RESEARCH ARTICLE

EFFECT OF OBESITY ON ESTRADIOL DEPLETIONIN POSTMENOPAUSAL WOMEN WITH HORMONE-SENSITIVE EARLY BREAST CANCER TREATED WITHADJUVANT ANASTRAZOLE.

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Abstract
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Background: Obese BC patients have increased total body aromatization which leads to increased serum estrogen level when compared with non obese patients, Recently it has been shown that BMI has an impact on the efficacy of AIs, mainly Anastrazole, in patients with breast cancer

Aim of the work: The aim of this study was to assess the effect of obesity on estradiol depletion in postmenopausal women with hormone-sensitive early breast cancer treated with Adjuvant upfront standard dose Anastrazole (1mg) after 6 months of treatment and its impact on survival.

Patients and Methods: This prospective cohort study was conducted at the Clinical Oncology and Nuclear Medicine Department - Zagazig University Hospitals. During the period of March 2013 to November 2016. The study included 100 postmenopausal women with hormonal receptors positive early breast cancer who received upfront Anastrazole 1mg/d . Patients were classified into two groups according to BMI, non-obese (BMI<30kg/m2) and obese (BMI≥30kg/m2) according to the WHO, a baseline serum estradiol and FSH were obtained for every patient prior starting Anastrazole therapy. Patients were followed up and monitored after 6 months for changes in serum estradiol level and FSH level . The primary end point of the study was , detection of BMI variation and its relation to changes in serum Estradiol and FSH levels Secondary end point was to compare the OS, DFS and adverse events between the two treatment groups

Results: One hundred patients were included, half of them were classified being obese with (BMI≥30) with mean BMI(35±5.8) while the other half was considered non obese (BMI<30) with mean BMI(24.5±4.4). Both groups were compared according to patient measures and tumor characteristics, regarding all (100) patients , Anastrazole significantly reduced the mean ESL from19.45±4.1 pg ml^{-1} to 11.13 ±3.1 pg ml^{-1} after 6 months of treatment (P <0.001). On the other hand , inverse changes in FSH serum level as the mean FSH serum level initially was 70.91±20.7 mIU ml^{-1} and then significantly increased to 75.78±19.3 mIU ml^{-1} after 6 months of treatment with Anastrazole (P <0.001). however after 6 months of Anastrazole treatment , the mean ESL of obese patients was significantly higher compared to non-obese patients (11.98 pg ml^{-1} VS 8.78 pg ml^{-1}) (P <0.001). and this difference reflected by significantly lower serum FSH level in obese compared to non-obese patients (64.98±14.7 mIU ml^{-1} vs 87.53±17.6 mIU ml^{-1}) (P <0.001). early results of survival analysis revealed 3y DFS in non-obese patients was 92% while it was 90% in obese patients with no significant difference between both groups (P=0.680) . 3y OS in non-

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obese patients was 96% versus 92%in obese patients with insignificant difference between both groups (P=0.374)

Conclusion: Anastrazole is less effective in suppressing the ESL in obese when compared with non-obese postmenopausal , hormonal sensitive early breast cancer patients.no statistically significant difference in preliminary 3year OS ,DFS between both groups .

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Introduction:-

In U.S Breast cancer is the most common malignancy and the second most frequent cause of cancer mortality in women.[1,2] And it is considered the first malignancy-affecting females in Egypt.[3]

 Obese postmenopausal women have an increased risk of breast cancer , cancer recurrence and death when compared with normal weight women . This higher risk could be due to an increased total body aromatization and subsequently elevated estrogen serum levels .[4]

Aromatase inhibitors (AIs) are the gold standard of adjuvant hormonal therapy in hormone receptor-sensitive postmenopausal women with breast cancer, It can be given either as upfront or after 2–3 years of tamoxifen .[5]

(AIs) block the aromatization of androgens to estrogens which occur in muscle and adipose tissue in postmenopausal women and thereby it depletes estrogen serum levels with subsequent improvement of disease-free survival and overall survival in the adjuvant as well as in the metastatic setting.[6,7]

 Obesity was found to have an impact on the effect of AIs ,specially Anastrozole, in patients with breast cancer. and it is not clear if the standard dose of anastrazole (1 mg) is sufficient to adequately suppress heightened aromatization related to obesity[8].

