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BRIEF REPORT

Effect of Coenzyme Q_{10}, Riboflavin and Niacin on Tamoxifen treated postmenopausal breast cancer women with special reference to blood chemistry profiles

Srinivasan Yuvaraj · Vummidi Gridhar Premkumar · Palanivel Shanthi · Kothandaraman Vijayasarathy · Sitthu Govindaswamy Dinakaran Gangadaran · Panchanatham Sachdanandam

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Abstract *Background* Tamoxifen (TAM) a non-steroidal antiestrogen, is widely used in adjuvant therapy for all stages of breast carcinomas and in chemoprevention of high-risk group. TAM also has estrogenic activity on liver and endometrium causing severe oxidative stress with various biochemical derangements. Coenzyme Q_{10}, Riboflavin and Niacin (CoRN) are well-known potent antioxidants and protective agents against many diseases including cancer. In this context, this study was undertaken to find if co-administration of TAM along with CoRN could alleviate the sole TAM-induced biochemical derangements in postmenopausal women with breast cancer. *Method* The vitamin supplementation with TAM was given for a period of 90 days. Blood samples were collected at the base line, 45th and 90th day during the course of treatment. Various blood chemistry profiles were assessed in 78 untreated, sole TAM treated and combinatorial treated group along with 46 age- and sex-matched controls. *Results* A statistically significant alteration in various blood chemistry parameters, such as serum total bilirubin (S. BIL), serum glutamate oxaloacetate transaminase (SGOT), serum glutamate pyruvate transaminase (SGPT), gamma glutamyl transpeptidase (γ-GT), uric acid (UA), lipoprotein lipase (LPL), lecithin: cholesterol acyl transferases (LCAT), potassium, calcium and Na^+, K^+-ATPase in sole TAM-treated group, was favorably reverted back to near normal levels on combinatorial therapy with CoRN. *Conclusion* TAM on co-administration with CoRN has a favorable impact on various blood chemistry profiles. However, large scale randomized studies over a longer time span are required to ascertain the safety and efficacy of co-administrating antioxidants with conventional chemotherapy.

Keywords Breast cancer · Tamoxifen · Postmenopausal · Biochemical derangements · Antioxidants

S. Yuvaraj · V. G. Premkumar · P. Sachdanandam (✉)
Department of Medical Biochemistry, Dr. ALMP-GIBMS, University of Madras, Taramani Campus, Chennai 600 113, Tamil Nadu, India
e-mail: psachdanandam2000@yahoo.co.in

P. Shanthi
Department of Pathology, Dr. ALMP-GIBMS, University of Madras, Taramani Campus, Chennai 600 113, Tamil Nadu, India

K. Vijayasarathy · S. G. D. Gangadaran
Department of Medical Oncology, Government Royapettah Hospital, Kilpauk Medical College, Chennai 600 014, Tamilnadu, India

Introduction

Breast cancer is one of the most prevalent cancers in women. Approximately 60% of breast cancer patients are aged 65 years or over [1]. Treatment of breast cancer is a combinatorial mode of surgery, chemo, radiation and hormonal therapy. Tamoxifen forms the major hormonal drug of choice by its estrogen antagonist property in mammary tissue, for a period of 5 years. Approximately 13% of women experience recurrence during the period of TAM therapy around second year [2]. In this subset of patients, treatment is only palliative and recurrent breast cancer is often incurable [3]. Therefore, a novel approach to the management of breast cancer has to be developed [4].

TAM does not produce visible side effects as nausea, vomiting, active infection, hair loss, etc., as in chemo or radiation therapy, but its prolonged administration for a period of 5 years causes severe biochemical derangements such as hypertriglyceridemia, hypercalcemia, deep vein

thrombosis in legs, increased risk of stroke, severe oxidative stress and red blood cell hemolysis resulting in hemolytic anemia [5–8]. Due to its estrogen-like action on liver and endometrium, there is an increased risk of hepatic and endometrial carcinoma. Adlard et al. found that patients experienced significant morbidity and toxicity while taking adjuvant TAM therapy [9] and TAM-induced fatty liver is observed in more than 30% of breast cancer patients [10]. Some results of aromatase (enzyme responsible for synthesis of estrogen) inhibitors have been shown to be encouraging in postmenopausal women; however, they have contraindicated results in premenopausal women with functioning ovaries [11]. These findings are preliminary with a median follow-up of only 7 years and no survival data are available. Until further data emerge, adjuvant TAM therapy would remain the standard for most of the breast cancer patients. Recent clinical trial results also support use of TAM as compared to aromatase inhibitors (AIs), as most of the Tamoxifen side effects do not continue after the 5-year treatment period [12, 13]. Hence, this study is focused on reducing the contraindications of sole TAM treatment with a vitamin combination of Coenzyme Q_{10} (CoQ_{10} 100 mg), Niacin (50 mg) and Riboflavin (10 mg).

