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Serum Cytokine Levels of Interleukin-1β, -6, -8, Tumour Necrosis Factor-α and Vascular Endothelial Growth Factor in Breast Cancer Patients Treated with Tamoxifen and Supplemented with Co-Enzyme Q_{10}, Riboflavin and Niacin

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Abstract: The prognostic significance of supplementing co-enzyme Q_{10} (CoQ_{10}), riboflavin and niacin (CoRN) along with tamoxifen to breast cancer patients was evaluated by measuring the serum cytokine levels of interleukin (IL)-1β, IL-6, IL-8, tumour necrosis factor α (TNF-α) and vascular endothelial growth factor. In the present study, 84 breast cancer patients were randomized to receive a daily supplement of CoQ_{10} 100 mg, riboflavin 10 mg and niacin 50 mg, one dosage per day along with tamoxifen 10 mg twice a day. Serum cytokine levels were elevated in untreated breast cancer patients (Group II) and significantly reduced after tamoxifen therapy for more than 1 year (Group III). When group III breast cancer patients were supplemented with CoRN for 45 days (Group IV) and 90 days (Group V) along with tamoxifen, a significant reduction in cytokine levels were observed ($P < 0.05$). Such a decrease in serum cytokine levels after CoRN supplementation in breast cancer patients may suggest good prognosis and efficacy of the treatment, and might even offer protection from metastases and recurrence of cancer.

Breast cancer is the most common cause of cancer-related deaths in women particularly in industrialized nations, and it is a significant public health problem. Although significant improvements in therapy have occurred recently, most deaths from breast cancer are still caused by metastases that are resistant to conventional treatment. Therefore, novel approaches to the management of breast cancer need to be developed [1].

Tamoxifen is a non-steroidal anti-oestrogen drug, which has led to an increase in both disease-free and overall survival of breast cancer patients after primary surgery [2]. A complicating factor is the relapse in breast cancer patients during tamoxifen therapy and in this subset of patients, treatment is only palliative and the recurrent breast cancer is incurable [3].

Earlier studies in our laboratory with co-enzyme Q_{10} (CoQ_{10}), riboflavin and niacin (CoRN) supplementation in rat mammary carcinoma was found to enhance antitumour activity by increasing the expression of the tumour suppressor gene MnSOD (manganese superoxide dismutase), thereby preventing cancer cell proliferation. It has also been to restore lipid peroxide levels and activities of the enzymatic and non-enzymatic antioxidants to near normal, thus demonstrating its mitochondrial antioxidant activity [4]. CoRN supplementation was found to prevent cancer cachexia by inhibiting host energy loss by increasing the gluconeogenesis pathway by the cofactors [flavin mononucleotide (FMN), flavin adenine dinucleotide (FAD^+), nicotinamide adenine dinucleotide (NAD^+), NADH, co-enzyme Q] of CoRN, which participate in oxidation-reduction reactions, numerous metabolic pathways and thereby enhance glycolysis, Kreb's cycle and adenosine triphosphate (ATP) production via the electron transport chain in the host tissue [5].

Cytokines stimulate cancer cell growth and contribute to locoregional relapse and metastases [6]. Permanent synthesis and release of these cytokines lead to increased serum cytokine concentration and act as markers of immunity status and immune system activation for prognosis and monitoring the course of cancer progression [7]. Angiogenesis is the formation of new blood vessels from the existing vasculature and is essential for the growth and metastasis of many solid tumours, including breast cancer. Expression of angiogenic cytokines in breast tumour correlates directly with the degree of the tumour and is an independent indicator of nodal metastases and disease-free survival [8]. Hence, in this study breast cancer patients undergoing tamoxifen therapy with CoRN were evaluated for their disease prognosis by measuring the serum cytokine levels of interleukin (IL)-1β, IL-6, IL-8, tumour necrosis factor α (TNF-α) and vascular endothelial growth factor (VEGF).

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Materials and Methods

Patients were recruited from the Medical Oncology Department of the Government Royapettah Hospital, Chennai, India, via their physicians

Table 1.

Characteristic of breast cancer patients in study Groups III, IV and V.

