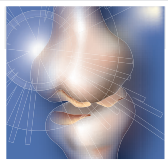
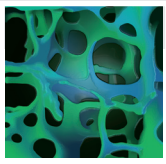




Bulletin Board

Adalimumab may be an effective treatment for juvenile rheumatoid arthritis

Results from a new study suggest that adalimumab may be an effective treatment for children suffering from juvenile rheumatoid arthritis. Juvenile rheumatoid arthritis, also known as juvenile idiopathic arthritis, is the most common form of arthritis affecting children. It is an autoimmune disorder characterized by joint swelling, stiffness and occasionally reduced motion. As the tumor necrosis factor (TNF) has been shown to have a pathogenic function in juvenile rheumatoid arthritis, the researchers assessed the effectiveness and safety of adalimumab, a TNF inhibitor derived from a fully human monoclonal antibody, in children.

The study included 171 patients aged 4 to 17 years suffering from active juvenile rheumatoid arthritis. All of the patients had been prescribed NSAIDs previously. After stratifying the patients according to methotrexate use, they were given 24 mg of adalimumab (brand name Humira®) per m^2 of body-surface area subcutaneously every other week for a total of 16 weeks. At this point, patients with an ACR Pediatric 30% (ACR Pedi 30) response were randomized to receive either adalimumab or placebo in a double-blind manner every alternate week for up to 32 weeks. This response measure is an indication of the improvement in symptoms of the patient.

In the group not receiving methotrexate, 74% of the patients were found to have an ACR Pedi 30 response at week 16, whereas in the group who had been treated with methotrexate, 94% had an ACR Pedi 30 response at this time point. The patients who had an ACR Pedi 30 response were the ones who had shown an improvement in the symptoms and were eligible for the next phase of the study. The researchers found that amongst the patients who did not receive methotrexate, 43% of those treated with adalimumab and 71% of those given placebo reported disease flares. The latter was the main outcome measure of the study. In the other group consisting of the methotrexate-treated patients, 37% of those treated with adalimumab experienced disease flares, as did 65% of those given placebo. These results were statistically significant.

After 48 weeks of treatment, the scientists found that the percentages of patients amongst the methotrexate-treated group, who had an improvement in their symptoms (as indicated by the ACR Pedi 30, 50 or 70 responses) were significantly greater for those treated with adalimumab compared with those receiving placebo. The differences between those receiving adalimumab and those receiving placebo in the group of non-methotrexate-treated patients were not statistically significant. The response rates were maintained for 104 weeks of treatment. A total of 14 serious adverse events, out of which half were serious infections, that could be related to adalimumab were reported in the study.

Owing to insufficient sample size and duration, the researchers could not establish the risks for rare adverse events. In addition, they were also unable to identify differences between patients treated with methotrexate and those not receiving it due to insufficient power of the study.

"Adalimumab, alone or in combination with methotrexate, appears to be an efficacious option for the treatment of children with polyarticular juvenile rheumatoid arthritis. Responses were sustained through 2 years of continued treatment," the authors stated.

Source: Lovell DJ, Ruperto N, Goodman S *et al.*; Pediatric Rheumatology Collaborative Study Group; Pediatric Rheumatology International Trials Organisation: Adalimumab with or without methotrexate in juvenile rheumatoid arthritis. *N. Engl. J. Med.* 359(8), 810–820 (2008).

in the news...

It has been suggested that rheumatoid arthritis researchers produce a database of healthcare claims data to aid in the understanding of the disease and adverse events related to it.

Novel claims database could provide improved understanding of complications associated with rheumatoid arthritis treatment

Researchers recommend collating healthcare claims information into a database as it could lead to a better understanding of the adverse events associated with rheumatoid arthritis.

> 'The team concluded that healthcare claims data, which provide information about medication use, would also accurately reflect the rate of adverse events in patients with rheumatoid arthritis.'

Previously it has been suggested that the complications observed in individuals with rheumatoid arthritis are more often side effects associated with therapy than related to the actual disease. Based on this assumption, disease severity becomes an important factor in estimating adverse event rate, since more severe disease will be treated more heavily.

With this in mind, the team concluded that healthcare claims data, which provide information about medication use, would also accurately reflect the rate of adverse events in patients with rheumatoid arthritis.

