International Journal of Advanced Research in Biological Sciences
ISSN: 2348-8069
www.ijarbs.com
DOI: 10.22192/ijarbs Coden: IJARQG(USA) Volume 4, Issue 12 - 2017

Research Article

DOI: http://dx.doi.org/10.22192/ijarbs.2017.04.12.014

Peroxisome Proliferator- Activated Receptor-gamma and Nuclear Factor-kappa B in Obese Breast Cancer Patients: Correlation with Omega-3 polyunsaturated Fatty Acids with Adjuvant Chemotherapy

Iman A. Sharaf [1,2*] , Maher A Kamel[2], Rasha A El-Tahan[2], Hanaa M Kohail[3], Mostafa A El Naggar[3]

[1]Faculty of Science; ALFaisaliah; Biochemistry Department; King Abdulaziz University; Jeddah - Saudi Arabia.
[2]Medical Research Institute; Biochemistry Department; Alexandria University; Alexandria - Egypt.
[3]Medical Research Institute; Department of Cancer Management and Research, Alexandria University; Alexandria – Egypt
*Corresponding Author: **Iman A. Sharaf,** Faculty of Science; ALFaisaliah; Biochemistry Department; King Abdulaziz University; Jeddah - Saudi Arabia.

Abstract

Background: PPAR-γ has been reported to affect cell proliferation/differentiation pathways in various malignancies. PPAR-γ negatively regulates NF- κB gene which is important in breast cancer progression.
Objective: The present study was designed to evaluate the relationship between PPAR-γ and NF-κB and the clinicopathological parameters of breast cancer women. The possible effects of adjuvant omega-3 fatty acid treatment with chemotherapy was also studied.
Methods: 40 obese breast cancer patients was subdivided into two groups(20 each),chemo group received chemotherapy alone and omega group received 2 gm n-3 daily wih chemotherapy and control group included 20 obese women. Serum PPAR-γ and NF-κB levels were conducted for all the studied groups.
Results: PPAR-γ was significantly lower than control .The level was decreased with increased positivity of ER, PR and increased with Her-2/neu in pre- and postmenopausal breast cancer patients. NF-κB significantly higher than controls and decreased with the increased positivity of ER, PR and Her-2/neu in pre- and postmenopausal breast cancer patients. Omega-3 FAs treatment with chemotherapy significantly enhances the level of PPAR-γ and decreases NF-κB level.
Conclusion: The using of omega-3 PUFA as adjuvant treatment may increase sensitivity of cancer cells for chemotherapy by targeting PPAR-γ /NF-κB signaling pathway through correction of their derangements.

Keywords: PPAR-γ, NF-κB ,Omega-3 Fatty Acids.

Introduction

Human obesity is a complex phenotype that results from a combination of elevated calorie intake and physical inactivity. Increased adipose tissue mass is associated with metabolic changes described as metabolic syndrome. In addition to cardiovascular disease and diabetes, epidemiological data demonstrated a link between obesity and multiple types of cancer. While age and gender are the two predominant risk factors for breast cancer, some risk factors remain modifiable, such as diet and obesity. Adult weight gain is correlated with increased breast cancer risk and is a poor prognostic factor. (1, 2)Tumor microenvironment provides a number of signals and resources to the tumor cells, promoting proliferation, survival, and motility. In that regard, adipocytes, or their precursor cells, may provide key factors in breast tissue needed for tumor development, progression, or even enable tumor cell invasion.(3)

Peroxisome proliferator-activated receptor-gamma (PPAR-γ); the master regulator gene of adipogenesis and plays a crucial role in insulin sensitization. Furthermore, PPAR-γ has been reported to affect cell proliferation/differentiation pathways in various malignancies. It is a ligand activated transcription factor, which belongs to the family of nuclear hormone receptors. It has been shown to be dysregulated in the obese population, and since obesity is a known risk factor for breast cancer development, PPAR- γ activity may have a role in breast cancer inhibition. Several studies have suggested that activation of PPAR-γ inhibits cell proliferation and induces apoptosis in vitro. (2, 4)

Nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) is transcription factor, which plays a key role in the control of genes involved in inflammation, cell proliferation, resistance to classical hormone-base therapies, and apoptosis. PPAR-γ negatively regulates several genes, including NF- κB gene. The ability of PPAR-γ to inhibit NF-κ B expression is important in breast cancer progression (5, 6).

Nuclear factor-κB translocation and signaling is reduced via the agonist effects of EPA and DHA on peroxisome proliferator-activated receptor gamma as well as interaction with the G protein receptor(GPR120), with expected reduction in inhibitors of apoptosis as well as cytokines, adhesion molecules, and metalloproteases .Additional preclinical studies suggest that EPA and DHA increase expression of BRCA1/2, phosphatase and tensin homolog (PTEN), and other proteins associated with cell cycle control and DNA repair.(7,8)

Various mechanisms have been proposed for the anti-proliferative effect of n-3 PUFAs (9). These include alterations in eicosanoid formation (10), lipid peroxidation initiated by free radicals (11), accumulation of cytotoxic lipid droplets (12), and specific changes in gene expression patterns. It was reported that alpha-linolenic acid regulated the growth of breast and cervical cancer cells through decrease in nitric oxide generation and increase in lipid peroxidation, leading to caspase 3-dependent apoptosis. The activity of several nuclear transcription factors, like peroxisome proliferator-activated receptors (PPARα/δ/γ), liver X receptors (LXRα/β), and sterol regulatory element-binding proteins (SREBP1/2), has been shown to be regulated by dietary PUFAs and their metabolites (13,14).

Several findings support the beneficial effect of n-3 PUFAs as chemopreventive and chemotherapeutic agents in the treatment of several chronic pathologies including cancer. N-3 PUFA is known ligands of PPAR-γ act by increasing the transcription of PPAR-γ and decreasing the transcription of NF-κB, and generally exerts tumor-suppressive effects. It was reported that combined administration of tamoxifen and n-3 PUFA is a promising new approach to breast cancer prevention. Because of its safety, this combination can quickly be translated to the clinic if its superiority can be supported by future studies.(15)Recent studieis suggested that increased intake of n3 fatty acids in the diet could help in the prevention as well as management of breast cancer(16).

The present study was designed to evaluate the circulating level of PPAR-γ and NF-κB in the obese breast cancer women in comparison with healthy obese women to study their regulation in cancer compared to obese status and also to study the relationship between PPAR-γ and NF-κB levels and the clinicopathological parameters of breast cancer women. The study also aimed to evaluate the possible effects of adjuvant omega-3 fatty acid treatment with chemotherapy on PPAR-γ and NF-κB levels.

Materials and Methods

The present study carried out on 60 obese individuals; 20 obese women served as control and 40 women (group II and III) who are histopayhologically proved breast cancer, and then referred to Cancer Management and Research Department, Medical Research Institute, Alexandria University for chemotherapy. According to the instructions of Ethics Committee, a signed consent will be received from all individuals enrolled in the study.

Exclusion criteria: all the studied subjects were free from diabetes, liver and kidney diseases.

The patients and control subjects were divided as follows:

Group (I); 20 obese women (BMI≥ 30 kg/m^2, WC> 94 cm) with no previous history of any malignant disease.

Group (II); 20 obese breast cancer patients (BMI≥30 kg/m^2, WC >94cm) undergo mastectomy, and then received thereafter the recommended chemotherapy course consisting of 6 cycles of FAC (5-Flourouracil 500mg/m^2, Adriamycin 50mg/m^2, and Cyclophosphamide 500mg/m^2) at three weeks interval.

