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Impact of Occupational Exposure to Low Dose Ionizing Radiation versus High Dose Exposure during Radiotherapy on Met Hb Levels

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ABSTRACT

Background: Ionizing radiation affects human health as it breaks the chemical bonds of the molecules and damages DNA through the manufacturing of free radicals, resulting in apoptosis of proliferative cells/ damage to erythrocytes which may influence the quality of RBC concentrates. The aim of the present investigation is to evaluate the effect of occupational exposure to low dose ionizing radiation versus high dose exposure during radiotherapy on met Hb levels. 150 individuals were included divided into two groups; group I, includes 50 radiation workers (RWs) compared to 25 healthy volunteers' as control group for radiation workers who never exposed to radiation in their work. Group II includes 50 breast cancer patients who were treated with post-operative radiotherapy compared to 25 matched age and sex healthy female volunteers' as control group who had never worked in radiation-related jobs. Methemoglobin was assayed by ELISA. Significant decrease in MCV and serum ferritin was observed among RWs in comparison to the control group. Methemoglobin levels and Reticulocyte % were significantly higher in RWs in comparison to the BCPs. Mean values of WBCs, HB and RBCs were significantly lower in BCPs when compared to RWs, while there was insignificant difference in the mean values of Ht, MCV, MCH and RDW. It is concluded that serum methemoglobin levels and Reticulocyte % can be used as biological markers for early assessment of the absorbed dose in radiation workers.

INTRODUCTION

The use of ionizing radiation (IR) in the medical field is a source of widespread concern. IR such as X rays, gamma (γ) rays and particles: α-particle, β-particle, protons and neutrons are being extensively used in diagnosis as well as in therapeutic use for cancer patients [1,2].

According to Mettler and Mosely (1987) [3] when a cell or tissue is exposed to radiation, several changes occur namely damage to the cell membrane through lipid peroxidation, damage to either one or both strands of deoxyribonucleic acid (DNA) & formation of free radicals which causes secondary damage to the cells. Radiation therapy can potentially cause direct damage to blood vessels by releasing reactive oxygen species (ROS), which break DNA strands and trigger an inflammatory response [4].IR exposure is known to have fatal effects on blood cells, particularly lymphocytes, which show a severe reduction (one day) after exposure and then recover [5,6]. The drop in peripheral blood cell counts that occurs within the first 48 hours of radiation exposure acts as a signal for not just the severity of the exposure, but also for therapy and prognosis [7]. When assessing radiation effects on the red bone marrow, both total dosage and dose rates must be taken into account. There is a scarcity of information on the consequences of different dosage rates for a particular accumulated dose [8]. On the other hand, Sanzari et al. [9] stated that the IR damage produces a considerable decrease in blood cell counts in a dose-dependent manner.

Methemoglobinemia is a disorder in which the methemoglobin (MetHb) level in the blood is greater than 1% of the total Hb level [10-12]. MetHb is generated when Hb is deoxygenated or when reactive oxygen species (ROS) oxidize the iron in the heme group of Hb from ferrous ($Fe2+$) to ferric ($Fe3+$) [13,14]. The erythrocyte is unable to transfer enough oxygen to

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the body tissue because the oxidized heme group is unable to link with an oxygen molecule, causing the oxygen dissociation curve to shift to the left and lowering oxygen release of other Hb molecules. Met Hb is commonly seen in concentrations of less than 1% of total Hb in RBCs which have Met Hb reductase such as cytochrome B5 reductase (CYB5R) which converts the Met Hb back to Hb [10,15].

The present study aims to evaluate the met Hb level in workers exposed to low dose ionizing radiation compared to breast cancer patients receiving high dose during radiotherapy.

SUBJECTS AND METHODS

The present study included 150 individuals divided into: 50 hospital RWs (Mean±SD of age 31.73 ± 5.69) exposed to small dose at least for two years matched by age & sex with 25 non-smokers healthy volunteers as a control group who were never exposed to radiation in their work (Mean±SD of age is 36.12 ± 5.07). Patients with breast cancer received post-operative high-dose radiation, with a dose of 44 Gray delivered in a daily fraction of 2.75 Gray given five times a week, were 50 in number matched by age & sex with 25 female healthy volunteers' as control group for them who never exposed to radiation in their work. Patients were chosen from those admitted to the University of Alexandria, Medical Research Institute. All BCPs were treated surgically with a modified radical mastectomy followed by adjuvant chemotherapy. After finishing chemotherapy, patients with breast cancer received post-operative high-dose radiation, with a dose of 44 Gray. Radiation therapy was delivered using a linear accelerator (LINAC) which customizes high energy X-rays.

