Serum resistin, adiposity, and insulin resistance in Saudi women: conflicting data or statistical flaws?

To the Editor: I have read with great interest the recently published article by Al- Harithy and Al- Ghamdi[1] in the *Annals of Saudi Medicine* and I appreciated the authors' efforts and work. However, I would like to make few comments on it because of the apparent conflicting results of different studies investigating the differences in resistin levels between healthy subjects and type 2 diabetics, which the author admitted in their discussion. The authors mentioned that "these conflicting data may reflect the lack of adjustment for potential confounding factors, i.e. age and body fat distribution".

I agree with the authors, partially, in their explanation. However, conflicting studies could also be attributed to nonfulfillment of certain prerequisites or assumptions before running a statistical model, a common problem in health research in which the authors themselves have fallen. The authors mentioned that "resistin concentrations were not correlated with BMI in lean subjects whereas there was a highly significant positive correlation between resistin and BMI in overweight/obese (OW/OB) nondiabetic and diabetic women". That means the authors have calculated a Pearson correlation coefficient between BMI and resistin level for each of the three studied groups separately. Albeit that the first and second group constituted 21 and 24 participants, respectively, the authors did not mention in their methodology that they tested the three groups for linearity before running Pearson's correlation for each. Linearity would be suspected given the paucity of participant numbers, especially for the first two groups. Pearson's correlation coefficient is a measure of linear association. Two variables can be perfectly related, but if the relationship is not linear, Pearson's correlation coefficient is not an appropriate statistic for measuring their association. If linearity is not met, we can use a transformation or one of the rank correlation methods.[2] I think it would also be better if the authors would pool the data of the three groups together (summing to 89 participants) and run a partial correlation between BMI and resistin adjusted for the type of group. Moreover, the results of any study should be consistent irrespective of the statistical tool used, especially if it is on the bivariate level. BMI was found to be significantly associated with resistin level by the ANOVA test (in Table 1). Accordingly, results of simple correlation should be in the same vein.

Moreover, when the authors mentioned in the results section that "HOMA-R were similar in lean and OW/OB subjects, but significantly higher in diabetic compared with non-diabetic women", they were semantically incorrect. The right description of what their data revealed is that there was no significant difference in HOMA-R between the lean and OW/OB groups, whereas the difference was significant between the lean and diabetic group as well as the OW/OB and diabetic group.

As regards the adjustment of confounding variables mentioned above, the authors, in the methods section, mentioned that "the findings from the bivariate correlation analysis were further explored using stepwise multiple linear regression analysis with resistin concentration as the dependent variables." I think it was better to enumerate the predictors or the independent variables in the regression model. If we look in Table 1 we could easily detect that many variables with strong co-linearity were significantly associated with resistin in bivariate analysis. The co-linearity of waist circumference with waist-hip ratio, and weight with BMI is manifest. Selecting one of any strongly co-linear variables should be done before running regression models.

Finally, I wish to close with what Altman et al[3] concluded in their study: "Statistical input to medical research is widely recommended but inconsistently obtained. Individuals providing such expertise are often not involved until the analysis of data and many go unrecognized by either authorship or acknowledgment."

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Season change bias in animal studies

To the Editor: In research, bias includes any systematic error in the

design, conduct, or analysis of the study. Bias can occur at all stages of research, from the selection of the population, how treatment is provided, to how and when outcome measurements are made.[1] One report reviewed more than 50 possible source of bias in analytic research.[2] Season change is a possible source of bias in animal studies that was not reported previously. We recently experienced this bias in evaluation of the biocompatibility of a new biomaterial with subcutaneous implantation in Sprague-Dawley white albino rat (male, mean weight, 200±25 g). During a longitudinal study, we obtained controversial results between summer and winter. All other variables were under control and we could not find any other source of bias. This source of bias could be attributed to hibernation in rodents,[3] altering the immunological, pathological, and behavioral responses. By changing the environment temperature and daylight duration (combination of natural and artificial light, not artificial light only) it can be controlled, relatively. Nevertheless, in subtle studies both investigators and readers of the medical literature should consider this source of bias.

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Remission of nephrotic syndrome in amyloidosis of familial Mediterranean fever following colchicine treatment

To the Editor: Familial Mediterranean fever (FMF) is an autosomal recessive disease characterized by recurrent inflammatory attacks of the serosal and synovial membranes and fever.[1] The main complication of the disease is the development of amyloidosis. In most FMF patients, colchicine treatment prevents inflammatory attacks and development of amyloidosis, whereas the inflammatory crises were not completely suppressed.[2] In the literature, cases of amyloidosis of FMF that regressed have rarely been reported.[3-5] We report two cases of nephrotic syndrome due to AA amyloidosis secondary to FMF who recovered colchicine treatment.

