Editorial

Looking Out for the Backside!

Recent estimates from the Arthritis National Data Workgroup identify 38 million Americans as having arthritis in 1990, with projections for this figure to rise to 60 million by the year 2020[1]. Moreover, osteoarthritis (OA) represents the leading form of arthritis among these aging adult Americans. Given the large population burden of OA, substantial effort has been expended over several decades at enhancing our understanding of the causes of OA. Many investigators have embarked upon case-control and cohort studies to further define the epidemiology and, specifically, risk factors for the development of OA.

Much of this research effort has focused upon OA of the appendicular skeleton, namely upon peripheral joints of the upper and lower extremities. No doubt, the daily impact in terms of pain, impaired function, and disability to individuals with advanced OA of the knee, hip, and hand warrant this attention. Further, the substantial volume of hip and knee replacement surgery performed annually in the United States necessitates ongoing investigation into the causes of such severe, endstage joint damage. An overriding goal remains to identify etiologic factors in order to prevent the development and progression of endstage disease before total joint arthroplasty for an irreversible osteoarthritic joint is the only remedy.

In comparison to the peripheral joints, however, less attention has been directed at investigating the causes and progression of OA of the axial skeleton, namely of the cervical and lumbar spine. It is in this area of lumbar spondylosis, or degenerative arthritis of the lumbar spine, that we read the report by Jordan, *et al*[2], in this issue of *The Journal*, which examined factors associated with OA of the lumbar spine in a community-based cohort in England. While the investigators gathered information on many conventional OA risk factors, what is particularly appealing about this report was the focus on body weight assessed at birth (and at 1 year of life), rather than limiting the assessment of body weight to young or mid-adult life, or at the time OA was diagnosed, characteristic of other similar studies[3-6]. Identification of such a relationship, if present, lends credence to the concept that development of OA may be predetermined, or programmed during early life, in fact, even at birth!

But consideration of a potential causal relationship between weight at birth and subsequent development of a chronic musculoskeletal disorder raises the question whether the link between the two is genetically determined. The report by Jordan, *et al*[2] is poised to address this consideration, inasmuch as the study participants also had their blood analyzed for polymorphisms of the vitamin D receptor gene.

With these considerations in mind, Jordan, *et al* gathered information on many conventional OA risk factors, including age, adult weight, height, occupation, cigarette smoking, alcohol consumption, and level of physical activity. Of particular note with regard to the 173 women and 219 men in the county of Hertfordshire who participated in the study and were born in the years 1920—1930, their birthweight was recorded by an attending midwife. Thus, the investigators were able to specifically examine the relationship of birthweight, and weight at 1 year of life, to the development of OA of the lumbar spine decades later. Blood samples were also drawn, enabling measurement of polymorphisms of the vitamin D receptor gene, as reflected in the title of the report.

From the analyses by Jordan, *et al*, we are informed that osteophytes were present in two-thirds of the men and among 60% of the women. Moreover, disc space narrowing was substantially less frequent than osteophytosis, occurring in only 16% of the men and 13% of the women. Interestingly, Jordan, *et al* found that the presence and severity of OA at the lumbar spine were related to both birthweight and to weight at 1 year of life. This association

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was only observed, however, in men. Further, and perhaps surprisingly, lumbar osteophytes were present more frequently among men with lower, rather than among those with higher, birthweights. In neither gender was birthweight or weight at 1 year related to disc space narrowing at the lumbar spine. The authors also report that among the men and women combined, the presence of the BB genotype, indicating absence of the Bsm-1 polymorphic site for the vitamin D receptor, was related to higher grade of osteophytes at the lumbar spine.

To view this article's focus and findings in context, one may revisit the examination of both traditional and relatively novel risk factors for OA. Jordan, *et al* specifically examined the relationship of body weight and of a genetic polymorphism to the risk of degenerative arthritis affecting the lumbar spine. Body weight has certainly been closely linked with OA in peripheral joints, particularly at the knee[4,5], also perhaps at the hip[3] and hand[8]. In contrast, relatively little attention has been directed at the relationship of body weight to axial involvement since Kellgren and Lawrence's initial observations[9].

As to the matter of heritability, interest in genetic factors as they may be related to development of OA has been appreciated for decades[10]. More than 60 years ago, Stecher noted among individuals with Heberden's nodes that mothers and sisters were disproportionately affected by the same bony enlargement of the proximal interphalangeal joint[11]. Subsequently, Kellgren and Moore demonstrated that beyond the relatedness of osteoarthritic finger joints among first-degree relatives, that Heberden's nodes were also associated with an increased prevalence of degenerative arthritis of the first carpometacarpal joint, the first tarsometatarsal joint, the knee joint, and the spine joints. However, the specific gene or allelic determinant(s) that contributed to this observed familial susceptibility to develop OA remained elusive.

A landmark publication that further enhanced and accelerated our understanding of the genetic contribution to OA was the demonstration of rather unique pedigrees with severe, highly penetrant, and early onset OA associated with mild chondrodysplasia. A specific allelic defect in the procollagen gene was defined that gave rise to this phenotype[12]. While the identification of this procollagen genetic defect, named COL2A1, provided key insight into how a well defined gene locus may give rise to incident OA, what has remained enigmatic is the determination of what genes contribute to OA, with its more characteristic phenotype, in the general population.

Alleles of the vitamin D receptor gene may furnish an additional important piece to this unraveling puzzle. In a recent population-based cohort of women, also from England, a Taq I polymorphism of the vitamin D receptor gene was related to a nearly 3-fold increased prevalence of knee OA[13]. In contrast, among a Belgian case-control study of postmenopausal women, those undergoing hip replacement for OA harbored no difference in frequency of the Bsm-I polymorphism of the vitamin D receptor gene compared to healthy controls, nor in polymorphisms for COL1A1 or COL2A1[14]. Moreover, in the Framingham Osteoarthritis Study, polymorphisms of the COL2A and VDR gene, both located on chromosome 12q, were not related to OA at either the knee or hand[15]. As to whether the vitamin D receptor polymorphism and its influence on OA risk might vary by ethnicity, no relation was observed in a case-control study from Japan focused upon women with OA of the hand, hip, and knee[16].

Importantly, Jordan, *et al* ascertained symptom status. The mere presence of radiographic disc narrowing, and of osteophytes at the uncovertebral margins and at apophyseal joints, does not in and of itself necessarily translate to a clinically meaningful outcome. In this vein, Jordan, *et al* report that the presence of back pain was not related to radiographic evidence of osteophytes or joint space narrowing. Therefore, one need bear in mind whether in such studies an observed relationship of birthweight, of vitamin D receptor polymorphisms, or of other measured risk factors is related to a clinically meaningful outcome, namely those persons with symptoms and radiographic evidence of OA of the lumbar spine.

One may also remain intrigued about a potential relationship of serum levels of vitamin D (1,25 hydroxycholecalciferol) to OA risk. Whereas in the Framingham cohort, lower levels of serum vitamin D were related to heightened risk of OA progression at the knee joint[17], in the report by Jordan, *et al* we are only informed that an interaction between the vitamin D receptor polymorphism and serum vitamin D levels was not observed. Finally, from a methodologic standpoint, it is important to encourage that such epidemiologic studies educate the reader about the magnitude of measured effects and not merely to rely on the measured P value[18]. In this way, a greater understanding may be ascertained from the completed endeavor.

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