Serum Androgens in Men with Rheumatoid Arthritis

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Abstract

Background: It has been hypothesised, that low serum concentrations of

androgen-anabolic hormones would play part in the aetiology of rheumatoid arthritis (RA). This study aimed to determine the role of low serum testosterone and DHEAs in men with rheumatoid arthritis.

Methods: a case control study was conducted on 73 male patients with rheumatoid arthritis and 73 healthy male age matched control at the Department of Rheumatology and medical rehabilitation, Rheumtologic outpatient, and the biologic centre, Basra teaching hospital, Basra Provence at the south of Iraq from February 2019 till March 2020.Full investigations including total serum testosterone(TST) and dehydroepiandosteron sulfate(DHEAs) levels and disease activity were measured for patients, TST and DHEAs were measured for controls. **Results**: The median total serum testosterone level of the patients and the control groups was; 2.2ng/ml and 7.8ng/ml respectively. The median DHEAs level of the patients and the control groups; 81mg/dl and 343mg/dl respectively. Men with low serum androgen levels and in particular low serum level of DHEAs and to less extent TST associated with negative rheumatoid factor and anti CCP. patients with high disease activity associated with lower androgen levels.

Conclusion: Men with rheumatoid arthritis have low levels of serum androgens, may related to the lack of the anti-inflammatory effects of androgens, lower androgen levels associated with negative serological markers and high disease activity. Androgen replacement may have associated with clinical improvement and low disease activity

Key words: *Dehehydroepiandosterone sulphate, Rheumatoid arthritis, Total serum testosterone.*

Introduction

Rheumatoid arthritis(RA) is a chronic autoimmune inflammatory disease that affects diffrent ethnic groups, Males are less likely to be affected than females. The peak incidence was at forties and fifties of age, but it will occur at any age. It is the most common form of inflammatory arthritis affects synovial joints. In early disease, the wrists, proximal interphalangeal, metacarpophalangeal, joints of the fingers, interphalangeal joints of the thumbs, and metatarsophalangeal are the most commonly affected joints in the body [(1)]. Additionally, chronic inflammation secondary to RA can lead to an increased risk of pulmonary and cardiovascular disease and changes in bone mineral density [(1)]. Rheumatoid arthritis affects 0.5–1% of the adults worldwide [(2)]. At 2010 the classification criteria of RA were revised, aiming to improve early diagnosis and management[(3)].

Auto-antibodies, like rheumatoid factor (RF) and antibodies to citrullinated protein antigens (ACPAs), are measured to diagnose RA disease [(4,5)]. RA associated with sex hormones abnormality[(6)]. The level of androgens decreases at the disease onset and may returns to the normal state after relieving the acute symptoms [(7)].

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Dehydroepiandrosterone sulphate (DHEAs) are the most abundant products of the adrenal gland secretions, but its functions yet unknown. The pathophysiology of gonad dysfunction is not clear during the illness, but the effects of cytokines and/or glucocorticoids can be noted [8]. Sexual hormones engage in immune responses, estrogen hormones intensify humoral immune responses, and progesterone and androgens considered as inhibitors of immune response [9]. The anti-inflammatory effects of androgens in physiological levels are proved [10]. The levels of serum testosterone and DHEAs in males and postmenopausal females with RA were low; hence, it is supposed that hypoandrogenism may be involved in the pathogenesis of RA [10]. Therefore it's important to study the relation of low (DHEAS) and RA and its severity. This study aimed to determine the role of low serum testosterone and DHEAs in men with rheumatoid arthritis

Patients and Methods

This case- control study was conducted on 73 male patients with rheumatoid arthritis and 73 healthy male age matched control at the Department of Rheumatology and medical rehabilitation, Rheumatologic outpatient, and biologic centre, Basra teaching hospital, Basra Provence at the south of Iraq from February 2019 till March 2020. The diagnosis of RA disease was approved by a single rheumatologist using the American College of Rheumatology/European League criteria (3). Patients with other rheumatologic, inflammatory and endocrine disorders were excluded from the study. Complete investigations including complete blood count(CBC) and erythrocyte sedimentation rate(ESR), RF, Anti CCP, total serum testosterone and DHEAs levels were measured for all participants, total serum testosterone and DHEAs levels were measured for controls, disease activity for patients measured using DAS28. A questioner about marietal status, number of children were completed by the patient and control groups. Informed permission was taken from all participants.

Statistical Analyses

statistical analysis, were performed with Chi squared and Mann-Whitney tests p-value less than 0.05, was considered significant.

