also been observed in other international studies. Temporal trends show a fall in mortality in females but not in males and this needs further evaluation.

OP4.32

Biochemical predictors of low bone mineral density and fracture susceptibility in Maltese postmenopausal women

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Introduction: Osteoporosis and fractures are complex skeletal conditions resulting from an interplay of genetic and environmental factors. The aim of the study was to investigate the association of biochemical levels of total serum calcium, total serum alkaline phosphatase (sALP) and serum albumin with bone mineral density (BMD) levels at the lumbar spine (LS) and femoral neck (FN), and with fracture risk in Maltese postmenopausal women. Levels were also correlated with age, years since menopause (YSM) and physical activity.

Methods: A case-control study of 1045 women was performed. Women who suffered a fracture were classified as cases whereas women without a fracture history were included as controls subdivided into normal, osteopenic or osteoporotic according to their BMD measurements. Blood specimens were collected following good standard practice and testing was performed by spectrophotometry.

Results: Calcium, and to a lower extent sALP, were correlated with FN BMD levels. Fracture cases, especially those who sustained a hip fracture, had the lowest levels of calcium, sALP and albumin relative to all other control groups. Biochemical levels decreased with increasing age, possibly increasing fracture risk. YSM was correlated with lower calcium levels in fracture cases (rho: 0.229, $p<0.01$). Biochemical levels significantly decreased with reduced physical activity in fracture cases. Moreover, reduced physical activity was associated with decreased BMD levels at the hip and spine.

Conclusion: Results suggest that levels of calcium, sALP and albumin could be indicative of fracture risk, whereas calcium levels and to lower extent sALP are indicators of hip BMD.

OP4.33

Aspirin impairs the carnitine shuttle pathway in redox-compromised yeast cells: implications for cancer chemoprevention and Reye's syndrome

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Introduction: Acetylcoenzyme A (acetyl-CoA) plays an important role in cellular metabolism. It is an essential substrate for energy production in the tricarboxylic acid (TCA) cycle. In yeast cells grown on ethanol as the carbon source, acetyl-CoA is generated in the peroxisomes and cytosol, and then transported into mitochondria by the carnitine shuttle pathway. We use yeast as a eukaryotic model since it offers large experimental advantages in conditions controlled by multiple genes.

Methods: The yeast strains used in this study are the wildtype Saccharomyces cerevisiae EG103 and the manganese superoxide dismutase (MnSOD)-deficient yeast strain EG110. Yeast cells were grown in rich ethanol medium (YPE) in the presence and absence of aspirin. Microarray analysis of gene expression profiles was validated by qPCR, in conjunction with preliminary enzyme activity studies.

Results: We observed that in MnSOD-deficient EG110 cells, aspirin exerts a significant inhibitory effect on acetylCoA synthetase. Moreover, aspirin downregulates components of the carnitine shuttle involved in the transport of acetylCoA to the mitochondria.

Conclusion: We conclude that this inhibitory effect of aspirin on the redox-compromised MnSOD-deficient yeast cells leads to energy failure and contributes to aspirin-induced apoptosis. Because several core cellular processes, such as apoptosis, are conserved among yeast and mammalian cells, these observations may contribute to our understanding of the mechanistic behaviour of aspirin in mammalian cancer cells which experience constantly higher levels of oxidative stress with respect to normal cells. These studies may also contribute towards understanding the involvement of aspirin in the molecular pathology of Reye's syndrome.

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OP4.34

Probing the structure and tumour-suppressor properties of manganese superoxide dismutase

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Introduction: Manganese superoxide dismutase (MnSOD) is an antioxidant and tumour suppressor protein located in the mitochondrial matrix, where it protects against oxidative stress generated during cellular respiration. The dismutation reaction converts superoxide into hydrogen peroxide and molecular oxygen. Since both superoxide and hydrogen peroxide function as signalling molecules, superoxide removal and hydrogen peroxide generation by MnSOD may result in being as crucial as the antioxidant protection provided by MnSOD. *Caenorhabditis elegans* MnSOD3 is of particular interest, as it has been identified as a component of the insulin regulated longevity pathway. Its catalytic mechanism is therefore, significant to the study of carcinogenesis and ageing.

Methods: The structures of *C. elegans* MnSOD as well as the MnSODazide complex have been determined by Xray crystallography, and the effect of the hydrogen peroxide reaction product on proliferation of chronic myelogenous leukaemia K562 cells was studied in the form of a biological assay.

Results: Azide acts as a superoxide substrate analogue and MnSOD inhibitor. The structure of MnSOD complexed with azide is the first that shows how the substrate is positioned in a tetrameric eukaryotic MnSOD. Azide binds endon to the manganese centre as a sixth ligand, demonstrating the arrangement of an extended hydrogen-bonded network necessary for the formation of a proton relay including His30, Tyr34, Gln142 and the manganese-bound solvent ligand.