Group (III); 20 obese breast cancer patients (BMI≥30 kg/m^2, WC >94cm) treated as in group **(II)**, and supplemented with a daily dose of n3-PUFAs (2.0 gm.) **(17)** in combination with the recommended chemotherapy regimen.

All patients were subjected to the following:-

- Full history taking.-
- Pathological diagnosis of breast stages II, III.-
- Clinical & radiological examinations-

Diagnosis of Obesity according to;

- Body Mass Index (BMI) (18)
- Waist Circumference (WC) (19)

Biochemical Analysis

- ***Laboratory investigations;***

- Complete Blood Count (CBC)**(20)**, Liver, and kidney Function tests.(21)
- Lipid Profile (Total cholesterol, Triglycerides, HDL, and LDL).

- ***Sample preparation;***

Peripheral venous blood sampleswere withdrawn from all subjects under study before and at the end of chemotherapy in groups **II, III** and from control group. The sample was left without anticoagulant for serum separation. Serum samples will be stored at -**70^{o}C** till used.

- ***Quantitative determination of PPAR-γ*** (22)and ***NF-κB levels*** (23)-

Determination of *PPAR-γ* and *NF-κB levels were measured* in serum by ELISA using a commercial kit according to the manufacturer's instructions.

Results

Clinical Data

The base line demographic and clinical data of the study populations are summarized in Table (1). It is clear that all of the study groups were of the matched age. All of the women under the study were obese as indicated by anthropometric measurements; weight, height and, BMI.

Table (1): Demographic Data of the Studied Groups

Parameters	Control Group (n=20)	Patients groups	
		Chemo (n=20)	Omega (n=20)
Age(year)	50.1±9.05	50.6±12.89	50.8± 10.89
Weight(kg)	86.9±6.1	91.15±15.84	88.0±9.89
Height(cm)	163.10±5.70	156.85±9.34[a]	157.25±5.83[a]
BMI(kg/m^2)	32.72±2.83	37.12±6.41[a]	35.66±4.17
WC(cm)	88.30±5.54	90.55±9.91	90.45±7.92

Data presented as Mean ± SD
a significantly different from control group by ANOVA ($p<0.05$)

Clinical Laboratory Parameters of the Different Studied Groups:

All the clinical data were within the normal range with the exception of the tumor marker CA15.3 which showed a significant elevation in the breast cancer patients (table 2).

Table (2) ; Clinical Laboratory Parameters in all Studied Groups

Parameters	Control Group (n=20)	Patients	
		Chemo Group (n=20)	Omega Group (n=20)
Hb	11.54±0.74	12.17±1.79	11.52±1.01
RBC	4.18±0.31	4.66±0.85	4.42±0.55
WBC	6.88±1.04	7.58±2.23	6.44±1.93
Platelets	267.40±42.49	334.20±99.70a	266.40±84.24[b]
Urea	37.50±8.30	28.15±10.79[a]	31.80±14.32
Creatinine(mg/dl)	0.774±0.135	0.66±0.148	0.751±0.164
Bilirubin (mg/dl)	0.656±0.171	0.569±0.145	0.525±0.107[a]
AST(U/L)	29.70±4.37	22.35±9.97	46.95±66.49
ALT(U/L)	32.10±3.51	20.95±10.63	54.70±110.60
Alkaline Phosphatase	59.90±17.84	81.65±31.67	88.600±28.14[a]
TG (mg/dl)	100.40±15.58	123.00±27.71**a**	132.80±27.72[a]
Cholesterol (mg/dl)	203.30±16.27	180.15±33.20	207.85±32.34[b]
HDL (mg/dl)	47.10±5.95	46.25±9.37	44.00±7.62
LDL (mg/dl)	132.40±21.06	109.80±37.34	137.40±34.45[b]
CA15.3 (U/ml)	7.20±4.53	56.23±44.72[a]	285.21±131.96[a,]**b**

Data presented as Mean ± SD

[a] *significantly different from control group by ANOVA ($p<0.05$)*

[b] *Significantly different from Chemo group by ANOVA ($p<0.05$)*

Pathological Features of Breast Cancer Patients:

The pathological parameters of breast cancer patients was described in Table (3); where, 70% of chemo group patients were grade II and 30% of patientswere grade III . 80% in the omega group of breast cancer patients were grade II and 20% were grade III. There was metastasis in bone, liver and/or lymph nodes in 65% in the chemo group and in 60% in the omega group. Moreover, the estrogen receptor was strong positive (++) in 50% in the chemo group but was weakly positive (+) in 55% in the omega group ,whereas the progesterone receptor was weakly positive (+) in about half number of both chemo and omega breast cancer patients .The Her-2/neu was weakly positive in 60% of omega group but was zero detected in 45% of the chemo group of breast cancer patients .

Table (3): Pathological Features of Breast Cancer Patients

Parameters	Patients	
	Chemo(n=20)	**Omega(n=20)**
Grade II	70% (14)	80%(16)
III	30% (6)	20%(4)
Metastasis	65%(13)	60%(12)
Yes	35%(7)	40%(8)
ER		
0	10%(2)	-
+	20%(4)	55%(11)
++	50%(10)	35%(7)
+++	20%(4)	10%(2)
PR 0	5%(1)	10%(2)
+	45%(9)	40%(8)
++	40%(8)	50%(10)
+++	10%(2)	-
Her-2/neu 0	45%(9)	15%(3)
+	35%(7)	60%(12)
++	10%(2)	15%(3)
+++	10%(2)	10%(2)

Data presented as percentage (number)

Kaplan-Meier Survival Curve:-

Follow up of the breast cancer women for 24 months indicated that the women who received adjuvant omega-3 treatment with chemotherapy showed a significant increase in the survival time compared to those women received chemotherapy alone. (Figure 1and table 4)

Table (4); The total levels of PPAR-γ (ng/ml) and NF-κB (ng/ml) in different studied groups before and after therapy

Parameters		Control Group (n=20)	Patients groups	
			Chemo (n=20)	Omega (n=20)
PPAR –γ	Before	1.14±0.412	0.78±0.33[a]	0.82±0.37 a
	After	-	0.79±0.17[a]	1.128±0.81[b]
	Difference	-	0.011±0.3	0.3±0.5
	% of Change	-	1.4%	36.6%
NF-κB	Before	0.56±0.597	0.84±0.32	0.98±0.29[a]
	After	-	0.91±0.32[a]	0.82±0.38
	Difference	-	0.07±0.44	-0.16±0.36
	% of change	-	8.3%	1.6%

Data presented as Mean ± SD

a *Significantly different from control group by ANOVA ($p<0.05$)*
b *Significantly different from Chemo group by ANOVA ($p<0.05$)*
c *Significantly different from the baseline value (before) by paired T-test ($p<0.05$)*

Serum PPAR-γ and NF-κB Levels (ng/ml) in Control and Breast Cancer Groups:

The statistical analysis of PPAR-γ and NF-κB levels are summarized in Tables (5). The results clearly indicated that, the breast cancer patients had a significantly lower level of serum PPAR-γ than control women and the base line value of the two breast cancer groups were comparable. The percent of change between before and after the treatment in the chemo group was 1.4% while in omega group was 36.6%

