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REVIEW ARTICLE

Role of hormones in cartilage and joint metabolism: understanding an unhealthy metabolic phenotype in osteoarthritis

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Abstract

Objective: Joint health is affected by local and systemic hormones. It is well accepted that systemic factors regulate the metabolism of joint tissues, and that substantial cross-talk between tissues actively contributes to homeostasis. In the current review, we try to define a subtype of osteoarthritis (OA), metabolic OA, which is dependent on an unhealthy phenotype.

Methods: Peer-reviewed research articles and reviews were reviewed and summarized. Only literature readily available online, either by download or by purchase order, was included.

Results: OA is the most common joint disease and is more common in women after menopause. OA is a disease that affects the whole joint, including cartilage, subchondral bone, synovium, tendons, and muscles. The clinical endpoints of OA are pain and joint space narrowing, which is characterized by cartilage erosion and subchondral sclerosis, suggesting that cartilage is a central tissue of joint health. Thus, the joint, more specifically the cartilage, may be considered a target of endocrine function in addition to the well-described traditional risk factors of disease initiation and progression such as long-term loading of the joint due to obesity. Metabolic syndrome affects a range of tissues and may in part be molecularly described as a dysregulation of cytokines, adipokines, and hormones (eg, estrogen and thyroid hormone). Consequently, metabolic imbalance may both directly and indirectly influence joint health and cartilage turnover, altering the progression of diseases such as OA.

Conclusions: There is substantial evidence for a connection between metabolic health and development of OA. We propose that more focus be directed to understanding this connection to improve the management of menopausal health and associated comorbidities.

Key Words: Osteoarthritis – Menopausal health – Metabolic syndrome – Estrogen.

Degenerative joint diseases, such as osteoarthritis (OA), lead to pain and physical disability. A worldwide estimate indicates that 10% of men and 18% of women aged 60 years or older have symptomatic OA.[1,2] Several independent lines of evidence support that OA affects the whole joint, including cartilage, bone, muscle, tendons, and synovium.[3] The primary clinical outputs of OA are pain and joint space narrowing, which is a result of cartilage erosion and subchondral sclerosis. It is therefore natural to view cartilage erosion as a surrogate endpoint in OA, the common denominator in all OA subtypes.

There is a missing link between the pathological outcome of OA, joint replacement, and the understanding of the initiators and drivers of OA that may vary at different stages of the disease. There is a clear lack of knowledge on the interactions between risk factors and progression of OA, as illustrated in Figure 1. At present, the understanding of risk factors and subpopulations of OA is a "hot topic," as such understanding may enable better disease understanding and, thereby, drug development for OA. OA is defined as the loss of cartilage and bone sclerosis of articular joints accompanied by joint pain, which is the obvious end result of years of disease progression in patients of different disease origins and history.

OA is significantly associated with an unhealthy metabolic phenotype (eg, overweight and hormonal dysregulation),

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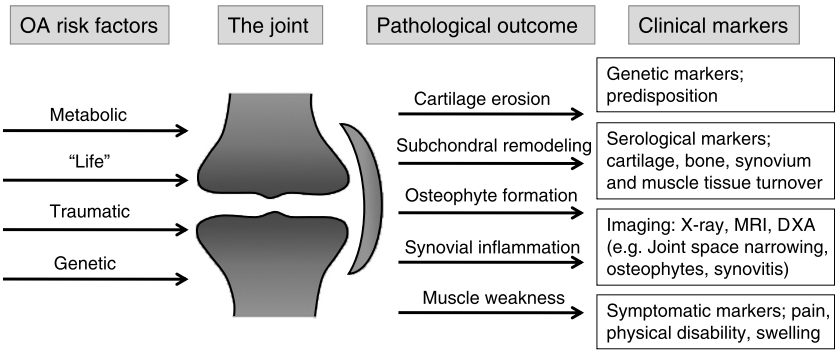