Coenzyme Q_{10} (CoQ_{10}) is a lipophilic molecule comprised of a benzoquinone ring structure linked to a polyisoprenoid chain of 10 isoprenes. CoQ_{10} is the only endogenously synthesized lipid-soluble antioxidant, present in all tissues and membranes. The protective effect is extended to lipids, proteins and DNA mainly because of its close localization to the oxidative events and the effective regeneration by continuous reduction at all locations. In the recent years, there is a growing body of evidence on protective role of CoQ_{10} in cardio-vascular diseases and cancer [14–16]. Riboflavin, in its active cofactor forms like flavin mononucleotide (FMN) and flavin adenine dinucleotide (FAD), participates in oxidation-reduction reactions in numerous metabolic pathways and in energy production via the respiratory chain [17]. Riboflavin captures reactive metabolites like Tamoxifen and carcinogens to form a complex and thereby, prevents formation of DNA adducts [18], DNA methylation and maintains genomic stability [19, 20]. Niacin is a precursor of nicotinamide adenine dinucleotide (NAD^+) and nicotinamide adenine dinucleotide phosphate ($NADP^+$) which is essential for a variety of oxidation-reduction reactions that comprise tissue respiration. In human cells, niacin deficiency has been shown to alter the expression of p^{53}, induce inherent genomic instability, and reduce survival following exposure to solar-simulated light [21]. Conversely, increased NAD^+ or more active NAD biosynthesis allows cells to recover more efficiently after DNA damage [21, 22]. Presently, niacin is one of the premier lipid lowering agents available to treat various CVD, with its first clinical utility dating back to 1950s [23]. In this context, efforts were undertaken to understand the benevolent role of CoQ_{10}, Riboflavin and Niacin on TAM-instigated biochemical derangements in postmenopausal breast cancer women.

Methods

Selection of patients

Seventy-eight consecutively treated postmenopausal women with resectable breast cancer were recruited from the Department of Medical Oncology, Government Royapettah Hospital, Chennai, India through their physicians according to the process approved by the institutional human ethical review board. Informed consent was obtained with explanation from all the subjects before entering into the study. The TAM-treated patients characteristics are given in Table 1. Age younger than 70 years with potentially curable and histopathologically confirmed breast cancer patients were recruited. Patients with diabetes mellitus, renal, hepatic diseases and patients who were on vitamin/estrogen supplementation were excluded from the study. Age and socio-economically matched healthy controls were recruited from the hospital visitors, who were non-blood related to the individuals with disease and who have no family history of cancer.

Blood sampling and study design

Blood samples were drawn by venous arm punctures into plain tubes and heparinized tubes. The serum/plasma were separated by centrifugation at 2,500*g* for 15 min and buffy coat was removed from the heparinized tubes, and packed cells washed thrice with physiological saline. The erythrocyte membrane was prepared by the method of Dodge et al. [24].

Blood samples were drawn from the disease-free, healthy, age-matched postmenopausal women (Group I), untreated breast cancer patients (Group II), breast cancer patients who were on Tamoxifen (20 mg a day, Nolvadex, AstraZeneca, India) therapy for more than a year (Group III), Group III patients after blood sample collection were recruited into Group IV and were supplemented with CoQ_{10} (100 mg Kaneka Q_{10}, Kaneka Corporation, Japan), Riboflavin (10 mg, Madras Pharmaceuticals, India) and Niacin (50 mg, Madras Pharmaceuticals) along with Tamoxifen (20 mg/day) and blood samples were drawn at the end of 45th day (Group IV). Group IV patients continued the same protocol and blood samples were collected at the end of 90th day (Group V).

