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From the Editor

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This is the third issue this year that is rich with papers from the region dealing with various topics. A case- control study from Jordan was designed to assess the relation between maternal anaemia in the third trimester and premature birth. A total of 200 women were included in the study and divided into two groups. Maternal anaemia was defined as haemoglobin level < 11g/dL and preterm delivery was defined as delivery prior to 37 weeks of gestation. Patients with haemoglobinopathies, systemic diseases. It was observed that maternal anaemia in the third trimester, at labour, was associated with an increased risk of prematurity.

Helvaci et al tried to understand whether or not there is a significant relationship between cholelithiasis or cholecystectomy and plasma lipids. One hundred and forty-four cases either with cholelithiasis or cholecystectomy for cholelithiasis were included. The authors concluded that there are significant relationships between cholelithiasis and parameters of the metabolic syndrome. Although the significantly lower prevalence of hyperbetalipoproteinemia probably due to the decreased amount of bile acids secreted during entrance of food into the duodenum and decreased amount of cholesterol absorbed in patients with cholelithiasis or cholecystectomy, the higher prevalence of hypertriglyceridemia may actually indicate its primary role as an acute phase reactant in the plasma.

A paper from Turkey, Lebanon and Australia looked at the effect of Triglyceride level on survival. The study included 478 cases (288 females and 190 males). Metabolic syndrome is a chronic inflammatory process mainly affecting the vascular endothelium all over the body and terminating with early aging and premature death. Hypertriglyceridemia may be one of the most significant reversible parameters of the metabolic syndrome, and it is better to have the lowest plasma triglyceride value as much as possible to live longer.

Haddad et al through descriptive study looked out the most common local side effects caused by inhalers in patients with Chronic Obstructive Pulmonary Disease (COPD). The effect of regular mouth rinsing with water after inhaler use in preventing these side effects was evaluated too. The authors concluded that local side effects of inhalers are common among COPD patients treated in KHMC. The most common side effects are throat and vocal complaints. Failure to adhere to mouth rinsing with water after inhaler use plays a major role in increasing the rates of these side effects.

A retrospective study from Yemen of descriptive patterns of findings seen in hysterectomy specimens based on records from Modern - histopathology laboratory in Aden. A total of 2544 specimens were analyzed during the 6 years period, to study the histopathological findings of these specimens. Most common pathology findings are, Endometrial hyperplasia 1481 (58.3%), Non neoplastic cystic lesion 1386 (54.5%), Chronic cervicitis 1363 (53.6%), Adenomyosis 793 (31.2%) follow by Leiomyoms 697 (27.4%). Other less frequent pathologies identified included atrophic endometrium, Inadequate secretory endometrial transformation, Gestational Trophoblastic disease, Endometroid adenocarcinoma, cervical prolapse. This study confirms that benign pathologies are more common in hysterectomy specimens than their malignant counterparts.

A randomized study from in which 40 patients with recurrent or advanced non–small-cell lung cancer (stage IIIB or IV) received paclitaxel and carboplatin (paclitaxel–carboplatin arm) (20 patients) or paclitaxel and carboplatin in addition to bevacizumab (paclitaxel–carboplatin–bevacizumab arm) (20 patients). The median overall survival was 15.5 months in the paclitaxel–carboplatin–bevacizumab arm as compared with 10.5 months in the paclitaxel–carboplatin arm (P=0.002). The authors concluded that the addition of bevacizumab to the chemotherapy add a significant value to the patients with non squamous nsclc in terms of response rate, progression free survival and overall survival however with significant side effects.

Helvaci et al investigate the role of Moderate anemia and metabolic syndrome. Age and sex-matched cases with a hematocrit value of less than 30% were collected into the first, less than 36% into the second, less than 40% into the third, and 40% or greater into the fourth groups. The study included 108 anemia patients. The anemia cases were mainly iron deficiency anemia and/or thalassemia minors. When we compared the first group with the second, the BMI and weight were significantly retarded in the first group (23.6 versus 26.9 kg/m2, p= 0.005 and 61.3 versus 69.9 kg, p= 0.008), whereas there were nonsignificant differences between the second, third, and fourth groups for both (p>0.05 for all). Although the significantly retarded BMI and weight in the first group, body heights were similar in the four groups (p>0.05 for all). The authors concluded that although the BMI and weight can be affected by moderate anemia, the height may strongly be determined by heredity. Since the excess weight may be a significant underlying cause of the metabolic syndrome, and the metabolic syndrome shortens human lifespan significantly, and there is no case with shortened survival due to iron deficiency anemia and/or thalassemia minors, an iatrogenic and moderate iron deficiency anemia with frequent blood donation may prolong human survival by decreasing the BMI and weight in the overweight and obese individuals.

Local side effects of inhalers in patients with COPD in KHMC

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ABSTRACT

Objective: To find out the most common local side effects caused by inhalers in patients with Chronic Obstructive Pulmonary Disease (COPD), treated in the pulmonary clinic in King Hussein Medical Center (KHMC). The effect of regular mouth rinsing with water after inhaler use in preventing these side effects was also evaluated.

Method: Descriptive study of 127 patients diagnosed to have Chronic Obstructive Pulmonary Disease (COPD) between January 2015 and January 2017 , treated in the pulmonary clinic in King Hussein Medical Center (KHMC). The rates of different local side effects of inhalers used in Chronic Obstructive Pulmonary Disease (COPD) were assessed in patients using inhalers regularly for more than 6 months, during their regular visit to the pulmonary clinic, using a questionnaire. The rates of regular mouth rinsing after inhaler use were evaluated as well.

Results: Of the 127 patients enrolled in our study, 93 patients (73%) were males. The mean(±SD) age was 68.0±7.6 years. The ages ranged between (47-79) years. 102 patients (80%) reported at least one adverse local side effect of inhalers .The most common local side effect was sore throat, affecting 29 patients (23%). Other side effects included dysphonia (18%), mouth ulcers (2%), oral candidiasis (5%), thirst (17%) and dry throat (21%). Out of the 102 patients who reported having local side effects of inhalers, 82 patients (80%) admitted that they don't rinse their mouth after inhaler use. Out of the 25 patients who didn't have adverse local side effects from the inhalers, only 2 patients (8%) admitted that they don't rinse their mouth regularly after inhaler use.

Conclusion: Local side effects of inhalers are common among COPD patients treated in KHMC. The most common side effects are throat and vocal complaints. Failure to adhere to mouth rinsing with water after inhaler use plays a major role in increasing the rates of these side effects.

Key words: COPD, Side effects, Inhalers

Introduction

Chronic Obstructive Pulmonary Disease (COPD) is considered one of the most common diseases worldwide. It is currently the fourth leading cause of death worldwide.(1) By 2020, COPD is expected to account for more than 3 million deaths annually, and to be the third leading cause of death worldwide.(2)

Inhaler therapy is considered the main mode of treatment of COPD. Bronchodilators, including Beta-2 agonists and anticholinergics, as well as inhaled corticosteroids, are considered to be the cornerstones in the management of COPD. (3) Despite the efficacy of inhaler therapy in managing COPD, adverse local side effects of these inhalers, especially inhaled corticosteroids, are common among these patients. (4-8) Those side effects are usually neglected and underestimated by both the patients and the physicians .(9,10) The different adverse local side effects of inhalers in COPD patients are poorly studied, and the information regarding the rates of these side effects are limited.(7) Direct questioning by the treating physician, as well as spontaneous patient reports regarding the different adverse side effects of inhaler therapy in COPD patients, are considered very important in detecting these side effects, and managing them properly and effectively. (11)

In our study, our aim was to assess the different adverse local side effects of inhalers in patients with COPD, treated in the pulmonary clinic in King Hussein Medical Center (KHMC). The effect of regular mouth rinsing after the use of inhalers in preventing these side effects was evaluated as well.

Materials and Methods

In our study, 127 patients who are diagnosed to have COPD, and who are regularly followed up and treated in the pulmonary clinic in KHMC, were enrolled in this study done between January 2015 and January 2017. Thorough explanation of the aims of the study was done to all the patients, after which a consent form was signed by all the patients prior to enrolling them in the study. Approval of the ethical committee was obtained in order to carry out the study. Inclusion criteria were as follows: age >40 years, current or former smokers, and an established diagnosis of COPD for at least 3 years. Exclusion criteria were as follows: immunocompromised patients, patients who received oral or parenteral corticosteroids for more than 2 weeks during the last 6 weeks , patients who suffered from an exacerbation requiring hospitalization during the last 6 weeks, patients who are not receiving inhaled corticosteroids as a part of their treatment, and patients who are non compliant to their inhalers.

After being enrolled in the study, all the patients were evaluated by a pulmonologist in the clinic. Information regarding the age and the gender of the enrolled patients were gathered. The type of inhalers used by the patients was recorded. Afterwards, the patients were asked to answer a questionnaire during their regular visit to the clinic. The questionnaire asked whether or not the patient suffered from any local side effect after using the inhalers. The side effects that were mentioned included the following: change of voice (dysphonia), oral ulcers, oral candidiasis, sore throat, thirst and dry throat. The patients

were also informed that they can mention any other local side effect, and they can choose more than one side effect if they have experienced them at any time during their treatment with the inhalers. The patients were asked to answer whether or not they are compliant to rinsing their mouth regularly with water after the use of their steroid inhaler.

The number and percentage of patients who developed each local side effect was calculated, and the number and percentage of those who were not compliant to regular mouth rinsing was assessed as well, and a comparison between the group of patients who developed local side effects and those who did not was done in order to assess the efficacy of mouth rinsing in preventing the local side effects of the inhalers.

Results

127 patients with COPD , who are using regular inhaler therapy were enrolled in this study. 93 patients (73%) were males. The mean (±SD) age was 68.0±7.6 years. The ages ranged between (47-79) years.

Overall, 102 patients (80%) reported at least one adverse local side effect. The most common side effect was sore throat, which was mentioned by 29 patients (23%). Dry throat, dysphonia and thirst were the next most common local side effects, mentioned by 21%, 18% and 17% respectively.

Chart 1 shows the number of patients who developed different local side effects of inhalers in this study.

Discussion

In our study, adverse local side effects of inhaler therapy in patients with COPD were found to be high, with about 80% of the patients having at least one local side effect. This proves that there is a high prevalence of local side effects of inhalers. Many other studies found the same observation regarding the prevalence of side effects of inhalers. (12-14) The most common side effects mentioned by the patients were mainly sore throat and throat dryness, both of which accounted for more than half the side effects mentioned by the patients (44% of all the patients, and 55% of those who had side effects). This was also observed by other studies, which found a high prevalence of throat symptoms in patients using inhalers. (12,13) Oral cavity side effects, such as oral candidiasis and oral ulcers were seen in only 7% of the patients. In other studies, the rates of oral cavity side effects vary widely, with studies estimating the prevalence of oral candidiasis to range between 0-70%. (4,5,15) This wide range may be caused by the dose of the inhalers, mainly the inhaled corticosteroid dose, and the duration of the therapy.

Thirst was observed as a side effect in 17% of the patients in our study. In one cross sectional study, this side effect was seen in 42-60% of the patients included in the study. (6) However, this high rate might be explained by the fact that this cross sectional study was conducted on patients with bronchial asthma rather than COPD, who were maintained on a high dose of inhaled corticosteroids.

local side effects of inhalers

- dysphonia
- mouth ulcers
- oral candidiasis
- sore throat
- thirst
- dry throat
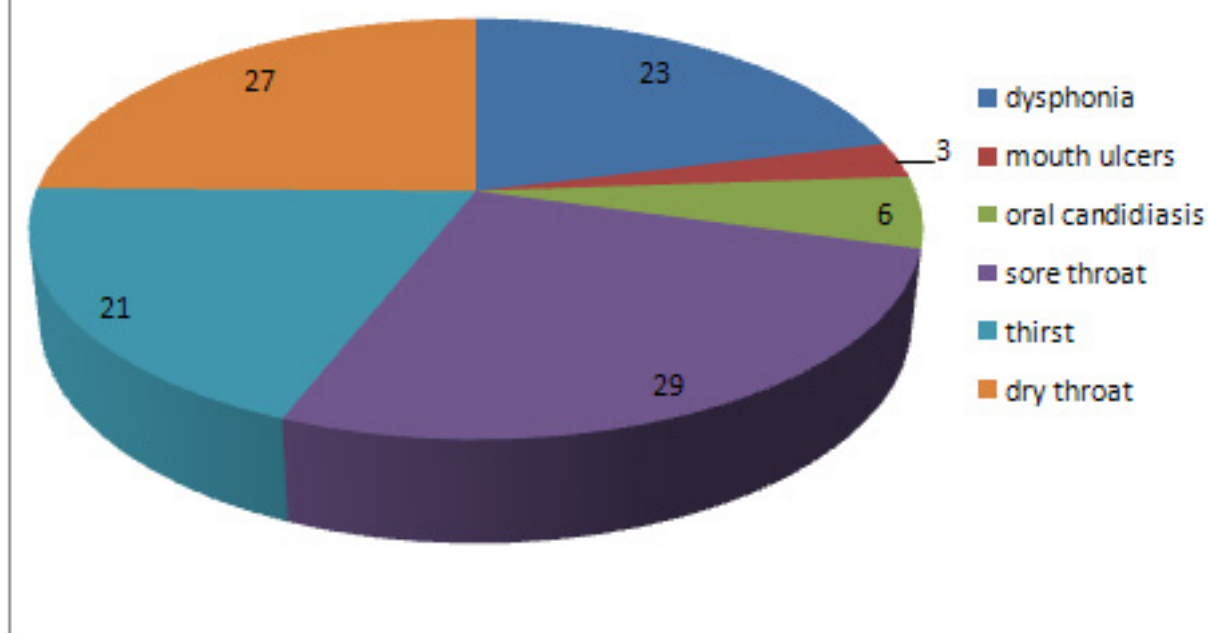
Dysphonia was mentioned as a side effect in our study by 18% of the patients. Many other studies found dysphonia to be a common side effect of inhalers, with rates ranging between 10-57%. (8,9,14) The most acceptable mechanism for dysphonia is attributed to the steroid component in the inhalers, which will lead to steroid myopathy affecting the vocal muscles, which causes a bilateral adduction deformity. (16,17)

Mouth rinsing was found to be a very effective method in preventing local side effects in our study. While 80% of the patients who developed local side effects didn't rinse their mouth regularly after the use of their inhalers, only 8% of the patients who didn't develop any local side effect in our study didn't rinse their mouth regularly after inhalers. This observation emphasizes the importance of oral hygiene maintenance and mouth rinsing in COPD patients using inhaler therapy, in order to prevent the occurrence of local side effects.

In conclusion, the rate of local side effects of inhalers in COPD patients is high. Mouth rinsing regularly is a very effective method to minimize these side effects. Taking into consideration the high rates of local side effects of inhalers, the attending physician is advised to regularly check for these side effects, and emphasize the importance of maintaining good mouth hygiene and mouth rinsing after inhaler use to his patients during each visit to the clinic.

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Association between maternal anaemia and premature birth

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ABSTRACT

Objective: This study was designed to assess the relation between maternal anaemia in the third trimester and premature birth.

