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REVIEW ARTICLE

Osteoarthritis: genes, nature–nurture interaction and the role of leptin

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Abstract Osteoarthritis (OA) is a common disease affecting patients at different ages regardless of gender or ethnicity. As with many chronic diseases, OA is thought to have a multifactorial aetiology, which is not fully understood. Whereas the pathophysiological process of OA can be analysed at a cellular and molecular level, the interaction between genes and lifestyle remains an important factor in the development of this disease. The expanding awareness of different genes that may play a role in OA, together with many chemical mediators thought to be associated with the progression of the disease, will help in better management of this condition. Some of the chemical mediators recently implicated in this condition are the adipokines (leptin, adiponectin and resistin). Few but consistent studies suggest that leptin in association with obesity could be an important factor in OA aetiology. Hence, this could establish a strong and direct molecular link between patient life style (nurture) and the pathological process of OA (nature). However, neither a clear mechanism nor a direct clinical association linking leptin to OA has yet been established. In this article, we explore some of the genetic and environmental factors in OA aetiology. We discuss leptin in obesity and assess its possible association with OA aetiology. This should emphasise the important role of health professionals in treating obesity in order to control OA symptoms and possibly progression.

Keywords Osteoarthritis · Gene · Homeostasis · Leptin · Environment

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Introduction

Osteoarthritis (OA) is a common progressive disease with a complicated aetiology affecting synovial joints and results in fibrillation of the extracellular matrix (ECM) and ultimately ulceration of the articular cartilage, leading to reduction in joint space [1, 2]. It effects 15 % of the world's population and is strongly associated with aging [3]. In the UK, approximately eight million people suffer from OA, and one million are undergoing some form of treatment [4]. All ethnic groups are affected [5], but the prevalence differs from one race to another. For example, it is more prevalent in the white Europeans and less so in black Africans, Indians and Chinese [5, 6]. OA is also more common in women [7] and strongly associated with obesity (knee) [8, 9] and manual jobs (hip and knee) [7, 10, 11], reflecting the complex interaction between genetics and environmental factors in its aetiological process (Fig. 1).

Gradual erosion of the articular cartilage in OA is preceded by compositional and mechanical changes in the ECM mediated by an imbalanced regulation of a plethora of complex molecules, such as metalloproteinases and multiple inflammatory factors [12–14]. This overwhelms the homeostatic processes of the articular cartilage, leading to its structural failure [15].

Genetic and environmental influences on the development of the disease

As with other chronic conditions, such as hypertension and asthma, OA has been classified as a common, multifactorial disorder with environmental and genetic causes [16, 17]. Its possible genetic basis was first recognised in the 1940s. Subsequent studies revealed that a twin or sibling of someone with OA was more likely to develop the disease than the

