

## Brief Communication

### Tuberculosis verrucosa cutis. Experience from eastern Turkey

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Tuberculosis verrucosa cutis (TBVC) is a paucibacillary form of cutaneous tuberculosis caused by exogenous reinfection in previously sensitized individuals. Inoculation occurs at sites of minor wounds or abrasions, and rarely from the patient's own sputum. The TBVC usually occurs on the hands in adults, and on the lower extremities in children. In western countries, TBVC is a rare form of cutaneous tuberculosis, however, in the Asian subcontinent it may be quite common.<sup>1,2</sup> A total of 304,566 patients were admitted to the dermatology outpatient clinics of Ataturk University Medical School Hospital, Erzurum, east of Turkey, between 1975 and 2005. One hundred and sixty eight (0.05%) patients diagnosed as cutaneous tuberculosis were retrospectively analyzed, 22 (13.09%) were found to have TBVC. Age ranged between 4-70, (mean age: 39.72 [male:female 0.83]). The localizations of lesions were: one (4.5%) head-neck region, 17 (72.3%) upper limbs, 5 (22.3%) lower limbs, and hand and foot involvement in one patient. Mean duration of lesion was 3.63 years, ranging one to 10 years. Seventeen (77.3%) tested positive for tuberculosis skin test, and 3 (13.6%) with positive culture results.

The incidence of TBVC varies in different regions and countries of the world, and is recently seen more frequently in Asia.<sup>1,2</sup> In a published prospective study of 20 years, 6% of all cases of cutaneous tuberculosis were TBVC.<sup>2</sup> In different regions, the ratio of TBVC was detected as 7% in Morocco,<sup>3</sup> 4% in Hong Kong,<sup>4</sup> and 18.95% in Pakistan.<sup>5</sup> In our study, the ratio of TBVC was detected as 13.1%. This frequency is lower than that of Pakistan, though higher than the others. Ho et al<sup>4</sup> reported that the mean age of TBVC in Hong Kong was 59.5, with male:female ratio of 0.25. In our study, the mean age was 39.72, with male:female ratio of 0.83, which was lower than the previous study in favor of male. The mean duration was detected at 11.3 years in a previous study,<sup>4</sup> however, it is 3.6 in our study.

Although TBVC occurs generally on the hands, the predilection sites for children are the lower extremities (knees, thighs, and buttocks). In Europe, TBVC lesions are most encountered on the hands, although the lower limbs and buttocks are the most frequently affected sites in eastern countries.<sup>2</sup> In our study, the most localized involvement was the upper limbs (72.3%) and the lower limbs (22.3%). Moreover, the ratio of positive Mantoux skin test was 77.3%. The laboratory diagnosis

of paucibacillary forms of cutaneous tuberculosis, such as TBVC, is difficult. Culture has a low sensitivity in paucibacillary conditions and may take several weeks to obtain available result, causing delays in initiating the therapy. In some studies, microscopy and culture are often negative.<sup>1</sup> We are unable to find any publications on the culture results in TBVC in the English literature, however, a positive culture was found in 13.3% in our study.

In conclusion, tuberculosis is still an important health problem in underdeveloped and developing countries. The TBVC is paucibacillary tuberculosis. The female ratio is close to the male ratio. It is commonly seen in a person who has high immunity, and is frequently localized on the upper limbs.

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### Echocardiographic approach of left ventricular dysfunctions in essential hypertension

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The prevalence of hypertension is 7-40%.<sup>1</sup> According to the results of the Third National Healthy, and Nutrition Examination Survey Study, 31% of the

hypertension patients are unaware of their conditions. The same study also found that only 53% of patients are under medical treatment. In 45% of the patients under medical treatment, blood pressure (BP) could not be lowered to desired levels.<sup>2</sup> These findings indicate that approximately 76% of the hypertension patients are not treated successfully; therefore, target organ damage develops which leads to a higher rate of mortality and morbidity. The goal of in our study was to compare the left ventricular echocardiographic (ECHO) parameters of essential hypertension patients assigned into different groups described as previously mentioned study.<sup>2</sup>

The study groups were designed as follows: group 1 (n=34); healthy individuals, group 2 (n=35); patients with essential hypertension newly diagnosed or previously diagnosed but received no drug for the prior month, group 3 (n=47); essential hypertension patients under medical treatment and with no left ventricular hypertrophy (LVH) on ECHO, and group 4 (n=67); essential hypertension patients under medical treatment and with LVH on ECHO. Patients with typical angina pectoris, diabetes mellitus, myocardial infarction, and chronic obstructive lung disease in their history, with high urea, creatinine, and glucose levels in biochemical parameters were excluded from the study. Also, patients with the regional wall motion abnormality, and with moderate or manifest valve dysfunction on ECHO were excluded from the study. The ECHO analyses were performed using a 2.5 Mhz transducer and the Hewlett-Packard Sonos 2500 system (Philips Medical Systems, Andover MA, USA). Standard ECHO parameters and pulsed wave tissue Doppler imaging (TDI) was used. Statistical analyses were conducted using a computer program, SPSS version 10:0. Results were given as mean  $\pm$  SD. One-way single-factor analysis of variance (ANOVA) test was used to compare the groups (Table 1).

