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IMPACT OF BODY MASS INDEX ON CHANGES IN ESTRADIOL AND FOLLICULAR STIMULATING HORMONE IN POSTMENOPAUSAL BREAST CANCER WOMEN RECEIVED ANASTRAZOLE IN MOSUL

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ABSTRACT

Background: Anastrazole is widely prescribed in recent years as a hormonal therapy for postmenopausal breast cancer women and as a new alternative for Tamoxifen. **Aim of the study:** is to measure estradiol levels in postmenopausal breast cancer women treated with anastrazole and compare them according to body mass index (BMI). To find out the level of FSH in those patients and to correlate the level of FSH with estradiol. **Subjects and Methods:** Twenty postmenopausal breast cancer women were tested for estradiol and FSH level using immunoassays retrospectively and patients were grouped according to their BMI. 10 other postmenopausal breast cancer women were also tested who didn't receive the therapy and taking them as a control group. **Results:** The results revealed that only 10% of the postmenopausal breast cancer women had a normal BMI. The overweight and obese patients represent the highest percentages. Estradiol levels in very obese postmenopausal breast cancer women were significantly higher than estradiol level in those overweight or less obese patients. While the reverse was noticed with FSH level, that's FSH level were less elevated in very obese women than in less obese or overweight postmenopausal breast cancer women. **Conclusion:** Anastrazole is less effective in reducing estradiol level in obese postmenopausal breast cancer women and it's less effective as BMI increased. Anastrazole is less reducing FSH level in obese patients compared to normal weight patients.

KEYWORDS: To find out the level of FSH in those patients and to correlate the level of FSH with estradiol.

INTRODUCTION

Breast cancer is a type of cancer originating from breast tissue, most commonly from the inner lining of milk ducts or the lobules that supply the ducts with milk. Cancers originating from ducts are known as ductal carcinomas, while those originating from lobules are known as lobular carcinomas. Breast cancer occurs in humans and other mammals. While the overwhelming majority of human cases occur in women, male breast cancer can also occur.[1,2]

Breast cancer incidence has increased in the past few years. It is rank one among all other types of cancer according to Mosul heath authorities.[3] Moreover, breast cancers are hitting younger women below age 30 years old started affect more spectrum of age group according to the last epidemiologic study made by Mosul health authority in 2011. According to Mosul health authority, most of cases diagnosed were lobular carcinoma. This raised the alarm in the medical authority and public concern. Ultimately the need for more researches on breast cancer treatment and follow up has largely adapted. Hormonal therapy comprises one of the most important comers in the quest of breast cancer treatment, as it's widely used for estrogen receptor positive women. That's why it's worth to measure the effectiveness and usefulness of these types of therapies in correlation with new challenging facts of breast cancer prevalence. This has set a high standard for this small study on hormonal therapy that s greatly adapted in the past few years.

Anastrozole (marketed under the trade name Arimidex by AstraZeneca, UK) is a non-steroidal aromatase-inhibiting ding approved for treatment of breast cancer after surgery, as well as for metastasis in postmenopausal women.[4]

It, as all other aromatase inhibitors, blocks the peripheral conversion of the adrenal androgens (androstenedione and testosterone) into estradiol and estrone in women. Aromatase inhibitors should not be considered in those women who have any ovarian function because blockage of peripheral aromatization will not block the ovarian production of estrogen and progesterone.[5,6]

Its Absorption is rapid, with T max at about 2 h. Food decreases C max by 16% and delays T max to 5 h. almost 40% of it is protein bound and metabolized in the liver (approximately 85% undergoes hepatic metabolism). The half-life is approximately 50 h; approximately 10% is excreted in the urine. The pharmacokinetics of anastrozole are not affected by age.[7]

It is indicated for advanced breast cancer in postmenopausal women with progression following Tamoxifen therapy; first-line treatment of postmenopausal women with hormone receptor-positive or hormone receptor unknown locally advanced or metastatic breast cancer; for adjuvant treatment of postmenopausal women with hormone receptor—positive early breast cancer.[4]

However, it is contraindicated for women who are or plan to become pregnant; premenopausal women; patients who have shown hypersensitivity reaction to the drug or any of the excipients.

