Background:
Telomeres are repetitive nucleotide sequences that protect the chromosome ends from DNA damage. Compelling data suggest that telomere attrition is associated with alteration in the DNA damage pathways, thereby inducing cell senescence. Idiopathic acquired aplastic anemia (AA) is a bone marrow (BM) failure disease characterized by pancytopenia and a hypoplastic fatty marrow. Several studies have reported shortening of telomere length (TL) in hematopoietic stem cells (HSCs) and lymphocytes in AA patients. The bone marrow mesenchymal stem cells (BM-MSC), which are the key cells of the BM niche, have garnered lots of interest as they are found to be functionally impaired in AA patients. However, a study highlighting telomere dysfunction in the BM-MSC of AA patients remains obscure. Therefore, we aim to study the telomere length shortening and its correlation with the alteration of genes involved in the telomere maintenance, DNA damage, and cellular senescence in AA patients.

Aims:
The study aims to evaluate the telomere length in BM-MSC of AA patients in comparison to that of controls. Further, it correlates the telomere length shortening with the alteration of genes involved in telomere maintenance, DNA damage, and cellular senescence in BM-MSC of AA patients.

Methods:
BM-MSC were harvested from the BM of newly diagnosed idiopathic acquired AA patients (n=20) and healthy control (n=12) after informed consent. The telomere length and the expression of genes associated with telomere maintenance, DNA damage responses, and cell senescence of the BM-MSC of AA patients were analyzed by real-time quantitative-PCR (RT-qPCR). The correlation between telomere shortening and expression of telomere maintenance, DNA damage, and cellular senescence associated genes was done using Pearson’s correlation. Student’s t-test and Mann Whitney test were used to compare differences between groups. All the results were analyzed using GraphPad Prism software. The data was represented as mean ± standard deviation, and p-value <0.05 was considered significant.

Results:
Twenty patients with idiopathic acquired AA (11 non-severe aplastic anemia (NSAA) patients and 9 severe aplastic anemia (SAA)) patients and 12 healthy controls were included in the study. The TL was significantly shorter in the BM-MSC of AA patients [0.77 (Range: 0.4 – 1.56) as compared to that of healthy controls [1.40 (range: 0.71 – 3.22); p=0.002] (Figure 1). The TL in BM-MSC was not influenced by age (p=0.360), disease severity, and other hematological parameters. A significant alteration was observed in the expression of genes involved in telomere maintenance, DNA damage, and cellular senescence with a positive correlation between the telomere length and telomere maintenance genes TRF2 (r=0.788; p=0.007), TPP1 (r=0.636; p=0.04) and TOP1 (r=0.676; p=0.03) as well as with...
gene involved in DNA damage responses CDKN1A ($r=0.667; p=0.03$) and ATM ($r=0.783; p=0.007$).

**Summary/Conclusion:**

This is the first study to highlight telomere shortening in the BM-MSC of AA patients. Furthermore, our study demonstrates that telomere shortening is in BM-MSC of AA patients is accompanied by altered expression of genes involved in telomere maintenance, DNA damage, and cellular senescence. These results shed new insight into that telomere attrition in the BM-MSC of AA patients could be attributable to DNA damage induced cell senescence or vice-versa. Overall, the findings of this study reveal that BM-MSC of AA patients potentially contributes towards the disease pathobiology.