Methods: A case-control study was conducted in Prince Hashim hospital and Prince Ali Hospital in the period between August 2015 and July 2016. A total of 200 women were included in the study and divided into two groups. Group A consisted of patients delivered between 24-37 weeks of gestation (case group), while Group B consisted of patients delivered after 37 weeks (control group). Maternal anaemia was defined as haemoglobin level < 11g/dL and preterm delivery was defined as delivery prior to 37 weeks of gestation. Patients with haemoglobinopathies, systemic diseases, Antepartum haemorrhage and multiple gestations were excluded from the analysis.

Results: In Group A, 47 patients were found to be anaemic while 53 patients had normal haemoglobin. In Group B, 29 patients were found to be anaemic while 71 patients had normal haemoglobin.

Conclusion: It was observed that maternal anaemia in the third trimester, at labour, was associated with an increased risk of prematurity.

Key words: Anaemia, Preterm delivery, Prematurity

Introduction

Anaemia is one of the most common nutritional disorders in the world. According to the WHO criteria, anaemia is defined as a blood haemoglobin concentration lower than 12 g/dL for non-pregnant women and lower than 11 g/dL for pregnant women.[1]

Prevalence of anaemia in Jordan is 20%, but among pregnant women this percentage reaches 32% according to a study conducted by the Jordanian Ministry of Health and UNICEF in 2009.[2][3]

Iron deficiency anaemia comprises the majority of all anaemia seen in pregnancy. Other causes of anaemia include vitamin B12 and folic acid deficiencies, hereditary anaemia, chronic infections and inflammations.[4][5]

Finding an association between anaemia in pregnancy and pregnancy outcomes has been investigated in many studies. Jain Preeti et al and Levey et al observed that mothers with anaemia have higher rates of preterm deliveries and low birth weight.[6][7]

The main purpose of the study is to find an association between anaemia and preterm delivery so that pregnant patients at risk are identified and effective management can be taken to prevent and treat anaemia.

Subjects and Methods

Our study was conducted on pregnant women admitted to the labour ward of Prince Hashim Hospital and Prince Ali Hospital between August 2015 and July 2016. The initial sample consisted of 253 patients, from whom we selected all who met the inclusion criteria, i.e. who were followed in outpatient department since early pregnancy, aged between 18-40 years and had a singleton pregnancy. Patients with multiple gestation, chronic illness, antepartum haemorrhage and unbooked patients were excluded and 200 patients remained for analysis. Data were collected from the interviews conducted with the patients and medical records; data were recorded on special forms designed for this purpose.

Information was analysed by using SPSS software.

Blood samples were drawn from patients at admission and haemoglobin level was estimated using a Sysmex KX-21 N machine (Swe Lab).

Anaemia in pregnant patients was defined according to WHO as haemoglobin level below 11g/dL.

Gestational age was calculated using Naegele's rule as the duration of pregnancy in weeks, i.e. from the first day of the last menstrual cycle to the date of delivery, and compared with ultrasound measurements in the first trimester and at admission.

Preterm birth was defined based on the WHO definition as delivery prior to 37 weeks of gestation.

Results

The population of the current study consisted of 200 patients divided into two groups. Group A comprised of preterm (cases) whilst Group B consisted of term (controls). In distribution of patients on the basis of anaemia, it was found that 47 patients (47 %) in group A were anaemic and 53 patients (53%) had normal haemoglobin. In group B, 29 patients (29%) were anaemic while 71 patients (71%) had normal haemoglobin. As Table 1 shows, the mean of haemoglobin in Group A was 10.30 and that of Group B was 11.19 . In distribution of patients on the basis of parity, in Group A there were 37 (37%) patients who were primigravidas and 63 (63%) patients who were multigravidas, while in Group B, 53 (53%) patients were primigravidas and 47 (47%) were multigravidas, as shown in Table 2.

In distribution of patients according to age, in Group A there were 20 patients (20 %) whose ages ranged from 18 to 25 years, 14 patients (14%) in the range of 25-30 years, 37 patients (37 %) in the range of 30-35 years and 29 patients (29%) who were aged between 35 and 40 years . In Group B there were 27 patients whose ages ranged from 18 to 25 years (27 %), 31 patients (31%) aged 25 to 30 years, 19 patients (19 %) in the range of 30-35 years, and 23 patients (23%) in the range of 35-40 years, as shown in Table 2.

In distribution of patients according to iron supplementation during pregnancy, in Group A there were 38 patients (38%) who received iron supplements and 62 patients (62%) who did not receive iron supplements. In Group B, there were 59 patients (59%) who received iron supplements and 41 patients (41%) who did not receive iron supplements, as shown in Table 2.

Discussion

Anaemia is defined as a decrease in the total circulating red cell mass below the normal ranges (8).

During pregnancy, iron deficiency and iron deficiency anaemia are the most common nutritional disorders.

Iron deficiency anaemia comprises 90% of all anaemia seen in pregnancy(WHO92). Malaria, hookworm infection, schistomiasis, chronic inflammations and inherited anaemia are other causes.(1)

Maternal anaemia is associated with premature delivery, low birth weight (9-11), IUGR (intrauterine growth retardation), IUD (intrauterine death), low APGAR score and perinatal death .(12).

In our study, the mean of haemoglobin in preterm group was 10.30 g/dL, which is lower than that in the term group, 11.19 g/dL. It was observed that maternal anaemia evaluated during the third trimester, i.e. at labour, is a risk factor behind prematurity. The effect associated with anaemia remained recognisable even after adjustment for potential confounding factors.

It was also observed that multiparity and older age were associated with an increased risk of preterm delivery.(13)

Our study showed that the percentage of patients who received iron supplements during pregnancy was low in the preterm group (38%), while the percentage in the term group was much higher (59%).

The results of our study were comparable to many previous studies that investigated the mutual relation between maternal anaemia and prematurity. This is exemplified in the study conducted by Scholl and Hedgier (14) that shows that maternal anaemia is associated with a 2-3 fold increased risk of premature delivery.

Conclusion

Based on the results of the current study, it can be concluded that anaemia is the most common nutritional deficiency in pregnancy and it is strongly associated with preterm delivery.

Educational efforts addressing the appropriate use of prenatal and antenatal care should be initiated to educate women about their health and the associated risks during pregnancy, especially anaemia.

Table 1: Distribution of patients according to Hb level

	G A (n = 100)		G B (n = 100)	
	No.	%	No.	%
Hb > 11 g/ dL	53	53%	71	71%
Hb < 11 g/ dL	47	47%	29	29%
Mean + SD	10.30 + 1.60		11.19 + 1.10	

Table 2:. Distribution of patients on the basis of age, parity and iron supplement

	G A (n = 100)		G B (n = 100)	
Age (years)	No.	%	No.	%
18 – 25	20	20 %	27	27 %
25 – 30	14	14 %	31	31 %
30 – 35	37	37 %	19	19 %
35 - 40	29	29 %	23	23 %
Parity				
PG	37	37 %	53	53 %
Multi	63	63 %	47	47 %
Iron supplement during pregnancy	38	38 %	59	59 %

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Paclitaxel-Carboplatin versus bevacizumab Paclitaxel-Carboplatin for treatment of Non-Small-Cell Lung Cancer

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ABSTRACT

Background: Lung cancer is considered as the leading cause attributed to cancer related deaths and approximately 85% of lung cancer patients have non-small-cell lung cancer (NSCLC) and Vascular endothelial growth factor (VEGF) is used to play the major role in regulation of angiogenesis in malignancies.

Aim: The aim of this study was to compare chemotherapy alone in comparison with addition of anti -vegf (bevacizumab) to chemotherapy and assessment of response rate , progression free survival, overall survival in patients diagnosed with non- squamous non small cell lung cancer in Saudi German hospitals in the period between March 2013 and February 2016.

Patients and methods: This study was held between March 2013 and February 2016 in Saudi German hospitals when we performed a randomized study in which 40 patients with recurrent or advanced non-small-cell lung cancer (stage IIIB or IV) received paclitaxel and carboplatin (paclitaxel-carboplatin arm) (20 patients) paclitaxel and carboplatin in addition to bevacizumab (paclitaxel-carboplatin-bevacizumab arm) (20 patients).

Results: The median overall survival was 15.5 months in the paclitaxel-carboplatin-bevacizumab arm as compared with 10.5 months in the paclitaxel-carboplatin arm (P=0.002) and the median progression-free survival was also significantly improved in the paclitaxel-carboplatin-bevacizumab arm reaching (8.4 months versus 5.9 in the paclitaxel-carboplatin arm) for a hazard ratio for disease progression of 0.67 (95% CI, 0.57 to 0.77; P<0.001) and the addition of bevacizumab to paclitaxel and carboplatin improved the response rate as (25 %) in the paclitaxel-carboplatin arm had a response versus (65%) in the paclitaxel-carboplatin-bevacizumab arm (P<0.001) and the rates of hypertension, bleeding, thrombocytopenia, neutropenia, febrile neutropenia, proteinuria were significantly higher in the paclitaxel-carboplatin-bevacizumab arm than in the paclitaxel-carboplatin arm. (P<0.05).

Conclusion: The addition of bevacizumab to the chemotherapy added a significant value to the patients with non squamous NSCLC in terms of response rate, progression free survival and overall survival however with significant side effects.

Key words: Lung cancer; Bevacizumab; Vascular endothelial growth factor

Introduction

Lung cancer is considered as the leading cause attributed to cancer related deaths and approximately 85% of lung cancer patients have non-small-cell lung cancer and there is global rise of lung cancer incidence with overall 5 years survival less than 15% .(1) Tumorogenesis is considered as a multistep process that depends on transformation from normal bronchial epithelium to overt lung cancer then continued accumulation of the genetic abnormalities influences the cancer invasion and development of metastases and resistance to the cancer treatment and that can take place throughout chromosomal instability mechanisms.(2) Several aetiological factors have been accused in NSCLC including cigarette smoking , exposure to radon , asbestos and genetic susceptibility.(3) NSCLC has 3 major histological subtypes, adenocarcinoma, large cell carcinoma and squamous cell carcinoma.(4) In early stages stage I and II, and selected cases of stage III, surgery is the corner stone of management followed by adjuvant chemotherapy but in late stages, the unresectable stage III the treatment is chemoradiation and in stage IV the treatment is double agent chemotherapy with or without biological target therapy .(5) After their growth within the bronchial wall and or the lung parenchyma primary lung malignant tumors invade the regional hilar and mediastinal lymph nodes through lymphatics then through the blood vessels to distant organs such as brain, liver and bone.(6) Biopsy can be performed through several methods including CT guided biopsy or bronchoscopic biopsy and even through thoracoscopy or thoracotomy and Positron Emission Tomography (PET scan) is a corner stone in staging and further assessment during treatment and follow up.(7)

Angiogenesis is a landmark for cancer in which there is an angiogenic switch from perturbation in the balance that normally exists between inducers and inhibitors which are produced by both tumor and host cells that lead to a high micro vessels density with overexpression of VEGF which is associated with poor outcome in NSCLC.(8) Vascular endothelial growth factor (VEGF) is used to play the major rule in regulation of angiogenesis in malignancies Increased VEGF expression in non-small-cell lung cancers is associated with increased risks of local recurrences, metastases, and deaths.(9) Preclinical studies have shown that a monoclonal antibody against VEGF (bevacizumab-avastin) can inhibit the growth of human malignant tumor cells (10).new target therapy agents are needed to overcome the intrinsic or acquired resistance limiting the efficacy of the common anti-tumoral agents (11).

This study was held in Saudi German hospitals and is a randomized study including patients with advanced non-small-cell lung cancer with no prior chemotherapy administration compared to paclitaxel and carboplatin protocol versus paclitaxel and carboplatin plus bevacizumab protocol with bevacizumab dose 15 mg /kg of body weight intravenously every 3 weeks.(12)

Patients and methods

This study was held between March 2013 and February 2016 in Saudi German hospitals as we performed a randomized study in which 40 patients with recurrent or advanced non-small-cell lung cancer (stage IIIB patient -pleural effusion- or IV) received paclitaxel and carboplatin (paclitaxel-carboplatin arm) (20 patients) or paclitaxel and carboplatin in addition to bevacizumab (paclitaxel-carboplatin-bevacizumab arm) (20 patients). Inclusion criteria were patients with an ECOG performance status of 0-2, and adequate hematologic, hepatic, and renal function and to be histopathologically proved newly diagnosed stage IIIB (pleural effusion) or stage IV non-squamous NSCLC or recurrent NSCLC with no prior chemotherapy.

Exclusion criteria were histologic evidence of squamous-cell cancer or central nervous system (CNS) metastases, pregnancy or lactation, significant cardiovascular disease and uncontrolled hypertension.

The primary end point was overall survival. In our study patients were randomly assigned to receive paclitaxel at a dose of 175 mg/m2 and carboplatin at a dose of area under the curve (AUC) 6 administered intravenously on day 1 (arm 1), or paclitaxel at a dose of 175 mg/m2 and carboplatin at a dose of area under the curve (AUC) 6 administered in addition to bevacizumab at a dose of 15 mg /kg given intravenously on day 1 and chemotherapy was repeated every 21 days for a total of six cycles unless there was disease progression or marked intolerable toxicity. Patients in the paclitaxel-carboplatin-bevacizumab group continued to receive bevacizumab alone every 3 weeks unless there was disease progression or marked intolerable toxicity.

Afterwards the baseline evaluation assessment took place every 9 weeks by PET scan assessment. Survival was measured as the period from randomization to death , and progression-free survival as the period from randomization to disease progression or death. Event-time distributions were estimated by the Kaplan-Meier method and estimated P values were two-sided and CIs were at the 95% level.

Results

The two groups were well balanced regarding baseline characteristics and the median number of cycles of therapy was five in the paclitaxel-carboplatin arm and seven in the paclitaxel-carboplatin-bevacizumab arm.

The median overall survival was 15.5 months in the paclitaxel-carboplatin-bevacizumab arm as compared with 10.5 months in the paclitaxel-carboplatin arm (P=0.002). Survival rates were 55% in the paclitaxel-carboplatin-bevacizumab arm as compared with 45% in the paclitaxel-carboplatin arm at 1 year and 27% as compared with 17% respectively at 2 years.

The median progression-free survival was also significantly improved in the paclitaxel-carboplatin-bevacizumab arm reaching (8.4 months versus 5.9 in the paclitaxel-carboplatin arm) for a hazard ratio for disease progression of 0.67 (95% CI, **0.57 to 0.77; P<0.001).**

The addition of bevacizumab to paclitaxel and carboplatin improved the response rate as (25 %) in the paclitaxel-carboplatin arm had a response versus (65%) in the paclitaxel-carboplatin-bevacizumab arm (P<0.001). (Table 1)

The rates of hypertension, bleeding, thrombocytopenia, neutropenia, febrile neutropenia, proteinuria were significantly higher in the paclitaxel-carboplatin-bevacizumab arm than in the paclitaxel-carboplatin arm (P<0.05).