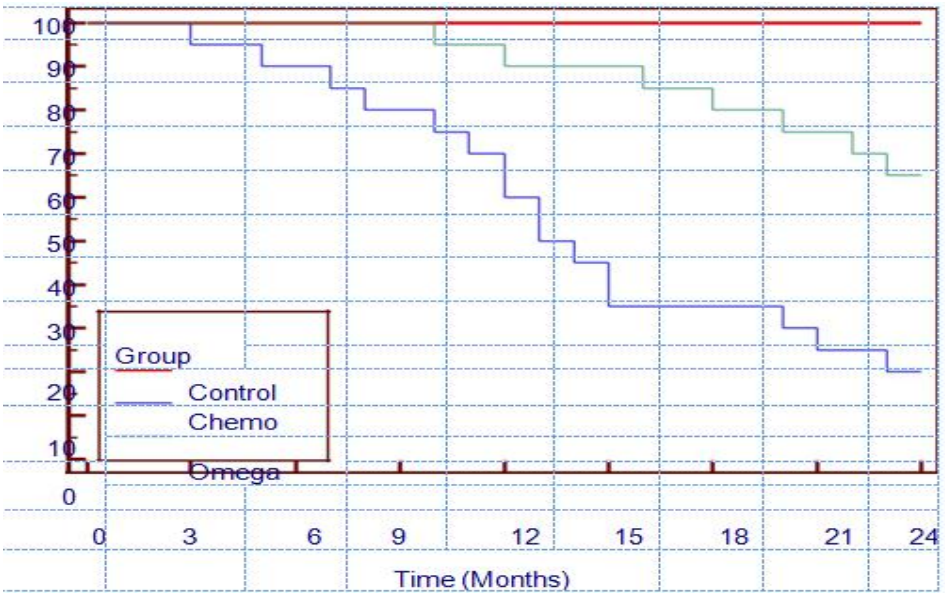
Table (5):Serum Levels of PPAR-γ (ng/ml) in the Pre- and Postmenopausal Breast Cancer Patients Before and After Treatment according to Pathological Markers

		Pre-menopause (n =17)		Post-menopause (n=23)	
		Before Tx	**After Tx**	**Before Tx**	**After Tx**
ER	**0**	1.71(1)	1.30(1)	-	-
	+	0.75±0.19(5)	1.05±0.19(5)	0.89±0.48(11)	1.15±1.1(11)
	+ +	0.73±0.13(8)	0.76±0.152(8)	0.77±0.35(9)	0.93±0.19(9)
	+ +	0.7±0.036(3)	0.78±0.151(3)	0.69±0.16(3)	0.82±0.22(3)
PR	**0**	1.71(1)	1.30(1)	1.48±1.1 1(2)	2.63±2.55(2)
	+	0.74±0.053(5)	0.854±0.166(5)	0.71±0.17(12)	0.87±0.24(12)
	+ +	0.73±0.16(11)	0.851±0.23(11)	0.84±0.37(7)	0.85±0.19(7)
	+ +	-	-	0.67±0.064(2)	0.90±0.092
Her-2/Neu	**0**	0.71±0.08(5)	0.74±0.12(5)	0.75±0.11(6)	0.85±0.08(6)
	+	0.74±0.18(9)	0.95±0.21(9)	0.75±0.33(11)	0.86±0.21(11)
	+ +	0.74(1)	0.64(1)	0.75±0.18(4)	0.91±0.34(4)
	+ +	1.2±0.72(2)	1.03±0.38(2)	1.48±1.1 1(2)	2.63±2.55(2)
Metastasis	**Yes**	0.67±0.11(7)	0.80±0.21(7)	0.84±0.44(18)	1.08±0.86(18)
	NO	0.87±0.32(10)	0.93±0.23(10)	0.71±0.097(5)	0.81±0.083(5)
Grade	**II**	0.72±0.15(12)	0.90±0.21(12)	0.82±0.45(17)	1.07±0.89(17)
	II	0.96±0.42(5)	0.83±0.29(5)	0.79±0.17(6)	0.89±0.25(6)

Data presented as Mean ± SD (number)

On the other hand, the statistical analysis of NF-κB levels indicated that, the breast cancer patients had significantly higher levels of serum NF-κB than control women. The base line values of the two breast cancer groups of patient were comparable. The chemotherapy alone cause a non-significant elevation of NF-κB while the adjuvant treatment with omega-3 cause a non-significant partial correction of NF-κB by about 1.6%.

Figure (1): Kaplan-Meier Survival Curve of Breast Cancer Patients



***Levels of PPAR-γ and NF- κB in Menopausal status*:**

Figure (2) represents the levels of serum PPAR-γ in the subjects of the present study stratified according to their menopausal status. It was shown that in the control obese women, the premenopausal women had significantly higher PPAR-γ level compared to the postmenopausal women.

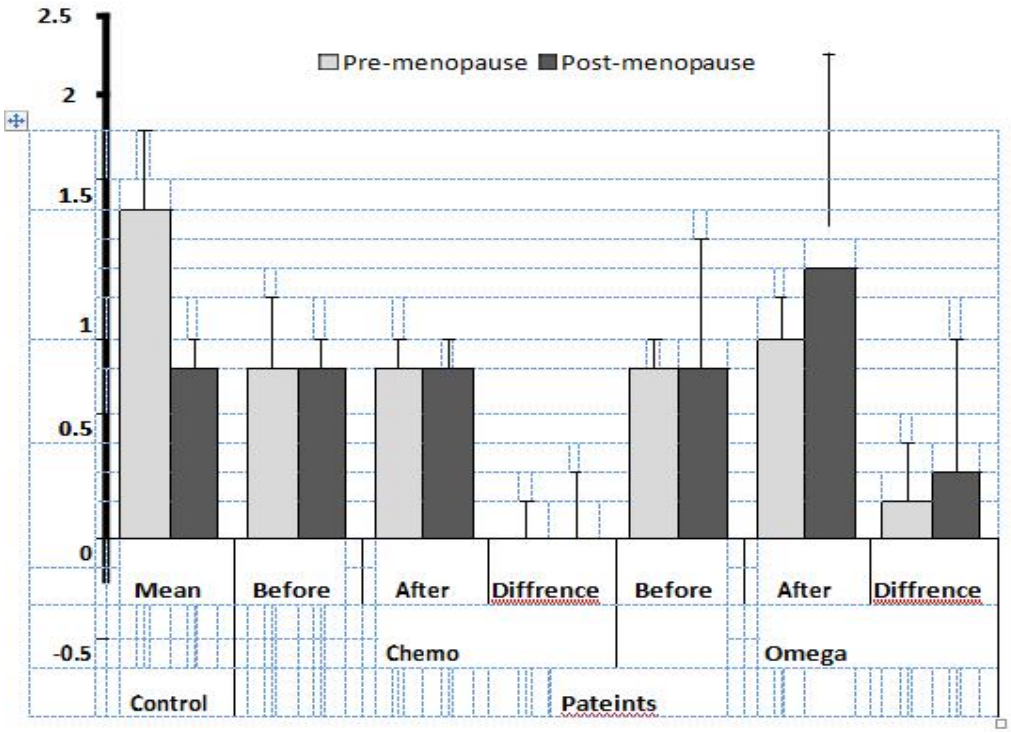


Figure (2); PPAR-γ levels (ng/ml) in control, pre- and postmenopausal breast cancer patients before and after therapy.
(*:significant difference between pre and post menopausal)

In the breast cancer women there was no significant difference observed between pre- and postmenopausal women at the base line values (before treatment). Premenopausal breast cancer obese women have significantly lower PPAR-γ level than control obese premenopausal women. The chemotherapy alone has no effect or even decreases the level of PPAR-γ in pre- and postmenopausal patients. While adjuvant treatment with omega-3 significantly increases PPAR-γ especially in the postmenopausal breast cancer obese women.

The mean values of PPAR-γ clearly indicated that, the breast cancer patients had a significantly lower level of serum PPAR-γ than control women and the base line value of the two breast cancer groups were comparable. Also no significant difference was observed between pre- and post-menopause breast cancer women while control premenopausal women had significantly higher level than postmenopausal women.