Data from a total of 120 patients from the Veteran's Administration (VA) Health System was pooled to create the claims-based index for rheumatoid arthritis severity (CIRAS); its accuracy was tested by comparing it to the medical records-based index for rheumatoid arthritis severity (RARBIS) database, a dataset that has been validated previously. Statistical testing demonstrated a moderate correlation between the two databases.

The authors believe that the CIRAS index could play an important role in improving the adjustment of rheumatoid arthritis disease severity in studies utilizing claims data. However, one of its limitations is that the data used to create it was mainly obtained from elderly men; however, the authors did not feel that its significance would be limited to this particular population.

> "CIRAS may be an important methodological tool for researchers studying rheumatoid arthritis treatment and complications using healthcare utilization data."

The authors also explained that they "plan on assessing the validity of CIRAS in other populations and will examine its ability to adjust for confounding and predictive validity for outcomes known to be associated with severe rheumatoid arthritis, such as future joint surgeries, higher medical care costs, and use of combination disease-modifying anti-rheumatic drugs."

"CIRAS may be an important methodological tool for researchers studying rheumatoid arthritis treatment and complications using healthcare utilization data," the authors stated.

Source: Ting G, Schneeweiss S, Scranton R *et al.*: Development of a health care utilization data based index for rheumatoid arthritis severity: a preliminary study. *Arthritis Res. Ther.* 10(4), R95 [Epub ahead of print] (2008).

Priority Paper Alerts

Vitamin D and chronic widespread pain in a white middle-aged British population: evidence from a cross-sectional population survey.

Atherton K, Berry DJ, Parsons T, Macfarlane GJ, Power C, Hypponen E: *Ann. Rheum. Dis.* (Epub ahead of print) (2008).

Causative factors for chronic widespread pain (CWP) include a variety of emotional and behavioral factors. Vitamin D deficiency has been proposed as one factor contributing to risk for CWP, and in this study the researchers assessed the correlation between vitamin D status and CWP in a nationwide sample consisting of white UK adults. An association between CWP and vitamin D status was observed in the female, but not the male, participants of the study. This association in women remained after adjustment for confounding lifestyle or social factors. However, further studies will be needed to establish if an increase in vitamin D intake could positively modify CWP risk.

The *FCRL3* -169T>C polymorphism is associated with rheumatoid arthritis and shows suggestive evidence of involvement with juvenile idiopathic arthritis in a Scandinavian panel of autoimmune diseases.

Eike MC, Nordang GB, Karlsen TH *et al.* *Ann. Rheum. Dis.* 67(9), 1287–1291 (2008).

Although the -169T>C SNP of the *FCRL3* gene has been shown to be linked with a variety of autoimmune diseases in Japanese populations, conflicting results have been obtained in other populations. In this study the authors studied this SNP in a Scandinavian panel of autoimmune diseases. Patients as well as healthy controls were genotyped for this SNP. The researchers found an association between the C allele and the homozygous C genotype and RA. The results also indicated an association between the SNP and JIA, which should be analyzed further in follow-up studies. They did not find a significant association between the SNP and any of the other autoimmune diseases included in this study. The authors concluded that their findings suggest that the -169T>C SNP plays a role in RA in ethnically diverse populations.

Study indicates increased risk for fractures in HIV-infected patients

In a new study, researchers have shown that there is a higher occurrence of fractures in HIV-infected patients compared with non HIV-infected patients, irrespective of gender and fracture site.