FIG. 1. Several broadly described risk factors or initiators of OA: metabolic components such as unhealthy phenotype and metabolic syndrome; "life," a miscellaneous term including age and less-defined time effects; trauma, both acute and chronic, with mechanical and accidental overtones; and genetics, resulting in predisposition to OA development and progression. All of these risk factors might be not only initiators but also drivers of OA by stressing the joint with different insults. These insults are poorly understood, creating a void between the risk factors and the pathological outcome. OA, osteoarthritis; MRI, magnetic resonance imaging; DXA, dual-energy x-ray absorptiometry.

life" (eg, age, wear and tear), acute trauma, and heredity.[4,5] However, the exact metabolic components that directly influence the development of OA are unclear. It is known that weight loss is an excellent short-term investment in joint loading for patients with combined obesity and knee OA.[6] A recent study in Japanese men and women showed a significant relationship between the presence of metabolic syndrome and knee OA.[7] Further evidence from an additional clinical study in patients with generalized OA (defined as symptomatic OA in at least two joints) demonstrated a statistically significantly increased vessel wall thickness of arteries as compared with participants without OA, even after adjustment for confounders such as sex, age, and body mass index (BMI).[8] Furthermore, a high degree of comorbidity between OA and unhealthy phenotype/type 2 diabetes (T2D)[9] accompanying cardiovascular diseases (CVDs) has been reported in several epidemiological studies.[10,11] In alignment with the missing factor, obese participants have been shown to have a higher prevalence of hand OA, which is a non–weight-bearing joint. This association has been supported by the association between OA and factors such as leptin.[12-15] Thus, there is abundant support for a metabolism-driven pathogenic effect on OA. Postmenopausal women have a higher prevalence of obesity[16] and would expectedly be more prone to an unhealthy phenotype. Thus, by achieving a better understanding on the association between OA and an unhealthy phenotype, physicians may become better equipped in managing postmenopausal health.

The molecular mechanisms affecting the initiation and progression of OA need to be elucidated. There seems to be a missing link between the current understanding of the diversities causing initiation and progression of OA and the confidence on and understanding of processes that cause joint deterioration and cartilage loss. As a plethora of pleiotropic signals seems to cause the same end result (hence, induction of the proteolytic destruction of cartilage), it may be an opportunity to revisit the risk factors for joint destruction rather than tunneling in on the clinical endpoint (eg, joint space narrowing and pain, resulting in joint failure and total joint replacement). Which molecular events predispose to this endpoint? Which parameters may accelerate disease progression? We hypothesize that an unhealthy metabolic phenotype can be the initiator, driver, or both initiator and driver of OA development.

KEY POINTS

OA is not just a disease measured by terminal endpoints such as pain and joint space narrowing. There seems to be a systemic component affecting the whole joint, where cartilage seems to be the surrogate marker of disease. At present, four main pieces of evidence suggest that the current understanding of OA may be revisited:

- Both weight-bearing and non–weight-bearing joints are equally affected in obese women, suggesting that systemic factors, which affect all joints, are involved.
- Circulating proinflammatory cytokines, such as tumor necrosis factor α, interleukin-1 (IL-1), and IL-6, are elevated in a subset of patients with OA without prior signs of inflammation, as in rheumatoid arthritis, indicating that systemic factors might be important in OA.
- Estrogen deficiency seems to augment OA progression, although estrogen does not block articular cartilage degradation. In alignment, estrogen replacement seems to counteract this deterioration. Estrogen receptors (ERs) are present in most—if not all—tissues, suggesting that the pleiotropic actions of estrogen on cartilage and all other tissues may be important in the progression of OA.
- Joint replacement and pain are highly divergent in patients. Whereas some have pain with little cartilage loss, others have complete loss (denudation) of articular cartilage without pain. Thus, it seems that additional and undescribed parameters are in part responsible for the representation of clinical symptomatic OA. In fact, there is little correlation between joint appearance assessed by Kellgren-Lawrence score and joint pain.

In the current context, evidence viewed in a new perspective suggests that metabolic syndrome is associated with OA and its molecular characteristics. However, what is the molecular evidence for a direct link between an unhealthy phenotype and the development of OA? How do systemic factors affect joint homeostasis? Velasquez and Katz[17] recently published a review

on OA and the different factors involved. In the current review, we carefully extend the molecular details from Velasquez and Katz[17] and Aspden[18] and continue the discussion on whether a subset of OA, characterized primarily by cartilage erosion, can be associated with systemic factors associated with an unhealthy metabolic phenotype. We give special emphasis to two scholarly examples of endocrine hormones—estrogen and thyroid hormone—that have been investigated thoroughly in the context of joint and cartilage health and that might be of key importance in the regulation of joint health. In addition, recent important research on adipokines is placed in the current context.

