161
MTDNA HAPLOGROUPS AND SERUM LEVELS OF SOD2, CATALASE AND GELSONIN: ROLE IN OSTEOARTHRITIS
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Purpose: To measure the serum levels of Manganese Superoxide dismutase (SOD2), Catalase and Gelsolin in order to evaluate their possible application as hypothetical biomarkers in OA together with the mtDNA haplogroups.

Methods: Serum concentrations of SOD2, Catalase and Gelsolin were measured by enzyme-linked immunosorbent assays (ELISAs) in 150 samples from Hospital Universitario A Coruña (77 healthy controls and 73 OA patients). Knee and hip radiographs from the subjects were classified according to Kellgren and Lawrence (K/L) scoring from Grade 0 to Grade IV. Appropriated statistical approaches were carried out in order to assess the incidence of diagnosis and haplogroups, as well as other variables, such as radiologic grade, gender, age and body mass index (BMI), on serum levels of the described enzymes.

Results: Serum levels of SOD2 were significantly increased in OA patients (36378.36±11161.54) compared with healthy controls (20830.11±30811.08), regardless of gender, age and BMI (p<0.001), and the higher the radiologic grade, the higher the serum levels of SOD2 (p<0.001). Serum concentration of Catalase showed a non significant trend towards higher levels in OA patients (218.8±27.68) compared to healthy controls (145.0±27.68), as well as increased levels in carriers of mtDNA haplogroup J (p=0.027). Finally, serum levels of gelsolin, an actin-binding protein related to oxidative stress and inflammation, appeared significantly decreased in OA patients (500999±43888.70) compared to healthy controls (511752.99±49709.35) (p=0.008), and significantly increased in carriers of the haplogroup U (520178.68±38409.87) (p<0.015).

Conclusions: The results obtained support that local inflammation and, specially, oxidative stress are key processes in the OA disease, and SOD2 appears as a candidate biomarker for prognosis of OA. The influence of the mtDNA haplogroups on serum levels of Catalase and Gelsolin could arise from the described different performance of the OXPHOS system among the mtDNA haplogroups.

162
SIMULATIONS TO ASSESS THE BEHAVIOR OF ORDERED VALUES FOR CHANGES IN KNEE CARTILAGE THICKNESS IN CLINICAL DRUG TRIALS
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Purpose: Change in cartilage thickness is an important aspect of osteoarthritis progression and is considered an alternative to joint space narrowing as a proof of concept efficacy endpoint. Detecting differences in population change between two or more cohorts with different exposures is a fundamental hypothesis in clinical trials for assessing treatments. Ordered values of change in cartilage thickness have been shown to be sensitive in detecting differences in thickness change between two cohorts, but the properties of this new metric have not been examined under conditions that mimic efficacy trials. The goal of this study was to assess ordered values of knee cartilage thickness change through the use of simulated clinical trials.

Methods: Simulation models were based on parametric models, i.e., they were based on theoretical distributions and estimates of population characteristics, or resampling of study data with adjustments to reflect beliefs about drug effects in a clinical trial. Three classes of simulation were examined:
1. Null case: Models with no difference between drug and placebo group were used to assess whether tests using ordered values show test bias, i.e., whether observed rate of statistical significance under the null hypothesis is different from the chosen Type I error for each individual simulated test.
2. Experimental models: Examined the effect of population characteristics, e.g., location and magnitude of change, on the sensitivity (power) for hypothesis tests (t and Wilcoxon rank-sum test) for change at fixed location regions and ordered values. These simulation models were constructed to exercise population characteristics rather than simulate realistic scenarios.
3. Observational models: Simulation models were constructed to examine 3 characteristics of drug effect: a reduction in proportion and/or magnitude change in fast progressors in the study population, and a general reduction in the magnitude of change (decline) in all subjects. Observational models were either resampling of OAI data at baseline and Year 2 or used parameters based on this data. The models cover conditions where differences exist in: fixed or random location for change in basic subpopulation; a fixed or random location for a fast progressor subpopulation; more than one random location for change in a fast progressor subpopulation. The basic subpopulation was based on distribution characteristics of OAI Incidence cohort.

Results: Results for the null case indicate that the t and Wilcoxon rank-sum tests were negligibly biased (proportion significant when α = 0.05 ranged from 0.93–0.96). The fixed location method was more powerful than the ordered values approach if change was restricted to the basic subpopulation. The ordered values approach was more powerful when fast progressors (thinning only) were present and change varied in location between individuals in the study. The two methods were equally sensitive when change was at fixed location and fast progressors were present. Test sensitivity was generally comparable for t and Wilcoxon rank-sum tests, but t tests were more powerful in some cases.

Conclusions: Testing based on ordered values method appears to be unbiased and is more sensitive than fixed location approach when fast progressors are present. Improved understanding of fast progressors in the population may be needed to optimize knee cartilage thickness change metrics in clinical trials.

163
TURNOVER OF SEVERAL DIFFERENT METALLOPROTEINASE DERIVED COLLAGEN SPECIES – A JOINT BIOCHEMICAL MARKER PANEL

Purpose: Joint degenerative diseases (JDD) are not only characterized by cartilage degradation, but it also affects the surrounding tissues such as muscle, bone and ligaments. In addition, it is known that both low and high grade inflammation associated with JDD affect several tissues in the body. Specific metalloproteinase (MMP) derived collagen fragments are released upon JDD to the circulation and measurement of those might give insight into tissue turnover upon JDD. The aim of the study was to investigate the diagnostic value of five novel assays measuring different collagen species. Ankylosing Spondylitis (AS) is characterized by gradual cementation of the vertebrae, a process which is described by excessive extracellular matrix remodeling of cartilage, bone and connective tissues. It was therefore interesting to investigate the level of different collagen species in AS.

Methods: Five newly developed ELISAs measuring MMP-degraded collagen fragments (neoepitopes) in serum of 40 AS patients and 40 age-matched controls were measured: Collagen type I (CO1), type II (CO2), type III (CO3), type IV (CO4) and type VI (CO6) as well as the bone formation marker osteocalcin.

Results: The levels of the five collagen neoepitopes were significantly higher in AS patients, except for osteocalcin. Cartilage degradation (CO2) was only significantly correlated with the basement membrane (CO4) in the AS patients. In contrast, CO3 was significantly correlated with all of the other collagen neoepitope markers. The highest diagnostic value was achieved when combining the CO2, CO3 and CO6 markers, AUC 87% (p<0.0001) and an odds-ratio of 15.6. Moreover, when combining markers there was a correlation with the clinical mSASS score (P<0.01, R=0.439)

Conclusion: Novel and unique biomarkers of tissue remodeling may provide diagnostic value and aid in understanding of the AS pathology. Each of the biomarkers tells a unique story and by combining them in a panel there, we found a strong correlation with the clinical score. We speculate that such panel will be a valuable tool for monitoring patients as effect of treatment, for prediction of responders and for diagnostic purposes for many JDD.