Results

Table 1 shows the demographic demonstration for patients and controls, there were 73 men patients of median age, and mean disease duration; 55 and 11.97(SD= 4.5), the mean numbers of children of patients and controls were 5.2(SD= 1.3)and 8.62(SD= 1.33) respectively. There were 73 controls with median age of 55. Serum levels of TST and DHEAs for both patients and controls are shown in table 2, the median total serum testosterone level of the patients group was 2.2ng/l that is lower than that of controls 7.8ng/l which is statistically highly significant with p value of 0.0001, the median DHEAs level for patients was 81mg/dl and 343mg/dl for controls, also result is statistically highly significant with p value of 0.0001.

Table 3: shows the relationship between TST and DHEAs levels in relation to the serological status; there were direct relationship between the negative rheumatoid factor and anti CCP and low androgen levels, result more obvious for patients with low level DHEAs and negative rheumatoid factor, results that are of statistical significance with p values less than 0.05. Low androgen levels directly correlated to high disease activity which is statistically highly significant with p value of 0.001, as shown in table 4.

Table 1: The demographic characteristics of patients and controls

Characteristics	Patients	Controls	P-value
Men	73	73	
Median age (year)	55	55	0.619
Disease duration (year)	11.97 (SD= 4.5)	------	------
No. of children	5.2 (SD= 1.3)	8.62 (SD= 1.33)	0.0001

Table 2: TST and DHEAs levels in both patients and controls

Characteristics	Patient	Controls	P-value
Total No.	73	73	
Median TST (ng/l)	2.2	7.8	0.0001
Median DHEAs (mg/dl)	81	343	0.0001

Table 3: TST and DHEAs levels in relation to serological status

	RF			Anti CCP		
	Positive	Negative	P-value	Positive	Negative	P-value
No.(%)	42 (57.5%)	31 (42.5%)	-------	55 (75.3%)	18 (24.7%)	-------
TST Median (ng/l)	3.1	2.0	0.0001	2.4	2.0	0.028
DHEAs Median (mg/dl)	107.5	78	0.0001	92.0	76.5	0.04

Table 4: TST and DHEAs levels in relation to DAS28

	Disease Activity		P value
	High DAS28	Low-Moderate DAS28	
TST Median (ng/l)	2.5	7.6	0.0001
DHEAs Median (mg/dl)	95	326	0.0001

Discussion

Over the past years, considerable interest has been dedicated towards circulating steroid hormones level in researches. Much research has been undertaken in view of the possibility that certain hormone profiles may predispose people to the development of illnesses such as coronary heart disease and cancer [11-13]. Hypoandrogenism may play a role in rheumatoid arthritis and/or appear as a complication of chronic inflammatory reaction. The higher levels of testosterone in young males may somewhat play protective roles against RA [14]. Clinical improvement after a successful treatment is followed by a rise within the level of serum testosterone in RA [15]. It should be noted that patients undergoing long-term treatment with glucocorticoids may experience hypoandrogenism [16]. Results of this study showed that total serum testosterone and DHEAs levels in men with RA were significantly lower than that of the control group. Also, this study showed that the normal levels may have protective effects on RA,

and the lower levels of serum testosterone may be caused by RA or may indicate the androgen role in the pathogenesis of RA. Our results were consistent with a study done by Pikwer M. et al who found an abnormal serum testosterone level was significantly lower in patients with RA and negative RF [17].

The low level of DHEAs found in our study are in agreement with an earlier report concerning men with established disease [18]. In a study done by Dessein et al. in South Africa on 38 patients with RA, the activity of hypothalamic-pituitary-adrenal axis was reduced and DHEAs levels in females and males with RA was low [19]. An attention has been paid on sex ratios of offspring of patients with RA; it has been hypothesised that the sexes of offsprings are partially controlled by parental hormone concentrations at the time of conception [20]. There is an evidence that women with RA are more likely to conceive with daughters rather than sons [21,22]. There is indirect evidence supporting the view that low androgen concentrations are involved in the aetiopathogenesis of RA [23]. In this study we found there was direct relationship between the negative serology of RF and anti CCP and low androgen level, especially for rheumatoid factor which may indicates an independent etiological effect of low androgens in the etiopathogenesis of rheumatoid arthritis. In this study the mean number of children in the patients group was less than that in the control group, result may correlate to the burden of the disease on the socioeconomic status of the patients or it may reflect the low fertility level in these patients. We found that patients with lower androgen levels were associated with high disease activity, this result is comparable to a study done by Cutolo M. who stated that; low serum testosterone and DHEAs associated with high disease activity in patients with rheumatoid arthritis [24].

Conclusions

Men with rheumatoid arthritis associated with low levels of serum androgens; this may have related to the lack of the anti-inflammatory effects of androgens. Men with lower levels of DHEAs and to less extent TST obviously associated with negative serological markers, disease activity strongly related to low androgen levels. Androgen replacement may have associated with clinical improvement and low disease activity.