Figure (3) represents the levels of serum NF- κB in the subjects of the present study stratified according to their menopausal status. In the control obese women, the postmenopausal women have a non-significant higher level of NF- κB compared to premenopausal women.

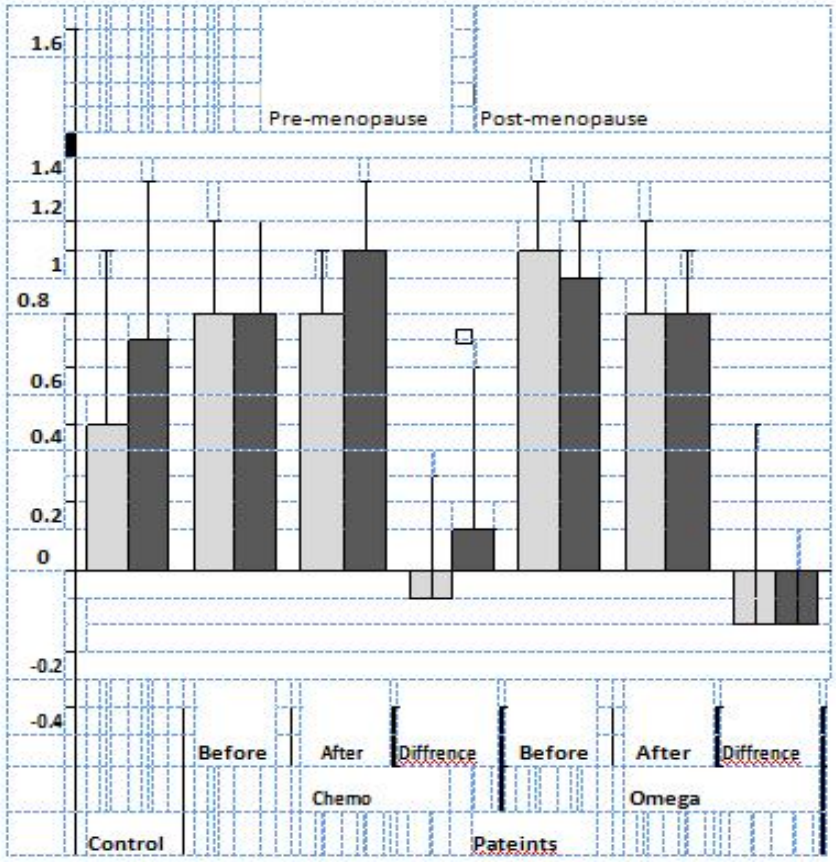


Figure (3); NF-κB levels (ng/ml) in control women, pre- and postmenopausal breast cancer patients(*:significant difference between pre and post menopausal)

In breast cancer obese women no significant difference observed between pre- and postmenopausal women. All breast cancer women show significant higher level of NF-κB. The treatment with chemotherapy alone has no significant effect on NF-κB while omega-3 adjuvant treatment produces a decrease in the circulating NF-κB especially in postmenopausal breast cancer women, however these decrease are not significant.

Pathological Markers and PPAR-γ levels;

The serum level of PPAR-γ appears to be affected by the pathological markers of cancer patients. Its level was decreased with the increased positivity of ER , PR and increased with Her-2/neu in both pre-and postmenopausal breast cancer patients. Also, the metastatic status affect PPAR-γ as its level was lower in premenopausal metastatic patients than those without metastasis. The higher grade of cancer was associated with higher PPAR-γ level in premenopausal

breast cancer patients. Note that this situation was reversed in postmenopausal breast cancer patients with respect to both the metastatic and grade relationship with the PPAR-γ level. (Table 5)

In table (6), the mean value of NF-κB indicated that, the breast cancer patients had significantly higher levels of serum NF-κB than healthy control women. The base line values of the two breast cancer groups of patient were comparable.

Table (6): Serum levels of NF-κB(ng/ml) in the Pre- and Postmenopausal Breast Cancer Patients according to their Pathological Markers

		Pre-menopause		Post-menopause	
		Before Tx	**After Tx**	**Before Tx**	**After Tx**
ER	**0**	0.69(1)	0.81(1)	-	-
	+	1.06±0.39(5)	0.93±0.38 (5)	1.014±0.21 (11)	0.89±0.26 (11)
	++	0.97±0.36(8)	0.76±0.21 (8)	0.85±0.32(9)	0.88±0.37 (9)
	++	0.695±0.13 (3)	0.79±0.26 (3)	0.60±0.17(3)	0.96±0.38 (3)a
PR	**0**	0.69(1)	0.81(1)	0.96±0.788 (2)	0.72±0.28 (2)
	+	1.056±0.498(5)	0.77±0.21 (5)	0.9±0.28(12)	0.92±0.29 (12)
	++	0.898±0.27 (11)	0.84±0.30 (11)	0.89±0.31(7)	0.77±0.29 (7)
	++	-	-	0.79±0.55(2)	1.33±0.07 (2)
Her-2/Neu	**0**	1.095±0.398(5)	0.78±0.199(5)	0.78±0.29(6)	0.93±0.36 (6)
	+	0.92±0.34(9)	0.84±0.32 (9)	0.97±0.25(11)	0.93±0.34 (11)
	++	0.82(1)	0.55(1)	0.82±0.43(4)	0.82±0.17 (4)
	++	0.62±0.099 (2)	0.94±0.19 (2)	0.96±0.078 (2)	0.72±0.28 (2)
Metastasis	**Yes**	0.91±0.41(7)	0.88±0.34 (7)	0.89±0.29(18)	0.84±0.31 (18)
	NO	0.95±0.31(10)	0.78±0.19 (10)	0.92±0.28(5)	1.09±0.24 (5)
Grade	**II**	1.03±0.32(12)	0.82±0.27 (12)	0.87±0.29(17)	0.89±0.31 (17)
	III	0.7±0.3(5)	0.81±0.27 (5)	0.98±0.27(6)	0.89±0.34 (6)

Data presented as Mean ± SD (number)

The serum level of NF-κB appeared to be affected by the pathological markers of cancer patients. Its level was decreased with the increased positivity of ER and PR in both pre-and postmenopausal breast cancer patients. Also, its level was decreased with Her-2/neu positivity in pre- and postmenopausal breast cancer patients. Also, the metastatic status affect NF-κB as its level was lower in both pre- and postmenopausal metastatic patients than those without metastasis. The lower grade of cancer was associated with higher NF-κB level in premenopausal breast cancer patients, but the vice versa was seen in postmenopausal breast cancer patients.

The study interested in the effect of omega-3 FAs on the circulatory levels of PPAR-γ and NF-κB. The results indicated that the omega-3 PUFAs adjuvant treatment with chemotherapy improve the response to chemotherapeutic drug. Omega-3 treatment significantly enhances the circulatory level of PPAR-γ and decrease NF-κB level while chemotherapy alone did not significantly improve it and even may worsen the situation.The response to therapeutic intervention in this study measured as survival time showed significant improvement by about 45% in the omega group in respect to the chemo group.