Results from the 100-month follow-up analysis of the ATAC trial confirmed that women receiving 1 mg of Anastrazole with a high body mass index> 35 at baseline had a higher incidence of recurrences than those with a low BMI < 23.[9] BMI effect has been confirmed in the extended adjuvant setting in the **ABCSG-6a trial** and even in premenopausal women in an analysis of the **ABCSG-12 trial**.[10,11] Recent findings regarding the impact of obesity on the efficacy of adjuvant hormonal treatment with aromatase inhibitors (AIs) for early-stage breast cancer have added to the debate on whether obese women benefit less from AI treatment regarding disease-free survival and overall survival.[8] And it became mandatory to evaluate if the dosing of Anastrazole , Is (1 mg) insufficient to adequately suppress aromatization related to obesity?

The aim of this study was to assess the effect of obesity on estradiol depletion in postmenopausal women with hormone-sensitive early breast cancer treated with Adjuvant upfront standard dose Anastrazole (1mg) after 6 months of treatment and its impact on survival.

Patients and Methods:- This   prospective cohort study was conducted at the Clinical Oncology and Nuclear Medicine Department - Zagazig University Hospitals During the period of March 2013 to November 2016. The study included 100 postmenopausal women with hormonal receptors positive early breast cancer who received upfront Anastrazole 1mg/d . Informed consent was obtained from all cases before enrolment in the study ,All the data obtained from the patients were confidential and used only for research purposes.

Eligibility Criteria and pretreatment evaluation :-
The eligibility criteria included , postmenopausal women, Histologically confirmed early primary breast cancer who has positive hormone receptor status(ER and/or PR) , ECOG performance scales of ≤ 2 , Patients who had completed initial therapy (i.e. surgical resection with or without adjuvant chemotherapy and radiation therapy), Patients started on adjuvant frontline hormonal treatment (Anastrazole 1 mg daily),no evidence of distant metastasis or local recurrence .

All the patients underwent pretreatment staging work up in the form of history and clinical examination ,complete blood picture (CBC), renal function test (RFT), and liver function tests (LFT) , Chest X-ray, pelvi abdominal ultrasound(US) and /or computed tomography(CT) scans and mammogram and US of contralateral breast. Brain CT or MRI and bone scan were done when indicated to exclude distant metastasis .

Treatment and follow up :-
All eligible patients received Anastrazole as an adjuvant frontline treatment with standard dose of Anastrazole 1mg/day. Patients were classified according to BMI into two groups , non obese or normal weight (BMI<30kg/m^2) and obese (BMI>30kg/m^2) by using equation BMI=mass (kg)/ height (m^2)according to the WHO (World Health Organization) and a baseline serum estradiol and FSH were obtained for each patient prior to starting Anastrazole therapy. Patients were followed up and serum estradiol and

FSH were monitored again 6 months after starting Anastrazole 1 mg daily to detect any changes in their levels . Adverse effects of the treatment were monitored (hot flashes ,bone pain, depression, dyspnea, headache, anorexia, dry mouth, nausea, abdominal pain) at baseline and after 6 months of treatment .Toxicity was analyzed according to National Cancer Institute-Common Toxicity Criteria (CTC) criteria version2. 1998, patients underwent physical examination, and monitored every 3 months for: Local recurrences: (chest wall, ipsilateral breast and lymphatic's), new contra lateral breast cancer and distant metastasis.

The primary end point of the study was , detection of BMI variation and its relation to changes in serum Estradiol and FSH levels Secondary end point were to compare the OS, DFS and adverse events between the two groups.

Statistical analyses:-
 All statistical calculations were performed using the SPSS 19.0 and MedCalc windows. The normality of continues data were assessed using Kolmogorov test, they were normally distributed. To compare the demographics and tumor characteristics between obese and non-obese patients , Student's t-test, x^2 test or Fisher's exact test was used. To compare means of serum levels before and after AI treatment we used paired T test. Overall Survival (OS) was calculated as the time from diagnosis to death. Disease Free Survival (DFS) was calculated as the time from surgery to reappearance of disease local, regional or distant. Local Recurrence Free Survival (LRFS) was calculated as the time from surgery to local or regional reappearance of disease. Distant Metastasis Free Survival (DMFS) was calculated as the time from surgery to distant reappearance of disease. These time-to-event distributions were estimated using the method of Kaplan-Meier plot, and compared using two-sided exact log-rank test. A p-value ≤ 0.05 was considered significant.