Characteristics	Number of patients	Percentage of patients
Age (years)		
Median – 57 years		
Range – 43–70 years		
Tumour size (T)		
T1	4	5
T2	33	39
T3	26	31
T4	21	25
Nodal status (N)		
N0	26	30.9
N1	44	52.4
N2	13	15.5
N3	1	1.2
N4	0	0
Metastasis (M)		
M0	84	100
M1	0	0
Histology		
Ductal invasive	82	97.6
Lobular invasive	2	2.4
Surgery		
Conservative	2	2.4
Mastectomy		
Simple	11	13
Radical	2	2.4
Modified radical	56	66.6
Patey's	10	12
Modified Patey's	1	1.2
No surgery	2	2.4
Family history of cancer		
Yes	9	10.7
No	75	89.3
Diet		
Mixed	80	95.2
Vegetarian	4	4.8
Treatment		
Tamoxifen alone	8	9.5
Chemotherapy + tamoxifen	40	47.6
Radiation + tamoxifen	26	31
Chemotherapy + radiation + tamoxifen	10	11.9

according to the process approved by the Institutional Human Ethical Review Board. Informed consent was obtained from all patients with due explanation of the study. They were aged 43 to 70 years with histopathology-confirmed breast cancer. Patients with diabetes mellitus, renal and hepatic diseases were excluded from this study. Patients' characteristics are given in table 1.

Study design. Three different groups of patient were recruited in the Groups I, II and III: Group I: 42 socio-economically and age-matched disease-free, healthy controls; Group II: 84 untreated breast cancer patients; Group III: 84 breast cancer patients treated for more than 1 year with tamoxifen; Group IV and V: Group III patients followed up for 45 days (Group IV) and 90 days (Group V) after supplementation with CoQ_{10} (100 mg), riboflavin (10 mg) and niacin (50 mg) one dosage per day along with tamoxifen (10 mg twice a day).

Patients were advised to take one capsule of CoQ_{10} (100 mg Kaneka® Q10, Kaneka Corporation, Osaka, Japan), one tablet of riboflavin and niacin (10 mg riboflavin and 50 mg niacin, Madras Pharmaceuticals, Chennai, India) and two tablets of tamoxifen (10 mg Nolvadex®, AstraZeneca, Bangalore, India) per day. All tablets were taken after breakfast, with a second tablet of tamoxifen after dinner. The patients were asked not to take any vitamin supplement during the study period. Compliance was checked by counting the number of tablets handed out to the patients and recollected at the end of the study.

Blood collection and cytokine assay. Five millilitre of blood was collected in a serum separator tube (Vacutainer; Becton Dickinson, Rutherford, NJ, USA) and immediately centrifuged after clotting at 500 g for 10 min. Serum samples were aliquoted in 1.0 ml fractions and were stored at –80°C. Serum cytokine levels were determined using the enzyme-linked immunosorbent assay (ELISA) kit according to the instructions provided by the manufacturer. The standard curves were prepared by using a group of serially diluted standards.

Serum IL-β level was determined using enzyme immunoassay (EIA) IL-1β kit (Immunotech SAS, Marseille, France), serum IL-6 (Quantikine, human IL-6 immunoassay; R&D Systems, Minneapolis, MN, USA), serum IL-8 (Quantikine, human IL-8 immunoassay; R&D Systems). TNF-α level was determined using ELISA kit and serum VEGF (Quantikine, human VEGF immunoassay; R&D Systems).

Statistical analysis were analysed with one-way analysis of variance (ANOVA) followed by least significant difference (LSD) test using Statistical Package for Social Science version 10.0 (SPSS, Chicago, IL, USA). Values are expressed as mean ± standard deviation. The values were considered statistically significant if the P-value was less than 0.05.

Results

The serum concentration of IL-1β, IL-6, IL-8, TNF-α and VEGF were compared between all the study groups and shown in table 2. Group II patients had serum cytokine levels of 340 ± 85.77 pg/ml (IL-1β), 26.8 ± 7.88 pg/ml (IL-6), 158.2 ± 46.55 pg/ml (IL-8), 28.6 ± 7.99 pg/ml (TNF-α) and 564.5 ± 147.88 pg/ml (VEGF), which were found to be significantly increased ($P < 0.05$) when compared to other groups. Group III patients treated with tamoxifen for more than 1 year had serum cytokine levels of 122.5 ± 30.89 pg/ml (IL-1β), 12.6 ± 5.25 pg/ml (IL-6), 78.2 ± 25.52 pg/ml (IL-8), 20.20 ± 5.69 pg/ml (TNF-α) and 337.20 ± 85.55 pg/ml (VEGF), which were found to be significantly reduced ($P < 0.05$) when compared to Group II, untreated patients. Group IV patients had serum cytokine levels of 45.3 ± 14.02 pg/ml (IL-1β), 6.2 ± 2.41 pg/ml (IL-6), 28.5 ± 17.85 pg/ml (IL-8), 9.2 ± 3.17 pg/ml (TNF-α), and 177.9 ± 50.6 pg/ml (VEGF). Group V patients had serum cytokine levels of 41.2 ± 11.17 pg/ml (IL-1β), 5.8 ± 1.97 pg/ml (IL-6), 21.8 ± 11.39 pg/ml (IL-8), 8.7 ± 2.95 pg/ml (TNF-α) and 164.2 ± 44.69 pg/ml (VEGF). Group IV and V patients who were supplemented with CoRN along with tamoxifen for 45 and 90 days, respectively, had serum cytokine levels significantly reduced ($P < 0.05$) compared to Group II and Group III patients.