Discussion

The increasing incidence of obesity and its co-morbid conditions poses a great challenge to global health. (24,25) Obesity disrupts the dynamic role of the adipocyte in energy homeostasis, resulting in inflammation and alteration of adipokine signaling. Additionally, obesity causes secondary changes that are related to insulin signaling and lipid deregulation that may also foster cancer development.(26)

PPAR-γ has been reported to affect cell proliferation/differentiation pathways in various malignancies. **(27)** It is negatively regulating several genes, including NF-κB, a key transcriptional factor involved in numerous disease processes, including inflammation. (28) The ability of PPAR-γ to inhibit NF-κB expression is important in breast cancer progression, since NF-κB has been shown to increase tumor cell invasiveness. (29) Altered expression of nuclear NF-κB has also been shown to prevent apoptosis. (30)

The results of the present study indicated that, the serum level of PPAR-γ was affected by the menopausal status as its level was significantly higher in control premenopausal obese women than postmenopause ones. The breast cancer patients have a significantly lower level of serum PPAR-γ than control women with no significant difference was observed between pre- and post-menopause women. On the other hand, serum level of NF-κB in the control obese women showed a significant higher level in postmenopausal compared to premenopausal. The breast cancer women have significantly higher circulating level of NF-κB than control obese women irrespective of the menopausal status.
The circulating PPAR-γ may reflect the overall body production .Its role in cancer development and potential as a target for cancer prevention and treatment strategies has been noted (31). Activation of PPAR-γ could possibly be an approach to induce differentiation in cells thereby inhibiting proliferation of a variety of cancers. In particular, breast tissue was found to express PPAR-γ in amounts greater than those found in normal breast epithelium. (32)

Decreased level of serum PPAR-γ may be associated with decreased activation of PPAR signaling and low nuclear levels of breast cancer gene 1 (BRCA1) which is considered as a tumor suppressor gene in breast and ovarian carcinomas. Over expression of BRCA1 induces genes in the apoptotic pathway with subsequent damage to DNA repair mechanisms. Pignatelli M *et al* (33) demonstrated that the DR1 element found in BRCA1 promoter is a functional PPAR-γ responsive element, which could mediate the expression of the endogenous BRCA1 gene. These findings offer a molecular basis for the regulation of the BRCA1 gene as well as the role of PPAR-γ as a protective factor in breast cancer tumors.

PPAR-γ is also known to regulate several genes involved in the regulation of tumor cell growth and metastasis. One of this genes is Na^+/H^+ exchanger 1 (NHE1); activated PPAR-γ is reported to arrest tumor cell growth by down regulating NHE1. (34) Interestingly, it was reported that exposure of breast cancer cell lines expressing high levels of PPAR-γ to natural ligands of PPAR-γ significantly inhibited NHE1 gene expression compared with noncancerous cells or cancer cell lines expressing low levels of PPAR-γ.(35)

Another important target of PPAR-γ is pro-inflammatory transcription factor; NF-κB. The ability of PPAR-γ to inhibit NF-κB expression is important in breast cancer progression, since NF-κB has been shown to increase tumor cell invasiveness as a result

of increased urokinase plasminogen activator (uPA) expression. (36) Altered expression of nuclear NF-κB has also been shown to prevent apoptosis. (37) Other studies have shown NF-κB is involved in mammary epithelial proliferation (38), and also chemoresistance in MCF-7 breast cancer cells. Tumors with constitutive NF-κB activation usually show increased resistance to chemotherapy It has been suggested that NF-κB may induce the expression of the multidrug resistance P-glycoprotein, involved in the development of resistance to chemotherapy drugs in many cancers. (39)

Inhibition of NF-κB improves the apoptotic response to radiation therapy. (40) Inhibitors of NF-κB activation can block the neoplastic transformation response. Indeed, inhibition of NF-κB through adenoviral delivery of a modified form of IκB, a specific inhibitor of NF-κB, has been reported to sensitize chemo-resistant tumors to the apoptotic potential of TNF-α and to the chemotherapeutic compound resulting in tumor regression. (41)

Also the results indicated that serum level of PPAR-γ appears to be affected by the clinicopathological parameters of cancer patients. Its level was increased with the Her2/neu positivity, this association can be explained by study which reported that Her-2/*neu* oncogene up-regulates PPAR-γ expression and modulates the sensitivity of breast cancer cells to PPAR-γ ligand therapy. (42) On the other hand PPAR-γ level was decreased with the increased positivity of ER and PR in both pre-and postmenopausal breast cancer patients. Also, the metastatic status affect PPAR-γ as its level was lower in premenopausal metastatic patients than those without metastasis. The higher grade of cancer was associated with higher PPAR-γ level in premenopausal breast cancer patients.

Similarly, NF-κB shows association with the clinicopathological parameters of the breast cancer patients. In contest to PPAR-γ; its level was decreased with the increased positivity of ER and PR in both pre- and postmenopausal breast cancer patients. Also, its level was decreased with Her-2/neu positivity in pre- and postmenopausal breast cancer patients. Also, the metastatic status affect NF-κB as its level was lower in both pre- and postmenopausal metastatic patients than those without metastasis. The lower grade of cancer was associated with higher NF-κB level in premenopausal breast cancer patients, but the vice versa was seen in postmenopausal breast cancer patients.

In line with these data, the cross talk between PPAR-γ and estrogen receptor pathways has been documented. (43) ER status in breast cancer plays a major role in the progression and metastatic potential of breast cancer in women. Breast cancer cells lacking the ER are usually more advanced and more difficult to treat than ER+ breast cancer cells. ER− women have more advanced breast cancer at the time of diagnosis than ER+ women. ER− breast cancer cells in women, regardless of age, are more likely to have tumor Grade III or IV with fewer Grade I and II tumor stages combined for each individual stage group.(44) Studies have suggested a strong correlation between fat intake and the elevated risk of ER+ breast cancer cells. The PPAR cascade was uniquely down regulated in ER+ cells in response to arachidonic acid and not altered in ER− cells. (45)

Although anti estrogens have provided effective endocrine therapies, a significant proportion of patients have acquired resistance to these drugs, others are intrinsically resistant. Hence, there is a requirement for alternative therapeutics to treat breast cancer. Development of selective anticancer agents based on the biological differences between normal and cancer cells is essential to improve therapeutic selectivity, sensitivity, and specificity. (46)

From present data it is clear that in breast cancer obese women there is a down regulation of PPAR-γ cascade associated with up regulation of NF-κB cascade which results in chronic inflammation, inhibition of apoptosis, cell survival, tissues invasion and metastasis. These make the activation of PPAR-γ pathway is a promising therapeutic approach. Thus, PPAR-γ agonists have been reported as new and potentially efficacious treatment of inflammation, diabetes, obesity and cancer. (47) All of these open the gates toward the usage of the natural PPAR-γ agonists; one of this promising agonist is omega-3 fatty acids. It has been suggested that these exogenous FAs may affect the tumorigenesis, cancer growth and metastasis process (48).

It was demonstrated that Higher intake of long-chain n-3 FA was associated with lower mammografic breast density, suggesting that increased long-chain n-3 FA intake could be a strategy for breast cancer prevention.(49).

It was demonstrated that an increased n-3 fatty acid intake and/or increased (n-3)/ (n-6) PUFA ratio in the diet is associated with a lower breast cancer risk. (50)

It was found that incorporation of docosahexaenoic acid(DHA) with the chemotherapeutic drugs epirubicine, cyclophosphamide, and 5-fluorourac can alter the treatment response in breast cancer patients. The high incorporating group was characterized by delayed time to tumor progression and longer overall survival (51) This observation correlates well with other studies showing that DHA incorporation differs between individuals due to dissimilar rates of metabolism, enzymatic activity, background diet, age, and sex. (52) There are currently several ongoing clinical trials where DHA or combinations of omega-3 FAs are being tested for cancer prevention, support, or therapy. (53)

In the current study omega-3 F was used in obese breast cancer women as a treatment strategy combined with chemotherapeutic drugs. The response to therapeutic intervention in this study measured as survival time showed significant improvement by about 45% in the omega group in respect to the chemo group.