The radiation workers were selected from Diagnostic Radiology and Radiotherapy Departments in Bahia hospital and National Cancer Institute, Cairo, Egypt. They worked six days a week, six hours each day for at least 2 to 6 years. The range of radiation dose was 1.2 – 6.0 mSV/year. Within the six months prior to blood collection, neither of them had received chemotherapeutic medications nor been exposed to ionizing radiation for diagnostic or therapeutic purposes. Personal dosimeters (film badge and pocket dosimeter) were used to measure the annual accumulated effective dosage. According to the Ethical Guidelines of the Medical Research Institute, Alexandria University, all participants were requested to freely volunteer for the study and informed written consents were obtained prior to their participation in the study. RWs with autoimmune illnesses, acute or chronic infections, a history of cancer, diabetes, heart disease, sepsis, hemolytic disorder, chronic renal failure, acute liver failure, smokers, or those taking oxidizing medicines were excluded from the study.

METHODS

A 5 ml venous blood sample were collected into EDTA tubes from radiation workers (during work shift), BCPs by the end of radiotherapy and from healthy controls.

All participants were subjected to the following

A detailed questionnaire concerning their habits, lifestyles, medical records and radiation exposure history. Complete blood counting (CBC) was determined by cell counter fully automated [16]. & Reticulocyte count [17]. Determination of serum ferritin levels was done by an automated quantitative enzyme linked fluorescent assay (VIDAS®). Iron was measured by colorimetric method (Biodiagnostic, Egypt) Methemoglobin concentration in plasma was estimated by enzyme-linked immunosorbent assay according to manufacture protocol (Cloud-Clone Corp, Houston, USA).

Statistical analyses

IBM SPSS software program version 20.0 was used to examine the data that was supplied into the computer (Armonk, NY: IBM Corp). The Kolmogorov-Smirnov test was employed to ensure that the distribution was normal. The independent t-test was used to compare two independent populations, and the paired t-test was used to compare two dependent populations. Correlations between the two quantitative variables were assessed using Pearson coefficient. Significance of the obtained results was judged at the 5% level.

RESULTS

Radiation dose and Working period are shown in Table (1).

Table (1): Radiation dose and working period of Radiation Workers

	Radiation Workers (n = 50)
Radiation Dose/year (mSV/year)	
Range	1.2 – 6.0
Mean ± SD	2.64 ± 1.22
Working period (Years)	
Range	1.0 – 27.0
Mean ± SD	10.20 ± 8.0

Hematological results of Radiation Workers

Range and mean ± S.D. of hematological results of radiation workers and control group showed that, the mean values of WBCs was significantly lower in RWs when compared to healthy volunteers (7.27 ± 1.77 vs 9.54 ± 2.87, p=0.006). Regarding mean corpuscular volume (MCV), it was significantly lower in radiation workers than in the control group (69.91 ± 6.13 vs 81.49 ± 6.57, p=0.001) (Figures 1-2).

There was no significant difference in the mean values of Hb, RBCs, hematocrit (Ht), red cell distribution width (RDW) and mean corpuscular hemoglobin (M.C.H) between radiation workers and the control group (14.01 ± 1.79 vs 14.30 ± 1.17, P=0.629, 5.18 ± 0.49 vs 5.06 ± 0.46, P=0.495, 41.27 ± 2.38 vs 40.58 ± 5.63, P=0.605, 13.93 ± 1.22 vs 13.52 ± 0.74, P=0.891, 27.63 ± 1.84 vs 27.68 ± 2.30, P=0.939 respectively).