Results:-
One hundred patients were included, half of them were classified being obese with (BMI≥30) with mean BMI(35±5.8) while the other half was considered non obese (BMI<30) mean BMI(24.5±4.4). Both groups were compared regarding patient measures and clinic pathologic characteristics , and both groups were comparable to each others as revealed in table (1).

Table 1:- baseline characteristics of the studied patients (n=100).

Patient characteristics	Non Obese X±SD (N=50)	Obese X±SD (N=50)	P-value
	No (%)	No (%)	
Age Mean±SD	54.6±8.7	54.2±8.1	0.49
Weight (kg)	67.2±10.5	73.8±14.6	0.00*
Height (cm)	158.6±5.3	162.3±5.2	0.00*
BMI (kg/m^2)	24.5 ± 4.4	35.8±5.8	0.00*
Early menopause ≤ 45y			
No	38(76.0%)	37(74.0%)	0.17
Yes	12 (24.0%)	13 (26.0%)	
Pathological type IDC ILC Other types	40 (80.0%) 7 (14.0%) 3 (6.0%)	37 (74.0%) 10 (20.0%) 3 (6%)	0.5
Tumor size(T) T1 T2 T3	4 (8.0%) 39 (78.0%) 7 (14.0%)	6 (12.0%) 38 (76.0%) 6 (12.0%)	0.81
Nodal state(N) N0 N1 N2	10 (20.0%) 22 (44.0%) 18 (36.0%)	12 (24.0%) 25 (50.0%) 13 (26.0%)	0.72
Grade (G) G1 G2 G3	6 (12.0%) 38 (76.0%) 6 (12.0%)	6 (12.0%) 37 (74.0%) 7 (14.0%)	0.61
Treatment modalities Adjuvant chemotherapy -No -yes	6(12.0%) 44(88.0%)	5(10.0%) 45 (90.0%)	0.65
Adjuvant radiotherapy -No -yes	9 (18.0%) 41 (82.0%)	7(14.0%) 43 (86.0%)	0.76
Oestrogen receptor			

Low expression(+)	4(8.0%)	5 (10.0%)	
Medium expression (++)	6 (12.0%)	9 (18.0%)	0.39
High expression(+++)	40(80.0%)	36(72.0%)	
Progesterone receptors			
Negative expression(-)	5(10.0%)	6(12.0%)	
Low expression(+)	6(12.0%)	8(16.0%)	0.18
Medium expression (++)	18(36.0%)	11(22.0%)	
High expression(+++)	21(42.0%)	25(50.0%)	
Her 2 neu status			
Negative	37(74.0%)	35(70.0%)	0.52
Positive	13(26.0%)	15(30.0%)	

Comparing Estradiol and FSH levels in all patients before and 6 months after treatment:-
On comparing Estradiol and FSH levels, we found that the mean estradiol serum level initially before the treatment was 19.45±4.1 pg ml^{-1} and then significantly reduced to 11.13 ±3.1 pg ml^{-1} 6 months after treatment with AI (P =0.00) **(Figure1)** . On the other hand ,   inverse changes in FSH serum levels have occured as the mean FSH serum level initially was 70.91±20.7 mIU ml^{-1} and then significantly increased to 75.78±19.3 mIU ml^{-1} after 6 months of treatment with   AI (P=0.00) **(Figure 1, 2)** .

Comparing Estradiol level between the studied groups before and 6 months after treatment:-
At baseline, a slightly higher mean estradiol serum level was detected in obese compared with non-obese patients (19.75±4.3 pg ml^{-1}*vs* 18.35±3.4 pg ml^{-1} respectively , P=0.8). After 6 months of treatment with an AI , significantly reduced the mean estradiol serum level in obese and non-obese patients (from 19.75±4.3 pg ml^{-1} to 11.98± 3.3 pg ml^{-1}, *p=0.00*, and from 18.35±3.4 pg ml^{-1} to 8.78±2.2 pg ml^{-1}, P=0.00 respectively) **(Figure 1)**