Omega-3 treatment significantly enhances the circulatory level of PPAR-γ and decrease NF-κB level while chemotherapy alone did not significantly improve these parameters.

Another report showed that dietary DHA-induced reduction in mammary tumors in a rat model was accompanied by a 60% increase in BRCA1 tumor suppressor protein. (54) Interestingly, n-3 fatty acid-enriched diets enhanced the efficiency of doxorubicin (55) and mitomycin C (56) in inhibiting tumor growth and strengthened the inhibitory effect of tamoxifen in estrogen dependent xenografts.These studies point to a potential value of n-3 fatty acids as adjuvant to standard chemotherapy. (58)

There are many molecular mechanisms by which omega-3 PUFA may exerts their potential effects on the cancer cells. First; Anti-inflammatory effect: n-3 PUF generally speaking, eicosanoids derived from n-6 PUFAs have pro-inflammatory whereas those derived from n-3 precursors have anti-inflammatory effects. (59) Therefore, utilizing dietry PUFA in a specific n-6:n-3 ratio may be an important chemopreventive tool in altering the growth characteristics of cancer cells.(60)

Second; anti-proliferative and pro-apoptotic effect; n-3 PUFA may increase tumor cell susceptibility to apoptosis by altering expression or function of apoptotic proteins, or by modulating activity of survival-related transcription factors such as NF-κB. N-3 PUFA may increase drug uptake or even enhance drug activation (e.g., in the case of some nucleoside analogue drugs). (61) The n-3 PUFAs might alter the growth of tumor cells by influencing cell replication, by interfering with components of the cell cycle or by increasing cell death either by way of necrosis or apoptosis. (62-64)

Moreover n-3 PUFAs down-regulate the expression of Her2/neu, a well characterized oncogene that plays a key role in etiology, progression and chemo sensitivity of various types of human cancer in which this oncogene is over-expressed. Her2/neu encodes transmembrane tyrosine kinase orphan receptor p185 Her2/neu, which regulates biological functions including cellular proliferation, differentiation, motility and apoptosis. (65)

Also, it was documented that dietary fish oil significantly suppressed the phospho-inositol 3 kinase (PI3 kinase) activity in the breast tumor, resulting in reduced Akt kinase and NF-κB p65 subunit phosphorylation and anti-apoptotic protein expression. In addition, **Ghosh-Choudhury T** *et al* (66), showed that the active constituents of fish oil, DHA and EPA, inhibit NF-κB transcriptional activation, resulting in attenuation of the antiapoptotic gene transcription which confirms our results of decreased NF-κB by omega-3 adjuvant treatment.

The third mechanism of omega-3 PUFA mediated action is its effect on signal transduction; N-3 PUFA as a long chain fatty acids are incorporated in the plasma membrane of growing cells which affect the membrane structure and functions.. N-3 fatty acids may alter cellular signaling by acting directly as ligands for nuclear receptors, including peroxisome proliferators-activated receptors (PPARs) (67) or retinoid X receptor alpha. (68) These nuclear transcription factors bind lipid ligands to regulate gene expression, thereby mediating biological functions ranging from lipid metabolism and homeostasis to cell differentiation and cell death. DHA was shown to induce cell apoptosis through activation of PPAR-γ. (69) All of these confirm the results of the present study which indicated 36.6% increase in level of circulating PPAR-γ with omega-3 adjuvant treatment while chemotherapy alone did not affect its level.

The results of the current study indicated that, the postmenopausal breast cancer women respond more efficiently for omega-3 PUFA with respect to PPAR-γ than premenopausal patients as indicated by higher level after treatment and higher difference in the level of PPAR-γ. The metastatic postmenopausal patients showed a good response by elevating PPAR-γ level. Also the high positivity for Her2/neu and lower positivity for ER and PR together with postmenopausal status may considered as a good prognostic marker for improvement of PPAR-γ.

On the other hand, the NF-κB lowering the effect of omega-3 adjuvant treatment appear to be not affected by the menopausal status. While in premenopausal patients showed small decrease in NF-κB level with chemotherapy alone, the postmenopausal patients showed elevation of its level. These may indicate that the postmenopausal patients at higher risk for increased inflammation and so at higher need for treatment with omega-3 PUFA. As with PPAR-γ, the high positivity for Her2/neu and lower positivity for ER and PR together with postmenopausal status may considered as a good prognostic marker for improvement of NF-κB. These finding suggested that the ER, PR and Her-2/neu status of breast cancer cell may play a role in the response of breast cancer cells for treatment with omega-3 fatty acids.

Conclusion

It is become clear that breast cancer obese women suffer from low circulating level of PPAR-γ and high level of NF-κB that may consider a cause and/or a consequence of cancer development. The using of omega-3 PUFA as adjuvant treatment may increase sensitivity of cancer cells for chemotherapy by targeting PPAR-γ /NF-κB signaling pathway through correction of their derangements.

Recommendation

- Further research is warranted to identify specific mechanisms by which n-3 PUFA increase chemotherapy efficacy

- The finding presented in this study warrant further investigation regarding the use of PPAR-γ ligands, such as n-3 PUFAs, in patients who are predisposed or already diagnosed with breast cancer.

Conflict of interest statement

We declare that we have no conflict of interest.

References

1. Vona-Davis L, Howard-McNatt M, Rose DP. Adiposity, type 2 diabetes and the metabolic syndrome in breast cancer. Obes Rev., 2007; 8: 395-408.
2. Howell A, Chapman M, Harvie M. Energy restriction for breast cancer prevention. Recent Results Cancer Res., 2009; 181: 97-111.
3. Boyd NF, Guo H, Martin LJ, Sun L, Stone J, Fishell E, et al. Mammographic density and the risk and detection of breast cancer. The New England Journal of Medicine .,2007; 356 (3): 227– 36.
4. Paltoo D, Woodson K, Taylor P, Albanes D, Virtamo J, Tangrea J. Pro12Ala polymorphism in the peroxisome proliferator-activated receptor-γ (PPAR-γ) gene and risk of prostate cancer among men in a large cancer prevention study. Cancer Letters., 2003; 191 (1): 67–74.
5. Jiang W, Zhu Z, McGinley JN, El Bayoumy K, Manni A, Thompson HJ: Identification of a molecular signature underlying inhibition of mammary carcinoma growth by dietary N-3 fatty acids.Cancer Res., 2012, 72:3795-806.
6. Jourdan M-L, Mahéo K, Barascu A, Goupille C, De Latour MP, Bougnoux P, et al.: Increased BRCA1 protein in mammary tumours of rats fed marine ω-3 fatty acids.Oncol Rep., 2007, 17:713-9.
7. Garg AK, Hortobagyi GN, Aggarwal BB, Sahin AA, Buchholz TA. Nuclear factor-kappa B as a predictor of treatment response in breast cancer. Curr Opin Oncol., 2003; 15 (6): 405-11.
8. Perkins ND. Integrating cell-signalling pathways with NF-κB and IKK function. Nat Rev Mol Cell Biol., 2007; 8 (1): 49–62.
9. Liu J, Ma DW. The role of n-3 polyunsaturated fatty acids in the prevention and treatment of breast cancer. Nutrients. 2014;6(11):5184–223.
10. Stoll BA. N-3 fatty acids and lipid peroxidation in breast cancer inhibition. The British journal of nutrition., 2002;87(3):193–8.
11. Rigas B and Sun Y. Induction of oxidative stress as a mechanism of action of chemopreventive agents against cancer British Journal of Cancer .,2008; 98, 1157–1160.