There were 9 deaths related to toxic effects of the treatment. Two deaths (from gastrointestinal hemorrhage and febrile neutropenia) occurred in patients in the paclitaxel-carboplatin arm and 7 occurred in the paclitaxel-carboplatin-bevacizumab arm; the difference between the groups was significant (P=0.001)(Table 1). Of the 7 deaths in the paclitaxel-carboplatin-bevacizumab group, 4 were due to pulmonary hemorrhage, and 3 due to febrile neutropenia.

Table 1:

	PACLITAXEL-CARBOPLATIN ARM	PACLITAXEL-CARBOPLATIN BEVACIZUMAB ARM	P- VALUE
Overall survival	10.5 M	15.5 M	0.002
PROGRESSION FREE SURVIVAL	5.9 M	8.4 M	<0.001
RESPONSE RATE	25 %	65 %	<0.001
DEATHS	2	7	0.001

Figure 1: Mediastinal mass
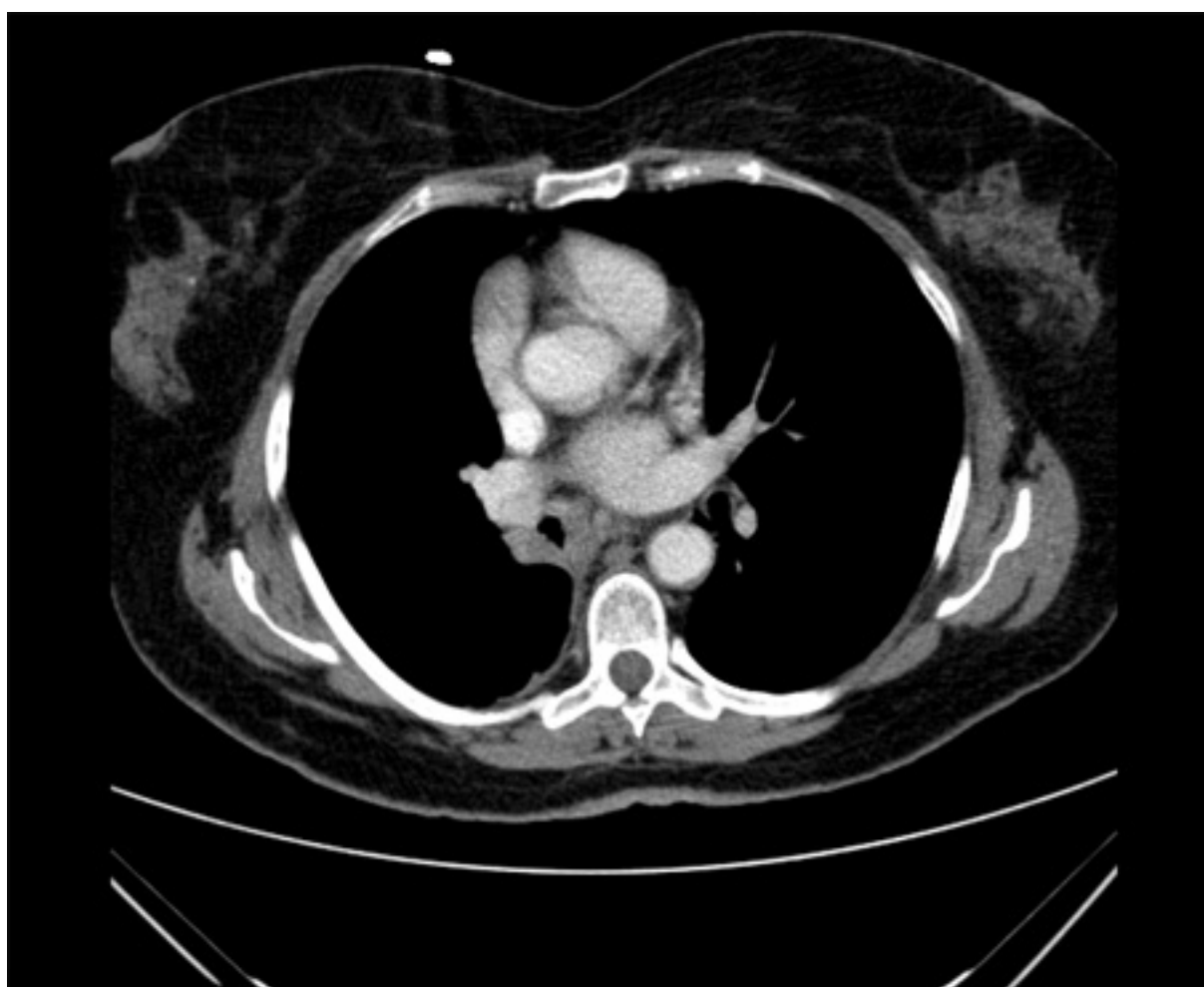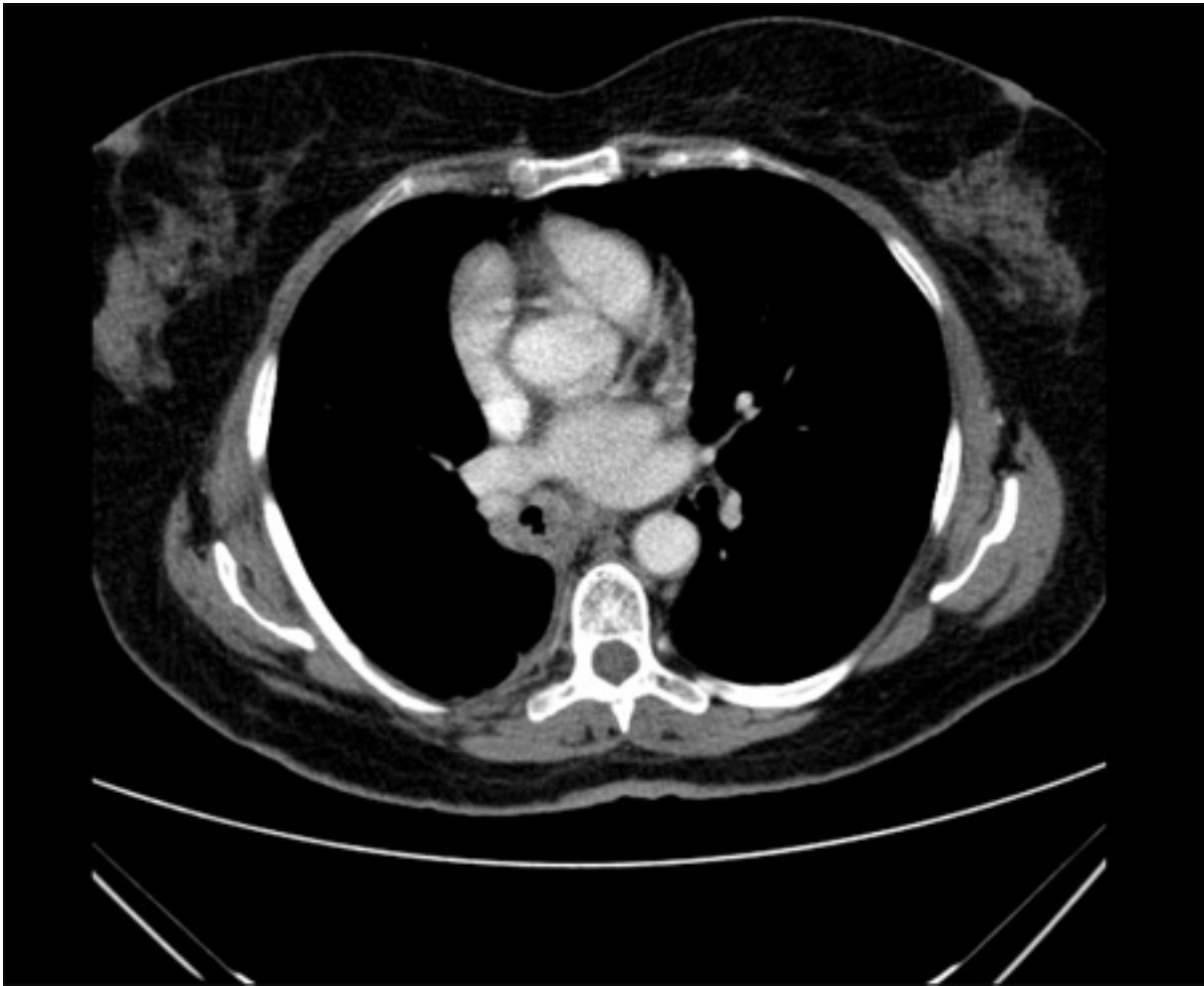
Figure 2 (above): Mediastinal mass

Figure 3: (below) Mediastinal mass

Figure 4: Left lung malignant mass (NSCLC)
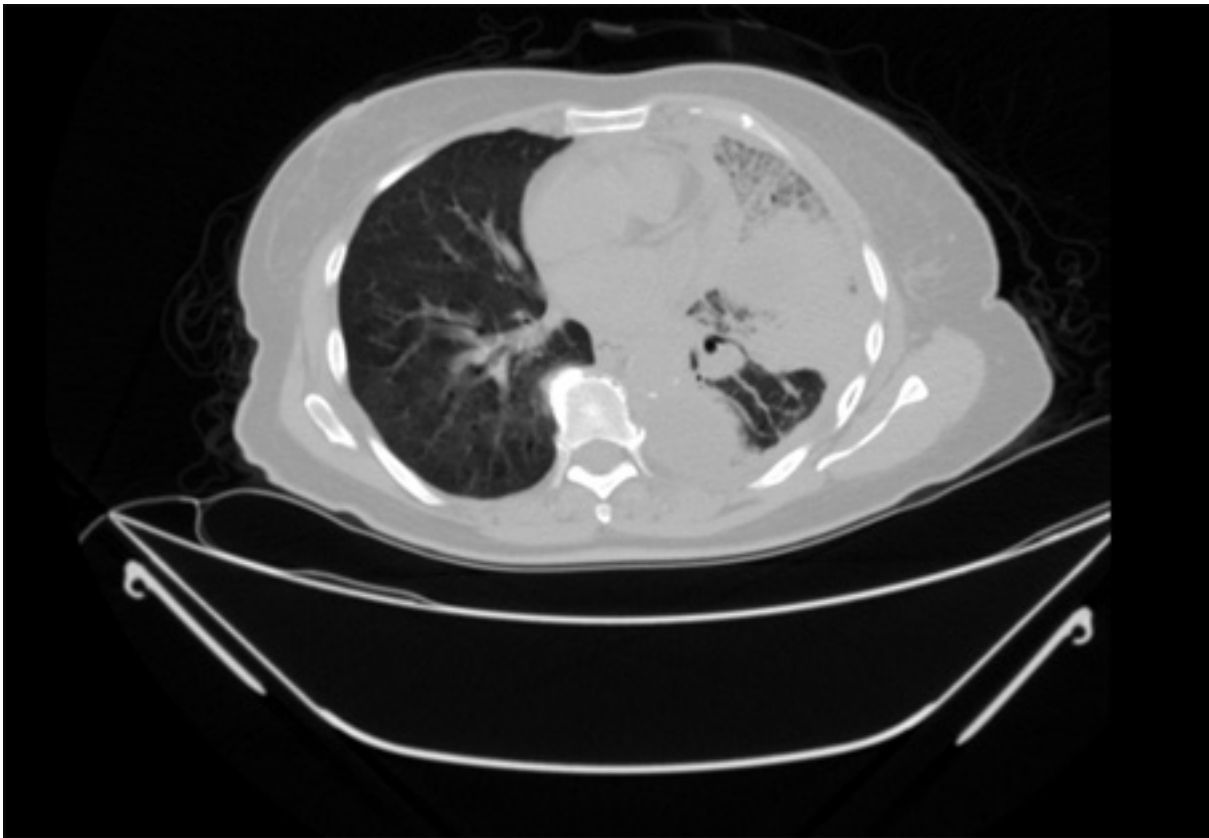
Figure 5: Left lung malignant mass (NSCLC)
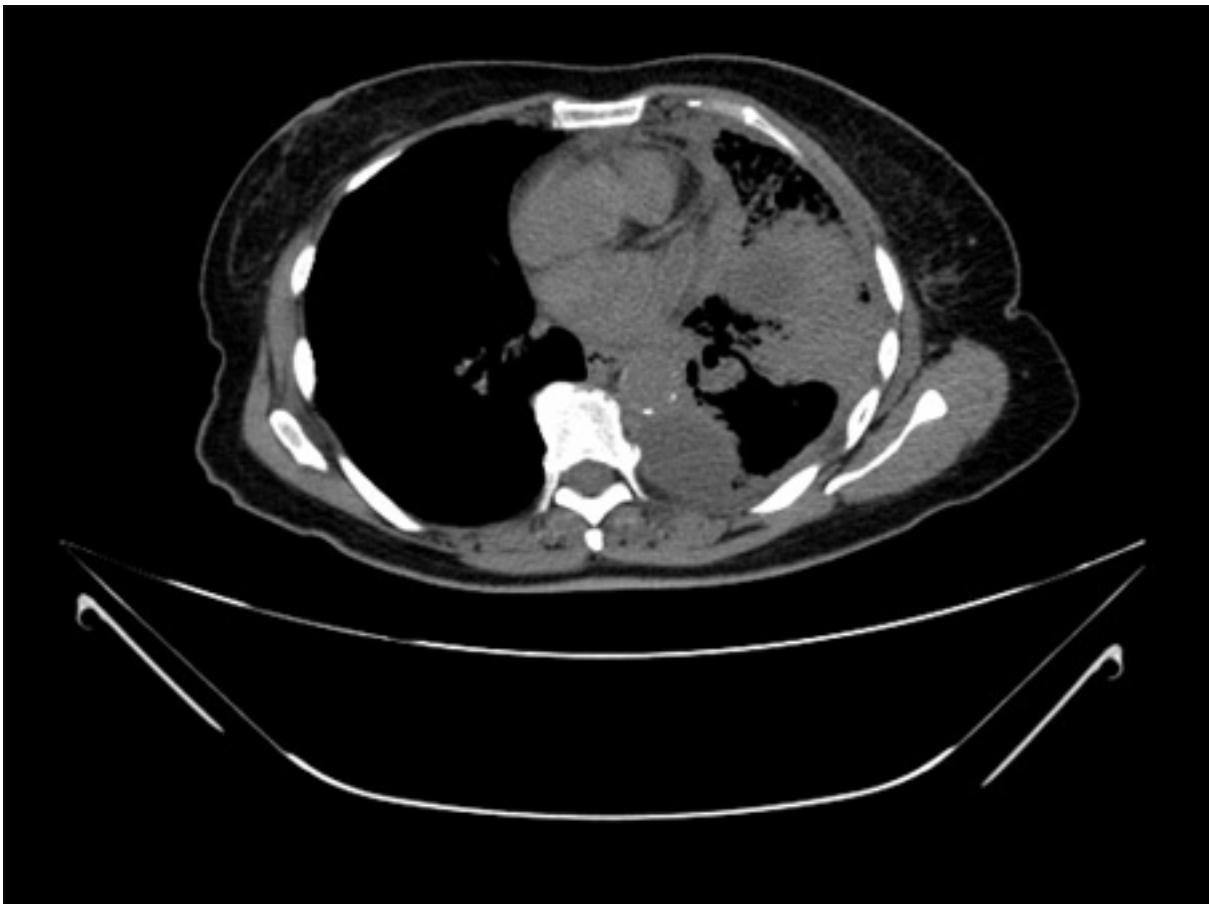
Figure 6: Right lung malignant mass (NSCLC)
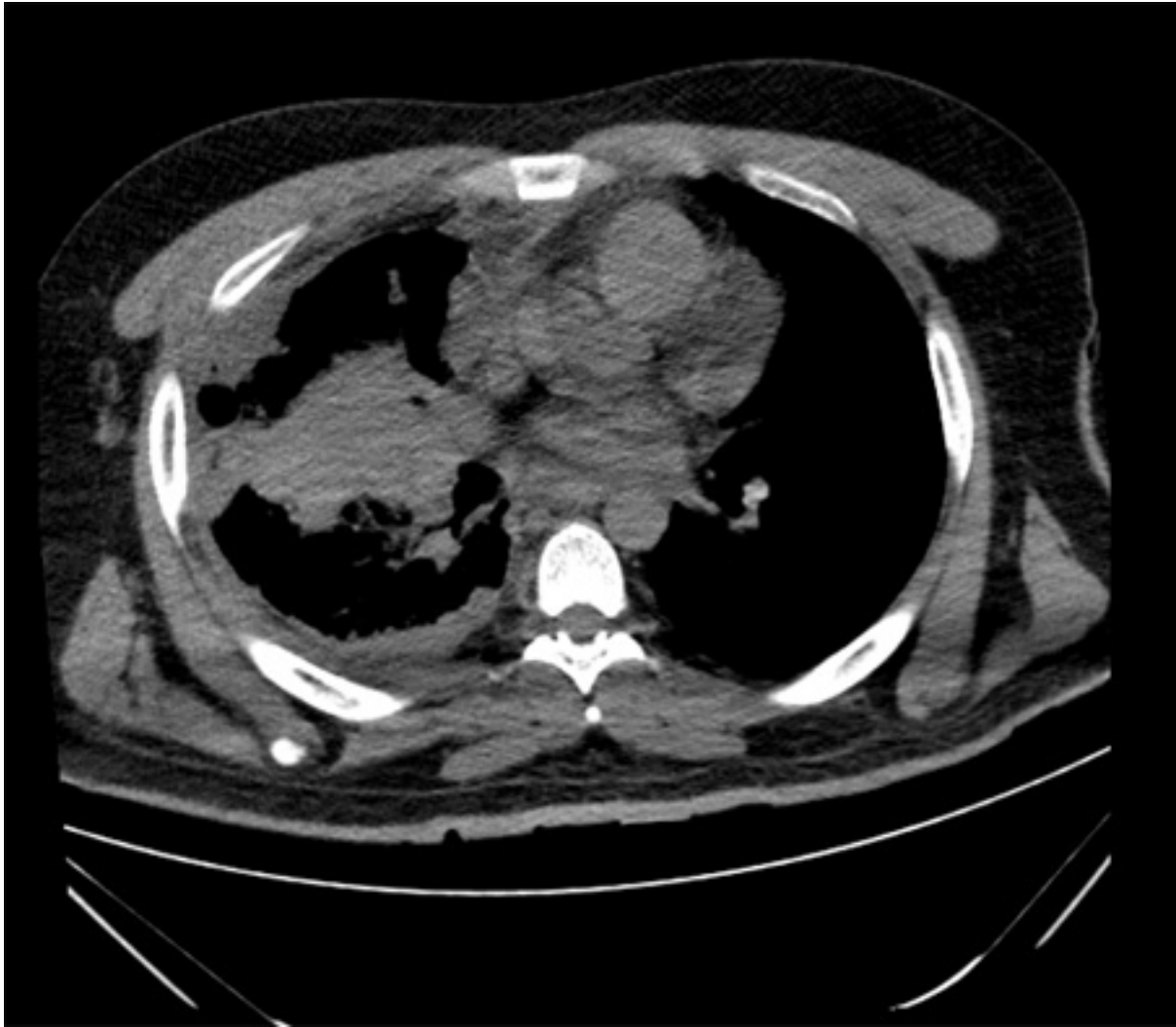
Discussion