REVIEW CRITERIA

Available English, written, peer-reviewed original research articles and reviews were searched for in the PubMed and Google Scholar databases using the following keywords in different combinations: osteoarthritis, cartilage, joint degenerative diseases, angiogenesis, bone, rheumatoid arthritis, metabolic syndrome, diabetes, obesity, estradiol, and thyroid hormone. Only literature readily available online, either by download or by purchase order, was included. No discrimination was made on the year of publishing. Current work is a journalistic review, which reviews current literature that may or may not support our hypothesis that hormones play central role in the development of OA.

PATHOGENESIS OF OA: DEGRADATION, REMODELING, VASCULARIZATION, AND INFLAMMATION

OA is characterized by cartilage erosion, subchondral remodeling,[19] osteophyte formation,[19] synovial inflammation,[20] and muscle weakness,[21] which emphasize a multifactorial disease representation. Although cartilage erosion, subchondral remodeling, and osteophytes are extensively described in the literature, less is known about the role of muscle weakness in OA. As mentioned in the introduction, a common biological and surrogate endpoint of OA is articular cartilage deterioration and loss. Healthy articular cartilage has a well-organized layer structure with different chondrocyte phenotypes: a superficial layer with discoid progenitor cells; a hypoxic midzone layer with latent spherical chondrocytes; a deep zone with metabolically active column chondrocytes; a calcified cartilage layer that acts as border between bone articular cartilages; and a vascularized and innervated subchondral bone layer.[22,23] In early OA, the protective superficial layer is lost, and the midzone cartilage is exposed to the synovial environment, which provides multiple factors that can induce latent chondrocytes to proliferate and express catabolic factors. Furthermore, the integrity of the interface between the cartilage and the subchondral bone is lost, inducing chondrocyte hypertrophy and apoptosis. This process is partly driven by subchondral bone vascularization, which exposes the cartilage to circulating factors such as hormones and proinflammatory cytokines, not to mention bone-derived catabolic and anabolic factors. In late OA, the cartilage is lost and the subchondral bone has expanded (Fig. 2). The joint becomes sclerotic and innervated. The take-home message is that

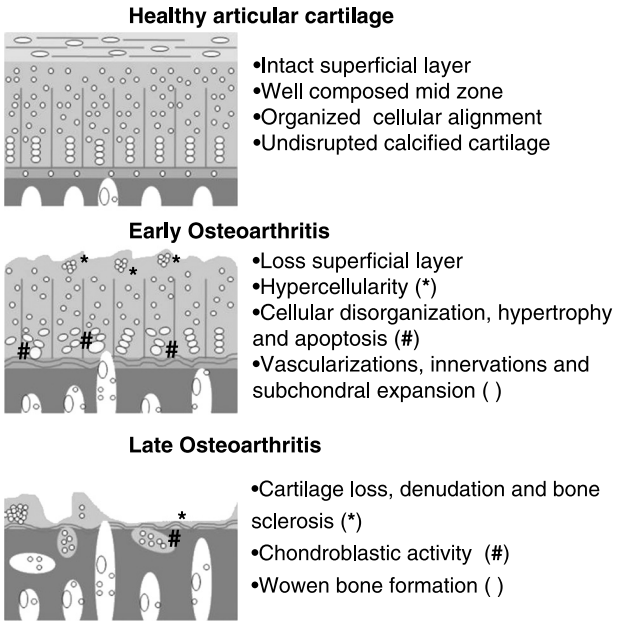

FIG. 2. The pathogenesis of osteoarthritis. Healthy cartilage is an organized tissue consisting of several chondrocyte layers: discoid, progenitor cells in the superficial layer; spherical, resting chondrocytes in the midzone; and metabolically active chondrocytes arranged in columns in the deep zone. As cartilage deteriorates, chondrocytes undergo a phenotypic shift, which alters their role and tremendously affects the microenvironment. Modified from Bay-Jensen et al.[23]

many different cell types from different tissues are involved in the pathogenesis of OA, and that these cell types will respond to systemic levels of many different factors. Thus, because the field accepts that OA should be considered a disease of the whole joint, we highlight that these tissues are more complex and undergo more regulation than the articular cartilage itself.