Serum bilirubin, protein, albumin, SGOT, SGPT, ALP, γ-GT, sugar, urea, creatinine, UA, LPL and calcium were

Table 1 Characteristics of the patients and their disease ($N = 78$ patients)

Characteristics	Years	*N*	%
Age (years)			
Mean	49		
Range	43–70		
Tumor size (T)			
T1		5	6.4
T2		31	39.7
T3		24	30.7
T4		18	23.0
Nodal status (N)			
N0		24	30.7
N1		41	52.5
N2		12	15.3
N3		1	1.2
N4		0	0
Metastasis (M)			
M0		78	100
M1		0	0
Histology			
Ductal invasive		76	97.4
Lobular invasive		2	2.5
Surgery			
Conservative		2	2.5
Mastectomy			
Simple		10	12.8
Radical		2	2.5
Modified radical		49	62.8
Patey's		9	11.5
Modified Patey's		2	2.5
No surgery		4	5.1
Family history of cancer			
Yes		9	11.5
No		69	88.5
Diet			
Mixed		73	93.5
Vegetarian		5	6.5

N, number of patients; %, percentage

determined by using commercial kit (Agappe Diagnostics, India). The activity of LCAT was assayed by the method of Legraud et al. [25] with modifications by Hitz et al. [26]. Concentration of serum sodium and potassium were determined by flame photometery [27]. Magnesium was determined by atomic absorption spectrophotometer. Activity of Na^+, K^+-ATPase in erythrocyte membrane was determined by the method of Bonting [28]. Ca^{2+}-ATPase was estimated as described by the method of Hjerten and Pan [29]. Mg^{2+}-ATPase was assayed by the method of Ohnishi et al. [30].

Statistical analysis

The experimental data were analyzed for significant differences by independent student *t*-test and paired *t*-test using Statistical Package for Social Sciences (SPSS, version 11.0, Chicago, USA). Values were expressed as mean ± standard deviation (SD). *P* value <0.05 was considered statistically significant.

Results

Table 1 depicts the characteristics of TAM-treated patients. Group I, comprised of healthy age and socio-economically matched postmenopausal women. Group II subjects were newly diagnosed and untreated postmenopausal women with breast cancer. Group III, IV and V are same patients followed on supplementation therapy for over a period of 90 days. The values of hepatic and renal function parameters are depicted in Tables 2 and 3. A significant ($P < 0.001$) decrease in serum protein, albumin and uric acid levels were observed in untreated Group II subjects, when compared to control Group I subjects, while γ-GT levels were significantly ($P < 0.05$) increased. TAM treated Group III subjects showed a mild increase in total protein, albumin and uric acid levels, however unfavorably increased ($P < 0.05$) serum bilirubin, SGOT, SGPT and γ-GT levels in group III subjects as compared to untreated and control subjects. On exogenous supplementation of CoQ_{10}, Niacin and Riboflavin along with TAM favorably decreased the serum bilirubin, SGOT ($P < 0.001$), SGPT ($P < 0.01$), and γ-GT ($P < 0.01$) levels while mildly increasing ($P < 0.05$) the uric acid concentration. No significant alterations were observed with respect to alkaline phosphatase, sugar, urea and creatinine levels in any of the groups.

The activity of lipid metabolizing enzymes such as lipoprotein lipase (LPL) and lecithin: cholesterol acyl transferases (LCAT) are expressed in Table 4. Group II patients showed a highly significant ($P < 0.001$) reduction in the activity of these enzymes when compared with their age-matched control (Group I). TAM therapy further, significantly ($P < 0.001$) decreased the activity of LPL when compared with the untreated breast cancer patients, whereas LCAT activity was mildly increased. The interesting observation of this study is that, combination therapy treated patients (Group V) experienced a significant ($P < 0.001$) increase in the activity of LPL as compared with TAM alone treated patients. Group V patients also showed a profound increase ($P < 0.01$) in LCAT activity, which was more than that of TAM alone treatment when compared with Group II patients. The values of serum minerals and membrane bound ATPases are depicted in

Table 2 Effect of Coenzyme Q_{10}, Niacin and Riboflavin on liver function test in postmenopausal breast cancer patients treated with Tamoxifen