In our study the addition of bevacizumab to chemotherapy regimen improved overall survival, progression-free survival and response rate in patients with advanced NSCLC.

Villett et al. stated that bevacizumab increases delivery of the drug to the tumor and the marvelous significant improvement in the response rate in this study and in previous randomized controlled studies of chemotherapy with addition of bevacizumab supports the data that bevacizumab improves overall survival, progression-free survival and response rate in patients with advanced NSCLC.(13)

Jubb AM et al stated in their study the use of bevacizumab in combination with platinum based chemotherapy in treatment of metastatic lung cancer stage IV patients resulted in improvement of response rate and progression free survival which is matching with the results revealed in our study.(14)

Among the 9 other deaths considered to be related to treatment in our study, 5 were due to haemorrhage either pulmonary or gastrointestinal and 4 were due to complications of febrile neutropenia and although neutropenia has not been associated with bevacizumab, however 3 patients in the paclitaxel-car-boplatin-bevacizumab group had grade 5 febrile neutropenia. Other studies had as that reported by Giantonio BJ et al and by Jubb AM et al revealed increased rates of neutropenia when bevacizumab was combined with chemotherapy.(14, 15)

The hypertension, and proteinuria in our study are due to bevacizumab. They were manageable and did not need a permanent stop of bevacizumab. This is matched with other literature as reported by Jubb AM et al and Kozloff M. et al in the study of treatment effects and side effects of bevacizumab (15,16).

Conclusion

The addition of bevacizumab to the chemotherapy added a significant value to the patients with non squamous NSCLC in terms of response rate, progression free survival and overall survival however with significant side effects.

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Hypertriglyceridemia may actually be an acute phase reactant in the plasma

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ABSTRACT

Background: We tried to understand whether or not there is a significant relationship between cholelithiasis or cholecystectomy and plasma lipids.

Methods: The study was performed in Internal Medicine Polyclinics on routine check up patients. All cases either with cholelithiasis or cholecystectomy for cholelithiasis were put into the first, and age and sex-matched control cases were put into the second groups.

Results: One hundred and forty-four cases either with cholelithiasis or cholecystectomy for cholelithiasis were detected among 3,437 cases, totally (4.1%). One hundred and sixteen (80.1%) of them were females with a mean age of 53.6 years. Obesity (54.8% versus 43.7%, p<0.01), body mass index (BMI) (31.0 versus 28.9 kg/m2, p<0.01), and hypertension (26.3% versus 13.1%, p<0.001) were significantly higher in the cholelithiasis or cholecystectomy group. Although the prevalence of hyperbetalipoproteinemia was significantly lower in the cholelithiasis or cholecystectomy group (9.7% versus 18.0%, p<0.05), hypertriglyceridemia (25.0% versus 18.0%, p<0.05) was significantly higher in them.

Conclusions: There are significant relationships between cholelithiasis and parameters of the metabolic syndrome including age, female sex, BMI, obesity, hypertension, and hypertriglyceridemia, so cholelithiasis may also be found among the terminal consequences of the metabolic syndrome. Although the significantly lower prevalence of hyperbetalipoproteinemia is probably due to the decreased amount of bile acids secreted during entrance of food into the duodenum and decreased amount of cholesterol absorbed in patients with cholelithiasis or cholecystectomy, the higher prevalence of hypertriglyceridemia may actually indicate its primary role as an acute phase reactant in the plasma.

Key words: Hypertriglyceridemia, metabolic syndrome, acute phase reactant, cholelithiasis, cholecystectomy

Introduction

Chronic endothelial damage may be the most common kind of vasculitis and the leading cause of aging, morbidity, and mortality in human beings (1, 2). Much higher blood pressure (BP) of the afferent vasculature may be the major underlying cause by inducing recurrent injuries on endothelium, and probably whole afferent vasculature including capillaries are involved in the process. Thus the term of venosclerosis is not as famous as atherosclerosis in the literature. Secondary to the chronic endothelial inflammation, edema, and fibrosis, vascular walls become thickened, their lumens are narrowed, and they lose their elastic natures that reduce blood flow to terminal organs and increase systolic BP further. Some of the well-known causes and indicators of the inflammatory process are sedentary life style, animal-rich diet, overweight, smoking, alcohol, hypertriglyceridemia, hyperbetalipoproteinemia, dyslipidemia, impaired fasting glucose, impaired glucose tolerance, white coat hypertension, and chronic inflammatory processes including rheumatologic disorders, chronic infections, and cancers for the development of terminal complications including obesity, hypertension, diabetes mellitus (DM), cirrhosis, peripheric artery disease (PAD), chronic obstructive pulmonary disease (COPD), chronic renal disease (CRD), coronary artery disease (CAD), mesenteric ischemia, osteoporosis, and stroke, all of which terminate with early aging and premature death. Although early withdrawal of causative factors may prevent irreversible complications, after development of cirrhosis, COPD, CRD, CAD, PAD, or stroke, endothelial changes cannot be reversed completely due to the fibrotic natures of them. The accelerator factors and terminal consequences were researched under the titles of metabolic syndrome, aging syndrome, or accelerated endothelial damage syndrome in the literature, extensively (3-6). On the other hand, gallstones are also found among one of the most common health problems in developed countries (7), and they are particularly frequent in women above the age of 40 years (8). Most of the gallstones are found in the gallbladder with the definition of cholelithiasis. Its pathogenesis is uncertain and appears to be influenced by genetic and environmental factors (9). Excess weight is a well-known and age-independent risk factor for cholelithiasis (10). Delayed bladder emptying, decreased small intestinal motility, and sensitivity to cholecystokinin were associated with obesity and cholelithiasis (11). An increased risk was confirmed in obese diabetics with hypertriglyceridemia (12), and plasma cholesterol levels were also found related with cholelithiasis (13). We tried to understand whether or not there is a significant relationship between cholelithiasis or cholecystectomy and plasma lipids.

Material and Methods

The study was performed in Internal Medicine Polyclinics of the Dumlupinar and Mustafa Kemal Universities on routine check up on patients between August 2005 and November 2007. We took consecutive patients below the age of 70 years to avoid debility induced weight loss in elders. Their medical histories including smoking habit, hypertension, DM, dyslipidemia, and already used medications and performed operations were learnt, and a routine check up procedure including fasting plasma glucose (FPG), triglyceride, high density lipoprotein cholesterol (HDL-C), low density lipoprotein cholesterol (LDL-

C), and an abdominal ultrasonography was performed. Patients with devastating illnesses including type 1 DM, malignancies, acute or chronic renal failure, chronic liver diseases, hyper- or hypothyroidism, and heart failure were excluded to avoid their possible effects on weight. Current daily smokers at least for the last six months and cases with a history of five pack-years were accepted as smokers. Cigar or pipe smokers were excluded. Body mass index (BMI) of each case was calculated by the measurements of the Same Physician instead of verbal expressions since there is evidence that heavier individuals systematically underreport their weight (14). Weight in kilograms is divided by height in meters squared, and underweight is defined as a BMI value of lower than 18.5, normal weight as lower than 24.9, overweight as lower than 29.9, and obesity as 30.0 kg/m2 or greater (15). Cases with an overnight FPG level of 126 mg/dL or greater on two occasions or already receiving antidiabetic medications were defined as diabetics (15). An oral glucose tolerance test with 75-gram glucose was performed in cases with a FPG level between 110 and 125 mg/dL, and diagnosis of cases with a 2-hour plasma glucose level 200 mg/dL or higher is DM (15). Patients with dyslipidemia were detected, and we used the National Cholesterol Education Program Expert Panel's recommendations for defining dyslipidemic subgroups (15). Dyslipidemia is diagnosed when LDL-C is 160 or higher and/or triglyceride is 200 or higher and/or HDL-C is lower than 40 mg/dL. Office BP was checked after a 5-minute of rest in seated position with a mercury sphygmomanometer on three visits, and no smoking was permitted during the previous 2 hours. A 10-day twice daily measurement of blood pressure at home (HBP) was obtained in all cases, even in normotensives in the office due to the risk of masked hypertension after a 10-minute education about proper BP measurement techniques (16). The education included recommendation of upper arm while discouraging wrist and finger devices, using a standard adult cuff with bladder sizes of 12 x 26 cm for arm circumferences up to 33 cm in length and a large adult cuff with bladder sizes of 12 x 40 cm for arm circumferences up to 50 cm in length, and taking a rest at least for a period of 5 minutes in the seated position before measurement. An additional 24-hour ambulatory BP monitoring was not required due to the equal efficacy of the method with HBP measurement to diagnose hypertension (17). Eventually, hypertension is defined as a BP of 135/85 mmHg or greater on HBP measurements (16). Cholelithiasis was diagnosed ultrasonographically. Eventually, all cases either with presenting cholelithiasis or cholecystectomy for cholelithiasis were put into the first and age and sex-matched control cases were put into the second groups. The mean BMI values and prevalences of smoking, normal weight, overweight, obesity, hypertension, DM, hypertriglyceridemia, hyperbetalipoproteinemia, and dyslipidemia were compared between the two groups. Mann-Whitney U test, Independent-Samples t test, and comparison of proportions were used as the methods of statistical analyses.

Results

Although the exclusion criteria, 25 cases with already presenting asymptomatic cholelithiasis and 119 cases with cholecystectomy for cholelithiasis were detected among 3.437 cases, totally (4.1%). One hundred and sixteen (80.1%) of them were females with a mean age of 53.6 years, so cholelithiasis is mainly a disorder of females in their fifties. Prevalences of smoking

Table 1: Comparison of cases with and without cholelithiasis

Variable	Cases with cholelithiasis or cholecystectomy for cholelithiasis	Control cases	p-value
Number	144	144	
Female ratio	80.5% (116)	80.5% (116)	
Mean age (year)	53.6 ± 9.3 (27-70)	53.6 ± 10.2 (28-70)	Ns*
Prevalence of smoking	18.0% (26)	19.4% (28)	Ns
Mean BMI† (kg/m2)	*31.0 ± 6.1 (19-51)*	*28.9 ± 5.7 (19-52)*	*≤0.01*
Prevalence of normal weight	*7.6% (11)*	*18.0% (26)*	*≤0.01*
Prevalence of overweight	37.5% (54)	38.1% (55)	Ns
Prevalence of obesity	*54.8% (79)*	*43.7% (63)*	*≤0.01*
Prevalence of hypertension	*26.3% (38)*	*13.1% (19)*	*≤0.001*
Prevalence of DM‡	20.8% (30)	19.4% (28)	Ns
Prevalence of hyperbetalipoproteinemia	*9.7% (14)*	*18.0% (26)*	*≤0.05*
Prevalence of hypertriglyceridemia	*25.0% (36)*	*18.0% (26)*	*≤0.05*
Prevalence of dyslipidemia	31.9% (46)	29.8% (43)	Ns

*Nonsignificant (p>0.05) †Body mass index ‡Diabetes mellitus

were similar in the cholelithiasis and control groups (18.0% versus 19.4%, p>0.05, respectively). Interestingly, 92.3% (133 cases) of the cholelithiasis group had excess weight and only 7.6% (11 cases) of them had normal weight. There was not any patient with underweight among the study cases. Obesity was significantly higher (54.8% versus 43.7%, p<0.01) and normal weight was significantly lower (7.6% versus 18.0%, p<0.01) in the cholelithiasis group. Mean BMI values were 31.0 and 28.9 kg/m2, (p<0.01) in the two groups. Probably parallel to the higher mean BMI values, prevalence of hypertension (26.3% versus 13.1%, p<0.001) was also higher in the cholelithiasis group, significantly. Although the prevalences of DM (20.8% versus 19.4%, p>0.05) and dyslipidemia (31.9% versus 29.8%, p>0.05) were also higher in the cholelithiasis groups, differences were nonsignificant probably due to the small sample sizes of the groups. Although the prevalence of hyperbetalipoproteinemia was significantly lower in the cholelithiasis or cholecystectomy group (9.7% versus 18.0%, p<0.05), hypertriglyceridemia (25.0% versus 18.0%, p<0.05) was significantly higher in them (Table 1).