Importantly, vascularization or angiogenesis of calcified cartilage and synovium is a common pathology in OA.[24] Subchondral bone vascularization permeabilizes the calcified cartilage and gives access to bone cells (ie, osteoclasts and osteoblasts) and circulating factors such as glucose,[25] which in turn will remodel the subchondral bone, degrade the cartilage, and initiate a "vicious circle" in which a subpopulation of chondrocytes (hypertrophic) produces angiogenic factors in response to hypoxia.[26,27] Hypertrophy will lead to apoptosis, calcification, and thickening of the subchondral bone.

Chondrocytes are known to respond to proinflammatory stimuli by decreasing the synthesis of cartilage matrix components and by increasing the synthesis of the enzymes responsible for cartilage destruction—aggrecanases and matrix metalloproteinases.[28] There is general acceptance that a low-grade systemic inflammatory component[29,30] contributes to symptoms and augments many pathological changes in OA.[31,32] Recently, high-sensitivity C-reactive protein has been investigated within OA studies to assess its relationship with such a chronic inflammatory state. Although the serum high-sensitivity C-reactive protein was below the acute-phase level, there was a strong and positive association with both BMI and knee OA.[33,34] As evidence for a central involvement of inflammation in OA accumulates, special care must be

taken in data interpretation inasmuch as a correlation does not mean causality per se. With the emergence of new concepts, researchers are faced with the traditional "hen-or-egg" problem. Is inflammation the consequence of OA or vice versa? At present, there is ample evidence that they are linked, and evidence on the causes of this low-grade inflammation needs to be presented. Central fat may be one of those features shifting the balance.

OA AND FAT DISTRIBUTION

It has been established that there is a strong interrelation between obesity and menopause symptoms. It is generally accepted that obesity is a primary risk factor for OA; the most apparent and accepted explanation for this is that increased mechanical stress (resulting from increased body weight) on weight-bearing joints is expected to increase the risk of OA,[35] especially with a valgus alignment.[36] Arguments that this does not fully explain the underlying mechanism come from the fact that the association between obesity and the non–weight-bearing hip joint is much less clear.[37] In alignment, support for a metabolic component was described in a recent systematic review on non–weight-bearing OA, giving moderate evidence for a positive association between weight or BMI and hand OA.[13] Together, these data indicate that metabolic changes caused by obesity may have an additional etiological influence on OA susceptibility, phenotype, and progression. It seems that fat mass is important for OA; however, key evidence suggests that different types of obesity provide different metabolic phenotypes, which are of paramount importance in the current context. Only about half of normotensive and nondiabetic obese persons (BMI >30 kg/m^2) seem to have insulin resistance syndrome (ie, altered metabolic markers),[38] suggesting that fat distribution rather than amount of fat tissue is important. Indeed, recent cross-sectional and prospective clinical studies in postmenopausal women have indicated that two types of fat affect metabolic representation. Abdominal (or central) fat mass is associated with low-grade inflammation, low adiponectin concentrations, insulin resistance, and increased atherogenesis for aortic calcifications. Peripheral fat (located subcutaneously on legs and arms), on the other hand, seems to be rather protective and correlates with decreased inflammation, high concentrations of adiponectin, insulin sensitization, and less aortic calcifications in postmenopausal women.[39] A similar thinking may be applied to the OA field, in which we segregate fat distribution. Is there an association between the prevalence of OA and fat distribution and, indirectly, the release of protective factors from different types of fat? In that case, an unhealthy phenotype and the risk of OA development/progression cannot solely be based on BMI; rather, we need to think further about metabolic factors linking the metabolic phenotype to OA.

