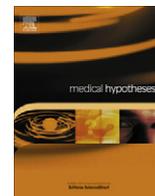


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Does diabetes hide osteoarthritis pain?

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ABSTRACT

Clinical practice and research efforts related to the highly prevalent and disabling disease, osteoarthritis (OA), have long been hampered by an inadequate case definition. Much of the difficulty is due to a lack of agreement between X-rays evidence of OA and a patient's report of pain at that site. Such discordance between reported pain and radiographic evidence of OA has been attributed to several factors. This paper proposes another possible explanation, for at least a portion of such patients. It is hypothesized that an insidiously increasing diabetic neuropathy, particularly in the lower extremity, while first causing some pain, may gradually inhibit the ability to feel pain which might have otherwise been reported by those patients without neuropathy. Many of these patients with early stage glucose dysmetabolism will proceed to develop overt type 2 diabetes; however, the pain-inhibiting neuropathy caused by glucose metabolism dysfunction may manifest long before such a diagnosis. The high prevalence of diabetes and pre-diabetic conditions, especially among the aged population, could mean that a substantial number of individuals with osteoarthritis will have both diseases to varying degrees over time. Validating and quantifying this hypothesized association would be useful to millions of persons and would significantly impact both research and clinical practice dealing with these major diseases of older persons.

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Introduction

Osteoarthritis (OA), the most common form of arthritis, is one of the most debilitating of all the chronic diseases that affect aging individuals. OA is characterized by cartilage erosion, development of osteophytes, varying degrees of changes to the underlying bone and synovial fluid, and the involvement of a variety of inflammatory components throughout the process [1]. The pathophysiology and main causes of OA have remained elusive, though research efforts have discovered some risk factors, such as age, gender, obesity, past injury, and genetic factors, among others [2–5].

The orthopedic community has been plagued for years by a poor association observed between joint pain and radiographic evidence of OA. This discordance is troubling to both clinicians and epidemiologists. In a 2008 systematic review of population studies, Bedson and Croft quantitatively described the problem for knee OA: “The proportion of those with knee pain found to have no radiographic osteoarthritis ranged from 15% to 76% and in those with radiographic knee OA (KOA) the proportion with pain ranged from 15% to 81%” [6]. Variation in case definitions and measurement of both OA and pain is one important factor for the observed discordance between joint pain and radiographic OA [6–8]. Another reason cited for the discordance may be the nature of the OA disease process. The location and type of pain receptors and their biochemical and biomechanical thresholds are some of the

factors that may be expressed differently through increasing stages of OA-related degeneration. Finally, the existence of comorbidities with overlapping, competing, or masking of pain likely contributes to the OA/pain discordance issue. Dieppe [9] and others [10] have suggested that OA might be too often studied in isolation, and researchers would be better served by considering the possibility of a shared etiology with other known systemic diseases. This claim is probably correct in the sense that diabetes, and its precursor metabolic conditions, are likely related to the development and expression of OA.

The hypothesis

Neuropathy caused by impaired glucose tolerance/diabetes mellitus inhibits the expression of pain due to osteoarthritis in the lower extremities among a portion of patients displaying radiographic osteoarthritis (Fig. 1).

Both OA and diabetes mellitus (DM) can be viewed as chronic disease processes characterized by early, undetected levels of biological change. Once initiated, the OA and DM pathological processes proceed by a decline in the conditions over time at individual-specific rates, dependent on various innate and environmental factors. Additionally, both of these diseases are associated with increasing age and thus, likely to be comorbid conditions [11,12]. Prediabetes, characterized by impaired glucose tolerance (IGT) and insulin resistance, will often gradually progress to overt DM: which, even at that symptomatic stage, may go undetected, undiagnosed, and untreated for some time [13]. While DM is associated