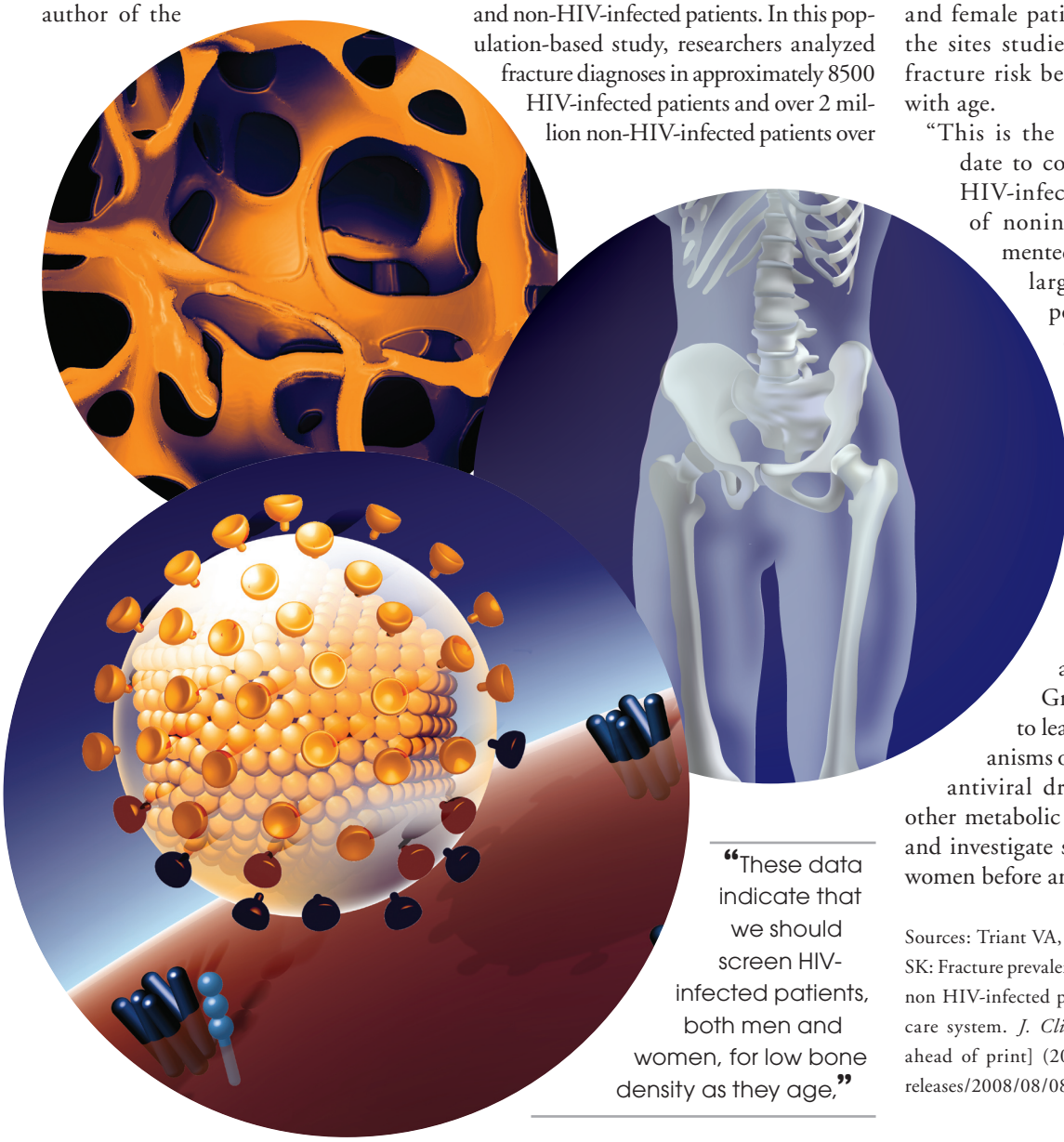
"Prior studies have indicated reduced bone density in HIV-infected patients, but little was known about whether fracture risk increased in this population," explained Steven Grinspoon, the lead author of the study. "These data are the first to suggest that there is a clinically significant increase in bone fractures among HIV-infected patients, using data from a large healthcare system."

Data from the Partners HealthCare System, which includes the Brigham and Women's Hospital and Massachusetts General Hospital in Boston, was utilized to compare fracture prevalence in HIV-infected and non-HIV-infected patients. In this population-based study, researchers analyzed fracture diagnoses in approximately 8500 HIV-infected patients and over 2 million non-HIV-infected patients over an 11-year period (from 1996 to 2008) and found that fracture prevalence increased by more than 60% in those infected with HIV relative to the controls.

The analysis revealed a significantly higher prevalence of spine, hip and wrist fractures in patients infected with HIV compared with HIV-negative patients. This increase in HIV-associated fracture prevalence was observed in both male and female patients for the majority of the sites studied. The HIV-associated fracture risk became more pronounced with age.