In May 1999, a 38-year-old man was admitted to the hospital because of attacks of FMF and nephrotic syndrome. Amyloidosis was proved by rectal biopsy. The laboratory findings included urinary protein excretion of 4 g/day, erythrocyte sedimentation rate 90 mm/h, serum creatinine 1.1 mg/dL, albumin 1.6 g/dL, and total protein 5.2 g/dL. Therapy with colchicine (1.5 mg/day) was initiated and was continued during the follow up. The proteinuria disappeared (50 mg/day) in October 2002. He remained proteinuria free during further follow up.

In July 2001, a 20-year-old girl was admitted to the hospital with fever, severe abdominal pain, arthralgia, myalgia, and swelling of the hands and feet. She had a history of recurrent abdominal pain and fever for 5 years. Physical examination showed pretibial oedema. Her blood pressure was 100/60 mmHg. Laboratory investigations revealed a hemoglobin level of 12.6 g/dL, a white blood cell count of 13 000/mm^3, an erythrocyte sedimentation rate of 79 mm/h, urinary protein excretion 4.3 g/day, serum creatinine 0.91 mg/dL, albumin 3.1 g/dL, and total protein 6.3 g/dL. Mutation analysis of the MEFV (gene for FMF) showed it to be homozygous for the M694 V mutation. A rectal biopsy showed amyloidosis. Colchicine treatment (1.5 mg/day) was started. The proteinuria decreased significantly, and the nephrotic syndrome disappeared at the third to fourth year of colchicine treatment.

The most severe manifestation of FMF results from the deposition of amyloid A protein.[1,2] The most common clinical manifestation of FMF-related amyloidosis is the development of nephrotic syndrome and eventually uremia. Patients are usually normotensive and non-hematuric.[1] Due to widespread use of colchicine, only a minority of FMF patients now present with amyloidosis. The frequency of amyloidosis differs among various ethnic groups and depends on whether patients are taking colchicine.[2] The introduction of long-term colchicine daily prophylactic therapy was shown to be highly effective in preventing or ameliorating the subsequent acute attacks of FMF and amyloidosis. Once it was believed that long-term treatment with

colchicine prevents amyloidosis in FMF patients, but it was not effective for amyloidotic kidney disease when it had reached the nephrotic stage. The presented cases demonstrate that reversal of the nephrotic syndrome by colchicines in amyloidosis of FMF. I conclude that colchicine is of paramount importance in preventing FMF amyloidosis; it may also arrest the progression of amyloidosis in those who already have it, and may even reverse proteinuria.

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Breast cancer in the south of Iran

To the Editor: Breast cancer arises from a multifactorial process. Recent attention has focused on genetic predispositions to breast cancer.[1,2] Furthermore, the effect of reproductive factors strongly supports a hormonal role in its etiology.[3,4] Earlier age at menarche[5,6,7] and later age at first full term pregnancy[6,7,8,9] have shown a significant increase in the risk of the disease. While numerous studies have been conducted in western counties to assess the epidemiology of breast cancer, there have been few studies on Middle East populations. Although breast cancer in Iranian women is the most common form of cancer,[10] few epidemiological studies have been conducted on its risk factors in this country. Age-adjusted incidence of the disease in Iran is estimated to be 22.4 per 100 000,[10] and epidemiological studies have found a lower age in Iranian patients compared with their western counterparts,[11] and a moderately rapid increase in incidence rate of the disease in recent years.[10] Now, the question arises as to whether or not breast cancer in the south of Iran is influenced by some specific risk factors established for high or moderate incidence areas. This case-control study was conducted from April 2002 to March 2004 in Bandar Abbas, Hormozgan, Iran to investigate this subject.

Eligible cases were incident (diagnosed within 2 years before the interview) breast cancer patients living in the region, and were entered into the study if they had a confirmed pathological primary breast cancer diagnosis from the pathology department of Bandar Abbas Shahid Mohammadi Hospital, which is the leading university-based hospital in the region. For each case three age-matched (±3 years) women were recruited from patients with no history of breast problems or neoplastic diseases who attended outpatient ophthalmology or dermatology clinics in the same hospital. After receiving informed consent, a structured questionnaire was completed at the time of recruitment. All interviews were carried out by two interviewers who had been thoroughly familiarized with the study protocol.