Discussion

Bile is formed in the liver as an isosmotic solution of bile acids, cholesterol, phospholipids, bilirubin, and electrolytes. The liver synthesizes water-soluble bile acids from water-insoluble cholesterol. About 50% of bile secreted during the fasting state passes into the gallbladder via the cystic duct. So gallbladder filling is facilitated during fasting. Up to 90% of water in the gallbladder bile is absorbed as an electrolyte solution, so bile acids are concentrated in the gallbladder and little amount of bile flows from the liver during fasting. Food entering the duodenum stimulates gallbladder contraction, releasing much of the body pool of bile acids to mix with food content and perform its several functions including solubilization of dietary cholesterol, fats, and fat-soluble vitamins to facilitate their absorption in the form of mixed micelles, causing water secretion by the colon promoting catharsis, excretion of bilirubin as degradation products of heme compounds from worn-out red blood cells, excretion of drugs and ions from the body, and secretion of various proteins important for the gastrointestinal functions. About 90% of bile acids is reabsorbed by the terminal ileum into the portal system. Bile salts are efficiently extracted by the liver, and secreted back into bile, so bile acids undergo enterohepatic circulation 10 to 12 times per day. The most clinical disorders of the extrahepatic biliary tract are related with the gallstones. In the USA, 20% of people above the age of 65 years have gallstones, and each year more than 500,000 patients undergo cholecystectomy. Factors increasing the probability of gallstones include age, female sex, and obesity. Highly water-insoluble cholesterol is the major component of most gallstones. Biliary cholesterol is solubilized in the bile salt-phospholipid micelles and phospholipid vesicles. The amount of cholesterol carried in micelles and vesicles varies with the bile salt secretion rate. In another perspective, cholelithiasis may actually be a natural defence mechanism of the body to decrease amount of bile acids secreted during entrance of food into the duodenum and decrease amount of cholesterol absorbed. Similarly, bile acid sequestrants including cholestyramine and cholestipol effectively lower serum LDL-C by binding bile acids in intestine and interrupting enterohepatic circulation of them.

Excess weight leads to both structural and functional abnormalities of many systems of the body. Recent studies revealed that adipose tissue produces leptin, tumor necrosis factor-alpha, plasminogen activator inhibitor-1, adiponectin, and other cytokines which act as acute phase reactants in the plasma (18, 19). For example, the cardiovascular field has recently shown a great interest in the role of inflammation in the development of atherosclerosis and numerous studies indicated that inflamma-

tion plays a significant role in the pathogenesis of atherosclerosis and thrombosis (1, 2). On the other hand, individuals with excess weight have an increased blood volume as well as an increased cardiac output thought to be the result of increased oxygen demand of the excessive fat tissue. The prolonged increase in blood volume can lead to myocardial hypertrophy and decreased compliance in addition to the common comorbidity of hypertension. In addition to them, the prevalences of high FPG, high serum total cholesterol, and low HDL-C increased parallel to the higher BMI values (20). Combination of these cardiovascular risk factors will eventually lead to an increase in left ventricular stroke with higher risks of arrhythmias, cardiac failure, and sudden cardiac death. Similarly, the prevalences of CAD and stroke increased parallel with the higher BMI values in some other studies (20, 21), and risk of death from all causes including cancers increased throughout the range of moderate to severe weight excess in all age groups (22). As another consequence of excess weight on health, cholelithiasis cases had a significantly higher BMI value in the present study (31.0 versus 28.9 kg/m2, p<0.01) similar to some other reports (8, 9). Probably as a consequence of the higher BMI values, the prevalences of hypertension (26.3% versus 13.1%, p<0.001) and hypertriglyceridemia (25.0% versus 18.0%, p<0.05) were also higher in the cholelithiasis group. The relationships between excess weight and elevated BP and hypertriglyceridemia were described in the metabolic syndrome (23), and clinical manifestations of the syndrome included obesity, dyslipidemia, hypertension, insulin resistance, and proinflammatory and prothrombotic states (24). The increased risk of cholelithiasis in obese diabetics with hypertriglyceridemia may also be an indicator of its association with the metabolic syndrome (10, 23). Similarly, prevalences of smoking (42.2% versus 28.4%, p<0.01), excess weight (83.6% versus 70.6%, p<0.01), DM (16.3% versus 10.3%, p<0.05), and hypertension (23.2% versus 11.2%, p<0.001) were all higher in the hypertriglyceridemia cases in another study (25). It is a well-known fact that smoking causes a chronic inflammatory process in the respiratory tract, lungs, and vascular endothelium all over the body terminating with an accelerated atherosclerosis, end-organ insufficiencies, early aging, and premature death thus it should be included among the major parameters of the metabolic syndrome. On the other hand, smoking-induced weight loss is probably related with the smoking-induced endothelial inflammation all over the body since loss of appetite is one of the main symptoms of disseminated inflammation in the body. In another explanation, smoking-induced loss of appetite is an indicator of being ill instead of being healthy during smoking (26-28). Buerger's disease (thromboangiitis obliterans) alone is also a clear evidence to show the strong atherosclerotic effects of smoking since this disease has not been shown in the absence of smoking up to now. On the other hand, as a parallel finding to the present study, the prevalences of hyperbetalipoproteinemia were similar in the hypertriglyceridemia and control groups (18.9% versus 16.3%, p>0.05, respectively) in the above study (25).

Although the mean age, female sex, BMI, obesity, hypertension, and hypertriglyceridemia indicated significant differences in the cholelithiasis or cholecystectomy group in the present study, there was no significant difference for the lipid parameters in another study (29). Whereas total cholesterol, triglycerides, and LDL-C were significantly reduced in patients on day

3 of surgery and 6 months after the cholecystectomy in another one (30). Similar to our results, significantly higher prevalence of cholelithiasis was found in patients with nonalcoholic fatty liver disease (NAFLD) (47% versus 26%, p<0.0001), and type 2 DM, overweight, obesity, and cholelithiasis were identified as independent predictors of NAFLD (31). Fifty six percent of patients with cholelithiasis had NAFLD compared with 33% of patients without (p<0.0001) (31). Age above 50 years, triglycerides above 1.7 mmol/l, overweight, obesity, and total cholesterol concentration were the independent predictors of cholelithiasis (31). So NAFLD may represent a pathogenetic link between the metabolic syndrome and cholelithiasis (31). Similarly, patients with type 2 DM had higher probability of having cholelithiasis, and age, female sex, and BMI were independently associated with cholelithiasis (32). Obesity may lead to fatty infiltration causing organ dysfunctions, and the higher BMI values were associated with steatocholecystitis in another study (33). As an opposite finding to our results, serum LDL-C values of patients with cholelithiasis above the age of 40 years were significantly elevated (p<0.05) in another one (34).

Although ATP II determined the normal triglyceride value as lower than 200 mg/dL (35), WHO in 1999 (36) and ATP III in 2001 (13) reduced this normal limit as lower than 150 mg/dL. Although these cutpoints are usually used to define limits of the metabolic syndrome, whether or not more lower limits provide additional benefits for human beings is unclear. In a previous study, patients with a triglyceride value lower than 60 mg/dL were collected into the first, lower than 100 mg/dL into the second, lower than 150 mg/dL into the third, lower than 200 mg/dL into the fourth, and equal to or greater than 200 mg/dL were collected into the fifth groups, respectively (23). Prevalence of smoking was the highest in the fifth group which may also indicate inflammatory roles of smoking and hypertriglyceridemia in the metabolic syndrome. The mean body weight increased continuously, parallel to the increasing value of triglyceride. As the most surprising result, the prevalences of hypertension, type 2 DM, and CAD, as some of the terminal end points of the metabolic syndrome, showed their most significant increases after the triglyceride value of 100 mg/dL (23). As one of our opinion, significantly increased mean age by the increased triglyceride values may be secondary to aging induced decreased physical and mental stresses, which eventually terminates with onset of excess weight and other parameters and terminal end points of the metabolic syndrome. Interestingly, the mean age increased from the lowest triglyceride having group towards the triglyceride value of 200 mg/dL, then decreased. The similar trend was also seen in the mean LDL-C and BMI values, and prevalence of WCH. These trends may be due to the fact that although the borderline high triglyceride values (150-199 mg/dL) is seen together with overweight, obesity, physical inactivity, smoking, and alcohol like acquired causes, the high triglyceride (200-499 mg/dL) and very high triglyceride values (500 mg/dL and higher) are usually secondary to both acquired and secondary causes such as type 2 DM, chronic renal failure, and genetic patterns (13). But although the underlying causes of the high and very high triglyceride values may be a little bit different, probably risks of the terminal end points of the metabolic syndrome do not change in these groups, too. For example, prevalences of hypertension and type 2 DM were the highest in the highest triglyceride value having group in the

above study (23). Eventually, although some authors reported that lipid assessment in vascular disease can be simplified by measurement of either total and HDL-C levels without the need of triglyceride (37), the present study and most others indicated a causal association between triglyceride-mediated pathways and parameters of the metabolic syndrome (38). Similarly, another study indicated moderate and highly significant associations between triglyceride values and CAD in Western populations (39).

As a conclusion, there are significant relationships between cholelithiasis and parameters of the metabolic syndrome including age, female sex, BMI, obesity, hypertension, and hypertriglyceridemia, so cholelithiasis may also be found among the terminal consequences of the metabolic syndrome. Although the significantly lower prevalence of hyperbetalipoproteinemia is probably due to the decreased amount of bile acids secreted during entrance of food into the duodenum and decreased amount of cholesterol absorbed in patients with cholelithiasis or cholecystectomy, the higher prevalence of hypertriglyceridemia may actually indicate its primary role as an acute phase reactant in the plasma.

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Moderate iron deficiency anemia in the treatment of metabolic syndrome

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ABSTRACT

Background: Body mass index (BMI), weight, and height may be due to various hereditary and environmental factors.

Material and methods: Age and sex-matched cases with a hematocrit value of less than 30% were collected into the first, less than 36% into the second, less than 40% into the third, and 40% or greater into the fourth groups of patients.

Results: The study included 108 anemia patients (101 females) with a mean age of 34.7 years (range 15-68). The anemia cases were mainly iron deficiency anemia and/or thalassemia minors. When we compared the first group with the second, the BMI and weight were significantly retarded in the first group (23.6 versus 26.9 kg/m2, p= 0.005 and 61.3 versus 69.9 kg, p= 0.008), whereas there were nonsignificant differences between the second, third, and fourth groups for both (p>0.05 for all). Although there was significantly retarded BMI and weight in the first group, body heights were similar in the four groups (p>0.05 for all).

Conclusion: Although the BMI and weight can be affected by moderate anemia, the height may strongly be determined by heredity. Since the excess weight may be a significant underlying cause of the metabolic syndrome, and the metabolic syndrome shortens human lifespan significantly, and there is no case with shortened survival due to iron deficiency anemia and/or thalassemia minors, an iatrogenic and moderate iron deficiency anemia with frequent blood donation may prolong human survival by decreasing the BMI and weight in the overweight and obese individuals.

Key words: Iron deficiency anemia, thalassemia minor, metabolic syndrome, weight, height

Introduction

Body mass index (BMI), weight, and height may be due to effects of various hereditary and environmental factors. Many studies assume that genes may be importantin these factors, and there is a common agreement that parents' heights affect the stature of the children (1, 2). External factors may also play a role on the body weight and height. It was shown in a previous study that rural and urban living conditions may cause up to a 30% of difference in weight and a 12% of difference in height (3). But there is still little known about genetic and environmental control of the BMI, weight, and height. On the other hand, anemia is defined as a reduction of hemoglobin in the red blood cells (RBCs), and millions of people suffer from it in the world. Iron deficiency anemia and alpha and/or beta thalassemia minors are the most common types of anemia seen in the world. Hemoglobin is the iron-rich protein of the RBCs that carries oxygen from the lungs to the body. The final consequence is a decrease in the blood's ability to carry oxygen to the body and supply it with the energy that it needs. So the important body processes including cell building, tissue repair, and muscular activity slow down in case of iron deficiency anemia. Dizziness and a decrease in mental acuity may result due to the lack of oxygen to the brain and heart failure due to the increased work of heart. Loss of appetite, palpitation, difficulty in concentration, depression, fatigue, coldness of extremities, pallor (reduced amount of oxyhemoglobin in the skin and mucous membranes), brittle nails, cessation of menstruation, breathlessness on exertion, glossitis (inflammation of the tongue), and angular cheilitis (inflammation of mouth corners) are the other common symptoms and signs seen with the iron deficiency anemia. All of the above symptoms are related to the decreased cell turnover and increased work of heart due either to the decreased oxygen supply or to the decreased iron supplement of tissues. We tried to understand possible effects of various hematocrit values on the BMI, weight, and height

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Material and Methods

The study was performed in the Hematology Polyclinics of the Mustafa Kemal University and Diskapi Yildirim Beyazit Education and Research Hospital on routine check up patients between August 2009 and August 2010. The medical history of all cases including already used medications was learnt, and a routine check up procedure was performed. Insulin using diabetics and patients with devastating illnesses including malignancies, chronic renal diseases, cirrhosis, hyper- or hypothyroidism, heart failure, thalassemia intermedia and major, sickle cell diseases (SCDs), and autoimmune hemolytic anemias were excluded to avoid their possible effects on the BMI, weight, height, or hematocrit values. Body weights and heights were measured, and the BMI of each case was calculated by the physicians instead of verbal expressions, since there is evidence that heavier individuals systematically underreport their weight relatively to the lighter ones (4). Weight in kilograms is divided by height in meters squared (5). Iron deficiency anemia and thalassemia minors were diagnosed with serum iron, iron binding capacity, ferritin, and hemoglobin electrophoresis performed via high performance liquid chromatography. Age and sex-matched cases with a hematocrit value of less than 30% were collected into the

first, less than 36% into the second, less than 40% into the third, and 40% or greater into the fourth group. Finally, the four groups were compared in between according to the mean BMI, weight, and height. Mann-Whitney U Test, Independent-Samples T Test, and comparison of proportions were used as the methods of statistical analyses.