"This is the largest investigation to date to compare fracture rates in HIV-infected patients with those of noninfected controls," commented Grinspoon. "This very large study group has the power to detect significant differences in risk for both men and women at critical sites, such as the hip and spine, risks that increased with age."

"These data indicate that we should screen HIV-infected patients, both men and women, for low bone density as they age," concluded Grinspoon. "We also need to learn more about the mechanisms of this bone loss – whether antiviral drugs, the virus itself, or other metabolic factors are responsible – and investigate specific fracture rates for women before and after menopause."



"These data indicate that we should screen HIV-infected patients, both men and women, for low bone density as they age,"

Sources: Triant VA, Brown TT, Lee H, Grinspoon SK: Fracture prevalence among HIV-infected versus non HIV-infected patients in a large U.S. healthcare system. *J. Clin. Endocrinol. Metab.* [Epub ahead of print] (2008); www.sciencedaily.com/releases/2008/08/080828084050.htm

Psychological therapies may alleviate arthritis pain

It is possible for sufferers of rheumatoid arthritis to ease their pain through the use of mental imagery techniques and hypnotherapy, according to a recent study from Bangor University, Wales, UK. Psychologists there believe that individuals can make use of such techniques to treat themselves as and when required, enabling them to lead a more active life.

'In this recent study, researchers examined the effect of psychological therapies – namely visualization techniques and hypnotherapy – on rheumatoid arthritis-induced pain and fatigue.'

Rheumatoid arthritis is a chronic autoinflammatory disease in which the immune system mounts an aberrant attack on the joints. The condition often leads to severe pain and disability, and can ultimately render sufferers unable to carry out day-to-day tasks.

Although there are a number of drugs available to treat rheumatoid arthritis, many patients do not respond well to conventional medication and, despite therapy, still experience a high level of pain. As a consequence, sufferers of chronic rheumatoid arthritis are increasingly turning to complementary and alternative medications in an attempt to lessen the painful symptoms of their debilitating condition.

In this recent study, researchers examined the effect of psychological therapies – namely visualization techniques and hypnotherapy – on rheumatoid arthritis-induced pain and fatigue, key symptoms that lead to loss of motility and prevent sufferers leading a full and active life.

One technique involved rheumatoid arthritis patients visualizing their pain in the form of a person. Having thanked the person for letting them know something was not right, they would then ask that person to leave. Participants then visualized the person's image going further and further away until it disappeared, theoretically leaving them free of pain.

The results of the study showed that imagery techniques such as this, as well as hypnotherapy, were effective at reducing pain and fatigue caused by rheumatoid arthritis. Patients were encouraged to take an active role in their own therapy, applying the visualization techniques to those areas of their life that were negatively affected due to rheumatoid arthritis. "By employing the techniques they were taught, (patients) were able to self-treat when necessary, allowing them to control their pain and enabling them to get on with enjoying life," says Bryan Bennett, one of the study's researchers.

Source: British Psychological Society: www.bps.org.uk

About the Bulletin Board

The Bulletin Board highlights some of the most important events and research in the field of rheumatology.

If you have newsworthy information, please contact:

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Determinants of premature ovarian failure in lupus patients identified

Novel research has revealed a possible association between premature gonadal failure (PGF) in patients with systemic lupus erythematosus (SLE) and several factors including cyclophosphamide use and disease activity. A number of menstrual problems can occur in women with SLE, of which PGF is one of the most serious. Previous work has shown that cyclophosphamide treatment and older age may act as predisposing factors to the development of PGF in lupus patients.

In this study, 316 women with SLE, all participants of the Lupus in Minorities: Nature vs Nurture (LUMINA) trial, a multiethnic US cohort, were assessed for indications of PGF, and almost 12% of the women were found to develop PGF during the course of the study.

"Identifying these factors has important implications for the preservation of reproductive function in women of child-bearing age."

The team confirmed the correlation between older age and cyclophosphamide use and an increase in the risk for PGF. In addition, the results also indicated that Texan-Hispanic ethnicity and higher disease activity increased PGF risk over time.

"Identifying these factors has important implications for the preservation of reproductive function in women of child-bearing age," commented Dr Graciela Alarcon, lead author of the study.