In our study, the clinical progress of the patients with essential hypertension, which did not cause mortality and morbidity was evaluated, placing in different groups at same time period. Absence of significant differences among groups as far as number of cases, age, gender, body mass index (BMI), and heart rate increased confidence in comparison of the results among groups. In group 2, the systolic and diastolic BP's were significantly higher compared to all other groups ( $p < 0.020$  for all groups). Compared to the group 3 and 4, the systolic BP of the group 1 was significantly lower ( $p = 0.017$  and  $p = 0.000$ ). Also, in group 1, diastolic BP was significantly lower compared to group 3 ( $p = 0.001$ ) and 4 ( $p = 0.002$ ). The left ventricular mass index (LMVI) in group 4 was significantly higher compared to all other groups ( $p < 0.001$  for all groups). However, LMVI was significantly higher in group 2 compared to groups

1 ( $p = 0.009$ ) and 3 ( $p = 0.004$ ). Considering the clinical progress of essential hypertension, differences in BP's and LVMI among the groups were expected results.

The diameter of the left atrium was significantly larger ( $p = 0.045$ ) in group 4 (with LVH) compared to the group 3 (with no LVH). The diameter of the proximal aorta was significantly larger in group 4 compared to group 3 ( $p = 0.024$ ) and the control group ( $p = 0.022$ ). Among the groups with essential hypertension, group 4 had significantly larger left ventricular end-diastolic diameter (LVEDD) compared to groups 2 ( $p = 0.001$ ) and 3 ( $p = 0.047$ ). The left ventricular end-systolic diameter (LVESD) in group 4 was significantly larger compared to group 3 ( $p = 0.001$ ). The relative wall thickness of the left ventricle was higher in group 4 compared to the control group ( $p = 0.001$ ). The increase in the measurements of LVEDD, LVESD, interventricular septum and posterior wall in group 4 might have been expected as described as features of LVH. However, the increase in the diameter of the left atrium and the proximal aorta was an interesting point that should be paid attention to, as it shows that changes in hypertension patients are not limited to the left ventricle, but the left atrium, and the proximal aorta are also affected. In addition, LVMI ( $p: 0.000$  correlation ratio: 29%) and the diameter of the left atrium ( $p: 0.000$  correlation ratio: 21%) were positively correlated with systolic BP; however, LVEDD, LVESD, and the relative wall thickness were not affected from the systolic and/or diastolic BP. These findings indicate that changes in the geometry of the left ventricle are not only related to systolic BP, but other factors are also involved, possibly neuro-humoral factors.

When the left ventricular filling flows were analyzed, the transmitral early velocity ( $V_e$ ) was not different among the groups; however, the transmitral left ventricle late velocity ( $V_a$ ) was significantly higher in group 4 compared to group 3 ( $p = 0.002$ ). So, the  $V_e/V_a$  rate was significantly lower in group 4 compared to group 3 ( $p = 0.016$ ). Among the other diastolic parameters, the  $V_e$ -deceleration time, atrial filling fraction (AFF) color M-mode flow propagation velocity, and pulmonary vein filling velocities (systolic, diastolic, and atrial velocities) were not different among the groups. The most prominent difference among the groups was observed in the isovolumetric relaxation time (IVRT). In group 4, the IVRT was significantly longer compared to all the groups ( $p < 0.001$  for all groups). The difference in IVRT naturally affected MPI rate. So, the MPI rate was significantly higher in group 4 compared to all groups ( $p < 0.001$  for all groups). The aortic velocity was significantly lower in group 2 compared to group 4 ( $p = 0.015$ ). However, the ventricular pre-ejection