Parameters U/L	Group I Control, normal age-matched, postmenopausal women (46)	Group II Untreated breast cancer women (78)	Group III Treatment with Tamoxifen (78)	Group IV 45 days after treatment with CoQ_{10}, Riboflavin and Niacin along with Tamoxifen (78)	Group V 90 days after treatment with CoQ_{10}, Riboflavin and Niacin along with Tamoxifen (78)
Bilirubin (T) (mg/dl)	0.67 ± 0.78	0.71 ± 0.07$^{a\ NS}$	0.98 ± 0.11$^{b***,\ c***}$	0.86 ± 0.09$^{d\ NS}$	0.81 ± 0.08$^{e\ NS,\ f\ NS}$
Total protein (g/dl)	7.41 ± 1.07	5.86 ± 0.87^{a***}	6.56 ± 0.78$^{b\ NS,\ c*}$	7.74 ± 0.91$^{d\ NS}$	7.91 ± 1.04$^{e*,\ f\ NS}$
Albumin (g/dl)	4.31 ± 0.57	2.98 ± 0.47^{a***}	3.88 ± 0.49$^{b\ NS,\ c*}$	4.41 ± 0.51$^{d\ NS}$	4.51 ± 0.42$^{e*,\ f\ NS}$
SGOT	22.17 ± 3.40	26.36 ± 3.19$^{a\ NS}$	34.17 ± 3.36$^{b***,\ c**}$	23.41 ± 3.12^{d***}	21.78 ± 2.79$^{e***,\ f\ NS}$
SGPT	15 ± 1.82	19.24 ± 2.10$^{a\ NS}$	23.17 ± 2.74$^{b***,\ c**}$	18.42 ± 2.77^{d**}	18.11 ± 2.57$^{e**,\ f\ NS}$
ALP	78.18 ± 8.76	98.41 ± 10.95$^{a\ NS}$	87.12 ± 11.51$^{b\ NS,\ c\ NS}$	86.47 ± 14.78$^{d\ NS}$	85.27 ± 14.24$^{e\ NS,\ f\ NS}$
γ-GT	21.17 ± 3.18	27.89 ± 3.32^{a*}	34.97 ± 3.38$^{b***,\ c**}$	27.11 ± 4.42^{d**}	24.27 ± 3.71$^{e***,\ f\ NS}$

Values are expressed as mean ± SD. Number of subjects are indicated in parentheses

Comparisons were made between: [a] Group I and Group II; [b] Group I and Group III; [c] Group II and III; [d] Group III and IV; [e] Group III and Group V; and [f] Group I and V

Statistical significance expressed as * $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$; NS, non significant

Table 3 Effect of Coenzyme Q_{10}, Niacin and Riboflavin on renal function test in postmenopausal breast cancer patients treated with Tamoxifen

Parameters	Group I Control, normal age-matched, postmenopausal women (46)	Group II Untreated breast cancer women (78)	Group III Treatment with Tamoxifen (78)	Group IV 45 days after treatment with CoQ_{10}, Riboflavin and Niacin along with Tamoxifen (78)	Group V 90 days after treatment with CoQ_{10}, Riboflavin and Niacin along with Tamoxifen (78)
Sugar (mg/dl)	75.28 ± 13.46	82.42 ± 15.17$^{a\ NS}$	85.31 ± 14.51$^{b\ NS,\ c\ NS}$	84.17 ± 13.36$^{d\ NS}$	86.28 ± 12.46$^{e\ NS,\ f\ NS}$
Urea (mg/dl)	28.42 ± 4.01	35.27 ± 4.51$^{a\ NS}$	32.25 ± 4.23$^{b\ NS,\ c\ NS}$	30.27 ± 4.41$^{d\ NS}$	30.36 ± 4.51$^{e\ NS,\ f\ NS}$
Creatinine (mg/dl)	0.71 ± 0.09	0.86 ± 0.17$^{a\ NS}$	0.81 ± 0.09$^{b\ NS,\ c\ NS}$	0.76 ± 0.07$^{d\ NS}$	0.74 ± 0.07$^{e\ NS,\ f\ NS}$
Uric Acid (mg/dl)	4.37 ± 0.47	3.06 ± 0.36^{a***}	3.31 ± 0.39$^{b**,\ c\ NS}$	4.46 ± 0.51^{d*}	4.55 ± 0.55$^{e*,\ f\ NS}$