Source: González LA, McGwin G Jr, Durán S *et al.*; LUMINA Study Group: Predictors of premature gonadal failure in patients with systemic lupus erythematosus. Results from LUMINA, a multiethnic US cohort (LUMINA LVIII). *Ann. Rheum. Dis.* 67(8), 1170–1173 (2008)

Hospitalizations may be associated with an increased risk of fracture among the elderly

A recent study published in the *Archives of Internal Medicine* suggests that, among the elderly, hospitalizations increase the risk of hip and other types of fracture. Rebekah Gardner (University of California, San Francisco, USA) and colleagues explain that hospitalization for fracture places a patient in the high-risk group for subsequent fracture, not only because the patient gains a history of fracture, but also owing to the hospitalization itself and its associated inactivity, which causes increased bone turnover and may decrease functional activity.

'Rebekah Gardner and colleagues explain that hospitalization for fracture places a patient in the high-risk group for subsequent fracture.'

The researchers conducted a prospective study of a cohort of 3075 black and white men and women aged 70 to 79 years. The participants were recruited from two communities from 1997 to 1998 and medical records were used to validate incident hospitalizations and fractures. Investigators were blinded to patient groups.

Analyzing the association between hospitalization, length of stay, number of admissions and risk of fracture, the researchers adjusted for age, race, sex and other potential confounding factors.

The study had a mean follow-up of 6.6 years. During this time 230 (66%) of the patients enrolled in the study were admitted to a hospital and 809 (26%) were admitted three or more times. Following adjustment for age, race and sex, the results demonstrated that those patients who recorded any hospitalization had a twofold increased risk of fracture; those who were hospitalized twice during the follow-up period were found to have a 2.42-fold increased risk of hip fracture. In addition, three or more hospital stays was associated with a 3.66-fold increased risk of fracture.

The authors caution that the observational nature of their study prevents them from demonstrating a causal relationship between hospitalization and fracture, but nevertheless state that hospitalization "appears to be a strong marker of increased fracture risk." They conclude that, "Hospitalization is an unrecognized opportunity to assess and reduce the risk of fractures in a very large number of elderly women and men."

'The results demonstrated that those patients who recorded any hospitalization had a twofold increased risk of fracture.'

Source: Gardner RL, Harris F, Vittinghoff E, Cummings SR: The risk of fracture following hospitalization in older women and men. *Arch. Intern. Med.* 168(15), 1671–1677 (2008).

How to keep muscles strong when in a cast

A major side effect of being in a cast after breaking a limb is muscle atrophy. An Israeli company, StimuHeal, believes it has developed a solution to this problem. The company has created an electrical stimulation device that is positioned under the cast and stimulates the muscles to keep them strong and minimize cast-induced atrophy.

The CEO of StimuHeal, Shlomi Cohen, describes the idea behind the device: "The initial thought behind the system was to enable patients with orthopedic injuries to efficiently use the immobilization period to reduce cast-induced atrophy. The problem after bone injury is that most patients are not active. Even though doctors are recommending them to be active, they aren't. Only after the cast is removed … do they start physical therapy."

The company first identified limitations that a current muscle-stimulating device, the Neuromuscular Electrical Stimulation (NMES), would face if used to stimulate muscles under casts. The NMES applies electrical impulses from a device through electrodes that are placed on the skin over the target muscle(s) for muscle rehabilitation, particularly after injury or stroke. However, StimuHeal recognized that if electrodes were placed under a cast, prolonged sweating would occur, which would be problematic. The company also had to overcome the potential problem of build up of lactic acid and CO_2 in the muscle, which they achieved by developing a microprocessor that is able to calculate a cycle for the muscles to rest.

'The company has created an electrical stimulation device that is positioned under the cast and stimulates the muscles to keep them strong and minimize cast-induced atrophy.'

The device, named MyoSpare™, can be used immediately after surgical or medical interventions. It is currently available in Israel and Europe and it is hoped to obtain US FDA approval in the next year. The device will not only cut physiotherapy costs, but also increase the speed of recovery after a serious injury.

Source: StimuHeal Inc. www.stimuheal.com/myospare

New treatment may help adults with difficult-to-treat gout

A new drug that regulates uric acid levels may provide relief to individuals suffering from gout who have failed to respond to other treatments.