## Echocardiographic approach

**Table 1 -** Parameters of left ventricular functions and geometry was demonstrated. (mean  $\pm$  sd)

Parameters	Group 1 (n=34)	Group 2 (n=35)	Group 3 (n=47)	Group 4 (n=67)
Systolic BP (mmHg)	126 $\pm$ 11	150 $\pm$ 13*	136 $\pm$ 13	140 $\pm$ 17
Diastolic BP (mmHg)	79 $\pm$ 3	97 $\pm$ 4*	84 $\pm$ 6	83 $\pm$ 6
LVMI (gr/m <sup>2</sup> )	89 $\pm$ 16	114 $\pm$ 50	89 $\pm$ 16	152 $\pm$ 38*
Left atrium (mm)	32 $\pm$ 5	33 $\pm$ 6	31 $\pm$ 5	35 $\pm$ 5*
Aort valve diameter (mm)	27 $\pm$ 4	28 $\pm$ 4	27 $\pm$ 4	29 $\pm$ 4*
LVEDD (mm)	47 $\pm$ 7	47 $\pm$ 6	46 $\pm$ 5	50 $\pm$ 6*
LVESD (mm)	32 $\pm$ 4	31 $\pm$ 5	30 $\pm$ 4	33 $\pm$ 5*
Relative wall thickness	0.35 $\pm$ 0.06	0.39 $\pm$ 0.07	0.39 $\pm$ 0.06	0.41 $\pm$ 0.08*
Va velocity (m/sc)	0.71 $\pm$ 0.16	0.73 $\pm$ 0.21	0.67 $\pm$ 0.16	0.81 $\pm$ 0.25*
IVRT (msc)	88 $\pm$ 16	87 $\pm$ 24	90 $\pm$ 13	109 $\pm$ 21*
MPI	0.47 $\pm$ 0.21	0.49 $\pm$ 0.14	0.47 $\pm$ 0.13	0.62 $\pm$ 0.17*
Aortic velocity (m/sc)	1.13 $\pm$ 0.20	1.05 $\pm$ 0.15	1.12 $\pm$ 0.21	1.19 $\pm$ 0.24*
IVCa velocity (cm/sc)	7.09 $\pm$ 1.69	7.55 $\pm$ 2.02	7.67 $\pm$ 1.92	6.73 $\pm$ 1.52*
Sa velocity (cm/sc)	9.57 $\pm$ 1.12	9.75 $\pm$ 1.76	9.57 $\pm$ 1.30	8.93 $\pm$ 1.61*
Q-Sa interval (msc)	192 $\pm$ 26	191 $\pm$ 28	198 $\pm$ 27	211 $\pm$ 53*
IVRb velocity (cm/sc)	5.88 $\pm$ 1.30	6.12 $\pm$ 1.01	6.36 $\pm$ 1.28	5.55 $\pm$ 1.22*
Ea velocity (cm/sc)	11.91 $\pm$ 2.28	11.78 $\pm$ 3.12	12.40 $\pm$ 2.49	9.87 $\pm$ 2.64*
Ea-Dt (msc)	137 $\pm$ 32	139 $\pm$ 29	136 $\pm$ 28	152 $\pm$ 33*
Ea VTI (cm)	1.59 $\pm$ 0.79	1.50 $\pm$ 0.29	1.53 $\pm$ 0.40	1.29 $\pm$ 0.31*
Q-Ea interval (msc)	539 $\pm$ 39	550 $\pm$ 44	549 $\pm$ 39	564 $\pm$ 44*
Q-Aa interval (msc)	780 $\pm$ 117	815 $\pm$ 114	815 $\pm$ 135	848 $\pm$ 134*

BP = blood pressure, LVMI = left ventricular mass index, LVEDD = left ventricular end-diastolic diameter, LVESD = left ventricular end-systolic diameter, Va velocity = left ventricle late diastolic velocity, IVRT = isovolumetric relaxation time, MPI = myocardial performance index,

IVCa = first tissue velocity of the isovolumetric contraction time, Sa = systolic tissue velocity, Q-Sa = time period between the electrocardiographic Q wave and Sa velocity, IVRb = negative velocity of the isovolumetric relaxation time, Ea = early diastolic tissue velocity, Ea-Dt = deceleration time of early diastolic tissue velocity, Ea VTI = early diastolic velocity time integrals, Q-Ea = time period between electrocardiographic Q wave and Ea tissue velocity,

Q-Aa = time period between electrocardiographic Q wave and Aa tissue velocity.

\* indicates significant differences among groups at  $p < 0.005$  level.

and ejection times were no different among groups. These findings may indicate that left ventricle diastolic functions gradually change in essential hypertension patients, especially those with LVH as a result of increase in the systolic BP and LVMI.

Among the pulse-wave TDI parameters of the isovolumetric contraction (IVCa) time, first tissue velocity of the IVCa time was significantly lower in group 4 compared to group 3 ( $p=0.026$ ). Second velocity of the isovolumetric contraction time, however, was not different among groups. The systolic tissue velocity (Sa) was significantly lower in group 4 compared to group 2 ( $p=0.039$ ). The Q-Sa, which represents the time period between the Q wave in simultaneous ECG and the Sa velocity obtained with the pulse-wave TDI method, was significantly longer in group 4 compared to group 2 ( $p=0.050$ ). Among the parameters of the

isovolumetric relaxation time of the diastolic period, positive tissue velocity was not different among groups; however, negative tissue velocity was significantly lower in group 4 compared to the group 3 ( $p:0.003$ ). The most prominent difference was observed in the early diastolic tissue velocity (Ea). In group with LVH (group 4), the Ea velocity was significantly lower compared to all groups ( $p < 0.001$  for all groups). The Ea deceleration time in group 4 was significantly longer compared to group 3 ( $p=0.037$ ). The Ea velocity time integral (VTI) in group 4 was significantly lower compared to groups 1 ( $p=0.020$ ) and 3 ( $p=0.007$ ). There were no significant differences among the groups as far as the pulsed-wave TDI late diastolic velocity (Aa) and Aa VTI. The time periods from the Q wave in simultaneous ECG to the Ea velocity (Q-Ea interval) and to Aa velocity (Q-Aa interval) were significantly longer in group