Comparing FSH level between the studied groups before and 6 months after treatment:-
Obese patients had significantly lower FSH serum level at baseline when compared with non-obese patients (60.34±15.7 mIU ml^{-1}*vs* 80.75±18.6 mIU ml^{-1}, (P<0.01). Six months after AI treatment increased FSH serum levels in obese and non obese patients (from 60.34±15.7 mIU ml^{-1}, to 64.98±14.7 mIU ml^{-1},and from 80.75±18.6 mIU ml^{-1}, to 87.53±17.6 mIU ml^{-1}, P=0.00 and P<0.05 respectively) (**Figure 2**)
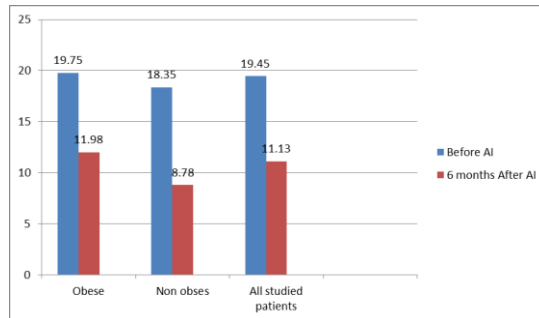

Fig 1:- Comparing Estradiol level in the studied groups before and 6 months after treatment.
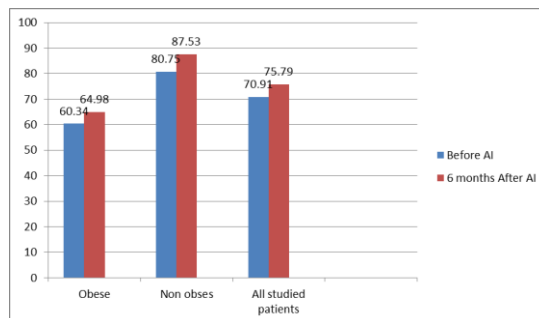

Fig 2:- FSH level in the studied groups before and 6 months after treatment

Comparing Estradiol level between the studied groups 6 months after treatment
however after 6 months of Anastrazole treatment , the mean ESL level was significantly higher in obese compared to non-obese patients (11.98±3.3 pg ml−1 VS 8.78±2.2 pg ml−1) (P <0.001) , and this difference reflected by significantly low serum FSH level in obese compared to non-obese patients(64.98±14.7 mIU ml−1 vs 87.53±17.6 mIU ml−1) (P <0.001) **(Figure 3).**
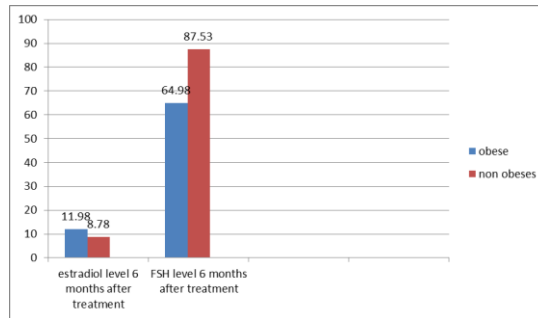

Fig 3:- Comparing Estradiol level and FSH levels 6 months after treatment in obese and non obese participants

Adverse event:-
No difference could be observed regarding the side effects of Anastrazole in obese versus non-obese patients at baseline as well as after 6 months of Anastrazole treatment. **(Table 2)**.

Table 2:- Adverse reactions in postmenopausal women initially and after 6 months.