Gout results from a build-up of uric acid in the blood; the elevated uric acid levels could be due to an increase in production or alternatively, due to problems with excreting it. The excess uric acid can form crystals and accumulate in joints, generally the big toe, foot, ankle or knee, provoking an inflammatory response in these tissues.

Patients are prescribed drugs such as allopurinol and probenecid, which help to lower uric acid levels in the blood, but some individuals cannot tolerate the medications or do not respond to them. A new drug called pegloticase was the focus of this Phase II trial.

"The generally accepted goal of therapy is to reduce serum urate concentrations to less than 6 mg/dl, and we found that pegloticase can do that very, very quickly," stated John Sundy, the lead author of the study. "Perhaps what is most important is that it did this in patients who had run out of therapeutic options."

"The generally accepted goal of therapy is to reduce serum urate concentrations to less than 6 mg/dl, and we found that pegloticase can do that very, very quickly."

The researchers assessed the efficacy of the drug in 41 patients in whom other treatments had failed. The participants were randomized to receive one of four doses – 4 or 8 mg every 2 weeks or 8 or 12 mg every 4 weeks – for a period of 12–14 weeks in total. They found that pegloticase was able to reduce the patients' uric acid concentrations within 6 h; the reduced uric acid levels were maintained for the course of the trial in the patients receiving 8 and 12 mg doses. While the treatment progressed, gout flares occurred in 88% of the participants. None of the patients had an anaphylactic reaction to the drug, and the majority of the adverse events appeared to be unrelated to treatment and were considered to be "mild or moderate in severity," by the researchers.

Source: Sundy JS, Becker MA, Baraf HS *et al.*: Reduction of plasma urate levels following treatment with multiple doses of pegloticase (polyethylene glycol-conjugated uricase) in patients with treatment-failure gout: Results of a Phase II randomized study. *Arthritis Rheum.* 58(9), 2882–2891 (2008).

Patients with inflammatory bowel disease or chronic liver disease likely to have vitamin D deficiency, two reports indicate

Two studies presented at the 73rd Annual Scientific Meeting of the American College of Gastroenterology have revealed that regular vitamin D monitoring may be of great importance in patients with particular gastroenterological disorders. The researchers found that individuals suffering from inflammatory bowel disease (IBD) or chronic liver disease were more likely to develop vitamin D deficiencies.

Vitamin D is essential for the growth and maintenance of healthy bones as it aids in the absorption of calcium. Deficiency of the vitamin can result in weak bones and increase the risk of osteoporosis-induced fractures.

On investigating vitamin D levels of over 500 IBD patients over time, scientists at the Medical College of Wisconsin (WI, USA) found that approximately 50% of the patients involved in the study were vitamin-D-deficient at some point, while 11% had severely low levels of the vitamin.

"All IBD patients, irrespective of their disease, disease location or nature, should have their vitamin D levels checked regularly and corrected aggressively when insufficiency is found," stated the lead researcher, Alex Ulitsky.

"All IBD patients, irrespective of their disease, disease location or nature, should have their vitamin D levels checked regularly and corrected aggressively when insufficiency is found."

The team from the University of Tennessee in Memphis (TN, USA) assessed vitamin D levels in more than 100 patients with chronic liver disease and observed vitamin D deficiency of some degree in approximately 92% of individuals, and at least a third of them were found to be severely lacking the vitamin. The latter was more common among patients with cirrhosis.

"Since deficiency is common among these patients, vitamin D replacement may hopefully prevent osteoporosis and other bone complications related to end-stage liver disease," explained Satheesh P Nair, lead researcher of the study.

Sources: Ulitsky A, Ananthakrishnan A, Skaros S *et al.*: Vitamin D deficiency in inflammatory bowel disease patients: association with disease activity and quality of life. Abstract P671. Presented at: *The ACG Annual Scientific Meeting and Postgraduate Course*, October 3–8, 2008; Jihad Arteh J, Sri Lakshmi Narra S, Satheesh Nair S: Prevalence of vitamin D deficiency in chronic liver disease. Abstract P90. Presented at: *The ACG Annual Scientific Meeting and Postgraduate Course,* October 3–8, 2008; www.sciencedaily.com/releases/2008/10/081006092645.htm

Latest research proposes that pain could be cause rather than symptom of osteoarthritis

A new study has revealed that pain is not only a symptom of osteoarthritis, but is in fact an intrinsic and detrimental part of the disease. Pain signals, which originated in arthritic joints and were processed at the spinal cord, appeared to exacerbate the spread of arthritis. Furthermore, the nerve pathways involved in conducting the pain signals seemed to transmit inflammation from the joints to the spine and back again, causing disease at both sites.