Results

The study included 108 anemia patients (101 females) with a mean age of 34.7 years (range 15-68). The anemia cases were mainly iron deficiency anemia and/or thalassemia minors. The female predominance of the anemia cases (93.5%) is due to the menorrhagia induced iron deficiency anemia in this age group. The mean hematocrit values were 23.4, 32.6, 37.7, and 41.6%, respectively, in the groups. The mean corpuscular volume (MCV) values were 58.3, 71.4, 83.3, and 85.5 fL, respectively, in them. When we compared the first group with the second according to the mean BMI and weight, both of them were significantly retarded in the first group (23.6 versus 26.9 kg/m2, p= 0.005 and 61.3 versus 69.9 kg, p= 0.008, respectively), whereas there were nonsignificant differences between the second, third, and fourth groups for both (25.1, 26.6 kg/m2 and 66.6, 71.8 kg, respectively, p>0.05 for all). Interestingly, although the significantly retarded values of the mean BMI and weight in the first group, the mean heights were similar in the four groups (161.0, 160.7, 162.1, and 163.1 cm, respectively, p>0.05 for all) (Table 1 - next page).

Discussion

Iron deficiency anemia is the most common type of anemia in the world, and mostly seen in children due to the increased iron requirement in growth and in women due to the increased iron requirement in pregnancy, lactation, and menstruation. For instance, nine to 11% of adolescent girls and women in childbearing age have iron deficiency, compared with less than 1% of young men in the United States (6). Similarly, the significantly lower MCV values of the anemia patients in the present study also indicate that the majority of cases with anemia are secondary to iron deficiency and/or thalassemias because both are the most common causes of microcytic anemias in the world. The female predominance (93.5%) and young mean age of the anemia patients (34.7 years) of the present study is due to the menorrhagia induced iron deficiency anemia since iron deficiency anemia can be caused by insufficent dietary intake of iron, insufficient absorption of iron, or blood loss which is often caused by menstruation. Iron deficiency anemia induced sign and symptoms may be due to the tissue hypoxia and/or iron deficiency alone since iron takes additional roles in the various tissues and enzymes in the body. Glossitis, angular cheilitis, koilonychia (spoon-shaped nails), and dysphagia due to formation of esophageal webs in the Plummer-Vinson syndrome may be some of the indicators of various roles of iron other than the hemoglobin in the body. Thus moderate anemia induced retarded BMI and weight in the present study may also be secondary to the various roles of iron in tissues and enzymes other than the hemoglobin alone. Thalassemias are the other most common causes of microcytic anemia in the world, particularly in the Mediterranean region. They are autosomal recessively inherited disorders. Normal hemoglobin is composed of two

Table 1: Characteristics of the study cases

Variables	Hematocrit value <30%	p-value	Hematocrit value <36%	p-value	Hematocrit value <40%	p-value	Hematocrit value ≥40%
Number	45		63		60		48
Mean age (year)	34.7 ± 12.0 (15-55)	ns*	34.8 ± 12.0 (16-68)	ns	34.8 ± 11.3 (16-68)	ns	34.6 ± 10.3 (18-54)
Female ratio	91.1% (41)	ns	95.2% (60)	ns	95.0% (57)	ns	93.7% (45)
Mean hematocrit value (%)	23.4 ± 3.9 (14-29)	0.000	32.6 ± 1.5 (30-35)	0.000	37.7 ± 1.0 (36-39)	0.000	41.6 ± 1.9 (40-48)
Mean MCV† value (fL)	58.3 ± 6.4 (46-77)	0.000	71.4 ± 5.5 (57-81)	0.000	83.3 ± 6.0 (64-92)	ns	85.0 ± 3.9 (78-93)
Mean body weight (kg)	61.3 ± 16.0 (38-104)	0.008	69.9 ± 18.1 (40-118)	ns	66.6 ± 12.6 (41-104)	ns	71.8 ± 16.1 (45-107)
Mean body height (cm)	161.0 ± 6.7 (145-179)	ns	160.7 ± 6.7 (147-179)	ns	162.1 ± 7.0 (149-182)	ns	163.1 ± 6.6 (151-180)
Mean BMI‡ (kg/m2)	23.6 ± 6.7 (15.0-47.5)	0.005	26.9 ± 6.8 (15.8-46.6)	ns	25.1 ± 5.0 (16.7-36.7)	ns	26.6 ± 5.6 (18.0-39.6)

*Nonsignificant (p>0.05) †Mean corpuscular volume ‡Body mass index

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pairs of alpha and beta globin chains. Alpha thalassemias result in a decreased alpha globin synthesis, causing an excess of beta chains in adults. The excess beta chains form unstable tetramers (called hemoglobin H) which have abnormal oxygen dissociation curves. Whereas in beta thalassemias, excess alpha chains bind to the RBC membranes causing membrane damage and they form toxic aggregates at high concentrations. Generally, thalassemias are prevalent in populations that evolved in humid climates where malaria is endemic since thalassemias protect these people from malaria due to the easy degradation of the RBCs. Alpha and beta thalassemias are also frequent in Turkey, especially in the Mediterranean region, and most of the cases with anemia in the present study have alpha thalassemias and/or beta thalassemias and/or iron deficiency anemia. Pathophysiologic mechanisms of the lower BMI and weight in the thalassemia cases may include anemia induced tissue hypoxia, increased cardiac activity, increased bone marrow activity, and increased splenic activity. In this field, iron deficiency anemia and thalassemia cases must be researched separately with increased number of cases in further studies. But it is obvious that neither the iron deficiency anemia nor the alpha and/or beta thalassemia minors do not shorten lifespan of the human being.

Normally the BMI and weight may be determined by a complex network of hormonal, nutritional, physical, and genetic factors. For instance, approximately 70 genes may take role in the regulation of bone mass (7), and some genes were shown to affect both the BMI and bone geometric parameters (8). The same results were also shown in animals that the results indicate substantial additive genetic control of Brahman body weight to hip height ratio (9). Leptin is a hormone produced mainly by adipocytes and it acts centrally to control the body weight (10). Leptin is also expressed on osteoblasts and acts as a skeletal growth factor and promotes bone mineralization (11, 12). The pleiotropic effect of leptin on the BMI and bone geometry may also be supported by the evidence of genetic correlation of leptin with the BMI and bone geometry (13). On the other hand, the body length growth velocity was found not to be affected by genes in some studies (14). Whereas we detected in the present study that although the significantly retarded BMI and weight in the moderate anemia (p< 0.05 for both), the heights were similar in all groups without any effect of anemia (p>0.05 for all). Similarly, in a previous study (15) performed on 122 patients (58 females) with the SCDs with a mean age of 28.6 years, although the BMI and weight were significantly retarded in the SCDs cases (24.9 versus 20.7 kg/m2 and 71.6 versus 57.8 kg, p= 0.000 for both) probably due to the accelerated vascular endothelial damaging process initiated at birth; the heights were similar in the SCDs and control groups (166.1 versus 168.5 cm, respectively, p>0.05) probably due to its hereditary nature.

Chronic endothelial damage may be the major cause of aging, morbidity, and mortality by causing disseminated tissue

hypoxia all over the body. Some of the well-known accelerators of the inflammatory process are physical inactivity induced excess weight, smoking, and alcohol for the development of irreversible consequences including obesity, hypertension (HT), diabetes mellitus (DM), cirrhosis, peripheric artery disease (PAD), chronic obstructive pulmonary disease (COPD), chronic renal disease (CRD), coronary artery disease (CAD), mesenteric ischemia, osteoporosis, and stroke, all of which terminate with early aging and death. They were researched under the title of metabolic syndrome in the literature, extensively (16, 17). The metabolic syndrome may be the most common type of vasculitis in the world, and leading cause of aging, morbidity, and mortality in human beings. Much higher blood pressure (BP) of the afferent vasculature may be the major underlying cause by inducing recurrent injuries on endothelium. Thus the term of venosclerosis is not as famous as atherosclerosis in the literature. Secondary to the chronic endothelial inflammation, edema, and fibrosis, vascular walls become thickened, their lumens are narrowed, and they lose their elastic natures that reduce blood flow and increase systolic BP further. Although early withdrawal of causative factors may prevent final consequences, after development of obesity, HT, DM, cirrhosis, PAD, COPD, CRD, CAD, mesenteric ischemia, osteoporosis, or stroke, endothelial changes cannot be reversed completely due to their fibrotic natures (18, 19). Other chronic inflammatory processes including SCDs, rheumatologic disorders, prolonged infections, and cancers may accelerate the process. Finally it is obvious that the metabolic syndrome terminates with a significantly shortened survival in human being (20).

As a conclusion, although the BMI and weight can be affected by moderate anemia, the height may strongly be determined by heredity. Since the excess weight may be a significant underlying cause of metabolic syndrome, and the metabolic syndrome shortens human lifespan significantly, and there is no case with shortened survival due to the iron deficiency anemia and/or thalassemia minors, an iatrogenic and moderate iron deficiency anemia with frequent blood donation may prolong human survival by decreasing the BMI and weight in the overweight and obese individuals.

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Lower the triglyceride, longer the survival

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ABSTRACT

Background: We tried to determine the safest triglyceride value in the plasma.

Methods: Check up cases with a triglyceride value lower than 60 mg/dL were collected into the first, lower than 100 mg/dL into the second, lower than 150 mg/dL into the third, lower than 200 mg/dL into the fourth, and equal to or greater than 200 mg/dL into the fifth groups, respectively.

Results: Study included 478 cases (288 females and 190 males), totally. Mean values of age, body weight, body mass index, triglyceride, and low density lipoprotein cholesterol and prevalences of smoking, white coat hypertension (WCH), hypertension, type 2 diabetes mellitus (DM), and coronary artery disease (CAD) increased nearly in all steps from the first towards the fifth groups, gradually and significantly (p<0.05).

Conclusions: Probably metabolic syndrome is a chronic inflammatory process mainly affecting the vascular endothelium all over the body and terminating with early aging and premature death. The syndrome has reversible parameters including sedentary life style, animal-rich diet, overweight, smoking, alcohol, hypertriglyceridemia, hyperbetalipoproteinemia, dyslipidemia, impaired fasting glucose, impaired glucose tolerance, WCH, chronic inflammations and infections and irreversible end points including obesity, hypertension, DM, cirrhosis, peripheric artery disease, chronic obstructive pulmonary disease, chronic renal disease, CAD, mesenteric ischemia, osteoporosis, and stroke. Hypertriglyceridemia may be one of the most significant reversible parameters of the syndrome, and it is better to have the lowest plasma triglyceride value as much as possible to live longer.

Key words: Triglyceride, metabolic syndrome, atherosclerosis, early aging, premature death

Introduction

Chronic endothelial damage may be the most common kind of vasculitis and the leading cause of aging, morbidity, and mortality in human beings (1-4). Much higher blood pressure (BP) of the afferent vasculature may be the major underlying cause by inducing recurrent injuries on endothelium, and probably whole afferent vasculature including capillaries are involved in the process. Thus the term of venosclerosis is not as famous as atherosclerosis in the literature. Secondary to the chronic endothelial inflammation, edema, and fibrosis, vascular walls become thickened, their lumens are narrowed, and they lose their elastic natures that reduce blood flow to terminal organs and increase systolic BP further. Some of the well-known causes and indicators of the inflammatory process are sedentary life style, animal-rich diet, overweight, smoking, alcohol, hypertriglyceridemia, hyperbetalipoproteinemia, dyslipidemia, impaired fasting glucose (IFG), impaired glucose tolerance (IGT), white coat hypertension (WCH), and chronic inflammatory processes including rheumatologic disorders, chronic infections, and cancers for the development of terminal complications including obesity, hypertension, diabetes mellitus (DM), cirrhosis, peripheric artery disease (PAD), chronic obstructive pulmonary disease (COPD), chronic renal disease (CRD), coronary artery disease (CAD), mesenteric ischemia, osteoporosis, and stroke, all of which terminate with early aging and premature death (5-9). Although early withdrawal of causative factors may prevent irreversible complications, after development of cirrhosis, COPD, CRD, CAD, PAD, or stroke, endothelial changes cannot be reversed completely due to their fibrotic nature. The accelerator factors and terminal consequences were researched under the titles of metabolic syndrome, aging syndrome, or accelerated endothelial damage syndrome in the literature, extensively (10-13). On the other hand, although its normal limits could not been determined clearly yet, hypertriglyceridemia is one of the significant indicators of the metabolic syndrome (14). Due to the growing evidence for a strong association between increased plasma triglyceride values and prevalence of CAD, Adult Treatment Panel (ATP) III adopts lower cutpoints for triglyceride abnormalities than did ATP II (15, 16). Although ATP II determined the normal triglyceride value as lower than 200 mg/dL in 1994, World Health Organisation (WHO) in 1999 (17) and ATP III in 2001 reduced its normal limit as lower than 150 mg/dL (15). Although these cutpoints are usually used to define limits of the metabolic syndrome, there are suspicions about the safest limits of plasma triglyceride values in the literature. We tried to determine the safest triglyceride value in the plasma.

Material and methods

The study was performed in the Internal Medicine Polyclinic of the Medical Faculty of the Dumlupinar University on routine check up patients between August 2005 and March 2007. Consecutive patients between the ages of 15 and 70 years were studied to prevent debility induced weight loss in elders. Their medical histories including hypertension, DM, dyslipidemia, and already used medications were learnt, and a routine check up procedure including an electrocardiography, fasting plasma glucose (FPG), triglyceride, and low density lipoprotein cho-

lesterol (LDL-C) was performed. Current daily smokers, at least with six pack-months, and cases with a history of five pack-years were accepted as smokers. Patients with devastating illnesses including type 1 DM, malignancies, acute or chronic renal failure, chronic liver diseases, hyper- or hypothyroidism, and heart failure were excluded to avoid their possible effects on weight. Additionally, anti-hyperlipidemic drugs or metformin users were excluded to avoid their possible effects on blood lipid profile (18). Body mass index (BMI) of each case was calculated by the measurements of the same physician instead of verbal expressions. Weight in kilograms is divided by height in meters squared (15). Cases with an overnight FPG level of 126 mg/dL or greater on two occasions or already receiving antidiabetic medications were defined as diabetics (15). An oral glucose tolerance test with 75-gram glucose was performed in cases with a FPG level between 110 and 126 mg/dL, and diagnosis of cases with a 2-hour plasma glucose level of 200 mg/dL or greater is DM (15). Additionally, office blood pressure (OBP) was checked after a 5 minute rest in seated position with a mercury sphygmomanometer on three visits, and no smoking was permitted during the previous 2 hours. A 10-day twice daily measurement of blood pressure at home (HBP) was obtained in all cases, even in normotensives in the office due to the risk of masked hypertension after a 10-minute education session about proper BP measurement techniques (19). An additional 24-hour ambulatory blood pressure monitoring (ABP) was obtained just in cases with a higher OBP and/or HBP measurement. It was performed with oscillometrical equipment (SpaceLabs 90207, Redmond, Washington, USA) set to take a reading every 10 minutes throughout the 24 hours. Eventually, hypertension is defined as a BP of 135/85 mmHg or greater on mean daytime (between 10 AM to 8 PM) ABP, WCH as an OBP of 140/90 mmHg or greater but mean daytime ABP of <135/85 mmHg (19). A stress electrocardiography was performed just in suspected cases as a result of the routine electrocardiography, and a coronary angiography was obtained just for the stress electrocardiography positive cases. Eventually, patients with a triglyceride value lower than 60 mg/dL were collected into the first, lower than 100 mg/dL into the second, lower than 150 mg/dL into the third, lower than 200 mg/dL into the fourth, and equal to or greater than 200 mg/dL into the fifth groups, respectively. The female ratio, values of the mean age, weight, BMI, triglyceride, and LDL-C, and prevalences of smoking, WCH, hypertension, DM, and CAD were detected in each group and compared. Mann-Whitney U test, Independent-Samples T test, and comparison of proportions were used as the methods of statistical analyses.