Adverse reactions	Before AI treatment			6 months of AI treatment		
	Non obese (N=50)	Obese (N=50)	P value	Non obese (N=50)	Obese (N=50)	
	No(%)	No(%)		No(%)	No(%)	P value
Hot flushes						
0	29(58.0%)	31 (62.0%)		27(54.0%)	28(56.0%)	
1	16(32.0%)	11(22.0%)	0.18	15(30.0%)	15(30.0%)	0.77
2	5(10.0%)	8(16.0%)		9(18.0%)	7(14.0%)	
Bone pain						
0	21(42.0%)	31(62.0%)		6(12.0)	7(14.0%)	
1	5(10.0%)	14(28.0%)	0.09	11(22.0%)	16(32.0%)	0.2
2	14(28.0%)	15(30.0%)		33(66.0%)	27(54.0%)	
Depression						
0	27(54.0%)	32(64.0%)		25(50.0%)	30(60.0%)	
1	13(26.0%)	13(26.0%)	0.12	16(32.0%)	9(18.0%)	0.07
2	10(20.0%)	5(10.0%)		9(18.0%)	11(22.0%)	
Dyspnea						
0	31(62.0)	29(58.0%)		20(40.0%)	26(52.0%)	
1	11(22.0%)	14(28.0%)	0.61	17(34.0%)	15(30.0%)	0.19
2	8(16.0%)	7(14.0%)		13(26.0%)	9(18.0%)	
Headache						
0	28(56.0%)	24(48.0%)		25(50.0%)	23(46.0%)	
1	13(26.0%)	21(42.0%)	0.11	17(34.0%)	15(30.0%)	0.36
2	9(18.0)	8(16.0%)		8(16.0%)	12(24.0%)	
Anorexia						
0	30(60.0%)	26(52.0%)		30(60.0%)	33(66.0%)	
1	11(22.0%)	16(32.0%)	0.28	12(24.0%)	6(12.0%)	0.27
2	9(18.0%)	8(16.0%)		8(16.0%)	11(22.0%)	
Dry mouth						
0	15(30.0%)	16(32.0%)		29(58.0%)	19(38.0%)	
1	25(50.0%)	21(42.0%)	0.30	11(22.0%)	13(26.0%)	0.17
2	10(20.0%)	13(26.0%)		10(20.0%)	18(36.0%)	
Nausea						
0	22(44.0%)	28(56.0%)		35(70.0%)	27(54.0%)	
1	15(30.0%)	13(26.0%)	0.20	9(18.0%)	9(18.0%)	0.14
2	13(26.0%)	9(18.0%)		6(12.0%)	14(28.0%)	
Abdominal pain						

0	27(54.0%)	23(46.0%)		17(34.0%)	14(28.0%)	
1	14(28.0%)	17(34.0%)	0.52	23(46.0%)	19(38.0%)	0.13
2	9(18.0%)	10(20.0%)		10(20.0%)	9(18.0%)	

Survival analysis:

Relapsed (local recurrence and distant metastasis) was more in obese group than non obese ,it occurred in 5 patients (10%) and 4 patients (8%) in both groups respectively with non-significant difference between both groups (p=1.000) after three years of follow up .Furthermore ,died patients in obese group were higher than non obese ,5 patients (10%) versus 3 patients (6%) respectively with insignificant difference between both group (p=0.715) **(Table 3)** .In addition, 3y DFS in non obese patients was 92% while it was 90% in obese patients with no significant difference between both groups (P=0.680) . 3y OS in non obese patients was 94% versus 90% in obese patients with insignificant difference between both groups (P=0.374) **(Figure 4)**.

Table (3): Comparison between non-obese and obese as regard treatment outcome.

Treatment outcome	**Non-obese (N=50)**			**Obese (N=50)**			**p-value**
	No(%)			No(%)			
Follow-up duration (months)							
Mean ± SD	35.78 ±1.01			35.24 ±2.34			---
Median (Range)	36	(30 – 36)		36	(26 – 36)		
Relapse							
No relapse	46	(92%)		45(90%)			1.000
Relapse	4	(8%)		5(10%)			
Disease Free Survival (DFS)							
Mean DFS (months)	35.44 month			34.44 month			0.680
(95%CI)	(34.71 – 36.17)			(33.14 – 35.74)			
1 year DFS	100%			100%			
2 year DFS	98%			90%			
3 year DFS	92%			90%			
Local recurrence							
No local recurrence	47	(94%)		45 (90%)			0.715
Local recurrence	3	(6%)		5 (10%)			
Local Recurrence Free Survival (LRFS)							
Mean LRFS (months)	35.67 month			34.44 month			0.439
(95%CI)	(35.13 – 36.22)			(33.14 – 35.74)			
1 year LRFS	100%			100%			
2 year LRFS	100%			90%			
3 year LRFS	93.9%			90%			
Distant metastasis							
No distant metastasis	48(96%)			46(92%)			0.678
Distant metastasis	2(4%)			4(8%)			
Distant Metastasis Free Survival (DMFS)							
Mean DMFS (months)	35.58 month			34.75 month			0.375
(95%CI)	(35 – 36.16)			(33.57 – 35.93)			
1 year DMFS	100%			100%			
2 year DMFS	98%			91.9%			
3 year DMFS	96%			91.9%			
Survival							
Alive	47(94%)			45(90%)			0.715
Died	3(6%)			5(10%)			
Overall Survival (OS)							
Mean OS (months)	35.80 month			35.39 month			0.374
(95%CI)	(35.52 – 36.08)			(34.81 – 35.97)			
1 year OS	100%			100%			
2 year OS	100%			100%			
3 year OS	94%			90%			