Values are expressed as mean ± SD. Number of subjects are indicated in parentheses

Comparisons were made between: [a] Group I and Group II; [b] Group I and Group III; [c] Group II and III; [d] Group III and IV; [e] Group III and Group V; and [f] Group I and V

Statistical significance expressed as * $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$; NS, non significant

Tables 5 and 6 respectively. A significantly ($P < 0.05$) decreased levels of serum sodium and all the membrane bound ATPases were observed in untreated breast cancer patients as compared to their normal counterparts, while the other serum minerals namely potassium, calcium and magnesium were significantly ($P < 0.001$) elevated. TAM administration favorably ameliorated the altered mineral and membrane bound ATPases levels, which was further corrected to near normal level on combinatorial therapy.

Discussion

More than 30 years of use of TAM is a testimony to its efficacy and overall safety profile. The side effect profile of TAM is well-known and well documented over the years; unlike AIs where the maximum median follow-up is less than 7 years. Of critical importance, is the fact that bone mass and bone density are favorably affected by TAM. This assumes significance in elderly postmenopausal patients when the bone density is already low [31]. As suggested by the EBCTCG analysis, the effect of TAM persists long after the drug has been stopped after 5 years, called as the "carry over phenomenon," while the absolute advantage in overall survival at 5 years in the TAM and no TAM arms is 4%, this difference increases to 9% at 15 years [32]. Such an effect has yet to be demonstrated by AIs. Under these circumstances the results of our study show that the deranged biochemical parameters with respect to serum total bilirubin, SGOT, SGPT, γ-GT and LPL in TAM treated group was ameliorated to normal level on co-administration of TAM with CoQ_{10}, Riboflavin and Niacin.

Table 4 Effect of Coenzyme Q_{10}, Niacin and Riboflavin on plasma lipid metabolizing enzymes in postmenopausal breast cancer patients treated with Tamoxifen

Parameters	Group I Control, normal age-matched, postmenopausal women (46)	Group II Untreated breast cancer women (78)	Group III Treatment with Tamoxifen (78)	Group IV 45 days after treatment with Co Q_{10}, riboflavin and niacin along with Tamoxifen (78)	Group V 90 days after treatment with Co Q_{10}, riboflavin and niacin along with Tamoxifen (78)
Lipoprotein lipase (μM free fatty acids liberated/ml plasma/h)	5.91 ± 0.60	4.85 ± 0.51[a]***	3.81 ± 0.33[b]***, [c]**	5.15 ± 0.57[d]***	5.47 ± 0.58[e]***, [f] NS
Lecithin: cholesterol acyl transferase (nM cholesterol esterified/ml plasma/h)	57.91 ± 5.97	44.88 ± 4.81[a]***	47.50 ± 5.73[b]***, [c] NS	53.47 ± 6.62[d] NS	54.91 ± 6.87[e] NS, [f] NS

Values are expressed as mean ± SD. Number of subjects are indicated in parentheses

Comparisons were made between: [a] Group I and Group II; [b] Group I and Group III; [c] Group II and III; [d] Group III and IV; [e] Group III and Group V; and [f] Group I and V

Statistical significance expressed as * $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$; NS, non significant

Table 5 Effect of Coenzyme Q_{10}, Niacin and Riboflavin on serum minerals in postmenopausal breast cancer patients treated with Tamoxifen

Parameters	Group I Control, normal age-matched, postmenopausal women (46)	Group II Untreated breast cancer women (78)	Group III Treatment with Tamoxifen (78)	Group IV 45 days after treatment with CoQ_{10}, Riboflavin and Niacin along with Tamoxifen (78)	Group V 90 days after treatment with CoQ_{10}, Riboflavin and Niacin along with Tamoxifen (78)
Sodium (M.Equi/l)	143.54 ± 16.65	112.45 ± 16.23[a]*	126.21 ± 14.26[b] NS, [c] NS	136.31 ± 14.21[d] NS	137.27 ± 14.71[e] NS, [f] NS
Potassium (M.Equi/l)	4.51 ± 0.51	6.67 ± 0.62[a]***	5.71 ± 0.60[b]**, [c]*	4.62 ± 0.52[d]*	4.56 ± 0.53[e]*, [f] NS
Calcium (mg/dl)	9.23 ± 1.41	13.27 ± 1.47[a]***	11.81 ± 1.22[b]*, [c] NS	10.51 ± 1.29[d] NS	10.44 ± 1.38[e] NS, [f] NS
Magnesium (mg/dl)	2.72 ± 0.30	3.67 ± 0.38[a]***	3.01 ± 0.35[b] NS, [c]*	2.78 ± 0.29[d] NS	2.41 ± 0.26[e] NS, [f] NS