In addition, follicle -stimulating hormone (FSI-I) is a hormone, that is synthesized and secreted by gonadotrophs of the anterior pituitary gland. FSFI regulates the development, growth, pubertal maturation, and reproductive processes of the body. FSH and luteinizing hormone (LH) act synergistically in reproduction.54 FSH is subject to estrogen feed-back from the gonads via the hypothalamic pituitary gonadal axis.[8,9]

The current study is aiming for measuring the estradiol level in postmenopausal breast cancer women treated with anastrazole and compare them according to body mass index (BMI), as well as finding out the level of FSH in those patients and to correlate the level of FSH with estradiol.

SUBJECTS AND METHOD

The study was performed retrospectively in Mosul nuclear oncology hospital. Where blood sample was collected for 20 postmenopausal breast cancer women. Patient samples were collected starting from June 2013 and continued tor 2 successive months under the ethical approval of medical committee in Mosul health directorate and by direct supervision of Dr. Ahmed Ali Albakr a clinical oncologist in the oncology department. Patients were selected according to the following criteria according to NICE guide line.[10]

Inclusion criteria were women who had postmenopausal breast cancer woman with estrogen receptor positive, measurable BMI and using aromatase enzymes inhibitors for more than 3 months.

While exclusion criteria were: Premenopausal women (e.g. those receiving pharmacologic ovarian ablation); Unknown estrogen receptor status; Handicap patient or unable to measure BMI; Very old age and unable to visit hospital regularly; Using aromatase enzyme inhibitors for less than 3 months and terminal stages.

In addition, 10 postmenopausal breast cancer women who had just started the therapy were included as a control group.

The blood samples of 20 patients and 10 control patients were collected. Three-five ml of blood samples were centrifuged and plasma was separated and serum was freezes within 1 hour of collection and made ready for later estrogen and FSH measurement. BMI data were also measured for those patients.

The 55 Patients were sub classified according to following criteria and from them 20 patients were selected.

1. Those who had just started the therapy (Control).
2. Those who had been long on therapy (more than 3 months).

The sample of the 55 breast cancer women were selected for BMI estimation patients classified depending on BMI according to WHO classification. BMI are calculated by dividing weight over square height and it's a good label for obesity and/or fat content.58

i. 18.5-25kg/m^2 healthy
ii. 25-29 kg/m^2 overweight
iii. 30-35kg/m^2 Class I obesity
iv. 35-40 kg/m^2 Class II obesity
v. > 40 kg/m^2 Class III obesity

Estradiol Measurement

Using highly sensitive immunoflourscent solid interphase technology with lowest detection limit of 9pg/ml. it was intended to measure estradiol levels among 20 patient serums in recovery fusion by adding low measurable estradiol fixed concentration to the patient's serums, previously measured with minividas and diluted with normal saline and calculating the possible error in 2 successive dilutions of 51 pg/ml and 31pg/ml. This was repeated twice and taking the mean which yield after dilution 23pg/ml and 12pg/ml respectively. Plotting these concentrations on graphic paper and dropping a line between the 2 dilutions. Same done with unknowns but instead of adding (51/2) pg/ml and (31/2) pg/ml to normal saline it was added to the unknown to measure possible appearance of difference.

Minividas has major limitation that it doesn't measure estradiol levels below 9pg/ml. Hence, it was intended to

increase the serum concentration by a fixed known concentration and by measuring the new concentration and subtracting the new addition it's possible to know what the estradiol concentration is.

(A) Very low cone, (non measureable) + (B) known cone, (measurable) + (C) error = D (total)[11]

B is known; C (error) is calculated. Then A = D (total) - (B + C)

FSH level

The I'[25]-hFSH IRMA system provides a direct quantitative in vitro determination of human Follicle Stimulating Hormone (hFSH) in human serum. hFSH can be assayed in the range of 0-180 mlU/ml using 100 ul serum samples.