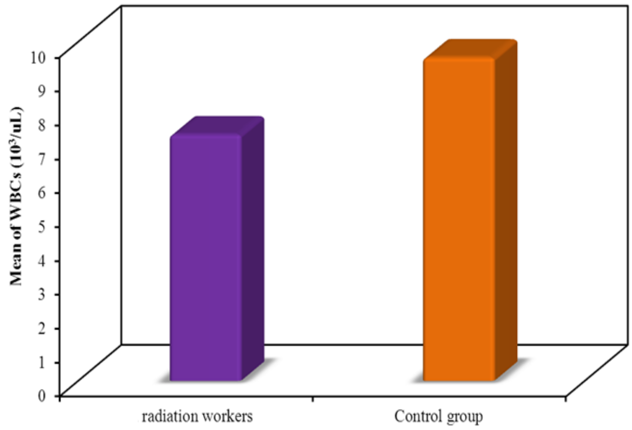

Fig. (1): Mean values of WBCs (10^3/uL) in radiation workers and control group

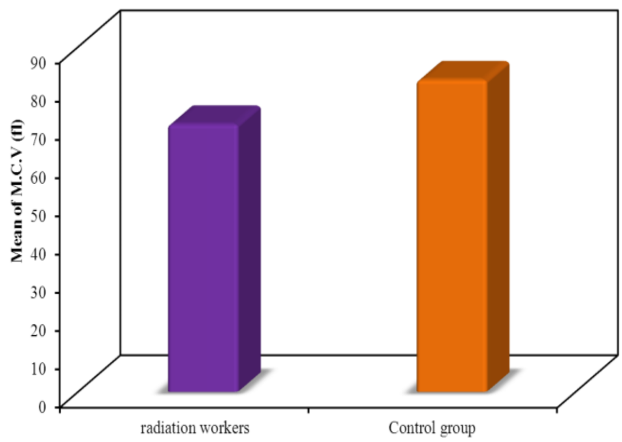

Fig. (2): Mean values of M.C.V (fl) in radiation workers and control group

Reticulocyte %, serum ferritin, iron and Methemoglobin levels in radiation workers

The mean value of the serum ferritin was 74.58 ± 54.45 in radiation worker while in healthy controls was 105.59 ± 61.68. There was a significant difference between them (P=0.002). As regards mean of serum iron, it was 83.66 ± 31.06 in radiation workers while in healthy controls was 83.06 ± 36.11 and there was no significant difference between the RWs and the controls (P=0.960). The mean serum methemoglobin was 2.34 ± 0.22 in radiation workers while it was 1.29 ± 0.19 in healthy controls. Serum methemoglobin was significantly higher in radiation workers compared to the control group (P<0.001). The mean value of reticulocyte % was 0.93 ± 0.36 in radiation workers, while it was 0.52 ± 0.20 in controls with a significantly higher in former than latter (P =0.026). (Table 2 and figures 3-5)

Table (2): Statistical analysis of serum ferritin, iron, Methemoglobin and Reticulocyte % in radiation workers as compared to control group

	Radiation workers (n = 50)	Control group (n = 25)	p
Ferritin (ng/ml)			
Range	6.50 – 169.0	14.0 – 198.20	0.002*
Mean. ± SD.	74.58 ± 54.45	105.59 ± 61.68	
Iron (µg /ml)			
Range	23.0 – 138.10	38.20 – 152.30	0.960
Mean. ± SD.	83.66 ± 31.06	83.06 ± 36.11	
Methemoglobin (mg/ml)			
Range	2.0 – 2.80	1.03 – 1.60	<0.001*
Mean. ± SD.	2.34 ± 0.22	1.29 ± 0.19	
Reticulocyte %			
Range	0.20 – 2.0	0.10 – 0.80	0.026*
Mean. ± SD.	0.93 ± 0.36	0.52 ± 0.20	

p: p value for comparing between radiation workers and control group

*: Statistically significant at p ≤ 0.05

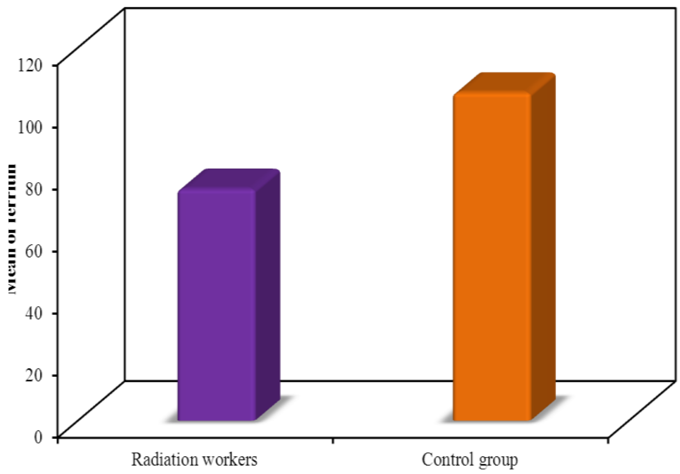

Fig. (3): The mean serum levels of ferritin (ng/ml) in radiation workers as compared to control subjects