METABOLIC AND HORMONAL FACTORS DRIVING OA: A METABOLIC LINK

OA is associated with systemic and circulating factors such as cytokines and hormones released as a function of an unhealthy phenotype. One possible way of investigating whether systemic factors may drive OA and provide a metabolic link (ie, filling the void; Fig. 1) is to investigate systemic hormones and their potential effects on joint pathology. Table 1 provides an overview on some of the systemic factors that may play an important role in regulating metabolic health and OA. These hormones are presently not considered standard risk factors for OA and may be part of metabolic dysfunction in metabolic OA.

Do stressed adipocytes directly affect cartilage? Adipokines, excreted in large amounts by central fat, regulate metabolic, skeletal, and reproductive processes.[49] Leptin is secreted by adipocytes and regulates body weight through its effects on food intake and energy expenditure,[54] and leptin deficiency is associated with severe obesity. The direct link between leptin and OA was demonstrated by a significant correlation between BMI, degree of cartilage destruction, and leptin concentrations in the synovial fluid of patients with advanced knee OA.[55] In alignment, it was shown that knee OA was observed twice as frequent in obese women with cardiometabolic clustering than in those without, indicating an overlap between these traits.[56]

One molecular rational for this correlation has been suggested to be a synergistic effect of ILs and leptin: costimulation of chondrocytes with IL-1β and leptin augmented the effects of IL-1β on joint degradation.[57,58] In complete alignment, Griffin et al[59] showed that the incidence of knee OA was not changed in extreme obese mice lacking leptin signaling. However, there were indications that subchondral remodeling was suppressed whereas trabecular bone volume was increased. Likewise, expression analyses of OA and healthy cartilage showed a peripheral up-regulation of leptin and its receptor in advanced OA cartilage, which was influenced by the BMI of the patients.[60] Whereas the current discussion is focused on cartilage, it should be noted that leptin, as a hormone, has pleiotropic effects.[54] Leptin is a major regulator of bone remodeling that acts on osteoblasts, thereby protecting mammals from osteoporosis (OP)[61] but increasing the risk of OA by affecting subchondral bone morphology.[62] Furthermore, recent research has revealed that leptin inhibits the endocrine function of the skeleton.[63,64]

Other important adipokines are currently being investigated for their relevance to OA. Adiponectin is a peptide produced by peripheral subcutaneous adipocytes. Accumulating evidence suggests that adiponectin confers protection against inflammation, atherogenesis, and diabetes,[65] and plasma levels of adiponectin were inversely correlated with fat mass and were lower in T2D and CVDs.[66] The role of adiponectin in joint homeostasis needs further attention and highlights the pool of factors that may be investigated and found important in the fat hypothesis.

The current discussion has focused on fat as central tissue, although it is well accepted that obesity affects other tissues that in turn may affect the joint. As an example, researchers have focused on obesity-related changes in muscles in relation to OA[67] and have documented a relationship. Directly or indirectly, fat and the metabolic representation associated with

TABLE 1. *Overview on some of the systemic factors that may play an important role in regulating both metabolic health and OA*