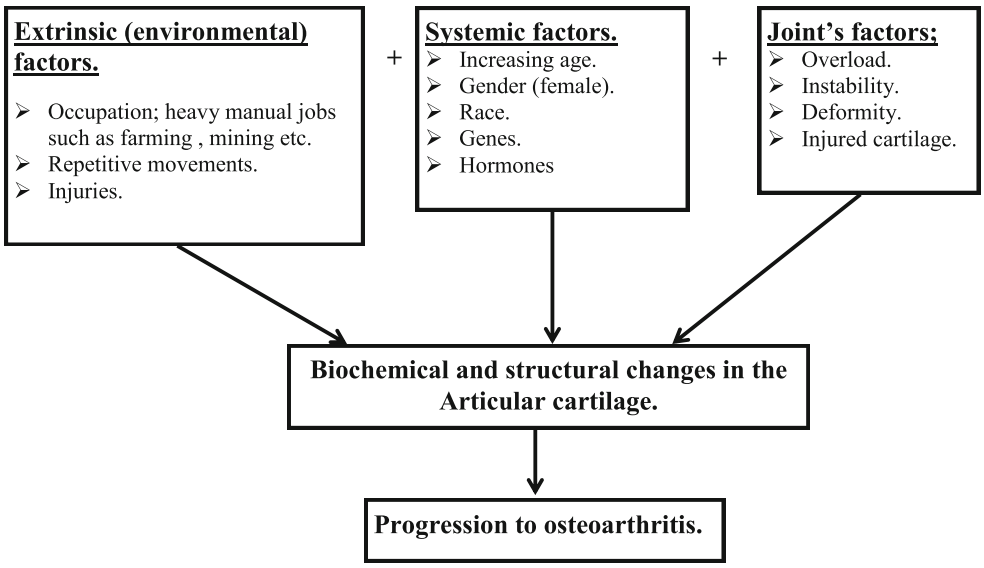

Fig. 1 Factors influencing the onset of osteoarthritis (OA). Many factors in isolation or combination can influence onset and progression of the disease

general population [16, 18]. Since then, the genetic influence on OA pathogenesis has consistently been shown by many epidemiological, twin-pair and family-clustering studies [18–21]. Genome-wide association and linkage-scan studies have uncovered a plethora of genes that may be implicated in OA aetiology [22], and now it is thought that the genetic influence could explain >50 % of the variations in susceptibility to this condition [16, 18]. It is evident that OA may have a polygenic inheritance mode transmitted in a non-Mendelian manner, whereby the interaction of many genetic defects may be responsible [19]. The severity of the disease is determined by the amount and the severity of gene defects.

Mercedes et al., in their review, listed more than 26 possibly important genes thought to harbour susceptibility to OA, with a variable level of involvement [18]. These include genes coding for structural proteins of the ECM, such as collagen type 2, and cytokines involved in the inflammatory process associated with this condition. Some genes discovered thus far do not pose a consistent increased susceptibility to OA development [18, 20]. However, the involvement of the interleukin 1 (*IL-1*) gene and the asporin gene (*ASPN*) have been the most compelling, showing a significantly strong statistical association [22]. Other genes thought to be of importance include that encoding vitamin D and its receptor, the oestrogen receptor α gene (Er-α) and the secreted frizzled-related protein 3 gene (*FRZB*) [16, 18, 19].

Following the announcement of the sequencing of the human genome in April 2003 [23], there has been considerable emphasis on the genetic role in the pathogenesis of diseases, including OA. This project created a base for further research into the mode of inheritance of genetic diseases based on isolating and cloning mutated genes [24]. The next important step in genetics is the human proteome project, which aims to identify all proteins present in tissues and cells and their alternations in relation to health and illness [25]. Researchers in other projects have diverted their attention into the possible involvement of mitochondria and mitochondrial DNA in the pathogeneses of OA [26]. Some studies demonstrate the association of certain mitochondrial DNA polymorphism with the severity of OA in the European population [18].

The role of the environment in OA aetiology has been demonstrated by directly linking OA to some jobs and activities undertaken by individuals [10, 27] (Table 1). In a cross-sectional study involving more than 10,000 people, Rossignol et al. [7] reported an increase in the prevalence of hip and knee OA in people involved in more physically demanding occupations, with an earlier incidence in women than in men. Activities involving kneeling, squatting and heavy lifting are associated with knee OA [30, 31], particularly in patients with a high body mass index (BMI) [11]. Framing and other heavy manual jobs are associated with hip OA [10, 27], whereas textile workers have a higher incidence of hand OA [7]. Despite the consistency in these studies, some authors report that the association between occupation and OA is weak [27], suggesting that another and more potent factor (or factors) may play a significant role in the aetiology of the disease.