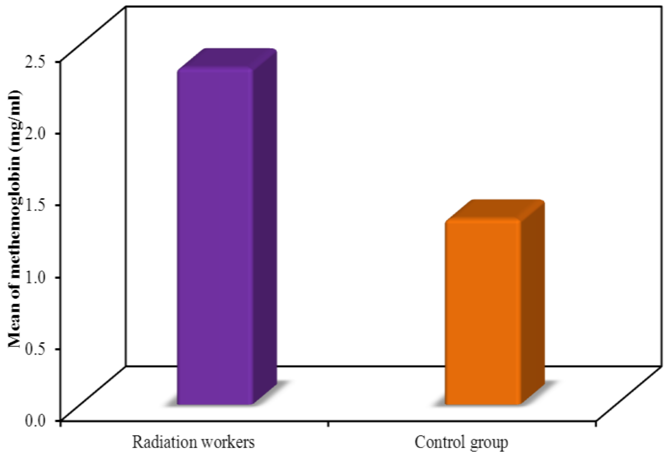

Fig. (4): Mean serum levels of Methemoglobin (mg/ml) in radiation workers as compared to control subjects

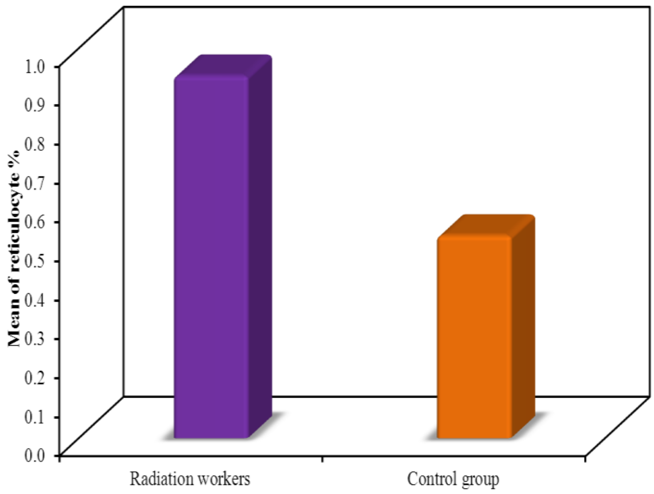

Fig. (5): Mean values of Reticulocyte % in radiation workers as compared to control subjects

Hematological results for breast cancer patients

The mean values of WBCs was significantly lower in BCPs either before or after radiotherapy in comparison with the control group (4.91 ± 1.20 versus 8.91 ± 2.53, $p1<0.001$, 3.74 ± 1.28 versus 8.91 ± 2.53, $p2<0.001$). Regarding Hb levels, it was significantly decreased in BCPs after radiotherapy when compared to the control group and before radiotherapy (11.67 ± 0.59 versus 13.8 ± 1.19, $p2<0.001$, 11.67 ± 0.59 versus 13.59 ± 1.05, $p3<0.001$). RBCs count was significantly decreased in BCPs after treatment when compared to control group and before radiotherapy (4.21 ± 0.25 versus 4.9 ± 0.51, $p2<0.001$, 4.21 ± 0.25 versus 4.93 ± 0.36, $p3<0.001$). There was insignificant difference in the mean values MCV, Ht, RDW and M.C.H between BCPs either before or after radiotherapy and the control group (Table 3).