12. Finstad HS, Dyrendal H, Myhrstad MC, Heimli H, Drevon CA. Uptake and activation of eicosapentaenoic acid are related to accumulation of triacylglycerol in Ramos cells dying from apoptosis. Journal of lipid research. 2000;41(4):554–63.
13. Pachikian BD, Essaghir A, Demoulin JB, Neyrinck AM, Catry E, De Backer FC, et al. Hepatic n-3 polyunsaturated fatty acid depletion promotes steatosis and insulin resistance in mice: genomic analysis of cellular targets. PloS one., 2011;6(8):e23365.
14. Xia S, Lu Y, Wang J, He C, Hong S, Serhan CN, et al. Melanoma growth is reduced in fat-1 transgenic mice: impact of omega-6/omega-3 essential fatty acids. Proceedings of the National Academy of Sciences of the United States of America., 2006; 103(33):12499–504.
15. Manni A, Xu H, Washington S, Aliaga C, Cooper T, Richie JP Jr, et al. The impact of fish oil on the chemopreventive efficacy of tamoxifen against development of N-methyl-N-nitrosourea-induced rat mammary carcinogenesis. Cancer Prev Res., 2010; 3: 322-30.
16. Prakash P. Mansara, Rashmi A. Deshpande, Milind M. Vaidya, Ruchika Kaul-Ghanekar Differential ratios of omega fatty acids (AA/EPA+DHA) modulate growth, lipid peroxidation and expression of tumor regulatory MARBPs in Breast Cancer Cell Lines MCF7 and MDA-MB-231.PLoS One., 2015; 10(9): e0136542.
17. Bougnoux P, Hajjaji N, Ferrasson M N , Giraudeau B, Couet C, Le Floch O. Improving outcome of chemotherapy of metastatic breast cancer by docosahexaenoic acid: a phase II trial. British Journal of Cancer 2010; 101: 1978–85.
18. Ewertz M, Jensen MB, Gunnarsdóttir KÁ, Højris I, Jakobsen EH, Nielsen D, et al. Effects of obesity in prognosis after early-stage breast cancer. J Clin Oncol .,2011; 29: 25-31.
19.. Hajian-Tilaki KO1, Gholizadehpasha AR, Bozorgzadeh S, Hajian-Tilaki E.Body mass index and waist circumference are predictor biomarkers of breast cancer risk in Iranian women.Med Oncol., 2011 Dec;28(4):1296-301.
20. Dacie JV, Lewis SM. Practical hematology. 8th Ed. J and A Churchil LTD, London., 1996, pp.49-82
21. Burtis CA, Ashwood ER, Bruns DE. Tietz Text Book of Clinical Chemistry and Molecular Diagnosis. 4th ed. Elsevier Saunders Company, St. Louis. 2006, pp. 802-3 (urea), 798-801(creatinine), 605-7(AST, ALT), 940-50 (lipid profile).
22. Brown P J, Smith-Oliver T A, Charifson PS, Tomkinson NC, Fivush AM, Sternbach DD, et al. Identification of peroxisome proliferator-activated receptor ligands from a biased chemical library. Chem Biol .,1997;4 (12): 909-18.
23. Ohsugi T, Horie R, Kumasaka T, Ishida A, Ishida T, Yamaguchi K, et al. In vivo antitumor activity of the NF-κB inhibitor dehydroxymethylepoxyquinomicin in a mouse model of adult T-cell leukemia. Carcinogenesis .,2005; 26: 1382-8.
24. Khandekar MJ, Cohen P, Spiegelman BM. Molecular mechanisms of cancer development in obesity. Nat Rev Cancer., 2011; 11: 886-95.
25. Trentham-Dietz A, Newcomb PA, Nichols HB, Hampton JM. Breast cancer risk factors and second primary malignancies among women with breast cancer. Breast Cancer Res Treat., 2007; 105: 195-207.
26. Bartsch H, Nair J, Owen RW. Dietary polyunsaturated fatty acids and cancers of the breast and colorectum: emerging evidence for their role as risk modifiers. Carcinogenesis .,1999; 20:2209-18.
27. Tontonoz P, Hu E, Spiegelman BM. Regulation of adipocyte gene expression and differentiation by peroxisome proliferator activated receptor-γ. Current Opinion in Genetics and Development .,1995; 5: 571–6.
28. Costa V, Foti D, Paonessa F, Chiefari E, Palaia L, Brunetti G. The insulin receptor: a new anticancer target for peroxisome proliferator-activated receptor-γ (PPAR-γ) and thiazolidinedione-PPARγ agonists. Endocrine-Related Cancer .,2008; 15: 325–35
29. Sliva D, Rizzo MT, English D. Phosphatidylinositol 3-kinase and NF-κB regulate motility of invasive MDA-MB-231 human breast cancer cells by the secretion of urokinase type plasminogen activator. J Biol Chem., 2002; 277: 3150–7.
30. Weldon CB, Burow ME, Rolfe KW, Clayton JL, Jaffe BM, Beckman BS. NF-κB-mediated chemoresistance in breast cancer cells. Surgery., 2001; 130: 143–50.
82: Woo CC, Loo SY, Gee V, Yap CW, Sethi G, Kumar AP. Anticancer activity of thymoquinone in breast cancer cells: possible involvement of PPAR-γ pathway. Biochem Pharmacol., 2011;464–75.
31. Sakharkar MK, Shashni B, Sharma K, Dhillon SK, Ranjekar PR, Sakharkar KR. Therapeutic implications of targeting energy metabolism in breast cancer. PPAR Res .,2013 : 2013 : 11 pages

