differences. Second, it can be used to explore the effects of various 'what if' scenarios that can demonstrate system wide and long-term effects that may result from changes in care processes. For example, two scenarios examined were: "What would happen if 1) primary care providers could manage more patients medically, ultimately referring fewer patients to specialists; and 2) primary care providers in all health zones adopted one zone's rheumatologist referral patterns for OA patients?" Such scenarios change the pathways through which simulated patients flow, the results of which can provide insight into intended and unintended effects on resource use and costs across the continuum of care over a lengthy time horizon.
Conclusions: Our SD model can be used as a decision-support tool to estimate changes in health care demands, resource requirements and costs over time and as a result of 'what if' scenarios. It is critically important to involve clinicians and decision-makers in the development of such tools to ensure they are appropriate representations of the system and to facilitate their adoption and continued use to inform decision making.

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QUADRICEPS MUSCLE STRENGTH AND ITS RELATIONSHIP TO RADIOGRAPHIC KNEE OSTEOARTHRITIS

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Purpose: Knee osteoarthritis (knee OA) is multifactorial disease and strongly affected by mechanical factors. The aims of the present study were to develop a lightweight muscle strength measuring device and investigate the relationship between knee OA and quadriceps muscle strength by epidemiological survey.
Methods: We developed portable quadriceps muscle training machine (QTM) and the accuracy of measuring was evaluated. Then, the relationship between radiographic knee OA and quantitative quadriceps muscle strength was investigated by epidemiological survey (Matsudai Knee Osteoarthritis Survey) using this device.
Results: Significant correlation was observed between QTM and BIODEX ($r=0.69, 0.82$). In Matsudai Knee Osteoarthritis Survey, 2032 knees in 1016 subjects (482 men and 534 women), average age was 65.9 ± 13.0 years old, were investigated. The prevalence of radiographic OA (grade II or higher upon Kellgren-Lawrence classification) was: 13%, 36.9%, 67.8%, and 86.5%, regarding women in their fifties, sixties, seventies, and eighties, respectively, and was 1.7%, 13.4%, 33.5%, and 66.2% regarding men, respectively. Quadriceps muscle strength declined following 50 years of age, and significant decline was observed in their sixties and seventies. Quadriceps muscle strength of OA group (grades II, III and IV) was significantly declined comparing with that of Non-OA group (grade-0 and I). Furthermore, tendency of the muscle strength level to decline with the progression of knee OA grade was particularly observed between grade 0 and grade I in both men and women and between grade I and grade II in men.
Conclusions: This is the first report in Japan that quantitatively evaluated the relationship between knee OA and quadriceps muscle strength in epidemiological survey, and we found the correlation between knee OA and the decline in quadriceps muscle strength. Furthermore, it suggests that the decline in quadriceps muscle strength may be more strongly related to the incidence of knee OA than its progression.

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ALTERED CARTILAGE PHENOTYPE IN MICE LACKING SIRT 1 GENE

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Purpose: Degenerative diseases of the cartilage, such as osteoarthritis, are age-related. The histone deacetylase Sirt 1 (silent information regulator 2 homolog 1) is thought to be an anti-aging protein. We previously demonstrated that Sirt 1 regulates apoptosis and cartilage-specific gene expression in human chondrocytes. To determine if Sirt 1 plays a protective role in cartilage homeostasis in vivo, we investigated Sirt 1 KO and Sirt 1 mutant mice to characterize their cartilage and try to understand the mechanisms underlying a phenotype, such as cartilage breakdown or apoptosis.
Method: Articular cartilage was harvested from hind paws and knees of 1-week to 6-month-old mice carrying wild type, null, or point mutations affecting the Sirt 1 gene. The cartilage was processed for histology and immunohistochemistry or used to establish cultures of chondrocytes.
Results: We found that articular cartilage tissue sections from Sirt1 KO mice and mutant mice, at any age, exhibited low levels of type 2 collagen, aggrecan, and glycosaminoglycans. In contrast, protein levels of MMP-8, MMP-9, and MMP-13 were elevated in the Sirt1 KO and mutant mice, leading to an increase of cartilage breakdown. The apoptotic process was shown to be elevated in these mice. Moreover, PTP1b (protein tyrosine phosphatase b)_a chondrocyte proapoptotic protein elevated in OA_was elevated in the Sirt1 KO mice.
Conclusion: The findings from these animal models demonstrated that Sirt1 KO mice and mice expressing a mutant allele of Sirt 1 presented an altered cartilage phenotype. The apoptotic process and the cartilage breakdown were elevated in these mice.

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NOVEL CANDIDATE GENES FOR STRUCTURAL FOOT DISORDERS: A GENOME-WIDE ASSOCIATION STUDY IN AN OLDER CAUCASIAN POPULATION

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Purpose: Structural foot disorders, such as hallux valgus, deformities of the lesser toes (toes 2-5) and plantar soft-tissue atrophy, commonly affect ~ 60% of older adults at the population level and are often linked with foot pain, chronic mobility limitations, and disability. Although, body weight and other environmental factors are considered possible causes of these foot conditions, the importance of genetics is commonly suspected in clinical observations of family aggregation. Previously, we reported strong heritability (h^2) for lesser-toe deformity (61% in men; 85% in women) and moderate h^2 for hallux valgus (~35%) and plantar soft-tissue atrophy (~20%) in older men and women, suggesting potential genetic predisposition to structural foot disorders. To identify their genetic determinants, we have undertaken a GWAS using 2.5M imputed SNPs (HapMapII CEU reference panel) to localize susceptible genes in the population-based Framingham Foot Study.
Methods: Structural foot disorders were indicated as present or absent and were assessed based on an atlas of pictorial depictions. Plantar soft tissue atrophy was determined by palpating the plantar fat pad at the forefoot and heel during a validated foot examination. Among 2,446 Framingham participants (mean age 66 yrs; 57% women; Caucasian), we identified 753 (31%), 764 (31%) and 665 (27%) participants with deformities of the lesser-toes, hallux valgus and plantar soft-tissue atrophy, respectively. A mixed-effect regression model was performed and adjusted for age, sex, weight and principal components of ancestral genetic background. A kinship covariance matrix was used to take into account within-family correlations among siblings. We filtered out SNPs with low imputation quality (O/E variance ratio of allele frequency < 0.3) and SNPs with MAF $< 1\%$. In addition, p-values were also adjusted for λGC.
Results: We found several associations achieved genome-wide significance ($p < 5x10\text{-}8$), i.e. SNPs on *TBC1D22A* and *OR5D13* gene for lesser-toe deformity. For hallux valgus, the most significant SNP ($p=4.9x10\text{-}7$) is located in *GATAD2B* gene. For plantar soft-tissue atrophy, the most significant SNP ($p=4.76x10\text{-}7$) is located near *ADAMTS16* gene. Pathway and gene-set analyses for the genome-wide significant and suggestive genes suggested significant clustering of genes involved in connective tissue disorders (such as oligoarticular arthritis, osteoarthritis and osteosclerosis). Of note, a few SNPs were reported to associate with longevity. These results are undergoing replication in independent samples.
Conclusions: In conclusion, our results identify novel candidate genes to further elucidate the etiology of structural foot disorders.