Results

The study included 478 cases (288 females and 190 males), totally. The mean ages of the groups increased up to the triglyceride value of 200 mg/dL, significantly (p<0.05 in all steps), then decreased nonsignificantly (50.5 versus 48.6 years, p>0.05). There were 117 smokers totally, and only 27.3% (32) of them were females. On the other hand, prevalence of smoking was the highest in the highest triglyceride value having group. The mean body weight increased continuously, parallel to the increasing value of triglyceride, whereas BMI increased up to the triglyceride value of 200 mg/dL, and then decreased. Similarly, the mean LDL-C reached its the highest value in the fourth,

Table   1:   Characteristics   of   the   study   cases

Variable	TG* value lower than 60 mg/dL	p-value	TG value lower 100 mg/dL	p-value	TG value lower than 150 mg/dL	p-value	TG value lower than 200 mg/dL	p-value	TG value equal to or greater than 200 mg/dL
Number	58		122		125		87		86
Mean age	33.9 ± 14.2	0.019	38.8 ± 13.8	0.001	44.8 ± 12.9	0.002	50.5 ± 11.2	ns	48.6 ± 10.9
Female ratio	72.4% (42)	ns†	65.5% (80)	ns	60.8% (76)	ns	56.3% (49)	ns	47.6% (41)
Prevalence of smoking	12.0% (7)	ns	14.7% (18)	0.01	23.2% (29)	ns	26.4% (23)	<0.001	46.5% (40)
Mean weight	64.9 ± 13.7	0.000	74.0 ± 15.6	0.017	78.5 ± 13.7	ns	79.6 ± 12.0	ns	80.3 ± 14.5
Mean BMI‡	24.4 ± 5.5	0.003	26.8 ± 6.0	0.001	29.3 ± 6.2	ns	29.5 ± 5.2	ns	28.8 ± 5.1
Mean TG value	51.3 ± 6.8	0.000	77.6 ± 10.9	0.000	122.2 ± 14.9	0.000	174.2 ± 14.7	0.000	263.7 ± 52.1
Mean LDL-C§ value	99.2 ± 23.1	0.000	116.9 ± 34.4	0.000	131.1 ± 30.1	0.010	142.0 ± 34.7	0.008	128.5 ± 39.1

*Triglyceride

†Nonsignificant (p>0.05)

‡Body mass index

§Low density lipoprotein cholesteroλ

Table 2: Associated diseases of the study cases

Variable	TG* value lower than 60 mg/dL	p-value	TG value lower than 100 mg/dL	p-value	TG value lower than 150 mg/dL	p-value	TG value lower than 200 mg/dL	p-value	TG value equal to or greater than 200 mg/dL
Prevalence of WCH†	20.6% (12)	<0.05	27.8% (34)	<0.01	40.8% (51)	ns‡	48.2% (42)	<0.01	32.5% (28)
Prevalence of hypertension	8.6% (5)	ns	9.0% (11)	<0.05	14.4% (18)	ns	12.6% (11)	ns	19.7% (17)
Prevalence of DM§	1.7% (1)	<0.001	6.5% (8)	<0.001	15.2% (19)	ns	14.9% (13)	ns	22.0% (19)
Prevalence of CAD‖	1.7% (1)	ns	1.6% (2)	<0.001	6.4% (8)	ns	4.5% (4)	ns	4.6% (4)

*Triglyceride

†White coat hypertension

‡Nonsignificant (p>0.05)

§Diabetes mellitus

‖Coronary artery disease

and decreased significantly in the fifth groups (48.2% versus 32.5%, p<0.01). As the most surprising result, prevalences of hypertension, type 2 DM, and CAD, as the irreversible end points of the metabolic syndrome, showed their most significant increases after the triglyceride value of 100 mg/dL (Table 2).

Discussion

Excess weight leads to both structural and functional abnormalities of many systems of the body. Recent studies revealed that adipose tissue produces leptin, tumor necrosis factor-alpha, plasminogen activator inhibitor-1, adiponectin, and other cytokines which act as acute phase reactants in the plasma (20, 21). For example, the cardiovascular field has recently shown a great interest in the role of inflammation in the development of atherosclerosis and numerous studies indicated that inflammation plays a significant role in the pathogenesis of atherosclerosis and thrombosis (1, 2). On the other hand, individuals with excess weight have an increased blood volume as well as an increased cardiac output thought to be the result of increased oxygen demand of the excessive fat tissue. The prolonged increase in blood volume can lead to myocardial hypertrophy and decreased compliance in addition to the common comorbidity of hypertension. In addition to them, the prevalences of high FPG, high serum total cholesterol, and low high density lipoprotein cholesterol (HDL-C) increased parallel to the higher BMI values (22). Combination of these cardiovascular risk factors will eventually lead to an increase in left ventricular stroke work with higher risks of arrhythmias, cardiac failure, and sudden cardiac death. Similarly, the prevalences of CAD and stroke increased parallel with the higher BMI values in some other studies (22, 23), and risk of death from all causes including cancers increased throughout the range of moderate to severe weight excess in all age groups (24). The relationships between excess weight and elevated BP and hypertriglyceridemia were described in the metabolic syndrome (14), and clinical manifestations of the syndrome included obesity, dyslipidemia, hypertension, insulin resistance, and proinflammatory and prothrombotic states (12). Similarly, prevalences of smoking (42.2% versus 28.4%, p<0.01), excess weight (83.6% versus 70.6%, p<0.01), DM (16.3% versus 10.3%, p<0.05), and hypertension (23.2% versus 11.2%, p<0.001) were all higher in the hypertriglyceridemia cases in another study (25). It is a well-known fact that smoking causes a chronic inflammatory process in the respiratory tract, lungs, and vascular endothelium all over the body terminating with an accelerated atherosclerosis, end-organ insufficiencies, early aging, and premature death thus it should be included among the major parameters of the metabolic syndrome. On the other hand, smoking-induced weight loss is probably related with the smoking-induced endothelial inflammation all over the body since loss of appetite is one of the main symptoms of disseminated inflammation in the body. In another explanation, smoking-induced loss of appetite is an indicator of being ill instead of being healthy during smoking (26-28). Buerger's disease (thromboangiitis obliterans) alone is also a clear evidence to show the strong atherosclerotic effects of smoking since this disease has not been shown in the absence of smoking up to now. On the other hand, the prevalences of hyperbetalipoproteinemia were similar in the hypertriglyceridemia and control groups (18.9% versus 16.3%, p>0.05, respectively) in the above study (25).

Although ATP II determined the normal triglyceride value as lower than 200 mg/dL in 1994 (16), WHO in 1999 (17) and ATP III in 2001 (15) reduced this normal limit as lower than 150 mg/dL. Although these cutpoints are usually used to define limits of the metabolic syndrome, whether or not more lower limits provide additional benefits for human beings is unclear. In the present study, patients with a triglyceride value lower than 60 mg/dL were collected into the first, lower than 100 mg/dL into the second, lower than 150 mg/dL into the third, lower than 200 mg/dL into the fourth, and equal to or greater than 200 mg/dL were collected into the fifth groups, respectively. Prevalence of smoking was the highest in the fifth group which may also indicate inflammatory roles of smoking and hypertriglyceridemia in the metabolic syndrome. The mean body weight increased continuously, parallel to the increasing value of triglyceride. As the most surprising result, the prevalences of hypertension, type 2 DM, and CAD, as some of the terminal end points of the metabolic syndrome, showed their most significant increases after the triglyceride value of 100 mg/dL. As of our opinion, significantly increased mean age by the increased triglyceride values may be secondary to aging induced decreased physical and mental stresses, which eventually terminates with onset of excess weight and other parameters and terminal end points of the metabolic syndrome. Interestingly, although the mean age increased from the lowest triglyceride having group towards the triglyceride value of 200 mg/dL, then decreased. The similar trend was also seen in the mean LDL-C and BMI values, and prevalence of WCH. These trends may be due to the fact that although the borderline high triglyceride values (150-199 mg/dL) are seen together with overweight, obesity, physical inactivity, smoking, and alcohol like acquired causes, the high triglyceride (200-499 mg/dL) and very high triglyceride values (500 mg/dL and higher) are usually secondary to both acquired and secondary causes such as type 2 DM, chronic renal failure, and genetic patterns (15). But although the underlying causes of the high and very high triglyceride values may be a little bit different, probably risks of the terminal end points of the metabolic syndrome do not change in these groups, too. For example, prevalences of hypertension and type 2 DM were the highest in the highest triglyceride value having group in the present study. Eventually, although some authors reported that lipid assessment in vascular disease can be simplified by measurement of either total and HDL-C levels without the need of triglyceride (29), the present study and most others indicated a causal association between triglyceride-mediated pathways and parameters of the metabolic syndrome (30). Similarly, another study indicated moderate and highly significant associations between triglyceride values and CAD in Western populations (31).

As a conclusion, probably metabolic syndrome is a chronic inflammatory process mainly affecting the vascular endothelium all over the body and terminating with early aging and premature death. The syndrome has reversible parameters including sedentary life style, animal-rich diet, overweight, smoking, alcohol, hypertriglyceridemia, hyperbetalipoproteinemia, dyslipidemia, IFG, IGT, WCH, chronic inflammations and infections and irreversible end points including obesity, hypertension, DM, cirrhosis, PAD, COPD, CRD, CAD, mesenteric ischemia, osteoporosis, and stroke. Hypertriglyceridemia may be one of the most significant reversible parameters of the syndrome, and it is better to have the lowest plasma triglyceride value as much as possible to live longer.

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Histopathological findings in hysterectomy specimens:
A retrospective study

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ABSTRACT

This is a retrospective study of descriptive patterns of findings seen in hysterectomy specimens based on records from a Modern - histopathology laboratory in Aden.

A total of 2,544 specimens were analyzed during the 6 years period from January 2006 to December 2012, to study the histopathological findings of these specimens. The age of the patients at hysterectomy ranged from 16-80 years with a mean of 44.6, with the maximum patients (56.3 %) in the age group 41-50 years and less patients in less than 30 years.

Most common pathology findings are; Endometrial hyperplasia 1481 (58.3%), Non neoplastic cystic lesion 1386 (54.5%), Chronic cervicitis 1363 (53.6%), Adenomyosis 793 (31.2%) follow by Leiomyoma 697 (27.4%).

Other less frequent pathologies identified included atrophic endometrium, Inadequate secretory endometrial transformation, Gestational Trophoblastic disease, Endometroid adenocarcinoma, cervical prolapse.

This study confirms that benign pathologies are more common in hysterectomy specimens than their malignant counterparts.

Key words: Hysterectomy, endometrial hyperplasia, ovarian cystic lesion, chronic cervicitis.

Introduction

Uterus, a vital reproductive organ is subjected to many benign and malignant diseases. Many treatment options are available including medical and conservative surgical but hysterectomy still remains the most common gynaecological procedure performed worldwide (1).

The procedure is not well embraced in developing countries, thus, the clinical indication for the procedure should be justifiable, for age and parity of the women (2).

In response to the consistent demand for this procedure, hysterectomy has been identified as a key health care indicator in recent reports, to measure and compare hospital performance (3).

It is the definitive cure for many of its indications which include dysfunctional uterine bleeding, fibroids, utero-vaginal prolapse, endometriosis and adenomyosis, pelvic inflammatory disease, pelvic pain, gynaecological cancers and obstetric complications. Ultimate diagnosis is only on histology, so every hysterectomy specimen should be subjected to histopathological examination (4).

In Yemen, histopathological examination of hysterectomy specimens carries diagnostic and therapeutic significance. Prevalence of uterine and adnexal pathologies varies from nation to nation and from region to region (5)

The present study is aimed at detailed histopathological evaluation of all lesions of hysterectomy specimens. It provides an intact uterus and consequent control over tissue sampling and hence enabling determination of origin of particular lesion and to compare the findings with other researchers.

Material and Methods

Our study was a retrospective descriptive work analysis of 2,544 patients with hysterectomy, over a period of 6 years from January 2006 to December 2012. The information was gathered regarding age, and histological diagnosis and was analyzed by Excel program and tables performed according to the objectives of the study and compared to literature review.

Results

A total of 2,544 hysterectomy specimens between January 2006 to December 2012 were analyzed. The age range of the patients was 16 to 80 years, with a mean of 47.6 years.

Of these 2,544 cases, most of the cases were in the 41-50 years age group 1431(56.3%), which is the most common age group for contracting various diseases as shown in Table 1.

Table 2 revealed that out of the total hysterectomy specimens 1,481(58.3%) were Endometrial hyperplasia, atrophied endometrium 396 (15.6%) Tumor was present in specimens out of which 10 were invasive complete hydatidiform mole, 45 were endometrial adenocarcinomas , Malignant mixed mullerian tumour (MMMT) 6 (0.2%) cases and one case of choriocarcinoma.

Most common histopathological abnormality in myometrium was adenomyosis followed by Leiomyoma. Adenomyosis in 793 (31.2%), followed by Isolated leiomyoma was seen in myometrium of 697 (27.4%) hysterectomies, where in 163 (6.3%) myometriums, both were present together. Tumor was present in specimens out of which 31 was invasive by malignant endometrial carcinoma as shown in Table 3.

In Table 4 cervix from 2,377 (53.6%) specimens showed chronic cervicitis. Cervical intraepithelial neoplasia (CIN) I, CIN II, CIN III with chronic cervicitis (0.8%, 0.4, 0.3%) and flat condyloma (0.1%,0.6%), squamous cell carcinoma were seen in 22 specimens (0.9%) and Adenocarcinoma were 17 cases. Uterovaginal prolapse were 132 cases (5.2%).

Unremarkable Histopathology of the cervix were 655 cases (25.7%).

2,087 ovarian specimens were retrieved from the computerized database of the pathology department, from January 2006 to December 2013.

There were 1,386 (54.4%) non-neoplastic functional cysts.

The neoplastic were benign serous cystadenoma (2.5 %) and benign varian fibroma (0.9%), mucous cystadenoma (0.5%) and Mature cystic teratoma (Dermoid cyst) 0.5%.

The malignant were 21 cases of serous cystadeocarcinoma , 9 cases of mucinous cystadeocarcinoma , 2 cases undifferentiated carcinoma and 9 cases of Metastatic carcinoma, as appears in Table 5 (page 36).

Discussion

Hysterectomy is the commonest gynecological operation and the rate of hysterectomy varies according to geographic distribution, patient and physician related factors (1).

Hysterectomy is second only to cesarean section as the most frequently performed major operation in the United States. Approximately 600,000 hysterectomies are performed annually in the USA, and more than one third of US women have had a hysterectomy by the age of 60 (6).