Reticulocyte %, serum ferritin, iron and Methemoglobin levels in breast cancer patients

The mean value of serum ferritin was significantly elevated in BCPs before radiotherapy than in the control group or after radiotherapy treatment (273.4 ± 68.15 vs 101.3 ± 59.2, $p1=0.001$, 273.4 ± 68.15 vs 163.6 ± 82.79, $p3=0.003$, respectively). It significantly decreased after radiotherapy and became insignificantly higher than the control group (163.6 ± 82.79 vs 101.3 ± 59.2, $p2=0.082$). Mean of serum iron was significantly elevated in BCPs after radiotherapy than in control group or before radiotherapy treatment (149.0 ± 93.81 vs 80.1 ± 35.2, $p1=0.006$, 149.0 ± 93.81 vs 80.98 ± 27.35, $p3=0.001$, respectively). Insignificant difference was found between serum iron and BCPs before radiotherapy and the control group (80.98 ± 27.35 vs 80.1 ± 35.2, $p2=0.884$). The mean value of serum methemoglobin was significantly elevated in BCPs after radiotherapy than in the control group or before radiotherapy treatment (2.12±0.13vs 1.3 ± 0.2, $p2<0.001$, 2.12±0.13vs 1.93 ± 0.12, $p3<0.001$, respectively). The level of this parameter was significantly higher before radiotherapy treatment than in the control group (1.93 ± 0.12 vs 1.3 ± 0.2, $p1<0.001$). The mean value of Reticulocyte % was 0.51 ± 0.20 in the control group, 0.50 ± 0.32 in BCPs before radiotherapy and was 0.33 ± 0.19 after radiotherapy treatment. An insignificant difference was found in Reticulocyte % between BCPs either before or after radiotherapy in comparison to the control group.

Hematological parameters in radiation workers in comparison to breast cancer patients after radiotherapy

The range and mean ± S.D. of hematological results of radiation workers in comparison to after radiotherapy treatment in BCPs are illustrated in Table (4). The results revealed that, the mean values of WBCs, Hb and RBCs were significantly lower after radiotherapy treatment when compared to radiation workers (3.74 ± 1.28 vs 7.27 ± 1.7, $p<0.001$, 11.67 ± 0.59 vs 14.01 ± 1.79, $p<0.001$, 4.21 ± 0.25 versus 5.06 ± 0.49, $p<0.001$). There was no significant difference in the mean values of Ht, MCV, MCH and RDW between radiation workers and BCPs after radiotherapy (40.58 ± 5.63 vs 39.59 ± 4.22, $P=0.621$, 79.91 ± 6.13 vs 75.55 ± 3.04, $P=0.231$, 27.63 ± 1.84 vs 26.54 ± 0.88, $P=0.084$, 13.93 ± 1.22 vs 12.38 ± 0.40, $P=0.464$, respectively).

Table (3): Statistical analysis of Hematological results of BCPs (before and after radiotherapy) in comparison to control group

	Control group (n = 25)	Breast Cancer Patients (n = 50)				
		Before radiotherapy	After radiotherapy	p_1	p_2	P_3
WBCs (10^3/uL)						
Range	5 – 10.3	3.77 – 6.04	1.96 – 5.71	<0.001*	<0.001*	0.101
Mean. ± SD.	8.91 ± 2.53	4.91 ± 1.20	3.74 ± 1.28			
M.C.V (fl)						
Range	80 – 90.2	78.54 – 85.16	73.30 – 81.20	0.879	0.091	0.611
Mean. ± SD.	82.5 ± 7.1	81.85 ± 3.49	75.55 ± 3.04			
Hb (g/dl)						
Range	12.0 – 14.5	11.90 – 14.70	11.0 – 12.90	0.160	<0.001*	<0.001*
Mean. ± SD.	13.8 ± 1.19	13.59 ± 1.05	11.67 ± 0.59			
RBCs(10^6/uL)						
Range	4.2 – 5.01	4.50 – 5.03	4.0 – 4.87	0.182	<0.001*	<0.001*
Mean. ± SD.	4.9 ± 0.51	4.93 ± 0.36	4.21 ± 0.25			
Ht (%)						
Range	36.0 – 43	36.60 – 45.90	35.60 – 45.60	0.990	0.286	0.345
Mean. ± SD.	40.1 ± 5.5	41.25 ± 4.90	39.59 ± 4.22			
RDW (%)						
Range	12 – 14	12.60 – 13.80	11.90 – 13.80	0.401	0.524	0.461
Mean. ± SD.	12.8 ± 0.81	12.70 ± 0.11	12.83 ± 0.40			
M.C.H (pg)						
Range	20 – 30	25.54 – 27.27	25.65 – 27.80	0.116	0.149	0.659
Mean. ± SD.	26.2 ± 2.41	26.41 ± 0.91	26.54 ± 0.88			

p_1: p value for comparing between control group and breast cancer patients before radiotherapy
p_2: p value for comparing between control group and breast cancer patients after radiotherapy
p3: p value for comparing between before and after radiotherapy in breast cancer patients.
*: Statistically significant at $p \leq 0.05$.