Values are expressed as mean ± SD. Number of subjects are indicated in parentheses

Comparisons were made between: [a] Group I and Group II; [b] Group I and Group III; [c] Group II and III; [d] Group III and IV; [e] Group III and Group V; and [f] Group I and V

Statistical significance expressed as * $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$; NS, non significant

Disturbance or strain rendered to the liver cells breaks the membrane and the cell organelles, hence leaking the liver enzymes (SGOT, SGPT and ALP) into the circulation. These liver enzymes under cancer condition talks about the involvement of metastasis, stage and prognosis of the disease. In the present study, a significant increase in γ-GT levels with decrease in albumin, protein and uric acid levels were found in the untreated breast cancer patients when compared to control subjects. The observed significant increase in S. BIL, SGOT, SGPT and γ-GT levels in TAM treated patients depicts TAM-induced hepatotoxicity which is in line with several published reports [33–35]. The observed elevated levels of the above marker enzymes on TAM-treatment could be attributed to the higher affinity of TAM for hepatic tissues than any other tissues, forming DNA adducts and initiating carcinogenesis [36]. Combinatorial therapy of TAM with CoRN significantly decreased the elevated liver parameters SGPT, SGOT and γ-GT to near normal levels, while increasing the albumin, total protein and uric acid levels. Riboflavin administration was found to increase the total flavins which have the capacity to capture reactive metabolites of TAM and other carcinogens to form a complex and thereby prevent formation of DNA adducts [18]. Recent experimental studies have shown the prevention of TAM induced hepatotoxicity by decrement of aminotransferase to near normal levels on exogenous supplementation with antioxidants. Riboflavin and Niacin neutralize hydroxyl and superoxide radicals [37, 38], while CoQ_{10} quenches singlet oxygen and polyunsaturated fatty acid radicals [39]. CoQ_{10} also helps in regeneration of Vitamin C and Vitamin E in conjunction with Niacin and Riboflavin to boost glutathione

Table 6 Effect of Coenzyme Q_{10}, Niacin and Riboflavin on erythrocyte membrane bound adenosine triphosphatases in postmenopausal breast cancer patients treated with Tamoxifen

Parameters (μM Pi liberated/mg protein/min)	Group I Control, normal age-matched, postmenopausal women (46)	Group II Untreated breast cancer women (78)	Group III Treatment with Tamoxifen (78)	Group IV 45 days after treatment with Co Q_{10}, riboflavin and niacin along with Tamoxifen (78)	Group V 90 days after treatment with Co Q_{10}, riboflavin and niacin along with Tamoxifen (78)
Na^+K^+-ATPase	0.532 ± 0.05	0.454 ± 0.04[a]*	0.493 ± 0.05[b]*, [c]*	0.517 ± 0.53[d]*	0.527 ± 0.05[e]*, [f] NS
Ca^{2+}-ATPase	0.241 ± 0.03	0.186 ± 0.02[a]**	0.213 ± 0.02[b] NS, [c]*	0.223 ± 0.02[d]*	0.238 ± 0.02[e]*, [f] NS
Mg^{2+}-ATPase	0.834 ± 0.08	0.662 ± 0.07[a]*	0.753 ± 0.08[b] NS, [c] *	0.787 ± 0.08[d]*	0.813 ± 0.09[e]*, [f] NS

Values are expressed as mean ± SD. Number of subjects are indicated in parentheses

Comparisons were made between: [a] Group I and Group II; [b] Group I and Group III; [c] Group II and III; [d] Group III and IV; [e] Group III and Group V; and [f] Group I and V

Statistical significance expressed as * $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$; NS, non significant

metabolism. CoQ10 and Riboflavin have also shown to have nephro-protective effect by alleviating its deficiencies [40–42]. Experimental studies have shown TAM to have renal toxicities in rat kidney by formation of DNA adducts in kidney, a gender based toxicity screening of TAM in experimental animals showed that female rats were found to be highly susceptible to renal toxicity with high creatinine levels, when compared to their male counterparts [43], and enhanced urinary bladder tumor formation in conjunction with arsenic [44, 45]. However, in our study apart from a mild decrease in uric acid concentration, we did not find any significant change with respect to renal parameters in untreated and TAM treated group when compared to control subjects.