OA and role of obesity and leptin

Many mechanisms are proposed for the degenerative process in the articular cartilage [13]. OA progression is broadly divided into three stages [1]: stage I involves breakdown of the cartilage matrix by proteolytic enzymes; stage II involves

Table 1 Occupation and osteoarthritis. Some occupational activities have been associated with osteoarthritis of the main joints

Occupational hazard	Reference citations
Hip	
Heavy manual work	[27, 28].
Tasks involving uncomfortable joint position	[7].
Female cleaners	[7].
Female postal workers	[29].
Male farmers	[7, 27, 29].
Builders	[7, 29].
Fire fighters and food-processing workers	[29].
Knee	
Tasks involving uncomfortable joint position	[7].
Repetitive bending, kneeling, squatting	[28, 30, 31].
Carrying loads	[32].
Carpenters and miners	[33].
Female cleaners	[7, 29].
Fire fighters	[29].
Construction workers	[29, 31].
Hand and wrist	
Movements repetition, such as bending and twisting	[7, 28, 34]
Work at a pace set by a machine	[7, 34]
Textile workers	[7]
Female cleaners	[7]
Technicians and assemblers	[35]
Elbow	
Heavy physical work	[36]
Foundry workers	[37]

further damage to the articular cartilage, fibrillation and erosion, together with the release of products into the joint space; stage III is characterised by inflammatory responses as a result of ingestion of products and synthesis of proinflammatory cytokines and proteases. Some inflammatory components include tumour necrosis factor alpha (TNF-α) and interleukin-1, (IL-1), which lead to the slowing of ECM synthesis and increased catabolic activities of metalloproteinases [14, 38].

The biomechanical effect of weight is thought to exacerbate the degenerative process and symptoms of OA directly by excessive loading of the joints and indirectly by stimulating mechanoreceptors on the surface of chondrocytes [39, 40]. Activation of these receptors is thought to induce production of inflammatory mediators and metalloproteinases responsible for cartilage destruction [41]. Nevertheless, whereas excessive weight is considered an aetiological factor, it does neither explains the association of hand OA with obesity [15, 42] nor the high risk of developing OA in more than one joint in the same individual [43]. Some authors argue that the only role of biomechanical load is to determine which joint manifests the first symptoms [15], and that OA is driven by systemic and metabolic processes other than the biomechanical influence of weight [44, 45], hence the presence of OA in non-weight-bearing joints.

Using the example of knee OA, Clockaerts et al. [46] suggested that the accumulation of immune cells, adipocytes and nerve fibres (peptidergic C fibres) in the infrapatellar fat pad (IFFP) influences cartilage metabolism, which provides an insight into other possible mechanisms that may be implicated in OA, especially in non-weight-bearing joints [44].

Adipose tissues are known as excess-fat-storage tissues but are now recognised as a form of connective tissue containing adipocytes, fibroblasts, leucocytes and macrophages involved in the process of inflammation [47, 48]. They produce ILs, growth factors including TNF-α, which are known to have an influence on OA [46]. Furthermore, adipose tissue secretes adipokines such as leptin and resistin [49]. These are found at increased concentration levels in obese individuals, hence their possible implication in cartilage metabolism and OA [50, 51]. Lack of exercise and a diet high in fat content are associated with increased levels of leptin within the serum [52]; conversely, reduction in BMI is associated with reduction in leptin serum levels [53]. This may suggest that the body's natural homeostatic control system for leptin within the joint fails to restore the normal homeostatic balance of leptin within the joint in obese individuals.

Leptin is a 16-kDa, nonglycosylated peptide hormone encoded by the obese (*LEP*) gene [54]. Leptin enters the circulation, crossing the blood–brain barrier to act on the hypothalamus to control food intake and energy expenditure [55]. It is involved in regulating other physiological processes, including lipid homeostasis, thermogenesis [56], insulin secretion [57], reproductive functions [58], angiogenesis and immune function [59, 60]. It is also shown to regulate bone growth directly by inducing osteoblast proliferation, collagen synthesis and bone mineralisation or indirectly by releasing antiosteogenic factor [17]. It is thought that leptin has an anabolic effect on cartilage by stimulating TGF-β and insulin-like growth factor (IGF) [44, 61]. Furthermore, leptin is classified as an adipocytokine because it shares common structural properties with IL-6 cytokines [54] and therefore is thought to play a role in the immune response [62].