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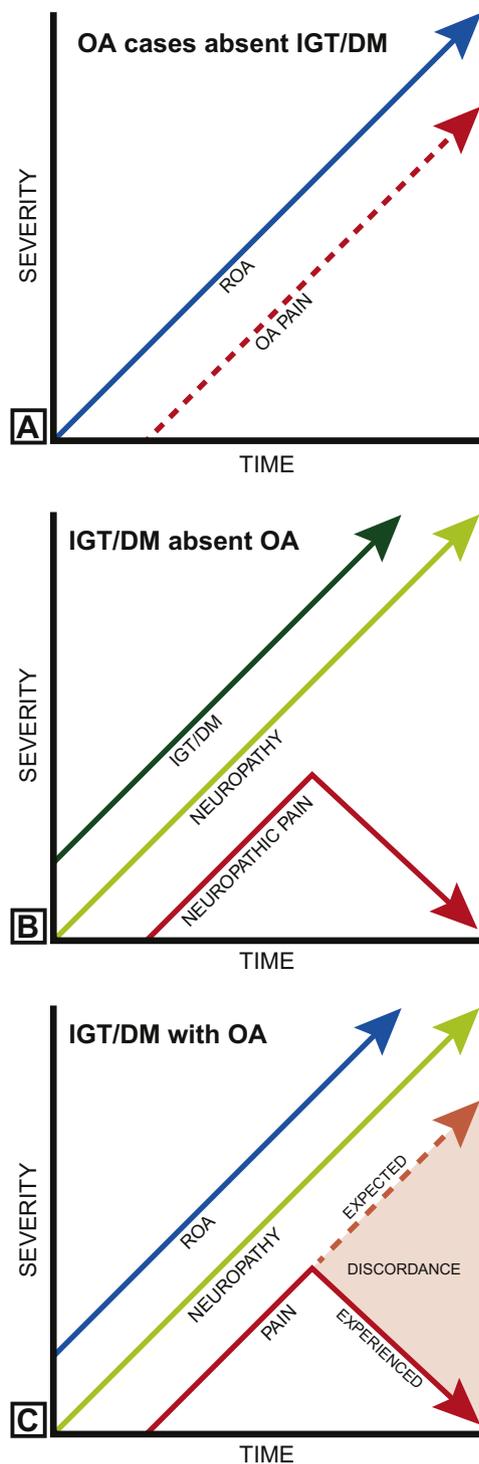


Fig. 1. General schematic of pain discordance occurring with osteoarthritis and impaired glucose tolerance or diabetes mellitus disease progression. (A) As OA progresses in those without IGT/DM, ROA worsens and pain is expected to increase. (B) In those without ROA, as IGT/DM increases and the length of time a person experiences IGT/DM increases, diabetic neuropathy increases. Early neuropathy may be experienced as pain. In later stages, neuropathy may be experienced as lack of sensation; consequently no pain. (C) As both OA and IGT/DM progress, ROA and neuropathy increase in severity. In earlier stages, pain may result from either or both diseases. As sensation is lost in later stages due to neuropathy, less pain is experienced than would be expected from the increasing OA. The pain/ROA discordance is the difference between the expected and experienced pain. *Acronym key:* OA, osteoarthritis; IGT, impaired glucose tolerance; DM, diabetes mellitus; ROA, radiographic osteoarthritis.

with many complications, diabetic neuropathy, generally defined by structural and functional peripheral nervous system impairment, is the most commonly diagnosed diabetic complication with prevalence estimates ranging from 45% to 50% of diagnosed diabetics [14]. The etiology of this condition is not clearly understood, but has been shown to be influenced by factors such as poor insulin regulation, diabetes duration, and height [15]. As the IGT/DM condition is left untreated, the resultant neuropathy causes sensory and motor axonal degeneration resulting in paresthesias, loss of proprioception, numbness, and loss of peripheral sensation [16]. The feet and ankles are particularly subject to these symptoms [15,17–19]. In less common cases these symptoms may manifest in the knees and upper extremity as well [11].

The suggested hypothesis seeks to explain a substantial portion of the radiographic OA/pain discordance by theorizing that it is the result of a gradual metabolic process of impaired glucose metabolism and a subsequent pain-suppressing neuropathy. We propose that many of those individuals who display unequivocal radiographic evidence of OA, yet report no associated pain, may be suffering from a chronic sensorimotor diabetic neuropathy and experience a blunting of the OA-related pain, which would otherwise be more severe. Dose–response would be expected based on relative joint location and on severity of OA, with the OA/pain discordance more pronounced in the distal joints and with increasing severity of OA for persons with more advanced diabetic neuropathy. For example, the OA/pain discordance would be greater in the foot, relative to the knee and the hip and greater for joints with more radiographic evidence of OA. The hypothesized causal relationship between impaired glucose metabolism and lack of reported pain associated with radiographic OA has biological plausibility. The current understanding of the etiology and pathogenesis of diabetic neuropathy supports this concept.

Evaluation of the hypothesis

One of the earliest studies of the association between OA and DM, conducted by Waive et al. in 1961, examined the radiographic severity of OA in the hands, spine, hips, knees, and feet of diabetics and age- and sex-matched non-diabetic controls [12]. They found that not only was OA more prevalent and more severe among the diabetics, but that it also presented at a younger age in the diabetics, as compared to the controls. These differences were noted across all joints examined but only reached statistical significance in the knees and feet, supporting our hypothesis that diabetic neuropathy would preferentially alter the OA disease manifestation in the more distal joints of the lower extremity. Hence, it is expected that the discordance between joint pain and radiographic OA would be the greatest in the feet, given the high prevalence of diabetic neuropathy in this group of joints. Most epidemiological studies of the OA discordance issue have focused on the knee, leaving the discordance largely unexamined in the foot [1–6].