Principle of Method

The technology uses two high affinity monoclonal antibodies in an immunoradiometric assay (IRMA) system. The I125 labeled signal antibody binds to an epitope of the FSH molecule spatially different from that recognized by the biotin-capture-antibody. The two antibodies react simultaneously with the antigen present in standards or samples, which leads to the formation of a capture antibody antigen-signal antibody complex, also referred to as a "sandwich". During 2-hour incubation period with shaking immune-complex is immobilized to the reactive surface of streptavidin coated test tubes. Reaction mixture is then discarded, test tubes washed exhaustively, and the radioactivity is measured in a gamma counter. The concentration of antigen is directly proportional to the radioactivity measured in test tubes. By constructing a calibration curve plotting binding values against a series of calibrators containing known amount of hFSH, the unknown concentration of hFSH in patient samples can determined.

1) Equilibrate reagents and samples to room temperature before use.
2) Label coated tubes in duplicate each standard (S1-S6), control serum and samples.
3) Homogenize all reagents and samples by gentle mixing to avoid foaming.
4) Pipette 100 µl of standards, control and samples into the properly labeled tubes. Use rack to hold the tubes. Do not touch or scratch the inner bottom of the tubes with pipette tip.
5) Pipette 200 µ1 of tracer into each tube.
6) Seal all tubes with a plastic foil. Fix the test tube rack firmly onto the shaker plate. Turn on the shaker and adjust an adequate speed such that liquid is constantly rotating or shaking in each tube.
7) Incubate tubes for 2 hours, shaking at room temperature.
8) Add 2.0 ml of diluted wash buffer to each tube. Decant the supernatant from all tubes by the inversion of the rack. In the upside-down position place the rack on an absorbent paper for 2 minutes.
9) Return the tube-rack to an upright position, and repeat step-8 two more times.
10) Count each tube for at least 60 seconds in a gamma counter.
11) Calculate the hFSH concentrations of the samples as described in calculation of results or use special software.

Table: the assay procedure of FSH measurement using IRAM.

Tubes	Total	Standard	Control	Sample
Standard		100		
Control			100	
Sample				100
Tracer	200	200	200	200
Shake for 2		hours at room temperature		
wash buffer		2000	2000	2000
Decant the fluid and blot on filter paper				
Wash buffer		2000	2000	2000
Decant the fluid and blot on filter paper				
Wash buffer		2000	2000	2000
Decant the fluid and blot on filter paper				
Count radioactivity (60 sec/tube)				
Calculate the results				

Calculations and graphs were based on Microsoft excel and student t test were used to find the p-value. P-value will be considered significant when $p < 0.05$ or $p < 0.01$.

RESULTS

Figure 1 and Figure 2 shows samples of 55 women were selected for BMI estimation. Where 3 out of 55 were normal weight with BMI < 25kg/m2 representing 5.5%, 18 out of 55 were overweight with BMI 25- 29.9 kg/m2 representing 33% of the population, 21 patients out of 55 were class I obesity with BMI 30-34.9 representing the larger portion of 38% of total population, 11 out of 55 were class II obese with BMI 35 - 39.9 kg/m2 and representing 18% of the population, finally 5.5% of population were class III obese (very obese).[12]

BMI it's obvious from this figure that only less than 10% had normal weight. The overweight and obese patients represent the highest percentages.