Compliance was estimated to be 100% in all the patients, based on counting the remaining CoRN tablets at the end of the study. The supplements were well tolerated and no side-effects were reported by any of the participants.

Table 2.
Comparison of cytokines interleukin (IL)-1β, IL-6, IL-8, tumour necrosis factor α (TNF-α) and vascular endothelial growth factor (VEGF) levels in breast cancer patients and controls.

	Groups					P-value comparison between groups								
	Group I (42)	Group II (84)	Group III (84)	Group IV (84)	Group V (84)	I/II	I/III	I/IV	I/V	II/III	II/IV	II/V	III/IV	III/V
IL-1β	26.5 ± 7.88	340 ± 85.77	122.5 ± 30.89	45.3 ± 14.02	41.2 ± 11.17	0.000	0.001	0.442	0.547	0.000	0.000	0.000	0.004	0.002
IL-6	3.2 ± 0.876	26.8 ± 7.88	12.6 ± 5.25	6.2 ± 2.41	5.8 ± 1.97	0.000	0.001	0.257	0.324	0.000	0.000	0.000	0.020	0.014
IL-8	5.3 ± 2.84	158.2 ± 46.55	78.2 ± 25.52	28.5 ± 17.85	21.8 ± 11.39	0.000	0.000	0.129	0.275	0.000	0.000	0.000	0.002	0.001
TNF-α	5.2 ± 1.42	28.6 ± 7.99	20.2 ± 5.69	9.2 ± 3.17	8.7 ± 2.95	0.000	0.000	0.165	0.222	0.006	0.000	0.000	0.001	0.000
VEGF	122.8 ± 35.6	564.5 ± 147.88	337.2 ± 85.55	177.9 ± 50.6	164.2 ± 44.69	0.000	0.000	0.265	0.400	0.000	0.000	0.000	0.003	0.001

Units of measure for all the tests were pg/ml. Number in parentheses represent number of patients. Least significant difference (LSD) was used to validate the differences. The values were considered significant if the P-value was less than 0.05.

Discussion

The incidence of breast cancer is almost identical all over the world, but the incidence of its clinical malignant state is much higher in Western countries [9]. Dietary and environmental factors are thought to play a role in the progression of a tumour from its latent into its clinical phase and if certain dietary factors and supplements delay tumour progression in the latent phase, it is not unlikely that they may also be effective in delaying tumour progression in an established tumour [10].

In this study, supplementation of CoRN to breast cancer patients was found to decrease the serum cytokine levels of IL-1β, IL-6, IL-8, TNF-α and VEGF. A reduction in serum cytokine levels contribute to reduction in tumour burden [6]. CoQ_{10} plays an important role in electron transport chain [11], functions as an antioxidant, prevents lipid peroxidation [12] and increases the phagocytic activity in tumour-induced mice [13]. Several clinical trials administering CoQ_{10} to cancer patients have indicated a tumour-suppressive effect [14–17]. In breast cancer patients, CoQ_{10} (90 mg/day) administration showed complete regression and an increased dose of 390 mg/day of CoQ_{10} for 5 years showed complete regression of metastases in these patients [16]. CoQ_{10} was found to increase the levels of serum IgG in patients, which is attributed to the increase in transcriptional and translational increase in the levels of CoQ_{10} apoenzymes [13].