'Pain signals, which originated in arthritic joints and were processed at the spinal cord, appeared to exacerbate the spread of arthritis.'

"Until relatively recently, osteoarthritis was believed to be due solely to wear and tear, an inevitable part of aging," explained Stephanos Kyrkanides, senior author of the study. "Recent studies have revealed, however, that specific biochemical changes contribute to the disease, changes that might be reversed by precision-designed drugs. Our study provides the first solid proof that some of those changes are related to pain processing, and suggests the mechanisms behind the effect."

Pain and inflammation have a long documented association; previous research has demonstrated that inflammation-inducing substances can also cause the sensation of pain if injected. The focus of this study is the proinflammatory, signaling molecule interleukin 1-β (IL-1β), which plays a role in the immune system.

'Pain and inflammation have a long documented association; previous research has demonstrated that inflammation-inducing substances can also cause the sensation of pain if injected.'

The team used genetically modified mice to show that overexpression of IL-1β in peripheral joints led to an increase in the production of IL-1β in the pain processing centers of the spinal cord. Conversely, when they upregulated IL-1β production in spinal cord astrocytes, the immune cells of the CNS, they found an increase in osteoarthritic symptoms in the joints. The effects were reversed when IL-1β signaling was inactivated.

"Our study results confirm that joints can export inflammation in the form of higher IL-1β along sensory nerve pathways to the spinal cord, and that higher IL-1β inflammation in the spinal cord is sufficient in itself to create osteoarthritis in peripheral joints," Kyrkanides concluded. "We believe this to be a vitally important process contributing to orthopedic and neurological diseases in which inflammation is a factor."

Sources: Fiorentino PM, Tallents RH, Miller JN *et al.*: Spinal interleukin-1β in a mouse model of arthritis and joint pain. *Arthritis Rheum.* 58(10), 3100–3109 (2008); www.sciencedaily.com/

Gene region that may play an important role in juvenile idiopathic arthritis is identified

The genetic variant that is suggested to play an important role in juvenile idiopathic arthritis (JIA) is on chromosome 9 in a region housing two genes *TRAF1* and *C5*. Researchers understand that the TRAF1 gene codes for a protein that regulates tumor necrosis factor, which has well-known associations with JIA. The responsible genes may be a 'master switch' for the control of the disease.

"There are only a few genes that may act as master switches like this to regulate autoimmune diseases," explained Dr Finkel, chief of Rheumatology at The Children's Hospital of Philadelphia, PA, USA. He added, "This switch we discovered probably has to be an 'ON' gene, and when it interacts with other genes and environmental triggers, a child may get juvenile arthritis."

"We think this finding may be a clue to the specific disease pathway that leads to arthritis."

While the cause of JIA is unknown, results from this study back up past research that shows arthritis arises in a genetically susceptible individual due to environmental factors. A total of 67 patients undergoing treatment for JIA were compared to 1952 healthy control subjects, and the genes were identified.

"We think this finding may be a clue to the specific disease pathway that leads to arthritis," commented Dr Behrens, a pediatric rheumatologist at Children's Hospital. "We currently use medicines called tumor necrosis factor blockers to treat children with JIA. However, not all children respond to these drugs, and other children may develop severe allergic reactions and other side effects. If we can fully identify all the genes that interact with environmental risk factors, we might develop more targeted treatments with fewer side effects."

The study utilized the high-resolution genome-wide association approach, and this was said to markedly enhance the ability to identify disease genes in complex disorders such as JIA, Furthermore, the genes could possibly be a common genetic factor predisposing to all seven forms of the disease.

The researchers say further study is needed to determine whether the *TRAF1* or *C5* genes are altered in the disease.

Source: Behrens EM, Finkel TH, Bradfield JP *et al.*: Association of the *TRAF1-C5* locus on chromosome 9 with juvenile idiopathic arthritis. *Arthritis Rheum.* 58(7), 2206–2207 (2008).