Altered lipid composition in malignant condition modifies the activity of certain lipid metabolizing enzymes which leads to striking changes in the pattern of integrated metabolism which may be the reason for the observed levels in the untreated group. Vitamin C deficiency observed in the cancer condition could also account for depressed LPL activity [8, 46]. An important observation of this study is that, during TAM treatment, the activity of LPL is reduced significantly in postmenopausal breast cancer women, while lecithin: cholesterol acyl transferase (LCAT) was slightly increased. The reason for abnormally decreased LPL activity may be attributed to alteration in apo cII, the apoprotein that regulates LPL activity [47]. Takagi et al. have also observed that LPL deficiency in patients with hypertriglycerdemia [48]. Combination therapy of CoRN with TAM increased the lipid metabolizing enzyme activity with augmentation of ascorbic acid and Vitamin E levels [8]. As discussed earlier, CoQ_{10} may form a redox interaction with other lipid-soluble antioxidants such as vitamin E by regenerating it from its phenoxyl radical form which increases the LPL and LCAT activity [49]. Love et al. have also proposed that TAM treatment to postmenopausal breast cancer women increases the concentration of apo AI, which in turn may increase LCAT activity [50]. Niacin, CoQ_{10} and Vitamin E plays a prominent role in the transesterification reaction, thus reducing the triglycerides in the VLDL component [51].

In the present study a significant decrease in serum sodium with increase in potassium, calcium and magnesium levels were observed in untreated group, which was favorably modulated to near normal level by sole TAM and combinatorial therapy. Active calcium transport and resultant low calcium concentration are the necessary conditions for active Na^+, K^+ transport. Since, sodium and calcium are thought to be competitive at number of membrane sites; it seems likely that high concentration of Ca^{2+} in cancer cells competes with sodium at sodium specific sites at the inner surface of the membrane [52] and this may be reason for the observed decreased sodium levels in the untreated group. Also, failure of sodium pump results in a depletion of plasma sodium and rise in plasma potassium concentration. This leads to hyponatremia and hypercalcemia which are the most common electrolytic abnormalities in cancer conditions. The components of combination therapy (CoQ_{10}, Niacin and Riboflavin) reduce the calcium level in the extra cellular fluids. Vitamin E seems to prevent the calcium release from the storage vesicles, which is augmented by CoQ_{10} [8, 53]. Moreover, combination therapy components, especially Riboflavin by excessively increasing the concentration of reduced glutathione successfully counter the release of calcium from the storage vesicles [54]. The calcium lowering potential of combination therapy components, in turn prevents high calcium induced peroxidative damage and hence, prevents the formation of echinocytes (rich in diacylglycerol, the peroxidative product of membrane phospholipids) and subsequent reactions that end in cell lysis. The overall amelioration effect of the combinatorial therapy may normalize sodium potassium pump thus, regulating the sodium and potassium contents to more

normal convenient levels. Erythrocyte membrane Na^+, K^+-ATPase, Ca^{2+}-ATPase and Mg^{2+}-ATPase regulates intracellular ion homeostasis. The activities of these membrane ATPases are greatly affected by free radicals, lipid peroxides and ATP levels. The observed significant decrease of all the ATPases in the untreated group might be due to the elevated lipid peroxidation and reduced ATP synthesis under cancer condition [55]. TAM by its membrane stabilizing property and anti-lipid peroxidation property favorably increased the membrane ATPases, which was further increased to normal level on combinatorial therapy.

Overall, the data from this study suggest that TAM on CT with CoRN has a favorable impact with respect to various blood chemistry profiles (mainly liver and lipid parameters). Though there has been wider acceptance and documented evidence of favorable impact of CT of antioxidants along with conventional chemotherapy, fewer studies do have contradictory findings of antioxidants having no impact on overall disease-free survival. It will take a large scale randomized study over a longer time span to ascertain the accuracy of this scenario.

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