4 ( $p=0.021$ ) compared to group 1 ( $p=0.050$ ). These changes may be indicative of systolic and diastolic dysfunction in essential hypertension patients who developed LVH. Considering the late opening of the mitral valve as evidence of diastolic dysfunction,<sup>3</sup> the prolonging of the Q-Ea and Q-Aa intervals may also be other indicators of diastolic dysfunction. The Q-Sa interval was prolonged, and the IVCa and Sa velocities were decreased in patients with LVH (group 4). Since, we know that decreased Sa velocity is predicted<sup>4</sup> to systolic dysfunction, these findings might support the interpretation that systolic dysfunctions occurred. This interpretation would be more meaningful considering the findings of the study by Fukuda et al<sup>5</sup> that the prolonging in the Q-Sa interval is highly sensitive in revealing systolic dysfunction. The most important limiting factor in our study was that a similarity in drug use among patients with essential hypertension could not have been established. In patients who developed LVH, multiple drugs were generally used. The second limiting factor arose when exclusion of atherosclerotic coronary artery disease in essential hypertension patients. The coronary angiography might have been helpful in this matter. However, our study commission did not find this procedure ethical.

As LVH develops in essential hypertensive patients, LVESD, LVEDD, the diameter of the left atrium, and diameter of the proximal aorta are increased and subsequently, systolic and diastolic dysfunction develop. Although the diastolic dysfunction can be revealed by standard ECHO as well as pulsed-wave TDI parameters, systolic dysfunction, however, can be revealed only by pulsed-wave TDI parameters.

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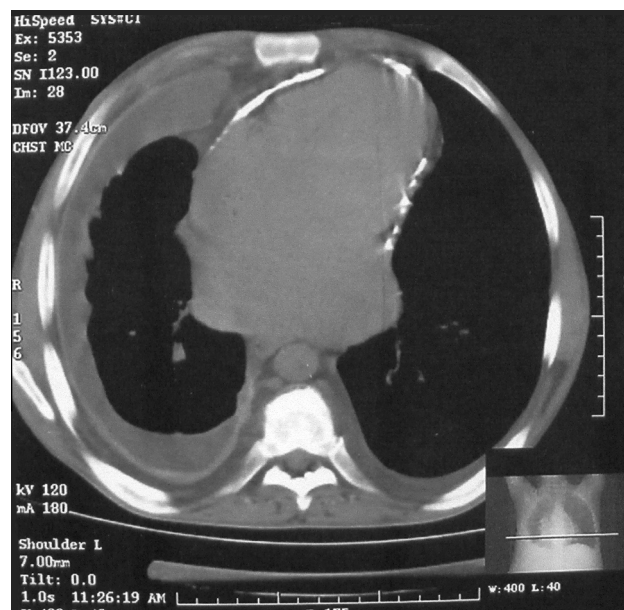
## Constrictive pericarditis presenting as recurrent ascites for 10 years

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Constrictive pericarditis (CP) is a very important pericardial disease and an underestimated and sometimes unrecognized cause of severe chronic ascites. The varied etiologies of CP parallel those of acute pericarditis and etiologies can be broken down by frequency into common (idiopathic, infectious [bacterial], radiation-induced, post-surgical); less common (infectious [fungal], neoplasms, uremia, connective tissue disorders, drug-induced, trauma, myocardial infarction) and rare forms (toxic or metabolic, intrapericardial instrumentation, hereditary [Mulibrey nanism syndrome], chemical trauma and chylopericardium).<sup>1-4</sup> We report a patient with chronic constrictive pericarditis and heavy pericardial calcification in whom the natural history of the disease has not been discovered despite 10 years of medical treatment. This should be rare in today's world of medicine and begs attention to the role that general practitioners play in early disease recognition and hence correct treatment. A 20-year-old male, nonsmoker, normotensive, nondiabetic, laborer from a rural area of Kashmir valley had 10 years history of recurrent ascites, for which he was under the supervision of a local practitioner in their place. Two to 3 liters of straw-colored fluid was drained every now and then and the patient would resume to his routine work. During this period he was never requested to go for investigations or hospitalization. The interval between the first and the second drainage of ascitic fluid was 3 years and afterwards the drainage was needed more frequently (after an interval of 6 months to one year). After a 10-year illness, deterioration in the functional status was observed and the patient was admitted to the Medical College Associated Hospital with cough and mucoid expectoration, breathlessness,