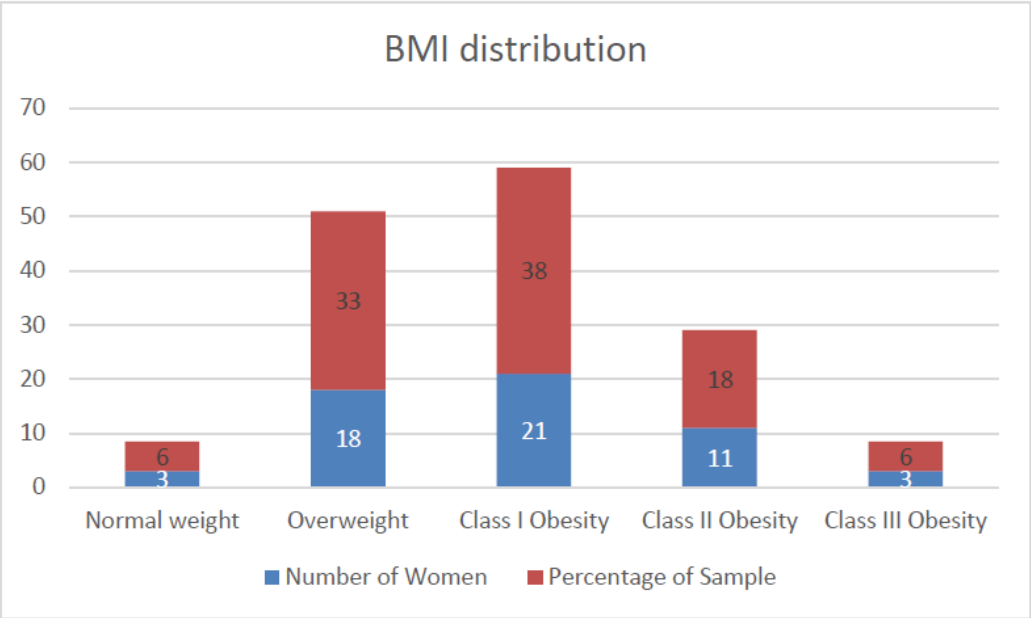

Figure 1: Breast cancer women distribution according to their BMI.

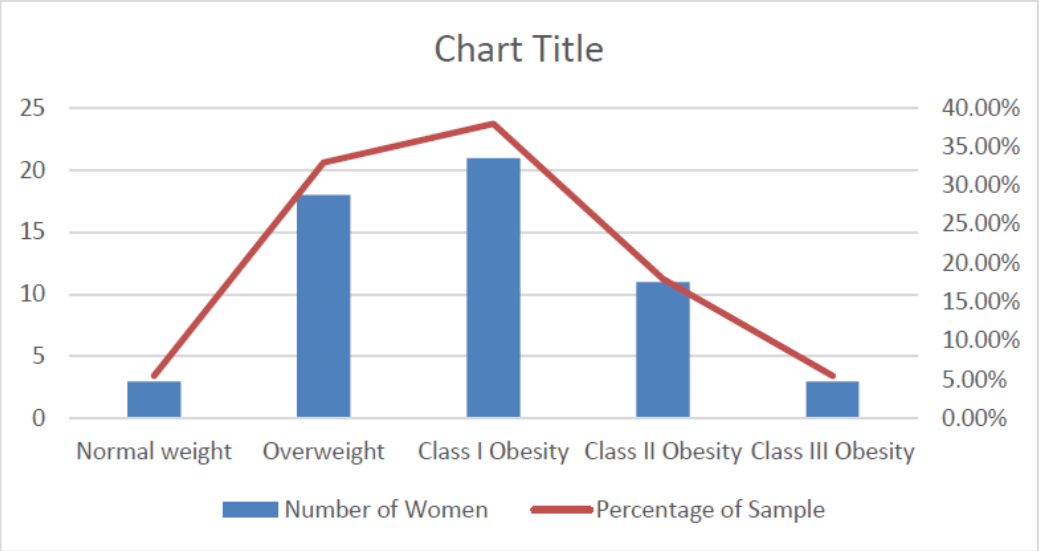

Figure 2: Breast Cancer patient distribution according to BMI.

Table 1 shows estradiol concentration in 20 postmenopausal patients used anastrazole classified according to their BM1. It is obvious from this table that 10 patients with BMI 25-35kg/m2 had low level of estradiol in the mean of 3.1 pg/ml, while 10 patients with higher BMI > 35 kg/m had high level of estradiol with mean of 4.9pg/ml. when the P value between the 2 groups were significant and was <0.05 (using student t test). The reduction of estradiol from control group (mean estradiol were 25 pg/ml) was significant with very low p value (P<0.01).

Table 1: estradiol reduction in two groups each group composed of 10 different BMI levels of BMI in postmenopausal breast cancer women.

BMI kg/m2	No of patients	mean Estradiol level
25-35	10	3.3± 0.6
>35	10	4.9± 0.7
Control Group	10	~25 pg/ml

With respect that pretreated group estradiol value was variable 17-30 pg/ml with mean 25 pg/ml ± 0.9. Even with least reduced group in obese women p value were significant p<0.05.