An increased level of freely circulating leptin in blood plasma is thought to diffuse into the joint space [61]. The high levels of leptin in the synovial fluid are detected by sensory receptors for leptin on chondrocytes [61, 63]. It induces its effects by stimulating the leptin receptor, which is encoded by the LEPR gene with at least five isoforms existing in humans. The leptin receptor (OB-Rb) activates the Janus kinase/signal transducer, an activator of the transcription signal transduction (JAK/STAT) pathway [54] (Fig. 2).

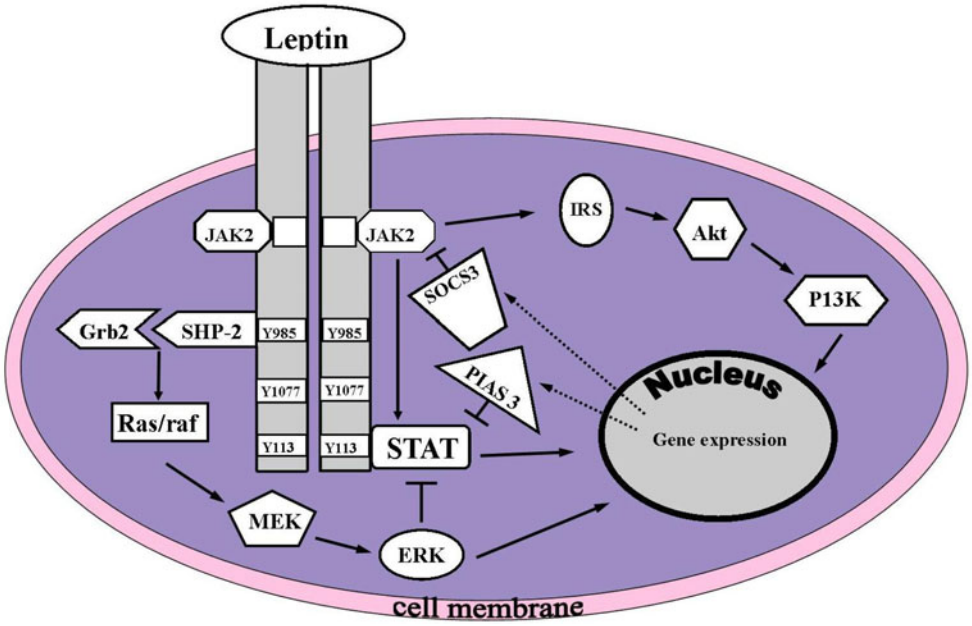

Fig. 2 Mechanism of leptin Intercellular signaling. Upon leptin binding to the leptin receptor (OB-Rb), the Janus kinase/signal transducer and activator of transcription (JAK/STAT), mitogen-activated protein kinase/extracellular signal-regulated kinase (MAPK/ERK) and phosphatidylinositol 3-kinase (PI3K) pathways are activated. *Akt* protein kinase B; *Grb-2* growth-receptor-bound 2; *IRS* insulin receptor substrate; *MEK* mitogen-activated protein kinase kinase; *PIAS3* protein inhibitor of activated signal transducer and activator of transcription 3 (STAT3); *Raf* MEK-kinase; *Ras* G-protein; *SHP2* domain-containing protein-tyrosine phosphatase; PTPN11, *SOCS3* suppressor of cytokine signalling-3. Reproduced with kind permission from [60]

In obese individuals, there is an increase in leptin serum and synovial fluid levels [50, 61]. In OA articular cartilage, an increased level of leptin messenger RNA (mRNA) is found in chondrocytes [63] in association with an increased level in synovial fluid [50, 61, 63]. Demund et al. demonstrated a correlation between the level of leptin expression by chondrocytes and the increased grade of cartilage destruction [61]. Even when comparing OA and normal cartilage in the same joint, Simopoulou et al. found an increased expression of leptin and its receptors on chondrocytes inhabiting the OA cartilage zones [63].

