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DNA DAMAGE IN VASCULAR SMOOTH MUSCLE CELLS PROMOTES PREMATURE AGEING AND ARTERIAL CALCIFICATION IN CHILDREN ON DIALYSIS

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Children on dialysis develop medial vascular calcification and have a cardiovascular mortality risk equivalent to the very elderly general population. Emerging evidence has shown that dysregulated mineral metabolism is associated with premature ageing and vascular calcification. However, the mechanisms driving premature ageing in response to dysregulated mineral metabolism are not understood. This study examined whether vascular smooth muscle cells (VSMCs) from children on dialysis exhibited features of premature ageing both in vivo and in vitro in comparison to disease-free children, and further investigated the underlying mechanisms. In vivo, vessels from children on dialysis displayed elevated levels of oxidative DNA damage, shown by 8-oxo-dG staining and this correlated with increased expression of the senescence markers p16 and p21. VSMCs cultured from dialysis vessels exhibited limited growth potential and elevated levels of DNA damage shown by increased γH2AX and pATM/ATR nuclear foci and comet assay. DNA damage was exacerbated by treatment with Ca and P both in vitro and in vivo resulting in persistent DNA damage signalling, increased p16 and premature senescence in dialysis VSMCs in vitro. Increased levels of DNA damage in dialysis VSMCs was associated with osteogenic differentiation shown by increased expression of Runx2 and BMP2, as well as increased calcification in response to Ca and P treatment. Cytokine array analysis showed that dialysis VSMCs displayed a proinflammatory secretory phenotype which promoted osteogenic differentiation of mesenchymal precursor cells in co-cultures. Importantly, children on dialysis showed elevated circulating levels of a number of these inflammatory factors including BMP2, OPG and IL6 which correlated with increased vascular stiffening and calcification. In summary, chronic mineral dysregulation in chronic kidney disease induces DNA damage at least partially via oxidative stress, which promotes osteogenic differentiation and calcification to accelerate premature VSMC ageing. This study indicates a therapeutic window for either antioxidant reagents or drugs that target DNA damage signalling to protect dialysis patients from several cardiovascular complications.