Table (4): Comparison between radiation workers and BCPs after radiotherapy according to hematological parameters

	Radiation workers (n = 50)	BCPs After radiotherapy (n = 50)	p
WBC (10^3/uL)			
Range	4.61 – 10.30	1.96 – 5.71	
Mean ± SD.	7.27 ± 1.77	3.74 ± 1.28	<0.001
Hb (g/dl)			
Range	10.50 – 17.0	11.0 – 12.90	
Mean ± SD.	14.01 ± 1.79	11.67 ± 0.59	<0.001
RBC (10^6/uL)			
Range	4.02 – 5.96	4.0 – 4.87	
Mean ± SD.	5.06 ± 0.49	4.21 ± 0.25	<0.001
Ht (%)			
Range	29.40 – 50.60	35.60 – 45.60	
Mean ± SD.	40.58 ± 5.63	39.59 ± 4.22	0.621
MCV (fl)			
Range	69.77 – 96.0	83.30 – 91.20	
Mean ± SD.	79.91 ± 6.13	75.55 ± 3.04	0.231
M.C.H (pg)			
Range.	24.42 – 33.40	25.65 – 27.80	
Mean ± SD.	27.63 ± 1.84	26.54 ± 0.88	0.084
RDW (%)			
Range	11.60 – 16.10	11.90 – 12.80	
Mean. ± SD.	13.93 ± 1.22	12.38 ± 0.40	0.464

p: p value for comparing between radiation workers and BCPs after radiotherapy
*: Statistically significant at $p \leq 0.05$

Reticulocyte %, serum ferritin, iron and Methemoglobin levels in radiation workers in comparison to breast cancer patients after radiotherapy

The mean levelof serum ferritin was 163.6 ± 82.79 in BCPs after radiotherapy while for radiation workers was 74.58 ± 54.45. Significant difference it was found in radiation workers when compared to BCPs after radiotherapy (P =0.008). Mean of serum iron was 80.98 ± 27.35 in BCPs after radiotherapy while for radiation workers, it was 83.66 ± 31.06. No significant difference was detected when comparing radiation workers to BCPs after radiotherapy (P =0.814). As regards the mean of serum methemoglobin, it was 2.12 ± 0.13 in BCPs after radiotherapy while for radiation workers was 2.34 ± 0.22. Serum methemoglobin was significantly higher in radiation workers in comparison to BCPs after radiotherapy (P =0.006). Finally mean of Reticulocyte % was 0.33 ± 0.19 in BCPs after radiotherapy while for radiation workers, it was 0.93 ± 0.36. Reticulocyte % was significantly higher in radiation workers when compared to BCPs after radiotherapy (P =0.002). (Table 5 and Figures 6-8).

Table (5): Statistical analysis of mean serum levels of ferritin, iron, Methemoglobin, Reticulocyte % in radiation workers as compared to BCPs after radiotherapy

	Radiation workers (n = 50)	BCPs After Radiotherapy (n = 50)	p
Ferritin (ng/ml)			
Range	6.50 – 169.0	55.70 – 255.6	0.008*
Mean. ± SD.	74.58 ± 54.45	163.6 ± 82.79	
Iron (µg/ml)			
Range	23.0 – 138.10	47.60 – 118.7	0.814
Mean. ± SD.	83.66 ± 31.06	80.98 ± 27.35	
Methemoglobin (mg/ml)			
Range	2.0 – 2.80	1.98 – 2.30	0.006*
Mean. ± SD.	2.34 ± 0.22	2.12 ± 0.13	
Reticulocyte %			
Range	0.20 – 2.0	0.20 – 0.60	0.002*
Mean. ± SD.	0.93 ± 0.36	0.33 ± 0.19	