Riboflavin influences epithelial integrity, tissue flavin concentrations, rate of prostaglandin biosynthesis and glutathione metabolism [18]. Riboflavin administration was found to decrease the risk of developing cancer by increasing the levels of total flavins, which has the capacity to capture reactive metabolites thereby decreasing the carcinogen binding to cellular macromolecules like DNA [19]. Riboflavin deficiency enhances the risk of oesophageal cancer development at the initiation and promotion stages [18]. In addition to redox functions in energy metabolism, niacin, in the form of NAD^+ participates in a variety of adenosine diphosphate (ADP)-ribosylation reactions, which is responsible for the majority of polymer synthesis and which plays an important role in DNA-damage response including repair, maintenance of genomic stability and signalling events of apoptosis [20,21].

High levels of serum cytokines are associated with resistance to chemo-endocrine therapy and poor prognosis in breast cancer patients [22]. Cytokines are low molecular weight glycoproteins secreted by inflammatory and tumour cells, which can regulate cell functions in an autocrine or paracrine fashion [23]. IL-1β is a pro-inflammatory regulatory cytokine, which plays a key role in breast cancer progression by regulating the functions of tissue and immune cells within the tumour microenvironment via expression of IL-1β receptors. IL-1β is known to induce the expression of a wide number of cytokines including angiogenic cytokine IL-8 [24]. IL-6 not only regulates VEGF expression, but increases aromatase activity in both stromal cells and tumour cells. IL-6 promotes osteoclast formation and inhibits dendritic cell differentiation, thus facilitating metastatic growth,

promotes cell migration by activating mitogen-dependent protein kinase pathway and inhibits apoptosis [25]. TNF-α induces IL-6 production by macrophages and other cell types and conversely, IL-6 can inhibit TNF-α secretion by mononuclear cells. Pro-inflammatory cytokines such as TNF-α and IL-6 could exert a potential role in promoting the local recurrence of breast cancer [26]. IL-8 is an angiogenic chemokine, which plays an autocrine role in modulating survival and proliferation of tumour cells; its expression is enhanced by VEGF and both are modulated by hypoxia [27]. Serum VEGF stimulates proliferation of tumour blood vessels and increases vascular permeability, which contributes to tumour cell extravasations and metastasis formation. High serum levels of VEGF reflect a large tumour mass or a rapid rate of angiogenesis due to greater vascular permeability [28].

Serum cytokine levels were found to be very high in breast cancer untreated Group II when compared to the other groups and our findings are in accordance with earlier studies, which have reported elevated serum cytokine levels in pre-operative and untreated breast cancer patients when compared to treated patients [27–30].

Group III patients treated for more than 1 year with tamoxifen had serum cytokine levels significantly reduced ($P < 0.05$) compared to Group II. The results showing beneficial effect of tamoxifen on breast cancer patients are in line with earlier studies, which have proved that the antitumour activity of tamoxifen is due to its anti-oestrogenic activity, mediated by competitive inhibition of oestrogen binding to oestrogen receptors [31]. Consequently, tamoxifen inhibits the expression of oestrogen-regulated genes, including growth factors and angiogenic factors secreted by the tumour that may stimulate growth by autocrine or paracrine mechanisms [32].

When Group III patients were subsequently treated with CoRN for 45 days (Group IV) and 90 days (Group V), there was a significant decrease ($P < 0.05$) in cytokine levels. These results are in accordance with earlier reports, which have shown that CoQ_{10}, riboflavin and niacin decrease the cytokine levels [33–35]. CoQ_{10} has been reported to protect the skin from free-radical damage by suppressing the increased levels of IL-1, IL-6, matrix metalloproteins and prostaglandin-E2 [33]. Riboflavin produces antiseptic effect by decreasing the level of pro-inflammatory cytokines IL-1β, TNF-α, IL-6, IL-8, monocyte chemotactic protein-1, γ-interferon and inducible nitric oxide synthase [34]. Treatment with niacin possibly attenuated the bleomycin-induced increase in pro-inflammatory cytokines such as IL-1, TNF-α and IL-6 and thereby shows its antifibrotic activity in preventing lung fibrosis [35].

In conclusion, this study suggests that serum levels of IL-1β, IL-6, IL-8, TNF-α and VEGF, which are stimulators of angiogenesis as well as factors for cancer cell proliferation and growth, are reduced after CoRN supplementation. Thus, supplementation of CoRN to tamoxifen therapy may provide a better prognosis by reducing the risk of cancer recurrence and metastases. More importantly, the relation between dietary supplementation and cancer treatment may also have therapeutic implications in the future.

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