95%CI: 95% confidence interval.

p<0.05 is significant.

(A)   (B)

(C)   (D)
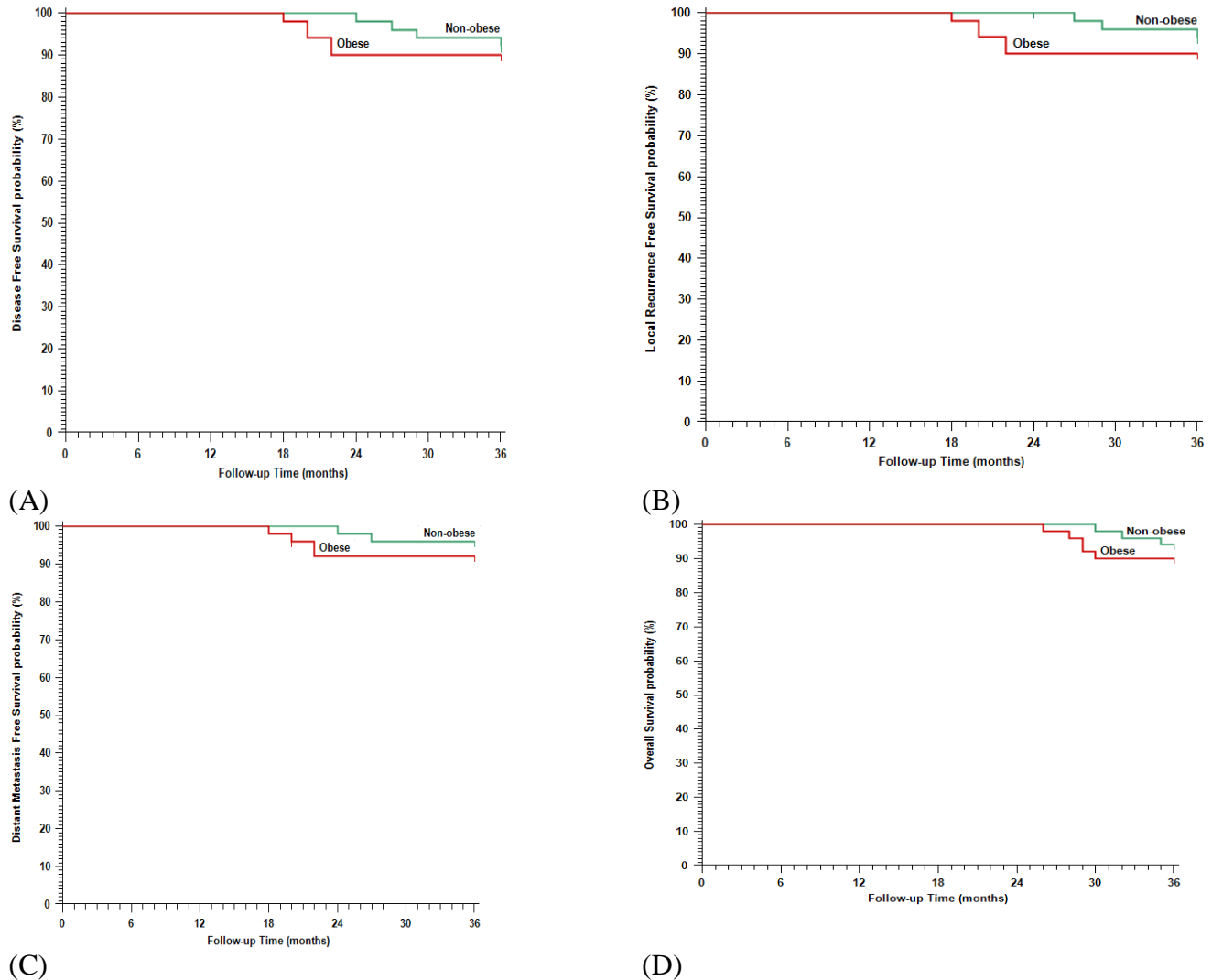
Figure (4): Kaplan-Meier plot: (A) Disease Free Survival (DFS); (B) Local Recurrence Free Survival (LRFS); (C) Distant Metastasis Free Survival (DMFS) and (D) Overall survival (OS).