Odds ratios from univariate logistic regression were used to estimate the relative risk of breast cancer associated with the various factors and their predictive effects. Based on the univariate analysis, the odds ratios were adjusted for potential confounding variables; 95% confidence intervals (CIs) for each of the odds ratios were calculated. A forward multivariate logistic regression model was used for significant associated risk factors and $P<0.05$ was considered statistically significant.

Of 173 women with breast cancer who were newly diagnosed, 168 patients entered the study as cases and 504 women were selected as controls. There were no significant differences between cases and controls with regard to parity, history of breast feeding, history of induced or spontaneous abortion, oral contraceptive use, menopausal status, age at menopause, HRT use, history of previous benign breast disease and tobacco exposure. Breast cancer history in first-degree relatives was a significant risk factor (OR 7.09, 95%CI 4.06-12.26). Women with a younger age at menarche (<13 years old) were found to be at higher risk for breast cancer than women with older age of menarche (OR 4.00, 95%CI 1.82-9.84). The results show that never-married women demonstrated a higher risk of breast cancer than the others (OR 2.69, 95%CI 1.38-7.12). Breast cancer risk was significantly greater in women whose first full-term pregnancy was at age 30 years or more in comparison with the others with a first full-term pregnancy at a lower age (OR 7.79, 95%CI 4.25-

9.12). Furthermore, it was shown that more than five full-term pregnancies would be expected to correlate with an increase in the risk of breast cancer (χ^2 = 111.12, P<0.05).

In the forward multivariate logistic regression analysis, in addition to those factors which were significantly associated with breast cancer, parity and breast feeding, factors with relatively high but not statistically significant odds ratios, were included in the model. The final model revealed that in addition to those factors, which were significant in univariate logistic regression analysis, a history of breast feeding is a significant factor in decreasing risk of breast cancer (OR 0.68, 95%CI 0.12-0.97) but nulliparity is still not significant.

Although the results cannot be generalized, the findings suggest that the associations between some known risk factors for breast cancer may differ in the south of Iran as compared with other populations. Intensive study of developing countries might reveal other important risk factors in these populations.

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Cardiovascular findings in patients with psoriasis

To the Editor: Psoriasis is a common, genetically determined, inflammatory and proliferative disease of the skin. The etiology of psoriasis has not exactly been determined.[1] Besides atypical psoriasis, other forms have been observed, including forms with systemic sympthoms, associations with some skin disorders, gout, hypocalcaemia, intestinal disease and malabsorption, anterior uveitis, myopathia and cardiovascular disorders.[1-4] Variations in lipid metabolism, diabetes mellitus, renal failure and malignancies may be associated with psoriasis.[3,5-7]

An increased incidence of occlusive vascular disease has been reported in psoriatic patients in retrospective studies. Because associations between psoriasis and cardiovascular disorders have been seen so often, we aimed to investigate cardiovascular findings in psoriatic patients. Thirty-six patients with histopatologically proven psoriasis, 21 female and 15 male, aged 13-77 years, applied to the dermatology outpatient clinic of Celal Bayar University and were enrolled in our study. Psoriasis area and severity index (PASI) values were calculated for all patients. Informed consent was obtained from each patient. Complete blood count (CBC), erythrocyte sedimentation rate (ESR), biochemical analysis, lipid levels, chest radiography, electrocardiography, echocardiography and exercise electrocardiography (according to the Bruce protocol) were performed on the patients. Diastolic and systolic functions were examined with echocardiography. For diastolic functions peak early (E) wave velosity, peak atrial (A) wave velosity, E/A ratios, E wave deceleration time (EDT) and isovolemic relaxation time (IVRT) were calculated. For systolic functions, end-systolic and end-diastolic volumes were calculated and then EF (ejection fraction) was determined. Ischemic findings were examined with electrocardiography and exercise electrocardiography. All tests were applied to the 20 volunteers in the control group and the results were compared with the patient group. Data obtained from the patient and control groups were analyzed by SPSS for Windows. In the statistical analyses, Fisher's exact test and Student's t test were used.

The mean age of psoriatic patients was 44.7 (±14.9) years and the median value was 46.5 years.