In laboratory studies on mice, leptin induces formation of proteoglycans, IGF and TGF-β1 in a dose-dependant response [54, 61], as well as IL1B, gelatinase B (MMP-9) and human procollagenase 3 (MMP-13) expression [63], which confer detrimental effects on chondrocyte proliferation at high concentration levels [54, 63]. These studies suggest that leptin may be involved in regulating chondrocyte metabolism and the ECM composition in OA. In degenerative vertebral spine discs, leptin and its receptor have been detected at high concentration levels promoting proliferation of nucleus cells, which also suggests an important role for leptin in pathogenesis of intervertebral disc degeneration [64].

Laboratory findings provide convincing evidence of a possible role for leptin in OA pathogenesis. However, a few authors failed to establish a direct association between serum leptin (and other adipokines) and arthritis in the hand. In a study involving 44 patients, Massengale et al. [65] could not demonstrate any correlation between the grade of hand OA and the levels of serum adipokinase. This has been supported by a larger study involving more than 1,000 patients, in which the authors could not demonstrate a significant difference in serum leptin concentration levels in patients with OA (symptomatic and asymptomatic) and controls [66]. However, leptin was correlated with the visual analogue scale (VAS) for pain, which may yield support for its inflammatory role in OA [65, 67, 68]. The contradictory results between laboratory studies and recent clinical studies cast a shadow on the exact role of leptin in OA pathogenesis; however, the lack of correlation between serum levels of leptin and OA severity could be explained by the following:

1. Leptin may not have any role in OA initiation but could be a secondary response involved in the subsequent inflammatory phase following articular cartilage degradation. Hence the high levels of leptin found in zones affected by OA and low levels in normal cartilage within the same joint [63]. If the high concentration level of leptin in obese individuals plays a major role in OA initiation, then leptin expression would be distributed uniformly in all joint cartilage and would also result in uniform cartilage destruction. However, the existence of leptin as an inflammatory mediator in OA cartilage may still potentiate the degradation process [67, 68].

2. Leptin at a low concentration levels stimulates chondrocyte proliferation but inhibits proliferation at high concentration levels [63], which are only found in association with high BMI [61]. Therefore, its inhibitory role may manifest only in obese individuals. Hence the high serum leptin levels correlated with knee OA in patients with high BMI [67].
3. In OA, leptin concentration in synovial fluid is greater than that of serum levels [50, 67]. Hence, serum levels may not reflect true leptin synovial levels, which have a direct influence on articular cartilage. This could be the reason that studies by Massengale et al. [65, 66] failed to establish an association between serum leptin and hand OA.

In conclusion, biomechanical causes of OA in obesity play a vital role in OA progression, but the associated high levels of adipokines (such as leptin) in chondrocytes suggest a possible implication of leptin in OA pathogenesis. Studying the multifactorial aetiology and involvement of many complex processes in OA will continue to reveal different chemical mediators that may appear to have an association with OA pathogenesis. The difficulty will be distinguishing between molecules that play a role in OA initiation and progression phases and those that emerge as a localised secondary response to the condition. This may also explain why target therapy against some of the chemical components of OA has not yielded any clinical benefit [15].

Whatever the mechanisms linking obesity to OA—be it biomechanical or chemical—there should be a concerted effort to counteract the effect of obesity on joints. In fact, this provides a venue for health-care workers to help reduce progression and symptoms of OA associated with obesity. Obesity is a modifiable factor [69] that could be reduced or eliminated by education and support/guidance given by health-care professionals. This is important because the increasing epidemic of obesity worldwide could potentially lead to an increase in the incidence of OA.

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