Elevated vibration perception threshold (VPT) and decreased nerve conduction velocity (NCV), commonly employed markers of diabetic neuropathy, have been studied extensively in patients with IGT/DM [20] and to a lesser extent, in OA patients [21,22]. As the neuropathy increases in severity, the degree of nerve damage is typically evidenced by changes in VPT and NCV. Shakoor et al. demonstrated that both radiographic KOA [21] and radiographic hip OA (HOA) [22] were significantly associated with an increased lower extremity VPT at all sites tested, compared to age-matched subjects free of KOA or HOA, respectively. The VPT-tested sites were: near the big toe, on both sides of the ankle, on both sides of the knee (in KOA study). These results indicate significant vibratory sensation deficits of the lower extremity is a characteristic shared by subjects with diabetic neuropathy and by subjects with OA of

the knee and hip. These findings provide supporting evidence for our hypothesis and possibly indicate a shared underlying mechanism. A study examining subjects with both IGT/DM and KOA or HOA would refine the understanding of this relationship.

Although studies directly refuting the hypothesis have not been located, several primary concerns have been identified. First, it must be recognized that not all OA researchers are in agreement that a significant discordance between radiographic evidence of OA and reported pain even exists. Several studies have demonstrated a moderate to strong correlation between pain and radiographic OA [23–25]. Most recently, Neogi et al. examined the association between pain and radiographic KOA in two large cohort studies, with results demonstrating “a strong dose–response relation between severity of radiographic knee osteoarthritis and knee pain, as measured by three characteristics: presence of frequent knee pain, consistency of knee pain, and severity of knee pain” [23]. These researchers accurately emphasized the potential for confounding to afflict epidemiological investigations of the association between pain and radiographic OA, given the highly subjective and individual nature of pain and the imperfect assessment methods employed. However, many other researchers [24,26–29] have found evidence for a substantial discordance between pain and observed radiographic evidence of OA, indicating that this issue is far from completely understood. The proposed hypothesis also allows for the partial explanation of pain/radiographic OA discordance by considering the natural history of IGT/DM neuropathy. Typically, the neuropathy first presents as pain and then as it progresses, sensation diminishes until sensation is no longer experienced. The extensive variability in the literature on the discordance between pain and radiographic OA points to the need for further investigation of this complex phenomenon.

There are several possible explanations for the OA/pain discordance issue derived from the considerable variability in the definition and measurement of both OA and pain. Spector and Hochberg eloquently describe the challenges presented by this discordance on the conduct and interpretation of epidemiologic investigations of OA [30]. Bedson and Croft identified a few of the reasons for the OA/pain disparity, including the number and aspect of the radiographs taken for OA assessment purposes [6]. Additionally, the most commonly used method of assessing x-rays for evidence of OA, the Kellgren–Lawrence (K/L) scale, has been criticized for utilizing composite scores derived by combining a number of elements, regardless of whether or not all of the individual components have been found to be associated with pain. The composite scores are based on overall impressions rather than specific counts and measurements, and do not assess the severity of each element separately [3].

The definition of pain also varies by study; pain may be defined by including or excluding the degree of functional limitations and disability, and definitions vary significantly according to frequency, severity, and duration of the reported pain [6]. Such extensive variability in pain definition renders it nearly impossible to compare pain across various studies. Clearly, efforts are required to develop a standardized pain index to quantify pain in an objective, consistent manner across study protocols. There have been attempts to include pain grading as a component of OA assessment, such as the development of the Western Ontario and McMaster Universities Arthritis Index (WOMAC), which takes into account severity of pain and functional limitation [31]. As more studies are conducted and the OA and pain measurements are refined, we expect the OA/pain discordance issue to decrease, but not disappear.

Another related consideration is that the literature does not yet exist, even in a piecemeal fashion, to support the hypothesis. Detailed studies examining OA/pain discordance in the foot, relative to the knee and hip have not been conducted. Nor have studies demonstrating the possible discordance with respect to the hand, another distal site that may be affected by similar neuropathic

and OA processes. The details of the underlying physiological and biochemical mechanisms have also not been fully elucidated and described. Finally, when investigating the hypothesis it is important to account for disease progression in both OA and IGT/DM. OA pain may occur in different structures at different levels of severity during different stages of disease progression. Likewise, it is known that diabetic neuropathy is expressed differently as it worsens [16]. Stages of both diseases need to be considered when describing their interaction, further complicating the matter. There is a gap in the literature on this aspect as well.