Discussion:-

Aromatase inhibitors (AIs) are the gold standard of adjuvant hormonal therapy in hormone receptor-sensitive postmenopausal women with breast cancer, It can be given either as upfront or switching after 2–3 years of tamoxifen .5

The Obesity increases the risk of breast cancer-specific mortality,[12,13,14] while maintaining a moderate weight may have a positive impact on breast cancer survival.[15] It is a well-known fact that obesity increases total-body aromatization which leads to increased serum estrogen level when compared with non-obese [10,16,17]. Obesity was found to have an impact on the effect of AIs ,specially Anastrazole, in patients with breast cancer. and it is not clear if the standard dose of anastrazole (1 mg) is sufficient to adequately suppress heightened aromatization related to obesity[8].

In this study we assessed the effect of obesity on estradiol depletion in postmenopausal women with hormone-sensitive early breast cancer treated with Adjuvant upfront standard dose Anastrazole (1mg) after 6 months of treatment and its impact on survival .

The study included One hundred patients , half of them were classified being obese with (BMI≥30) with mean BMI(35 ± 5.8) while the other half was considered non obese (BMI<30) mean BMI(24.5 ± 4.4). Regarding all (100) patients , Anastrazole significantly reduces the mean ESL from19.45 ± 4.1 pg ml−1 to 11.13 ± 3.1 pg ml−1 after 6 months of treatment (P =0.00) . Inverse changes in FSH serum levels as the mean FSH serum level initially was 70.91 ± 20.7 mIU ml−1 and then significantly increased to 75.78 ± 19.3 mIU ml−1 after 6 months of treatment with Anastrazole (P=0.00).The initial lower FSH level than ESL is due to the negative feedback of ESL. In obese patients , a slightly higher mean estradiol serum level was detected at baseline

compared with non-obese patients (19.75±4.3 pg ml^{-1}*vs* 18.35±3.4 pg ml^{-1}, *P*=0.8). 6 months of treatment with an AI significantly reduced the mean estradiol serum level in obese and non obese patients (from 19.75+4.3 pg ml^{-1}, to 11.98 +3.3 pg ml^{-1} (p=0.00) and from 18.35+3.4 pg ml^{-1}, to 8.78+2.2 pg ml^{-1} respectively, (*P*=0.00)) .

Obese patients had significantly lower FSH serum level at baseline when compared with non-obese patients (60.34+15.7 mIU ml^{-1}*vs* 80.75+18.6 mIU ml^{-1}, (*P*<0.01). Six months of AI treatment , increased FSH serum levels in obese and non obese patients (from 60.34±15.7 mIU ml^{-1}, to 64.98±14.7 mIU ml^{-1},and from 80.75±18.6 mIU ml^{-1}, to 87.53±17.6 mIU ml^{-1},(*P*=0.00) and (*P*<0.05) respectively) . However after 6 months of Anastrazole treatment the mean ESL was significantly higher in obese compared to non-obese patients (11.98 ±3.3 pg ml^{-1}1 VS 8.78+2.2 pg ml−1) and this difference reflected by significantly lower serum FSH level in obese compared to non-obese patients(64.98+14.7 mIU ml−1vs 87.53+17.6 mIU ml−1)**.** And we concluded that Anastrazole is less effective in suppressing the ESL in obese when compared with non-obese patients, as regard the toxicity and the preliminary 3y DFS and OS there was no significant statistical difference between obese and non obese patients.