In Pakistan, the rate of hysterectomy is quite high because it is the only surgical option available if the patient is not responding to medical treatment(7).

Many women in Africa and Nigeria in particular are reluctant to undergo this procedure because of the socio-cultural attachment to procreation and taboos associated with lack of menstruation(2).

Few studies have been performed describing the pathologic findings in hysterectomy specimen and examining the relationship between the preoperative clinical indication and pathologic diagnosis (8).

In the present study, the mean age of patients was 47.6 years and age range from 16 to 80 years which was nearly similar to findings by others (7,9,10).

The peak age for the procedure in our study was the fourth decade (41–50 years) as has been observed in other studies (9).

In the current work we found endometrial hyperplasia was the commonest histopathological finding with 58.3%.

Lee (11) reported that endometrial hyperplasia was confirmed in 95%, a somewhat higher figure than we found and less results 16% were found in Nepal by Ranabhat et al (5).

Table 1: Distribution of patients according to age groups

Age group (years)	No	%
< 30	50	2.0
31-40	535	21.0
41-50	1431	56.3
51-60	397	15.6
>60	131	5.1
Total	2544	100

Table 2: Histopathological findings in Endometrium hysterectomy specimens

Histopathology	No	%
Endometrial hyperplasia	1481	58.3
Atrophic endometrium	396	15.6
Gestational Trophoblastic disease or hydatidiform mole (complete and partial mole)	222	8.7
Inadequate secretory endometrial transformation	216	8.5
Endometrial hyperplasia and Polyp	139	5.5
Endometroid adenocarcinoma	45	1.7
Endometritis	21	0.8
Invasive gestational trophoblastic disease	10	0.4
Atrophic endometrium with polyp	5	0.2
MMMT	6	0.2
Choriocarcinoma	1	0.04
Normal Endometrium	2	0.08
Total	2544	100

Table 3: Histopathological findings in myometrium

Histopathology	No	%
Adenomyosis	793	31.2
Benign Leiomyoma	697	27.4
Leiomyoma and adenomyosis	163	6.4
Invasion by malignant endometrial carcinoma	31	1.2
Chronic Myometritis	12	0.5
Leiomyosarcoma	10	0.4
Normal	838	32.9
Total	2544	100

Table 4: Histopathology of cervix

Histopathology	No	%
Chronic cervicitis	1363	53.6
Chronic cervcitis with CIN-I	21	0.8
Chronic cervicitis with CIN-II	9	0.4
Chronic cervicitis with CIN-III	8	0.3
Uterovaginal prolapse	132	5.2
Inflammatory endocervical polyp	37	1.5
Flat condyloma without dysplasia	72	2.8
Flat condyloma with CIN-I	4	0.1
Flat condyloma with CIN-II	15	0.6
Flat condyloma with CIN-II	1	0.04
Cervical Leiomyoma	21	0,8
Squamous cell carcinoma	22	0.9
Adenocarcinoma	17	0.7
No cervix	167	6.6
Normal	655	25.7
Total	2544	100

Table 5: Histopathology of ovaries

Histopathology	No	%
Non neoplastic cystic lesion	1386	54.5
Ovarian endometriosis	16	0.6
Ovarian fibroma	22	0.9
T.B Oopheritis	3	0.1
Ovarian Bilharziasis	2	0.1
Ovarian abscess	1	0.0
Ovarian hemangioma	1	0.0
Benign serous cystadenoma	63	2.5
Benign mucinous cystadenoma	13	0.5
Mature cystic teratoma (Dermoid cyst)	12	0.5
Malignant serous cystadeocarcinoma	21	0.8
Malignant mucinous cystadeocarcinoma	9	0.4
Granulosa cell tumor	6	0.2
Sertoli Leydig cell tumor	3	0.1
Gonadoblastoma	2	0.1
Yolk sac tumor	1	0.04
Clear cell carcinoma	1	0.04
Benign transitional cell (Brunner) tumor	1	0.04
Non Hodgkin's Lymphoma	2	0.1
Undifferentiated carcinoma	2	0.1
Metastatic carcinoma	9	0.4
Normal	511	20.1
No ovaries	457	18
Total	2544	100

Endometrial hyperplasia is either idiopathic or occurs due to associated diseases or conditions. It can also be transformed to endometrial carcinoma and patients with endometrial hyperplasia must be treated properly and carefully followed up (12).

The exact pathogenesis of endometrial polyps is not fully elucidated, but they are thought to originate as a localized hyperplasia of the basalis, perhaps secondary to hormonal influences (13).

In our study the association between endometrial hyperplasia and hyperplastic endometrial polyp were 139 (5.5%) cases.

This figure approaches that seen by Kelly et al (14) with (3.1%) in all cases of endometrial hyperplasia in his study period. Other studies have found that incidence of endometrial polyps in endometrial hyperplasia range between 11 and 29% (15).

In the present study we found atrophic changes in 396 cases (15.6%), nearly approximate to that seen by Ranabhat et al (5) with 13% and that seen by Pity et al (16) from Iraq with 10.4 %.

A higher figure was seen in study by Thamilselvi et al (17) with 26%.

This may justify the sample size in our study.

Other authors were in discordance with our study, Gousia et al (18) reported 5.44%, and results reported by Sarawathi et al (19) with 2.44%.

In the present study inadequate secretory transformation were 216 (8.5%) cases, which was similar to other findings (20).

It is higher than that seen by Zeeba et al (21) with 1.8% and higher than our result was reported by Sarfraz et al (22) with 24%.

Chronic endometritis is commonly seen in the reproductive age due to either retained products of conception, pelvic inflammatory diseases or other pregnancy related conditions.

In our study 21 (0.8%) cases showed chronic endometritis of all hysterectomy samples, which approximate with the finding of Sajjad et al (23) which was 1% and completely lower than that seen by Ranabhat et al (5) which was 9.5%.

We found in our study endometrial adenocarcinoma were in 45 patients (1.7%). This finding is similar to that found by others (5,16), but it was completely lower than those reported by Patel (24) from Australia 10.5%, and by Gebauer et al (25) from Germany with 16%.

Gestational Trophoblastic Disease (GTD) refers to a wide spectrum of interrelated conditions ranging from benign hydatidiform mole (HM), invasive mole to malignant choriocarcinoma (26).

These regional variations have been reported with many speculative factors such as ethnic origin, blood group, age, parity, diet and nutrition, contraception, socio-economic status, immunologic factors and genetic constitution (27).

In our study we found 222 (8.7%) cases of GTD of the total hysterectomies samples, only 10 cases were invasive gestational trophoblastic disease at the time of pathological diagnosis and one case of choriocarcinoma.

In the Kingdom of Saudi Arabia (KSA) fifty-nine cases of hydatidiform mole, 36 complete hydatidiform mole (CHM) and 23 partial hydatidiform mole (PHM) and 2 cases of choriocarcinoma were observed, out of 64,762 pregnancies registered at Security Forces Hospital, Riyadh, KSA, during an 11 year period (27).

In a study in Nepal, there were 17 (37.8%) cases of hydatidiform mole, 6 (13.3%) of invasive mole and 22 (48.8%) patients of choriocarcinoma (28).

A malignant mixed Mullerian tumour (MMMT) of the uterine corpus is an extremely rare and aggressive malignancy, comprising only 1–2% of uterine neoplasms (29).

In our study there were 6 (0.2%) cases of MMMT. In the study of Rajshekar SK only four cases of MMMT were diagnosed representing 20% of his sample (30) and this variation in the frequencies may support our justification related to sample size and study design.

In the current study adenomyosis was the commonest lesion of the myometrial pathology and represented 31.1% followed by leiomyoma 27.4%. Adenomyosis appears also to be the commonest pathology and similar to our findings reported by others (5,22,31).

The present study revealed that leiomyoma was also the commonest pathology and it was 27.4%. Reported frequencies vary in different countries and it was 26% in KSA (32), and 36% and in Kurdistan/Iraq (16), in Nigeria 48%(33) and 17% in India (34) and only 8% in Sweden (35).

Some of the hysterectomy specimens show more than one lesion in the body of uterus, of which coexistence of adenomyosis and leiomyoma are the most common (34).

In the present study there was 6.4% showing coexistence of adenomyosis and leiomyoma. In other study increasing to 56% when adenomyosis with concomitant leiomyoma are included (31) and it was 19% reported by Sarfraz et al (21) and 5.6% reported by Qamar et al (7).

Leiomyoma was the commonest lesion of uterine corpus followed by adenomyosis.

This was similar to findings of other studies (16,32,33,36,37).

Geographical and racial influences are thus apparent on the prevalence of uterine leiomyoma and the prevalence of risk factors in terms of quantities and type. Early menarche, delayed menopause, decreased parity, obesity and lack of exercise are some of the risk factors of leiomyoma (5).

Among the cervix uteri, chronic cervicitis was the main pathological finding in the present study and accounted for 53.6%. This figure is nearly similar to that reported by Jamal et al (36) which was 41.5% and to that reported by Qamar et al (7) which was 31%.

A higher figure of chronic cervicitis seen in Nepal women by Jha et al was 96.4% (37); the variation may be related to different reproductive health procedures. Iin Yemen almost all males are circumcised which minimizes vaginal infection.

In our study 37 (1.5%) cases showed dysplasia of various degrees with chronic cervicitis and 20 (0.7%) cases showed cervical condyloma with dysplasia.

A premalignant lesion, Cervical intraepithelial neoplasia (CIN) was seen in 3.0% in a study by Thamilselvi et al (17) and 0.8 % reported by Ranabhat et al (5).

The low incidence of CIN in our study may related to the reproductive life style, where the women are restricted to single sexual partner , while the CIN is more common with sexually transmitted disease of HPV, which is more frequent in multiple sexual partner women .

The diagnosis of uterovaginal prolapse was based on clinical as well as pathological findings (38).

In our study Hysterectomies done for utero-vaginal prolapse were found in 132 (5.2%). This finding was higher than that reported by Pity et al (16) which was 2(0.5%), while less than the findings reported by Butt et al (39) with (11%) and less than 17% reported by Adelusola et al (33).

The present study revealed only 0.9% of all the samples of hysterectomy showing invasive squamous cell carcinoma at the pathological study.

This finding was nearly similar to that reported by Ranabhat et al (5), Gousia RR et al (18) and Bani et al (40) which were 0.6%, 0.3% and 0.6% respectively.

This low incidence may be related to reproductive health in Arab and Muslim countries where most of the women are restricted to one sexual partner and a Muslim habit for washing and vaginal douches after sexual intercourse and a high incidence of HPV infection in European countries play an important role in cervical dysplasia and carcinoma.

In the present study adenocarcinoma were 17 (0.7%) cases.

Garud et al in 1981 described adenocarcinoma of cervix also carries considerable percentage i.e. 15-20% of all invasive carcinoma of cervix (41), while Sanyal et al (42) noted it as 2% among all cervical lesions.

The most common lesions encountered in the ovary include functional or benign cysts and tumors and benign ovarian neoplasms occur at any age whereas malignant ovarian neoplasms are more common in the elderly (43,10).

Ovarian tumors are one of the major causes of gynaecological problems in females and present with marked variation in their histological types. Relative frequency of these lesions is different for Western and Asian countries (10).

We found in our current study, the most common pathological finding of the ovaries in all hysterectomy samples were benign (functional) cysts and were 54.4%.

Our finding was nearly similar to that reported by Mansour (44) in KSA where the benign non neoplastic ovarian cysts comprise 47.5%, while the data from South East Asia shows that 90.5% of ovarian cysts were benign (45), less results were reported by Gupta et al (46)with 2.77% and 20% by Ranabhat et al (5).

Surface epithelial tumours were the major histological type of ovarian tumours followed by germ cell tumours as the commonest ovarian cyst seen in most of the literature (8).

In our study, the most common surface epithelial tumors was benign serous cyst adenoma 2.5% followed by mucinous cystadenoma 0.5% , which approximate the finding seen by Jha et al (37) with 4.5% for benign serous cystadenoma, 3.1% for mucinous cystadenoma and 25.7% of benign surface epithelial tumors were serous cyst adenoma and 6.7 % were mucinous cyst adenoma reported by Pity et al (16) in their study, which was lower than that seen by Abdullah et al (38) where serous cystadenoma represented 44.6% and mucinous cystadenoma 13.6%. The low figure in our study may be related to the study sample, where we are selected only hysterectomy samples and excludes all cases with simple ovarian cystectomies.

In our study malignant serous cystadenocarcinoma were the most common malignant ovarian neoplasm and represented 0.8% of the cases followed by mucinous cystadeocarcinoma 0.4% and this figure approximates the data published by Jha et al (37) where 3.4% of his cases are malignant serous cystadenoma and 0.8% were malignant mucinous cystadenoma.

The higher result with data published by the others, and it's 33.3% for malignant serous cystadenocarcinoma and 15.4% for malignant mucinous cystadenocarcinoma seen by Abdullah et al (38) and in Nepal malignant serous cystadenocarcinoma account for 21.1% and 22.2% of malignant mucinous cystadenocarcinoma found by Jha et al (37) and the low figure in our study related to the type of study sample.

Approximately 95.0% of ovarian germ cell tumors are mature cystic teratomas in the western world (47).

In this study mature cystic teratoma (Dermoid cysts) account for 12 (0.5 %) of all ovarian tumors. A study in Pakistan (48) reported a high figure of 38%.

A mature cystic teratoma is a benign neoplastic ovarian lesion that occurs during reproductive life and is more common in young females during active reproductive life and usually treated by simple cystectomy and this may justify the low incidence in our study where the hysterectomy is the sample study and not ovarian cystectomy.

Other ovarian tumours are rare in our study and it was 0.6% for ovarian fibroma which is similar to that reported by Jha et al (37) with 0.9%.

Granulose cell tumor was 6(0.2%) in our study and it is similar to other findings (37,49).

In the present study ovarian endometriosis accounted for 16 (0.6%), which was similar to that seen by Gousia et al (17) with (0.61%). Also, our finding was less than that observed by Randabhat et al (5) which was 8.9% and less than that seen by Ahsan et al (30) with 13%.

Ovarian endometriosis is a benign condition usually treated by simple ovariectomies, which justify the low figure in our study which is based on hysterectomy samples.

In the present study metastatic carcinoma to ovaries (secondary) accounted for 9(0.4%) which was lower than that seen by Abdullah et al (38) with 13(15.5%) and 4(2.4%) reported by Jha et al (10).

The low figure in our study does not reflect the low incidence in our patients but may be related to big sample size in our study (2,450 cases) as well as the type of sample study and most cases of metastatic carcinoma to ovaries are with advanced stages of either breast or GIT cancer, where there is no indication orfor hysterectomies.

Conclusion

Hysterectomy still remains the widely used treatment modality even in developed countries. The ultimate diagnosis is only on histology, so every hysterectomy specimen should be subjected to histopathological examination. Histopathological analysis correlates well with the pre-operative clinical diagnosis for hysterectomy.

Most of the pathologies are still benign; malignancies are also detected on hysterectomy specimens, but very rarely. A yearly audit should be conducted in every institute to collect data and to analyze the pattern of indications and types of histopathological lesions and pattern of diseases.

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