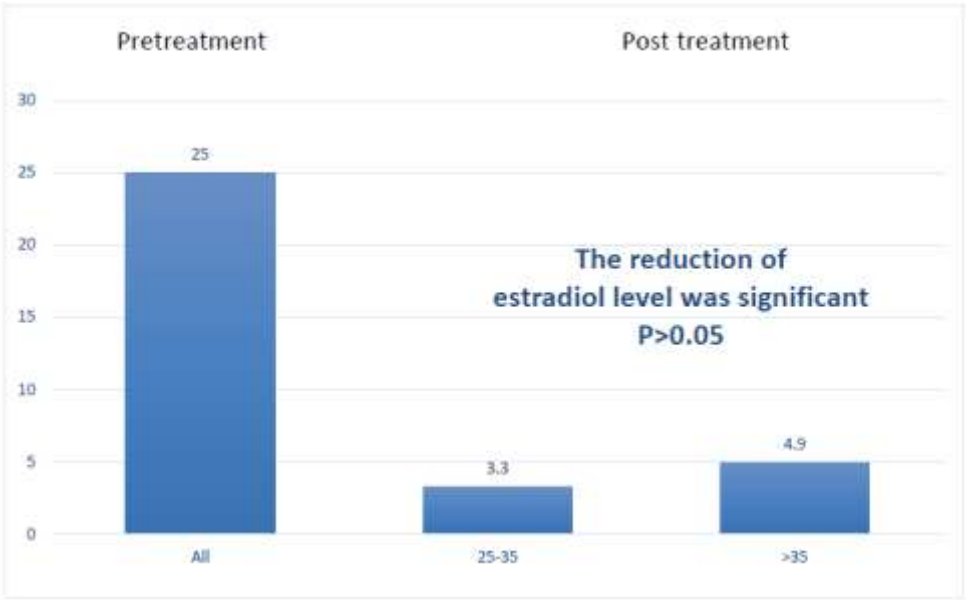

Figure 3: the change of estradiol level reduction in respect to BMI in the 2 group study design.

Table 2 FSH serum level was highly correlated with BMI and estradiol level. Mean FSH in the group of low estradiol and low BMI margin was 84mIU/l. While mean FSH in the group of higher estradiol and higher BMI was 66 mIU/1 with significant change with BMI and estradiol that's $p < 0.01$.

Table 2: FSH level in correlation with BMI and estradiol.

BMI	Mean Estradiol Pg/ml	FSH mIU/1
25-35	3.3± 0.6	84 ± 18.2
>35	4.9± 0.7	66 ± 12

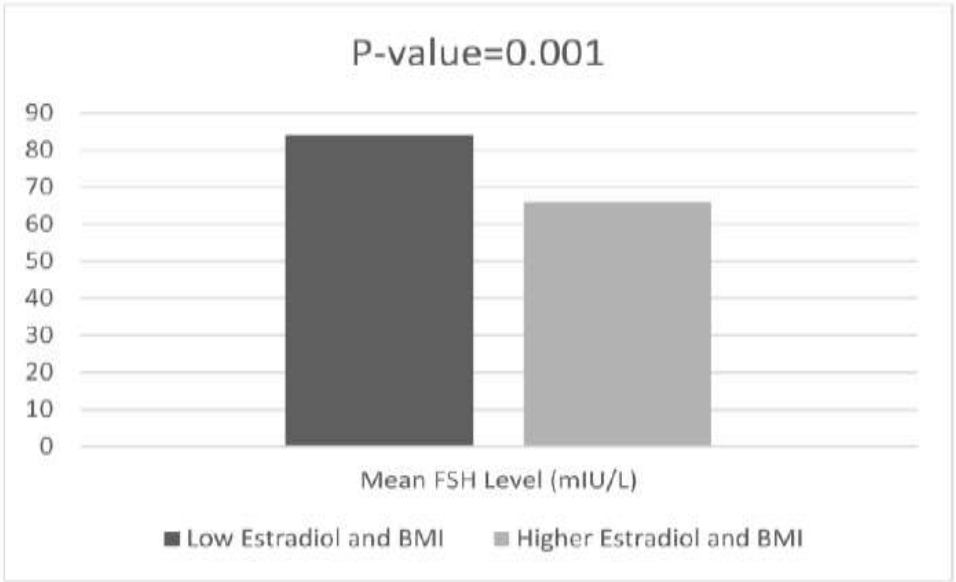

Figure 4: shows significance of the mean FSH level between those above the mean of FSH increase and FSH low.