Duration of disease varied from 1-35 years. The range of PASI values were 0.7-23.6. Laboratory findings revealed anemia in three patients (8.3%), high ESR, tricgylceride (TG), cholesterol and low density lipoprotein (LDL) levels in 4 (11.1%), 5 (13.9%), 14 (38.9%) and 14 (38.9%) patients, respectively. High density lipoprotein (HDL) levels were found to be low in 7 (19.4%) psoriatic patients. There was no anemia in the control group. ESR was high in 5% of cases, whereas high levels were also observed in TG (5%), cholesterol (35%), and LDL (35%). HDL levels were normal in all control cases. Chest radiograms were normal for both groups. Electrocardiographies were pathologic in three patients. One of them had P pulmonale and early repolarization at precordial derivations; the second had a 2 mm Q-wave at DII, DIII and aVF; the third had negativity of T at DI, aVL, V5-6 and an intraventriculary conduction disorder. In the control group, electrocardiography was pathologic in one person. He had an absence of R at V1-2 and rS at DIII and aVF. EF values and systolic functions with echocardiography were normal for all cases. Diastolic dysfunction was determined in 15 (41.7%) patients, but in the control group it was seen in 5 (25%) persons. Ischemia was not seen in the electrocardiography and exercise tests in the patient group, but it was seen in one case (5%) in the control group. In the patient group, exercise times ranged between 2.34 and 14.59 minutes. Mean exercise time (MET) values were calculated for determining exercise performance. MET values varied from 4.6 to 17.2 minutes in the patient group and were normal in all patients. MET values were also normal in control cases. Both cardiac and exercise capacities were adequate in all cases. A hypertensive answer to exercise was seen in 4 (11.1%) psoriatic patients, but only in 1 (5%) control case.

Psoriasis is a disorder that is characterized by abnormal proliferation and regeneration of keratinocytes, acute and chronic inflamation and microangiopathic changes.[8] Because of these microangiopathic changes, there are pathologic findings and complications at internal organs,[9] causing cardiovascular disorders and variations in lipid methabolism.[4,6] Altered renin-angiotensine system activity and increased endothelin levels disturb circulation in psoriatic patients, so that cardiovascular disorders may occur.[5,8] Ena et al reported that the prevelance of hypertension, cardiovascular disorders and diabetes mellitus increased in psoriasis. Also, they found high cholesterol and trigylceride levels and low HDL levels.[5] Seçkin et al attributed increased atherosclerosis risk to changes in lipid and lipoprotein composition in psoriatic patients and determined that lipoprotein (a) levels were increased in psoriasis, depending on the severity of the disease.[10] Cardin et al found elevated blood cholesterol in children with psoriasis, as in adult subjects with psoriasis.[11] Pietrzak et al demonstrated a statistically significant decrease in HDL cholesterol concentration and a statistically significant increase in triglyceride concentration in psoriatic patients.[12] In our study, we found that 13.9% of our patients had high TG levels, 38.9% had high cholesterol, 38.9% had raised LDL levels, and 19.4% had low HDL levels. Low HDL levels were significant ($P<0.05$), whereas the differences between the TG, LDL and cholesterol levels in the two groups were not statistically significant ($P>0.05$). There was no correlation between lipid levels and PASI scores of psoriatic patients. The differences in CBC, ESR, urine analysis, electrocardiography and echocardiography findings were statistically insignificant ($P>0.05$).

Torok et al reported cardiovascular complications in 18 of 137 psoriasis patients in their study (3 myocardial infarction, 5 angina pectoris, 3 deep vein thrombosis, 6 superficial thrombophlebitis, and 1 sudden death). They proposed that psoriasis was not a predisposing factor for cardiovascular complications except for psoriatic arthritis.[4] In our study, we found no ischemic findings in the patient group. Systolic functions and exercise capasities were adequate in all cases. According to echocardiography, there was diastolic dysfunction in 41.7% of patients. Although the electrocardiographic and echocardiographic differences were not significant between the two groups, diastolic dysfunction and a hypertensive answer to exercise were prominent in the patient group (41.7% versus 25%).

As a result, we want to draw attention to the low HDL levels and diastolic dysfunction in psoriatic patients in our study. Our data suggest that psoriasis patients must be considered as a group at risk for cardiovascular disease. Thus, regular cardiological follow-ups must be performed in psoriatic patients in order to eliminate the cardiovascular risk factors.

This letter was presented at the International Symposium on Psoriasis 2000 at the Dead Sea, 7–10 September 2000, Israel.