New York Heart Association (NYHA) class II-III and fatigue. He was diagnosed as tuberculous ascites and was started on antitubercular medications, diuretics and other symptomatic treatment. He was referred to the cardiology department for further evaluation and treatment. On examination the patient looked emaciated. His neck veins were distended and he had a positive Kussmaul's sign. The pulse rate was 90/min, irregular blood pressure 120/80 mm Hg and chest examination suggestive of bilateral pleural effusion more on the right side. Cardiac examination revealed irregular heart rate with S3 (diastolic knock, which was also palpable). Abdominal examination revealed abdominal wall edema, ascites, and hepatomegaly. Investigations revealed hemoglobin 12.8 g/dl, normal white blood cells and platelet counts. The erythrocyte sedimentation rate was 30 mm. Liver function tests revealed serum bilirubin 1.2 mg/dl, total proteins 5.6 gms/dl, serum Albumin 2.6 gms/dl, alanine aminotransferase 45U/l and aspartate aminotransferase 50U/l. Blood sugar and kidney function tests were normal. Ascitic fluid was straw-colored and transudative. Bacterial cultures were negative. There were no malignant cells. It was acid-fast bacilli negative. Tuberculin test was negative. Electrocardiogram showed diffuse low voltage and atrial fibrillation. Echocardiography showed aortic root 26 mm, left atrial dimension 69 mm, left ventricular end diastolic dimension 34 mm, left ventricular end systolic dimension 14 mm and ejection fraction 86%. There was a septal bounce. Mitral E velocity was 1 m/sec, a velocity 0.2 m/sec and E/A ratio was suggestive of restrictive filling pattern. There was more than 25% respiratory variation in E velocity across the mitral valve and more than 40% variation in E velocity across tricuspid valve. Inferior vena cava diameter was 42 mm with no respiratory variation. Chest x-ray showed bilateral pleural effusion, cardiomegaly and pericardial calcification. Contrast enhanced CT scan of the chest revealed pericardial thickness of 15 mm with gross pericardial calcification (Figure 1). Right heart catheterization revealed right atrial (RA) mean pressure 23 mm Hg, right ventricle (RV), 40/26 mm Hg, pulmonary artery (PA) 40/30 mm Hg (mean 28) and pulmonary capillary wedge pressure mean 25 mm Hg. All suggestive of CP. The patient was initially offered symptomatic treatment in the form of drainage of ascitic fluid, a loop diuretic and spironolactone. He was later subjected to surgical decortication, but the patient died during the procedure.

Constrictive pericarditis represents the end stage of an inflammatory process of varying etiologies involving the Pericardium. The constrictive process can follow an initial insult by as little as several months.<sup>3,5</sup> At an earlier stage the patient may present with features of systemic



**Figure 1-** Contrast enhanced CT scan of the chest revealed pericardial thickness of 15 mm with gross pericardial calcification.

venous congestion. Signs and symptoms ascribable to elevated pulmonary venous pressure may also appear with disease progression. Pericardial calcification is seen in a small number of patients and raises the suspicion of tuberculous pericarditis.<sup>4</sup> Surgical pericardiectomy is the only definitive treatment and is associated with 5-15% perioperative mortality.<sup>3</sup> The highest mortality occurs in patients with NYHA class III and class IV perioperative symptoms.

In conclusion, while evaluating and treating a patient with ascites, CP should be suspected and ruled out early as this is a potentially reversible cause which can be treated with less mortality as compared to the late stages of disease when operative mortality is considerably higher.

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### Ultrastructure study of postmenopausal endometria of tibolone, conjugated estrogen + medroxyprogesterone acetate and tamoxifen users

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The ultrastructure of the normal endometrium was first described by Nilsson.<sup>1</sup> Although there were data available related to the ultrastructure of the endometria of the patients under the different hormone therapies (unopposed estrogen, progestin, clomiphene citrate, danazol, cyproterone acetate) and diseases such as endometrial carcinoma,<sup>2</sup> the endometria of the postmenopausal women receiving different treatment modalities currently available were not well studied ultrastructurally using the transmission electron microscope (TEM). The response of the ultrastructure of endometrial cells in the postmenopausal endometrium to unopposed estrogen replacement therapy was studied previously.<sup>3</sup> The aim of this researcher was to understand the ultrastructural pathogenesis of endometrial carcinoma. Ultrastructural similarities were found between estrogen treated postmenopausal endometrium and endometrial adenocarcinoma. It has been reported that the ultrastructure of the postmenopausal endometrium resembled the late proliferative phase endometrium of the normal cycle when estrogen replacement was given alone. However, Ludwig<sup>4</sup> studied the ultrastructural effects of progestational agents on the endometrium. In this study, we aimed to investigate the ultrastructural effects of 2 different hormone replacement therapy (HRT) regimens [tibolone and conjugated estrogen (CE) + medroxyprogesterone acetate (MPA)] and tamoxifen on the postmenopausal endometrium by TEM.