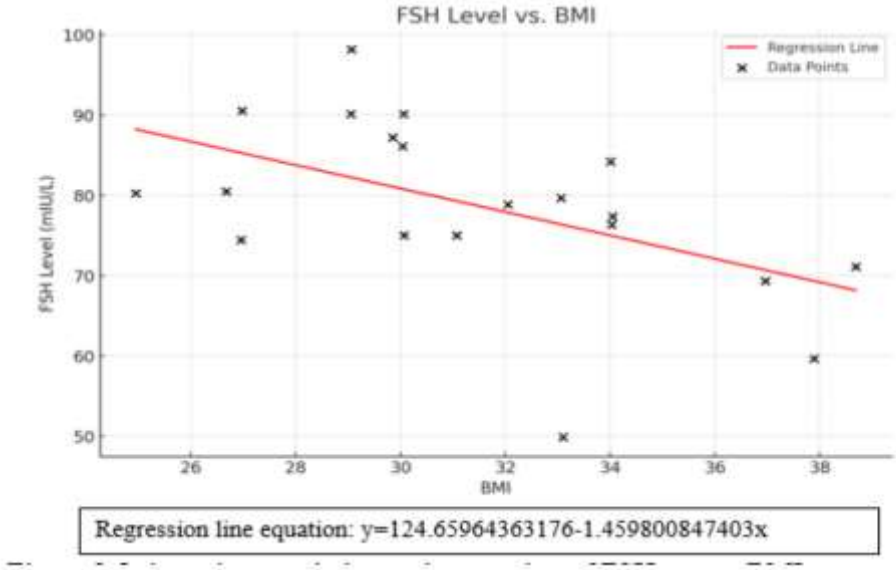

Figure 5: shows the correlation and regression of FSH versus BMI.

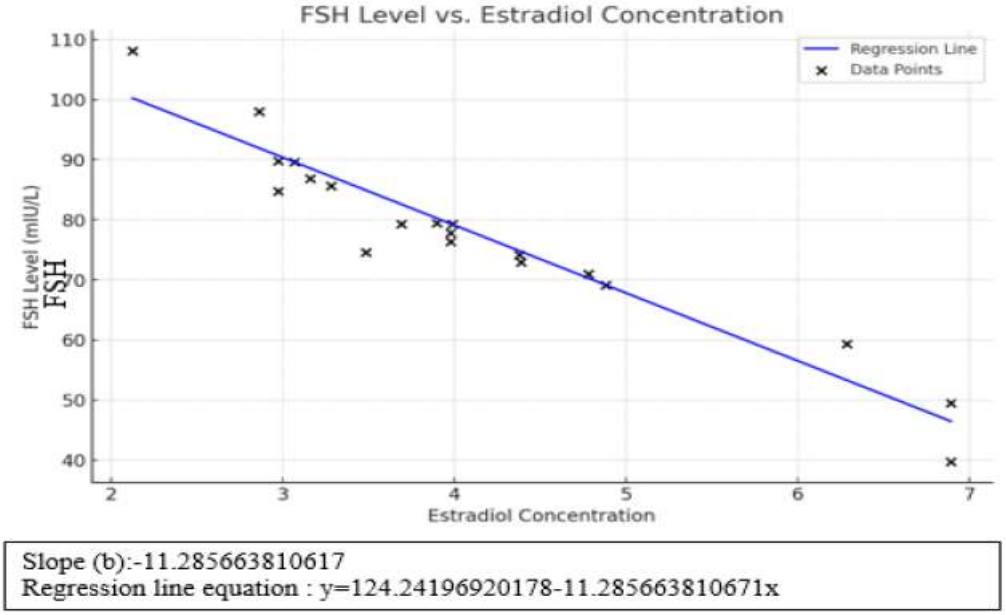

Figure 6: FSH correlation and regression versus estradiol measured.