Hypothesis testing

Recognizing that no single study can sufficiently evaluate the proposed hypothesis, population-based, clinical, and laboratory studies all stand to contribute to the scientific investigation of its merit. Epidemiological studies would need to examine a variety of relevant factors, such as height, weight, glucose metabolism (non-fasting serum test of HbA1c), KL scoring of X-rays across the hip, knee, and foot joints, WOMAC index to assess pain and function, and a detailed neurological evaluation (including nerve conduction capability and vibration, thermal, and electrical sensory perceptions). All variables mentioned have been used in various combinations in prior studies of OA or IGT/DM; however, the techniques have not been combined in studies reported in the literature. It bears emphasis that detailed information on pain and OA imaging is necessary to develop a reliable method for OA assessment in the lower extremity, allowing for the valid investigation of the role that IGT/DM plays in the manifestation of OA-generated pain. Given the inherent difficulty in assessing tissue changes and biochemical processes in human population studies, laboratory studies conducted on mice models of comorbid OA and IGT/DM likely would offer greater insight into the molecular pathogenesis by providing histological and biochemical analyses of the affected tissues for each stage of disease.

Consequences and discussion

Both OA and IGT/DM are highly prevalent and debilitating diseases that are destined to assume a larger role affecting the health of the United States population in the coming years, primarily due to aging of the population and the obesity epidemic. The conservative 2008 estimates yielded an OA prevalence of 27 million, based on OA of the knee, hip and hand [32], and other extrapolations have projected a doubling in the prevalence of OA between 2000 and 2020 [33]. According to 2007 National Institutes of Health data, the prevalence of diabetes among Americans aged 60 years or older is 12.2 million, or 23.1% of all Americans above the age of 60 [13]. A published survey by the National Center for Health Statistics indicated that more than half of the 20 million American adults who have diabetes are also afflicted with OA [34]. The increasing incidence of obesity among younger individuals is likely to lead to even earlier onset of both IGT/DM and OA and more rapid OA progression resulting in an overall increase of disability due to OA at earlier ages, causing a marked increase in the total years of disease burden. Thus, the potential interaction of these underlying systemic disease mechanisms is of significant interest. If the hypothesis proves to be correct, that is, progressive neuropathy caused by an increasing impairment in glucose metabolism retarding the expression of OA-related pain in the lower extremities in a portion of patients displaying radiographic OA, there are clinical, public health, and research, ramifications.

Clinical

Clarification of reasons for the pain/ROA discordance would be useful to clinicians when assessing either diabetes or OA.

Endocrinologists and general practitioners could routinely screen patients with IGT/DM for OA in the lower extremities, particularly those who show altered biomechanics, to allow for early initiation of appropriate interventions, such as supportive footwear, supports, and physical therapy, to help maintain mobility, functionality, and slow disease progression. Rheumatologists and orthopedists could recommend that patients with early onset OA or rapidly progressing OA of the lower extremities be screened and treated for IGT/DM. Additionally, radiographically diagnosed OA without accompanying pain in that patient may signal an increased need for the testing of glucose levels. A beneficial byproduct of the research to prove this hypothesis may be improved and more refined clinical and radiographic OA definitions for the lower extremity joints. Such a result would contribute to improved epidemiologic studies of OA, leading to more precise estimates of risk factors.

Public health

Increasing awareness of the link between OA and DM through existing public health education avenues will provide additional impetus to change clinical practice as more informed patients query their health care providers. Earlier intervention in either DM or OA has demonstrated health benefits.

Research

The understanding that two systemic diseases, OA and IGT/DM, are interrelated in ways not previously envisioned provides a shift in the health research paradigm, which has tended towards the more specific, rather than inclusive, perspective. The ability to analyze large volumes of complicated and inter-related data provides the means to look at underlying disease mechanisms common to more than one health issue. Pharmaceutical treatments developed to target common mechanisms will reduce the per patient medication burden, resulting in fewer medication interactions, complications and errors. In addition, preventive methods may be more readily identified and implemented to mitigate disease initiation and progression.

Diabetic neuropathy as an explanation for a portion of the discordance between pain and OA identified on X-rays, is deceptively simple. Aging of the population and increasing obesity imply the potential public health impact of such an hypothesis. Underlying mechanisms that contribute to OA, IGT/DM, and neuropathy, are likely complex and may indeed be inter-related. Consequently, the studies designed to evaluate this hypothesis will yield results far beyond this circumscribed domain. The recognition that a portion of the observed discordance between pain and radiographic evidence of OA may be due to diabetic neuropathy will result in improved osteoarthritis case definition and interpretation. Such improvements would have a clear impact on both research and clinical practice dealing with this major disabling disease.

Conflict of interest

The authors have no conflicts of interest to declare.

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