Twenty postmenopausal women, 5 of whom were operated for breast cancer admitted to the Department of Obstetrics and Gynecology, Gazi University Hospital, Ankara, Turkey, during January 2005-December 2005 were included in this study. Patients were divided

into 3 groups (consisting of 5 women in each group) according to the regimen given. They were receiving either 2.5 mg/day tibolone, or 0.625 mg/day CE plus 5 mg/day MPA or tamoxifen 20 mg/day in each group for at least 6 months. Aside from these patients, 5 postmenopausal patients were selected as the control group. We performed pipelle endometrial biopsy on all patients. The endometrial specimen was fixed in 2.5% glutaraldehyde for 24 hours, washed in phosphate buffer (pH 7.4), post-fixed in 1% osmium tetroxide in phosphate buffer (pH 7.4) and dehydrated in increasing concentrations of alcohol. Then, the tissues were washed with propylene oxide and embedded in epoxy-resin embedding media. Semi-thin sections approximately 2 mm in thickness and ultra-thin sections approximately 60 nm in thickness were cut with a glass knife on an LKB-Nova (Sweden) ultra-microtome. Ultra-thin sections were collected on copper grids, stained with uranyl acetate and lead citrate and examined with TEM (Jeol JEM 1200 EX, Japan). Electron microscopy of the endometrial specimen showed moderately active cells with heterochromatic nuclei and moderately increased the number of organelles in the tibolone group. In the CE+MPA group, there were active cells with the increased number of endoplasmic reticulum, mitochondria, and Golgi apparatus. Contrary to the tibolone and CE+MPA groups, tamoxifen users have demonstrated inactive cells with the heterochromatic nucleus. All the organelles were the least in number in tamoxifen users among the 3 regimens. The details of ultrastructural findings of the tibolone, CE+MPA and tamoxifen have been shown in Table 1.

At the beginning of the normal menstrual cycle, endometrial cells are relatively undifferentiated. Estrogen causes cellular proliferation followed by differentiation during proliferative phase. Rough and smooth endoplasmic reticulum and the Golgi apparatus are poorly developed at the beginning of the cycle. Lysosome-like bodies and free ribosomes are abundant anywhere in the cytoplasm at this stage. Basal and apical cytoplasm contains mitochondria, which do not have cristae. During the late proliferative phase, the number of free ribosomes is decreased and lysosome-like bodies disappear. Smooth and rough endoplasmic reticulum and the Golgi apparatus become prominent. Ciliated cells are increased in number and lateral processes are seen near the base of the cells causing irregular appearance of cellular borders. Glycogen in the cytoplasm is present at this stage.<sup>1</sup> Ultrastructural changes in the secretory phase of the normal menstrual cycle endometrium are apical protrusions at luminal epithelial cells and secretory products within the glands' openings. Massive glycogen deposits are common while minimal lipid deposits are seen at the very late

## Ultrastructure study of postmenopausal endometria

**Table 1** - The ultrastructural findings of tibolone, CE+MPA and tamoxifen.

Electron microscopic findings of endometrium	Tibolone	CE+MPA	Tamoxifen
Celular activity	Normal	Hyperactive	Inactive
Nucleus	Heterochromatic	Euchromatic	Heterochromatic
Mitochondrial cristae	Prominent	Prominent	Prominent
Smooth endoplasmic reticulum	Ultrastructurally normal	Mild dilations	Ultrastructurally normal
Rough endoplasmic	Ultrastructurally normal	Ultrastructurally normal	Ultrastructurally normal
Free ribosomes	Normal in appearance	Normal in appearance	Normal in appearance
Golgi apparatus	Ultrastructurally normal	Highly dilated	Ultrastructurally normal
Secretory granules	†	‡	*
Glycogen deposits	*	‡	*
Lipid deposits	†	‡	*
Interdigitated lateral borders	Absent	Absent	Absent
Tendency for dehiscence	Absent	Absent	Absent
Perinuclear cisternae	Normal	Dilated	Dilated

\* A few, † Moderate in number, ‡ Abundant  
CE - conjugated estrogen, MPA - medroxyprogesterone acetate

secretory phase. Giant mitochondria, with the tubular cristal pattern are abundant to provide high energy during this phase. There is a tendency for dehiscence of cellular borders at the base which is interdigitated by lateral cytoplasmic processes.<sup>5</sup> Ultrastructure of the postmenopausal endometrium was described by Aycock et al<sup>3</sup> as decreased cytoplasmic complexity. Lateral cell borders are interdigitated, and cytoplasmic extensions are decreased. The cells had few cilia. There were highly developed Golgi apparatus, in contrast the number of free ribosomes was greatly reduced. Lysosome like bodies, lipid droplets, and glycogen granules were abundant in the postmenopausal endometrium. Ultrastructural effects of unopposed estrogen on postmenopausal endometrium<sup>2</sup> were irregular nuclei and an abnormally large number of structurally normal mitochondria present in the endometrial glandular cells. Abundance of ribo-nuclear protein, which is decreased in the late proliferative phase of the normal cycle, and the absence of glycogen deposits, which are present during the late proliferative phase of the normal cycle were striking findings in the estrogen-treated tissue. There were large lipid droplets which were not seen in the normal proliferative phase. In addition, perinuclear microfilaments were seen in the endometrial cells. The ultrastructural response of human endometrium to