DISCUSSION

The relationship between obesity and breast cancer is a complex one[13] & they are associated with breast cancer risk in qualitatively different ways before and after menopause (with decreased risk in premenopausal women and increased risk in postmenopausal women), whereas similar associations of obesity with prognosis are seen in pre- and postmenopausal women (obese women in both groups experience poorer outcomes). This complexity likely reflects, at least in part, the variable relationships between obesity and estrogen (a major contributor to the growth of hormone receptor—positive breast cancer) before and after menopause. Before menopause, obesity may interfere with normal menstrual cycle, potentially leading to reductions in estrogen levels. after menopause, increased production of estrogen in excess adipose tissue in obese women is associated with higher estrogen levels. It is likely that the complexity of the relationship between obesity and breast cancer also reflects important contributions of obesity-related factors other than estrogen to both breast cancer risk and prognosis.[14]

It's worth to note that degree of aromatization is differing from tissue to another, that's breast tissue, has higher level of aromatization. The concentration of estradiol in breast-carcinoma tissue is approximately 10 times the concentration in plasma,[15] probably in part because of the presence of intratumoral aromatase. Early evidence that intratumoral aromatase activity might help predict the response to aromatase inhibitors[16] remains to be confirmed in large-scale studies. Details on the control

and importance of the sources of aromatase have recently been published.[17,18]

From the above figures (1 and 2) the BMI distribution of breast cancer postmenopausal women is diverted toward overweight and to a lesser extent toward obesity. Meyerhardt et al[19] and McTiernan el al[20] discuss the evidence that links various aspects of energy balance (e.g., body size, physical activity, diet) to outcome in colorectal and prostate cancer and in breast and gynecologic cancers, respectively. They argue that sufficient evidence exists for some associations (e.g. the associations of physical activity with colorectal cancer and of physical activity and body size with breast cancer) that discussions with patient's and intervention research are warranted. Nonetheless, there are challenges to host factor interventional research. Although a questions remain regarding the needed duration of such diet and lifestyle changes to achieve an impact on tumor growth and progression and regarding how to sustain prolonged change in patients.

These works further proving that the higher weight in our postmenopausal women population (Mosul) might have great impact on both prognosis and incidence of breast cancer, assuming from the above figure that most of our patients were obese. In postmenopausal women and in premenopausal women with ovarian suppression, the major source of serum estrogens is the fat tissue, in which precursors are metabolized to estrogens by the enzyme aromatase.[20] Thus, an increase in BMI leads to an increase in total-body aromatization and, consequently, an increase in estrogen serum levels, which impact on breast cancer.[21,22] Taken together, this suggests that BMI[23] may serve as a useful surrogate parameter for total-body aromatization and eventually may be a practicable tool to tailor aromatase enzyme inhibitors therapy for individual patients.

The incidence of breast cancer increases with age, although the rate of increase slows after menopause,[24,25] early menarche, late menopause, and nulliparity increase the risk of breast cancer. Atypical lobular or ductal hyperplasia also increases the risk, and benign breast disease does so marginally.[26,27] Other risk factors are early exposure to ionizing radiation, long-term postmenopausal estrogen-replacement therapy, and alcohol consumption. The most important risk factor is a family history of breast cancer.[28,29] About 5 to 10 percent of all breast cancers occur in high-risk families.[30]

In the 20 postmenopausal breast cancer women, Estradiol was measured and estradiol mean level for those high BMI was higher than those with lower BMI level, with high confidence ($P < 0.05$) figure 3. Although the precise estradiol level measurement in postmenopausal breast cancer women are extremely difficult with current available commercial kits and methods. The estradiol level in this small scale study came to be parallel to previous works, Folkerd et al[31,32] measured estradiol retrospectively using radioimmunoassay after organic extraction with diethyl ether. On the other hand, Pfeiler G et al.[33] had higher estradiol level measured prospectively where Pfeiler used electrochemoileumensis. None of the estradiol level in all three studies were equal, but they were all parallel and came with the same fact that estradiol is less reduced in obese breast cancer postmenopausal women then in those with less BMI breast cancer postmenopausal women. This can be explained due to following reasons. different methodology was used in each one of these works, so it's not strange to obtain different estradiol levels.

The base estradiol level in Mosul patient might be higher than that elsewhere these studies were made.[34]

The kit used in Iraq might be of higher calibration level, although G Pfeiler had come with higher estradiol levels.