32. Pignatelli M, Cocca C, Santos A, Perez-Castillo A. Enhancement of BRCA1 gene expression by the peroxisome proliferator-activated receptor γ in the MCF-7 breast cancer cell line. Oncogene ., 2003; 22: 5446–50.
33. Akram S, Teong HF, Fliegel L, Pervaiz S, Clément MV. Reactive oxygen species-mediated regulation of the Na+-H+ exchanger 1 gene expression connects intracellular redox status with cells' sensitivity to death triggers. Cell Death Differ., 2006; 13: 628–41.
34. Venkatachalam G, Kumar AP, Yue LS, Pervaiz S, Clement MV, Sakharkar MK. Computational identification and experimental validation of PPRE motifs in NHE1 and MnSOD genes of human. BMC Genomics., 2009; 10:1-13.
35. Sliva D, Rizzo MT, English D. Phosphatidylinositol 3-kinase and NF-κB regulate motility of invasive MDA-MB-231 human breast cancer cells by the secretion of urokinase type plasminogen activator. J Biol Chem .,2002; 277: 3150–7.
36. Shao R, Karunagaran D, Zhou BP, Li K, Lo SS, Deng J. Inhibition of nuclear factor-κB activity is involved in E1A mediated sensitization of radiation-induced apoptosis. J Biol Chem .,1997; 272: 32739–42.
37. Weldon CB, Burow ME, Rolfe KW, Clayton JL, Jaffe BM, Beckman BS. NF-κB-mediated chemoresistance in breast cancer cells. Surgery 2001; 130: 143–50
39. Thevenod F, Friedmann JM, Katsen AD, Hauser IA. Up-regulation of multidrug resistance P-glycoprotein via nuclear factor-kappaB activation protects kidney proximal tubule cells from cadmium- and reactive oxygen species-induced apoptosis. J Biol Chem .,2000; 275: 1887-96.
40. Aggarwal BB, Shishodia S, Sandur SK, Pandey MK, Sethi G. Inflammation and cancer: how hot is the link? Biochem Pharmacol .,2006; 72:1605-2.
41. Wang CY, Cusack JC, Liu R, Baldwin AS. Control of inducible chemoresistance: enhanced anti-tumor therapy through increased apoptosis by inhibition of NF-kappa B. Nat Med .,1999; 5: 412-7.
42. Menendez JA, Lupu R, Colomer R. Targeting fatty acid synthase: potential for therapeutic intervention in Her-2/neu-overexpressing breast cancer. Drug News & Perspectives.,2005;18:375–85
43.. Keller H, Givel F, Perroud M, Wahli W. Signaling cross-talk between peroxisome proliferator-activated receptor/retinoid X receptor and estrogen receptor through estrogen response elements. Mol Endocrinol .,1995; 9: 794-804.
44. Wang X, Kilgore MW. Signal cross-talk between estrogen receptor alpha and beta and the peroxisome proliferator-activated receptor gamma1 in MDA-MB-231 and MCF-7 breast cancer cells. Mol Cell Endocrinol .,2002; 194: 123-33.
45. Alquobaili F, Miller SA, Muhie S, Day A, Jett M, Hammamieh R. Estrogen receptor-dependent genomic expression profiles in breast cancer cells in response to fatty acids. J Carcinog .,2010; 8: 17-41.
46. Fedele P, Calvani N, Marino A, Orlando L, Schiavone P, Quaranta A. Targeted agents to reverse resistance to endocrine therapy in metastatic breast cancer: where are we now and where are we going? Crit Rev Oncol Hematol., 2012; 84: 243-51.
47. Tyagi S, Gupta P, Saini AS, Kaushal C, Sharma S. The peroxisome proliferator-activated receptor: A family of nuclear receptors role in various diseases. J Adv Pharm Technol Res., 2011; 2: 236-40.
48. Goodstine SL, Zheng T, Holford, TR, Ward BA, Carter D, Owens PH. Dietary (n-3) / (n-6) fatty acid ratio: possible relationship to premenopausal but not postmenopausal breast cancer risk in U.S. women. J Nutr., 2003; 133: 1409-14.
49. Diorio C, Dumas I. Relations of omega-3 and omega-6 intake with mammographic breast density.Cancer Causes Control., 2014 Mar;25(3):339-51.
50. Mansara PP, Deshpande RA, Vaidya MM, Kaul-Ghanekar R. Differential Ratios of Omega Fatty Acids (AA/EPA+DHA) Modulate Growth, Lipid Peroxidation and Expression of Tumor Regulatory MARBPs in Breast Cancer Cell Lines MCF7 and MDA-MB-231.PLoS One., 2015 Sep 1;10(9):e0136542.
51. Bougnoux P, Hajjaji N, Ferrasson MN, Giraudeau B, Couet C, Le Floch O. Improving outcome of chemotherapy of metastatic breast cancer by docosahexaenoic acid: a phase II trial. Br J Cancer., 2009; 101: 1978–85.
52. Rusca A, Di Stefano AF, Doig MV, Scarsi C, Perucca E. Relative bioavailability and pharmacokinetics of two oral formulations of docosahexaenoic acid/eicosapentaenoic acid after multiple-dose administration in healthy volunteers. Eur J Clin Pharmacol., 2009; 65: 503-10.
53. Berquin IM, Edwards IJ, Chen YQ. Multi-targeted therapy of cancer by omega-3 fatty acids. Cancer Lett., 2008; 269: 363–77.

54. Jourdan ML, Maheo K, Barascu A, Goupille C, De Latour MP, Bougnoux P, et al. Increased BRCA1 protein in mammary tumours of rats fed marine omega-3 fatty acids. Oncol Rep., 2007; 17: 713–9.
55. Hardman WE, Avula CP, Fernandes G, Cameron IL. Three percent dietary fish oil concentrate increased efficacy of doxorubicin against MDA-MB 231 breast cancer xenografts. Clin Cancer Res., 2001; 7:2041–9.
56. Shao Y, Pardini L, Pardini RS. Dietary menhaden oil enhances mitomycin C antitumor activity toward human mammary carcinoma MX-1. Lipids. 1995; 30:1035-45.
57. Chen J, Hui E, Ip T, Thompson LU. Dietary flaxseed enhances the inhibitory effect of tamoxifen on the growth of estrogen-dependent human breast cancer (mcf-7) in nude mice. Clin Cancer Res., 2004; 10: 7703–11.
58. Pardini RS. Nutritional intervention with omega-3 fatty acids enhances tumor response to antineoplastic agents. Chem Biol Interact ., 2006; 162: 89–105.
59. Calder PC, Yaqoob P, Thies F, Wallace FA, Miles EA. Fatty acids and lymphocyte functions. Br J Nutr., 2002; 87: S31–S48.
60. Abel S, Riedel S, Gelderblom WC. Dietary PUFA and cancer. Proc Nutr Soc., 2014 Aug;73(3):361-7.
61. Biondo PD, Brindley DN, Sawyer MB, Field CJ. The potential for treatment with dietary long-chain polyunsaturated n-3 fatty acids during chemotherapy. J Nutr Biochem .,2008; 19: 787-96.
62. Serini S, Piccioni E, Merendino N, Calviello G: Dietary polyunsaturated fatty acids as inducers of apoptosis: implications for cancer. Apoptosis. 2009; 14: 135-52.
63. Field CJ, Schley PD. Evidence for potential mechanisms for the effect of conjugated linoleic acid on tumor metabolism and immune function: lessons from n-3 fatty acids. Am J Clin Nutr .,2004; 79: 1190S-8S
64. . Das UN. A radical approach to cancer. Med Sci Monit .,2002, 8: RA79-92.
65. Menendez JA, Vazquez-Martin A, Ropero S, Colomer R, Lupu R. HER2 (erbB-2)-targeted effects of the omega-3 polyunsaturated fatty acid, alpha linolenic acid (ALA; 18:3n-3), in breast cancer cells: the “fat features” of the “Mediterranean diet” as an “anti-HER2 cocktail”. Clin Transl Oncol .,2006; 8: 812-20.
66. Ghosh-Choudhury T, Mandal CC, Woodruff K, St Clair P, Fernandes G, Choudhury GG. Fish oil targets PTEN to regulate NF kappa B for down regulation of anti-apoptotic genes in breast tumor growth. Breast Cancer Res Treat., 2009; 118: 213-28.
67. Stoll BA. N-3 fatty acids and lipid peroxidation in breast cancer inhibition. Br J Nutr., 2002; 87: 193–8.
68. Fan YY, Spencer TE, Wang N, Moyer MP, Chapkin RS. Chemopreventive n-3 fatty acids activate RXR alpha in colonocytes. Carcinogenesis., 2003; 24: 1541–8.
69. Zand H, Rhimipour A, Bakhshayesh M, Shafiee M, Nour Mohammadi I, Salimi S. Involvement of PPAR-gamma and p53 in DHA-induced apoptosis in Reh cells. Mol Cell Biochem .,2007; 304: 71–7.

Access this Article in Online	
	Website: www.ijarbs.com
Quick Response Code	Subject: Medical Sciences
DOI:10.22192/ijarbs.2017.04.12.014	

How to cite this article:
Iman A. Sharaf , Maher A Kamel, Rasha A El-Tahan, Hanaa M Kohail, Mostafa A El Naggar. (2017). Peroxisome Proliferator- Activated Receptor-gamma and Nuclear Factor-kappa B in Obese Breast Cancer Patients: Correlation with Omega-3 polyunsaturated Fatty Acids with Adjuvant Chemotherapy. Int. J. Adv. Res. Biol. Sci. 4(12): 133-149. DOI: http://dx.doi.org/10.22192/ijarbs.2017.04.12.014