progestational agents.<sup>4</sup> Defective cilioneogenesis was the common response. The other findings of surface epithelium treated with progestogens were similar to a normal cyclic endometrium. In that study it has been found that progestins when combined with estrogens, administered for the control of bleeding, caused irregular proliferation of glands, focal proliferative hyperplasia and little marginal polyp formation near glandular openings. Investigation of the ultrastructure of endometrial carcinoma showed that there were 2 types of cells, named as type I and II.<sup>3</sup> Type I cells were larger than normal glandular cells with the less electron-dense cytoplasmic matrix than type II cells. The cells borders were interdigitated with lateral extensions and there was increase in the intercellular space. Microvilli and cilia were rare. Nuclear pleomorphism and giant atypical mitochondria in both cell types were present. Although smooth endoplasmic is relatively less highly developed, both rough and smooth endoplasmic reticulum occurred in large amounts. Free ribosomes and lysosome like bodies were more than in normal endometrium. Golgi apparatus was less developed. Glycogen and lipid deposits were abundant. Except an increase in the number of free ribosomes (characteristic of early proliferative phase), other findings of endometrial carcinoma resemble the early secretory phase.

In this study, in the patients receiving CE+MPA, the hyperactivity of all the organelles was striking. Ultrastructural changes caused by CE+MPA were similar to the late proliferative phase of the normal menstrual cycle. The most significant finding was euchromatic nucleus (a finding of cellular hyperactivity). There were active cells with increased number of endoplasmic reticulum, mitochondria, and Golgi apparatus. The cells had dilated Golgi apparatus. These findings implied increased synthesis capability of endometrial cells. Similar to estrogen-treated postmenopausal endometrium, lipid deposits were abundant. While glycogen deposits were present in the cells of the all regimens, CE+MPA users had the highest in number. The ultrastructure of the endometrium of tibolone users showed cellular activity between CE+MPA and tamoxifen users. Changes in organelles caused by tibolone were not as prominent as the CE+MPA. The nucleus was heterochromatic (a finding of normal cellular activity). The least active cells were present among tamoxifen users. The cells had the heterochromatic nucleus. The organelles were the least in number. However, none of these preparations showed ultrastructural similarities to unopposed estrogen use or endometrial carcinoma such as significantly increased number of free ribosomes, lysosome like bodies, smooth and rough endoplasmic reticulum, giant mitochondria, nuclear pleomorphism and perinuclear microfilaments.

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## Metformin discontinuation rate among patients with type-2 diabetes mellitus in Basrah, Iraq

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Metformin is a biguanide, first introduced in 1957 as an oral glucose-lowering agent, that reduces plasma glucose by decreasing hepatic glucose output and enhancing insulin-mediated glucose utilization (reduce insulin resistance).<sup>1</sup> The long-term blood glucose-lowering efficacy of metformin is broadly similar to sulfonylureas as monotherapy in patients who are not adequately controlled on nonpharmacological therapy. The sulfonylureas generally cause weight gain, while metformin does not, and may even reduce weight. It reduces plasma glucose by 2-4 mmol/L, corresponding to a decrease in glycated hemoglobin (HbA1C) by 1-2%. Metformin also appeared to be superior to sulfonylureas in cardiovascular protection and patient survival in UK Prospective Diabetes Study.<sup>2</sup> It is widely accepted as the first line drug, relatively effective, safe, and cheap. It improves hirsutism, normalizes menstrual cycles, and induces ovulation in a substantial number of patients with polycystic ovary syndrome.<sup>1</sup> Furthermore, metformin can be considered as a first-line agent for the prevention of type-2 diabetes.<sup>3</sup> The aim of the present work is to determine, in a cohort of patients with type-2 diabetes mellitus (DM), the discontinuation rate and causes of discontinuation of metformin use.