Possible test intei' action, explained by Folkerd and Pauwel works, where Folkerd and Mitch Dweetz[35,36] had made prior treatment for the serums using organic extraction, while G Pfeiler[37] used direct electrochemoileumensis. It might be possible to conclude that anastrazole was less efficient in reducing estradiol in obese women then in less obese or slim women. Even though this study gives a clear vision of how this drug is performing in obese women, who are actually the majority of our patient population, figure 3.2. As its shown earlier and it's hard to find patients with BMI less than 25kg/m in our postmenopausal breast cancer women to obtain golden standard for comparative study.

Ivana Sestak et al,[38] had also confirmed this observation clinically in term of recurrence and prognosis of breast cancer women in obese women. Three other previous studies had not shown such clinical observation of impact of BMI on efficacy of BMI on anastrazole efficacy in obese women, both in term of recurrence and prognosis.

The menopausal transition usually begins in the mid-to-late 40s and lasts about 4 years with menopause occurring at a median age of 51 years. Cigarette smokers undergo menopause about 2 years earlier than nonsmokers. During the early menopausal transition, estrogen levels are generally normal or even slightly elevated, 87 the level of follicle stimulating hormone (FSH) begins to increase but is generally in the normal range.[2]

As the menopausal transition progresses, hormone levels variable, but estrogen levels fall markedly and levels of follicular stimulating hormone increase.[9] After menopause, ovulation does not occur. The ovaries do not produce estradiol or progesterone but continue to produce testosterone. A small amount of estrogen is produced by the metabolism of adrenal steroids to

estradiol in peripheral fat tissue.

The level of FSH after menopause are remarkably elevated than premenopausal and is non-fluctuating (steady level) as its affected by negative feedback of estradiol[39] (figure 2). The FSH show high correlation with estradiol with $P < 0.001$ and correlation factor < 0.7 in twenty patients tested and the regression curve show the same (figure5, 6). In addition, we found that FSH had better correlation than estradiol against BMI in these patents. However, the correlation between BMI and FSH needs further investigations, as well as the normalization of FSH level postmenopausal Iraqi women in general[39], and postmenopausal breast cancer women in special. From all above evidences, BMI are greatly correlated with estradiol level as it was also found in this study. G.Pfeiler et al[36], measured the estradiol and FSH in postmenopausal breast cancer. It was obvious that FSH was synchnising in the way it was reduced when BMI and estradiol were elevated, and it was elevated where BMI and estradiol reduced.[37,38]

Elevated FSH levels could indeed be a valuable surrogate marker to establish a notion of effective endocrine treatment. All patients were believed in a positive effect of the anastrazole, but a proportion of obese patients stated that there was doubt in the effect of the anastrazole treatment. This loss of conviction in the efficacy of aromatase enzyme inhibitors is certainly a factor contributing to the complex issue of malcompliance shown in several studies. Such a marker has a potential of increasing concordance to therapy. The impact of BMI can be demonstrated even in a clinical routine laboratory by using FSH levels as a surrogate parameter for estradiol levels. This study established BMI as a predictive clinical factor concerning estrogen depletion under aromatase inhibitor treatment. This study adds to the evidence that important survival disadvantages under aromatase inhibitors therapy might be due to, at least in part, incomplete inadequate estrogen depletion in obese women.

CONCLUSIONS

Most of postmenopausal breast cancer women in Mosul were obese and overweight having high BMI. Anastrazole is less effective in reducing estradiol level in high BMI postmenopausal breast cancer women compared with less BMI. Anastrazole affect FSH level in reverse sequence compared to estradiol level. The increment in FSH level was more obvious than the decrease in estradiol levels which could be a suitable indicator for follow up treatment. Anastrazole is less effective in increasing FSH level in high BMI patients compared to less BMI.

Recommendations

It's highly recommended that Mosul state apply national reference range of the hormones and in special postmenopausal women. This type of work requires high quality projects performed by sophisticated laboratories. It was noticed through this work that estradiol measurement was too difficult and coasty and FSH is better biomarker for patient's follow up. However, this still needs large scale study. If proven that estradiol wasn't the marker of choice and from future. FSH measurement can be used to follow up treatment. Physician should think twice before choosing aromatase inhibitor as hormonal adjuvant therapy in very obese women.

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