p: p value for comparing between radiation workers and BCPs after radiotherapy

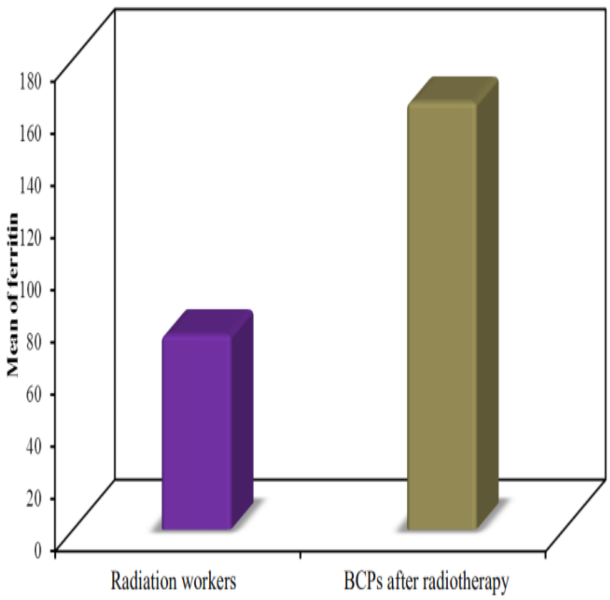

Fig. (6): Mean serum levels of ferritin in radiation workers as compared to BCPs after radiotherapy

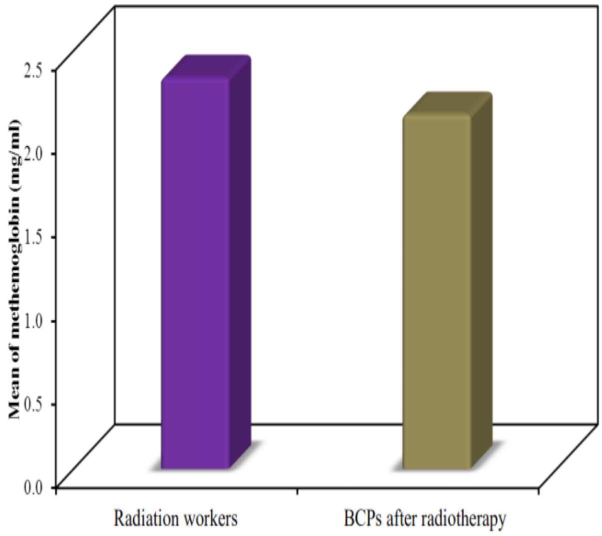

Fig. (7): Mean serum levels of Methemoglobin in radiation workers as compared to BCPs after radiotherapy

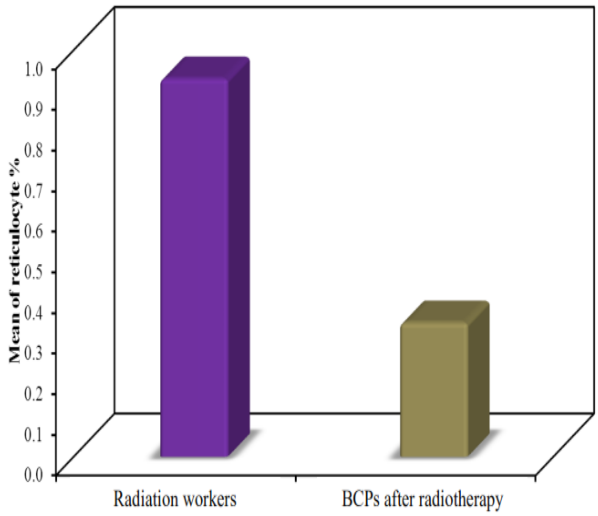

Fig. (8): Mean serum levels of Reticulocyte % in radiation workers as compared to BCPs after radiotherapy

DISCUSSION

Ionizing radiation is sometimes the single best treatment of cancer stopping it from spreading as it can provide a cure or control of the disease [18]. However, while having a central role in cancer therapeutics, it injures as well the normal cells by damaging their genetic material as DNA which is the principale target for the biological effects of ionizing radiation (IR). The indirect interaction of IR leads to hydrolysis of water molecules resulting in hydrogen and a hydroxyl free radical molecule [19]. Moreover, occupational exposure to IR increases the secretion of pro-inflammatory cytokines [20,21].

A biological dosimeter is an observable change in a biological parameter as a result of exposure to radiation. Biological dose assessment can help in the development of a treatment plan for radiation victims. Hematological changes in blood counts following IR exposure, on the other hand, are still the most sensitive biological evidences for radiation exposure [22].