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References

1. Kahlenberg JM, Fox DA. Advances in the medical treatment of rheumatoid arthritis. Hand Clin. 2011;27(1):11–20.
2. Bax M, Van Heemst J, Huizinga TWJ, Toes REM. Genetics of rheumatoid arthritis: What have we learned? Immunogenetics. 2011;63(8):459–66.
3. Aletaha D, Neogi T, Silman AJ, Funovits J, Felson DT, Bingham CO, et al. 2010 Rheumatoid arthritis classification criteria: An American College of Rheumatology/European League Against Rheumatism collaborative initiative. Arthritis Rheum. 2010;62(9):2569–81.
4. Demoruelle MK, Deane K. Antibodies to citrullinated protein antigens (ACPAs): Clinical and pathophysiologic significance. Curr Rheumatol Rep. 2011;13(5):421–30.
5. Puszczewicz M, Iwaszkiewicz C. Role of anti-citrullinated protein antibodies in diagnosis and prognosis of rheumatoid arthritis. Arch Med Sci. 2011;7(2):189–94.
6. Spector TD, Perry LA, Tubb G, Silman AJ, Huskisson EC. Low free testosterone levels in rheumatoid arthritis. Ann Rheum Dis. 1988;47(1):65–8.
7. Cutolo M, Wilder RL. Different roles for androgens and estrogens in the susceptibility to autoimmune rheumatic diseases. Rheum Dis Clin North Am. 2000;26(4):825–39.
8. Cutolo M, Balleari E, Giusti M, Monachesi M, Accardo S. Sex hormone status of male patients with rheumatoid arthritis: evidence of low serum concentrations of testosterone at baseline and after human chorionic gonadotropin stimulation. Arthritis Rheum. 1988;31(10):1314–7.

9. Cutolo M, Straub RH. Insights into endocrine-immunological disturbances in autoimmunity and their impact on treatment. Arthritis Res Ther. 2009;11(2):218.
10. Imrich R, Vigas M, Rovensky J, Aldag JC, Masi AT. Adrenal plasma steroid relations in glucocorticoidnaïve premenopausal rheumatoid arthritis patients during insulin-induced hypoglycemia test compared to matched normal control females. Endocr Regul. 2009;43(2):65–73.
11. Alexandersen P, Haarbo J, Christiansen C. The relationship of natural androgens to coronary heart disease in males: A review. Atherosclerosis. 1996;125(1):1–13.
12. Nomura AMY, Kolonel LN. Prostate Cancer: A Current Perspective. Epidemiol Rev. 1991;13(1):200–27.
13. Key TJ, Verkasalo PK. Endogenous hormones and the aetiology of breast cancer. Breast Cancer Res. 1999;1(1):18–21.
14. Harbuz MS, Perveen-gill Z, Lightman SL, Jessop DS. A protective role for testosterone in adjuvant-induced arthritis. Rheumatology. 1995;34(12):1117–22.
15. Lunenfeld B, Mskhalaya G, Zitzmann M, Arver S, Kalinchenko S, Tishova Y, et al. Recommendations on the diagnosis, treatment and monitoring of hypogonadism in men. Aging Male. 2015;18(1):5–15.
16. Mahabadi N, Doucet A, Lun Wong A, Mahabadi V. Glucocorticoid Induced Hypothalamic-Pituitary Axis Alterations Associated with Hypogonadotropic Hypogonadism. Osteol Rheumatol – Open J. 2019;1(1):30–4.
17. Pikwer M, Giwercman A, Bergström U, Nilsson JÅ, Jacobsson LTH, Turesson C. Association between testosterone levels and risk of future rheumatoid arthritis in men: A population-based case-control study. Ann Rheum Dis. 2014;73(3):573–9.
18. Mateo L, Nolla JM, Bonnin MR, Navarro MA, Roig-Escofet D. Sex hormone status and bone mineral density in men with rheumatoid arthritis. J Rheumatol. 1995;22(8):1455–60.
19. Dessein PH, Joffe BI, Stanwix AE, Moomal Z. Hyposecretion of the adrenal androgen dehydroepiandrosterone sulfate and its relation to clinical variables in inflammatory arthritis. Arthritis Res. 2001;3(3):183–8.
20. James WH. The hypothesized hormonal control of mammalian sex ratio at birth-A second update. J Theor Biol. 1992;155(1):121–8.
21. Deighton CM, Watson M, Walker DJ. RA sex ratios, HLADR, and testosterone. Ann Rheum Dis 1993; 52:244.
22. Brennan P, Silman A. Role of androgens in the aetiology of rheumatoid arthritis. Ann Rheum Dis 1996;55:404.
23. James WH. Rheumatoid arthritis, the contraceptive pill, and androgens. Ann Rheum Dis 1993;52:470–4.
24. Cutolo M. Androgens in rheumatoid arthritis: When are they effectors? Arthritis Res Ther. 2009;11(5):3–5