The study was conducted in a diabetes center in Al-Faiha Hospital, Basrah, Iraq. Patients were followed in the outpatient clinic from 6 months to 4 years. Patients discontinued from using other drugs by doctors for various reasons, such as treatment failure, contraindication, failed follow-up, or follow up of less than 6 months, were excluded from the study. From a total of 2,331 patients with type-2 DM, 1019 (43.7%) used metformin from January 2003 to December 2006. Patients were seen every 1-3 months, and were asked about metformin use in each visit. Metformin therapy was initiated (alone or with other drugs) with a single dose of medication (usually 500 mg) taken with the patient's largest meal to prevent gastrointestinal symptoms. Medication doses may be increased by 500 mg every 1-2 weeks, as indicated by the glycemic control, to a desirable blood glucose level, or the maximum recommended daily metformin dose of 2550 mg according to the recommendation.<sup>1</sup> Patients who are widowed, separated, single, or divorced were considered unmarried. Qualifications (years of school achievement)



were divided into 2 groups, 6 years and less, and above. The standing height and weight measurements were completed with the subjects wearing lightweight clothing, and without shoes. Height was measured to the nearest cm, and the weight to the nearest half-kilogram (kg). Body mass index (BMI) was calculated as body weight in kg divided by the squared value of body height in meters (kg/m<sup>2</sup>). Subjects who smoke at least one cigarette per day during the year before the examination were classified as smokers. The data analysis was performed using Statistical Package for Social Sciences version 8 (SPSS, Chicago, IL, USA).

The total number of patients was 1019 (mean age 51.72±10.8 year), 50.9% male, 86.6% married, 47.1% illiterate, 37.4% obese, 23.3% smoker, and 72.5% urban dwellers. The patient who discontinued metformin totalled 560 (54.9%). Demographic factors associated with discontinuations of metformin (Table 1) were male (OR, 0.7; 95% CI, 0.5-0.9; *p*=0.01), and age ≤50 years (OR, 0.6; 95% CI, 0.4-0.7; *p*=0.0001). No association between discontinuation and marital status, qualification, BMI, smoking state, or residency were observed. When these variables significantly associated with discontinuation were entered simultaneously into

a logistic regression model, only those age's ≤50 years remained significantly associated with discontinuation. The cause of discontinuation was 17.5% due to adverse effects, mainly gastrointestinal, such as diarrhea, colic, and cramps. Patients who stop taking the drugs do not believe in its hypoglycemic effects (66.7%), as no hypoglycemia occurs, or it does not cause marked immediate blood glucose lowering effect. No cause for discontinuation was seen in 15.7% of patients. More than half of our patients in this study stopped metformin against the medical advice. This complicated the management of our patients since using the sulfonylureas alone, or insulin alone, is not effective enough for glycemic control especially with the progress of diabetes.<sup>4</sup> Thiazolidinediones, a carbose as an oral agent, are not available widely in our country due to their high cost. Most of our people self medicate on sulfonylureas, a glibenclamide, which is cheap and available, even without prescriptions. More males, aged ≤50 years, discontinued metformin. A similar finding of older age-groups being more adherent to metformin prevention therapy than the young group was found by Walker et al.<sup>5</sup> Adverse effects as a cause of discontinuation of metformin were seen in 17.5%,

**Table 1** - Univariate association of metformin discontinuation with demographic factors.

Variables	Continued n (%)	Discontinued n (%)	OR	95% CI	<i>p</i> -value
<i>Gender</i>					
Male	214 (46.6)	305 (54.5)	0.7	0.5-0.9	0.01
Female	245 (53.4)	255 (45.5)			
<i>Age (years)</i>					
≤50	175 (38.1)	279 (49.8)	0.6	0.4-0.7	0.0001
>50	284 (61.9)	281 (50.2)			
<i>Marital status</i>					
Married	388 (84.5)	495 (88.4)	0.7	0.5-1	0.07
Unmarried	71 (15.5)	65 (11.6)			
<i>Qualification (years)</i>					
≤6	225 (49.0)	255 (45.5)	1.1	0.8-1.4	0.2
>6	234 (51.0)	305 (54.5)			
<i>Body mass index</i>					
<30	272 (59.3)	365 (65.2)	0.7	0.6-1	0.05
≥30	187 (40.7)	195 (34.8)			
<i>Smoking</i>					
Yes	101 (22.0)	137 (24.5)	0.8	0.6-1.1	0.3
No	358 (78.0)	423 (75.5)			
<i>Residency</i>					
Urban	334 (72.8)	405 (72.3)	1	0.7-1.3	0.8
Rural	125 (27.2)	155 (27.7)			

OR - odds-ratio, CI - confidence interval

which is comparable with literature, where up to 20% of patients have gastrointestinal side effects, and 10% cannot tolerate the drug.<sup>1</sup> Those who do not believe in its effect, have no cause, and hence stop therapy constitute 82.4%.

We conclude that in practice, maximal doses of the commonly used sulfonylureas will reduce HbA1C levels by 1.1-1.9%, the same range as metformin and thiazolidinediones.<sup>1</sup> The results show that we are dealing with a misconception of metformin, which is considered the first choice in the management of type 2 diabetes.<sup>1</sup> One of the cause of this misconception is probably the educational level of our subjects, as 47.1% were illiterate, despite 72.5% being from the urban areas.

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