In terms of the effects of ionizing radiation on hematological parameters, radiation workers had a significantly lower (MCV) than healthy controls, indicating erythrocyte microcytosis while in BCPs undergoing high dose irradiation the MCV it was within normal. This discrepancy could be explained by the fact that neither the duration nor the intensity of irradiation are responsible for this difference. The present results are supported by Linear no-threshold model (LNT). According to this model, it is postulated that all exposure to IR is harmful irrespective of how low it is as its effect is cumulative over time. This is obvious in the obtained results as RWs were exposed a dose below 20 Smv. It seems that the radiation effects are proportional to the dose but their severity is independent of the dose. LNT suggests that radiation causes harm at any dose level. Moreover, WBCs count was lower in radiation workers in comparison to control group yet it was within the normal range. WBCs were significantly lower in BCPs as high dose irradiation severely lowers lymphocytes by their effect on bone marrow cellularity. In agreement with our findings, El-Benhawy et al [23] and Davoudi et al [24] showed a significant reduction in WBCs among radiation field workers, especially with more than 5 years' experience. This makes them more vulnerable to acquire infection. Leukocytes are among the most sensitive cells to ionizing radiation and hence radiation can lower white blood cells, as a result, there would be a lowered immunity to viruses or bacteria. As fore the other parameters, namely Hb, RBCs, Ht, RDW, and M.C.H, there is no difference between the radiation workers and the control group.

In the present study, a significant increase was found in methemoglobin level in radiation workers compared to its level in control group. This could be explained by structural changes in Hb molecule. On the other hand IR produces reactive free radicals, namely the reactive oxygen species inducing a state of oxidative stress enhancing the production of methemoglobin which could be a biological marker of the harmful effect of IR over time. The mechanism of this kind of acquired methemoglobinemia is different from that of congenital methemoglobinemia [25]. The latter is a hereditary disorder caused by deficiency of NADPH–dependent methemoglobin reductase [26].

In consistence with the present results, Zhang et al [27] found that methemoglobin was increased in gamma-irradiated mice and this increase is dose dependent. On comparing BCPs exposed to high IR dose for a short duration, methemoglobin level significantly increased after irradiation, yet on comparing them to RWs its mean was significantly higher in workers. This reflects that the prolonged effect of radiation exposure is more harmful & not directed to specific organ than massive exposure on a short time period that is restricted to determined organs.

As regards the reticulocyte count in our study, it was higher in RWs which reflects a good compensatory function of the bone marrow. In patients with breast cancer, the bone marrow was hypo functioning possibly due to the effect of high dose irradiation which agrees with Younis et al [28].

In agreement with our results, Sun et al. [29] found that the percentage of Micronucleus formation in reticulocytes (MN-RET) reached a maximum between 24 and 32 hours after exposure to 1 Gy gamma-ray, indicating cytogenetic damage caused by clastogenic agents such as ionizing radiation. However, how ionizing radiation may affect the kinetics and magnitude of human MN-RET formation is still unknown.

Regarding the significantly lower ferritin level in some RWs in our study, it could be due to IR -induced ferritin degradation. In agreement with this fining Silva et al [30], suggested that oxidative stress induced by IR affects protein structure of ferritin leading to protein damage or degradation and make RWs susceptible for anemia. On the other hand, Nasri et al [31], found another explanation for this low level, that could be attributed to exposure to electromagnetic fields, a type of non-ionizing radiation emitted by cell phones added to ionizing radiation.

The obtained results confirmed that low dose IR over a long period is more injurious than a high dose over a short period of time. In agreement with the current study, Taqi et al [32], found that chronic exposure significantly altered hematological parameters while Talab et al [33] did not found such results.

CONCLUSIONS

Serum methemoglobin levels and Reticulocyte % can be used as biological markers for early assessment and monitoring radiation workers.

RECOMMENDATIONS

Radiation workers should regularly wear proper personal protective equipment at their work site and should get periodic medical surveillance including hematological profile with emphasis on Reticulocyte %, serum ferritin and Methemoglobin levels. Antioxidant drugs and vitamin C should be given to them as a routine supplement.

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All authors contributed significantly to this work. No funding to declare.

CONFLICT OF INTEREST

No conflict of interest is declared.

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