Pfeiler et al **(2013)** [10] studied the impact of BMI on FSH levels in breast cancer patients treated by AIs and their results showed that 40 patients were normal or overweight (non-obese: BMI 18.5–29.9 kg m^{-2}) and 28 were obese (BMI⩾30 kg m^{-2}). Aromatase inhibitors significantly suppressed estradiol serum levels (initially : 19.5 pg ml^{-1}, after 3 months: 10.5 pg ml^{-1}, *P*<0.01) and increased FSH serum levels (initially: 70.2 mIU ml^{-1}, after 3 months: 75.7 mIU ml^{-1}, *P*<0.05). However, after 3 months of AI treatment, estradiol levels of obese patients were non significantly higher compared with non-obese patients (12.5 pg ml^{-1}*vs* 9.0 pg ml^{-1}, *P*=0.1). This difference was reflected by significantly lower FSH serum levels in obese compared with non-obese patients (65.5 mIU ml^{-1}*vs* 84.6 mIU ml^{-1}, *P*<0.01).this results are in line with our results but doesn't reach statistical significance may be due to small sample size [10].

Furthermore, our prospective data are matched with the retrospective analysis by **Folkerd *et al* ,2012** [21], who stated that BMI has an impact on estradiol levels during AI treatment [20] and demonstrated that higher estradiol serum levels in obese compared with non-obese patients were observed – even though those differences are numerically small [21]

In our study ,there is opposed effects on FSH serum levels compared with estradiol serum levels during AI treatment. And this is in line with a trial conducted by **Shaw et al,2010** [22] which showed that , higher estradiol serum levels lower FSH serum levels via the negative feedback loop even in postmenopausal women. And we suggest that FSH can be used as a surrogate to ESL . In **Pfeiler et al ,2013** [10] study ,as in ours, observed no statistically significant difference between the two groups as regard the toxicity but they stated that with caution due to the small number of patients in their trial which is the same limitation in our study.

The results obtained from the **ATAC trial** confirmed lower efficacy of anastrozole treatment in women with obesity (BMI > 30) in terms of time to recurrence [7,9] .

This is in accordance with the findings of **Ewertz et al**, who investigated the efficacy of AIs in correlation with weight and found a survival benefit for women with a BMI < 30 after 10 years of follow-up and no group differences were found for the first 10 years of follow-up. [18]

Finally, **Pfeiler et al(2011)**,observed a 60% relative increase in risk of disease recurrence as well as a 2-fold increase in the risk for death in patients with excess weight compared with those with normal weight who received anastrozole therapy in the **ABCSG 12 trial**[8] . The authors strongly suggested that incomplete estrogen serum level suppression through inadequate Anastrazole dosing explains these findings, and they assume an AI dose adjustment according to body weight is essential for the optimization of treatment efficacy.[19-20] Dose finding studies showed that low dosages of anastrozole (1 mg) was able to nearly fully block the aromatase and thereby lower estradiol serum levels to a minimum .However, these studies included small number of patients [23].

Our preliminary results of survival analysis after three years of follow up were ,the relapse (local recurrence and distant metastasis) occurred more in obese group than non obese ,it occurred in 5 patients (10%) and 4 patients (8%) in both groups respectively with non-significant difference between both groups (p=1.000) .Furthermore ,died patients in obese group were higher than non obese ,5 patients (10%) versus 3 patients (6%) respectively with insignificant difference between both group (p=0.715) .In addition, 3y DFS in non obese patients was 92% while it was 90% in obese patients with no significant difference between both groups (P=0.680) .3y OS in non obese patients was 94% versus 90%in obese patients with insignificant difference between both groups (P=0.374) ,this is consistent with **Ewertz et al trial,**[18] who found no group differences between obese and non obese for the first 10 years of follow-up but a survival benefit for women with a BMI < 30 occurred after 10 years of follow-up and..Our explanation of insignificant survival results of our trial is , short follow up period which is one of limitations of our study but we are awaiting the final results after longer follow up period to see if there will be any significance between both groups regarding the outcome and survival or not. Furthermore , we recommend doing this study on larger number of patients with longer follow up period with addition of an important new point of research which is increasing the dose of Anastrazole according to BMI.

Conclusion:-

Anastrazole is less effective in suppressing the ESL in obese when compared with non-obese postmenopausal , hormonal sensitive early breast cancer patients .no statistically significant difference in preliminary 3year OS ,DFS between both groups .

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