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Effects of hormone replacement therapy and tıbolone on skın thıckness and bone ın postmenopausal women

To the Editor: This prospective, randomized study was undertaken to investigate the effects of hormone replacement therapy (HRT) and tibolone (T) on skin by ultrasonographic and histologic evaluation and on bone by bone mineral density (BMD). Forty nonsmoking postmenopausal women were randomized by block randomization to HRT or T. Of the 20 women in the HRT group, one had undergone hysterectomy and received conjugated equine estrogens 0.625 mg daily (*Premarin*, Wyeth); 19 women received conjugated equine estrogens 0.625 mg, medroxyprogesterone acetate 5 mg daily continuously (*Premelle* 5, Wyeth). The 20 women in the T group received tibolone 2.5 mg daily continuously (*Livial*, Organon). Both groups were treated for 12 months. One women in the HRT group and 3 women in the T group did not complete the study.

Skin thickness was measured by ultrasonography, three times (at initiation, at 6th and 12th months). Evaluations were performed at the right thigh 3 c m below the greater trochanter. Skin biopsies were performed two times (at initiation and at 12th month) at the marked location. BMD in the lumbar spine was measured by dual X-ray absorpsiometry (DXA) at initiation and at 12 months. When estimations were done for comparisons within each group using the ANOVA method, 11%±26% (mean±SD) of change could be detected with an α level of .05 and a power of 78%. The demographic characteristics (age, body mass index, menopause time, gravida, parity) of the two groups were comparable.

When evaluated by ultrasonography, a statistically significant increase in skin thickness compared with baseline was observed after 12 months of treatment (P=0.002) and from 6 to 12 months (P=0.001) within the HRT group (Table 1), but there was no statistically significant changes after the first 6 months compared with baseline (P=0.68). In the T group, the increase in skin thickness was statistically significant from baseline to the 6th and 12th months (P=0.01 and P=0.01)) but not between the 6th and 12th months (P=0.53). The tibolone group showed a significant increase on the ultrasonographic skin thickness measurement at the 6th month visit

Table 1. Skin thickness by ultrasonography at baseline, and 6th and 12th months.

	Group HRT (n=19)	Group T (n=17)
Baseline	1.989 ± 0.395	2.156 ± 0.378
6th month	1.956 ± 0.383	2.340 ± 0.308*†
12th month	2.222 ±0.407‡	2.393 ± 0.281†

*P<0.05 vs HRT, †P<0.05 vs. baseline, ‡P<0.05 vs. baseline and 6th month

Table 2. Baseline and 12 month measurements of skin thickness by skin biopsy and T scores for BMD.

	Group HRT (n=19)		Group T (n=17)	
	Skin thickness (mm)	BMD (T score)	Skin thickness (mm)	BMD (T score)
Baseline	3.070±1.134	-1.36 ± 1.02	2.784±1.116	-1.51±1.01
12th month	2.565±1.088	-1.09±0.97*	2.782±1.239	-1.34±1.07*

*P< 0.05 vs. baseline

compared with the HRT group (*P*=0.03). Histologic skin thickness differences at 12 months were not statistically significant compared with baseline in either the HRT (*P*=0.289) or T groups (*P*=0.996) (Table 2). There were no group differences in the histologic skin thickness measurements (*P*=0.29).There were statistically significant changes in T score after 12 months of treatment in the two treatment groups (*P*=0.007 in the HRT group, *P*=0.027 in the T group), but the responses in the two treatment groups were not significantly different from each other (*P*=0.269).

Most studies have measured the thickness of dermis, and dermis is composed virtually entirely of connective tissue. Subcutaneous tissue is an added variable and inclusion of the subcutaneous fat in the measurements results in uncertainty.[1] Therefore in order to obtain good accuracy in the measurements, high frequency ultrasonography has been used to determine skin thickness. Our study supports these results with the ultrasound technique, a sensitive, reproducible and valid technique for measurement of skin thickness.

Dermis thickness in skin biopsy may show wide variations related to how the specimen is cut; if the cut is not perpendicular to the skin surface, the thickness measurement will not be correct.[2] In concordance with others, significant increases in skin thickness were observed on the sonographic evaluation in our study, but not in the histologic examination in the two treatment groups. Skin and bone changes with estrogen deficiency at the menopause have been shown to be isochronal events.[3] In our results, both HRT or tibolone therapy was associated with increases in T scores. Although a small series, our results showed that HRT and tibolone had a benefical effect on skin thickness and on BMD in postmenopausal women.

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