruction and functional disorders of the joints, as well as with the influence of antirheumatic therapy.

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