Systemic factor	Origin	Metabolic indication	Joint indications
Adiponectin	Mainly secreted from white adipose tissue but also from bone marrow cells (eg, osteoblasts)	Adiponectin exerts pleiotropic effects on whole-body metabolism. Serum levels are inversely correlated with BMI and visceral fat accumulation. Serum levels are reduced in obesity and T2D. Hypoadiponectinemia is associated with metabolic syndrome.[40]	Adiponectin levels in plasma, serum, and synovial fluid decreased significantly as the severity of OA increased.[41] Serum and synovial levels of adiponectin were higher in patients with RA compared with healthy controls.[42] Increases induce MMP-3 and iNOS expression in human chondrocytes in vitro.[43]
Leptin	Primarily in white adipose tissue and various tissues	Increased secretion of leptin from adipose tissue inhibits food intake. Circulating levels are believed to have protective effects against an unhealthy phenotype.[44]	Leptin has been shown to be up-regulated in OA cartilage, and this local expression of leptin seems to have procatabolic effects on cartilage.[45,46] It seems to exert proinflammatory actions by enhancing MMP production in human OA cartilage.[47]
Resistin	Human resistin is made and secreted by macrophages	In vivo studies in rodents confirmed adipose tissue–specific expression of resistin and down-regulation by TZDs. Resistin expression is 15-fold greater in visceral adipose tissue than in subcutaneous adipose tissue in rodents.[48] As with leptin, resistin levels are higher in women, fall during fasting, and increase after eating, which is partly controlled by insulin and glucose.[49]	Circulating levels of resistin are not altered significantly in patients with OA or RA. An experimental model seems to be able to mediate joint inflammation; however, there is limited knowledge on its direct effect on the joint.[50]
Visfatin (nicotinamide phosphoribosyltransferase)	Released predominantly from macrophages rather than from adipocytes in visceral adipose tissue	Visfatin activates insulin receptors and has insulin-mimetic effects, lowering blood glucose and improving insulin sensitivity. There is strong evidence that visfatin increases with obesity, as demonstrated in a prospective cohort study where visfatin levels were augmented in morbidly obese participants compared with lean individuals.[51]	Visfatin is released from osteophytes and exerts a potential proinflammatory effect on surrounding tissue. Patients with OA had higher synovial visfatin concentrations, suggesting that visfatin might be involved in cartilage matrix degradation.[52] Furthermore, visfatin suppressed cartilage production by chondrocytes in vitro.[53]

The third column provides general insights into metabolic implications known to be affiliated with the given factor.
The references given are reviews recommended by the authors for further reading.
BMI, body mass index; T2D, type 2 diabetes; OA, osteoarthritis; MMP, matrix metalloproteinase; iNOS, inducible nitric oxide synthase; TZD, thiazolidinedione; RA; rheumatoid arthritis.

increased BMI (central or peripheral) seem to affect OA. Next, we will discuss two scholarly examples of how hormones exert a significant influence on joint and whole-body health.

Lessons learned from estrogen

The first example of a systemic regulator that affects many tissues is estrogen (eg, estradiol), which has a protective effect on skeletal tissues. Emphasizing the effects of estrogen is the fact that two types of ER, ER-α and ER-β, are widely but differentially expressed in most tissues and organs.[68] ER-α is highly expressed in the hypothalamus, where it plays a pivotal role in regulating food intake and energy expenditure by estrogens. ER-β, on the other hand, has an important role in tissue homeostasis such as bone and cartilage stabilization.[69] Each of the ERs is found in various splice variants and isoforms, underlining the complexity of estrogen regulation. No association between the genetic variants in ER isoform 1 (*ESR1*) and ER isoform 2 (*ESR2*) encoding ER-α and ER-β, respectively, and metabolic syndrome was observed among white women.[70] However, significant associations were detected between *ESR1* single nucleotide polymorphisms and metabolic syndrome, T2D, insulin sensitivity, fasting insulin, triglycerides, low-density lipoprotein, cholesterol, BMI, waist circumference, and subcutaneous adipose tissue area.[71] It seems probable that *ESR1* contributes to T2D and CVD risk via pleiotropic effects, leading to insulin resistance, poor lipid profile, and obesity.[72] Thus, a variety of results have shown that estrogen exerts important regulatory effects on health homeostasis. How does this translate into OA and joint homeostasis?

Postmenopausal women have a higher prevalence of OA and OP than age-matched men.[73,74] This may seem contradicting because OA is associated with elevated bone remodeling and OP is associated with decreased bone density. However, one should remember that OA and OP are diseases of different bone compartments and thus have different cellular involvements. Some have proposed an inverse relationship between OA and OP.[75,76] It has been demonstrated that women receiving estrogen therapy had a lower risk of developing radiographic knee and hip OA and that the protective effect increased with increasing duration of estrogen therapy.[73,77,78] This is in line with findings that bone turnover is also increased

owing to estrogen deficiency.[79] Mouritzen et al[80] found that urinary levels of cartilage and bone resorption markers (ie, C-terminal telopeptides of type I and type II collagens) were increased in postmenopausal women compared with premenopausal women. Since then, it has been shown that selective ER modulators given to postmenopausal women decrease the level of C-terminal telopeptides of type II collagen to about 50% of baseline (12-mo follow-up).[81] These markers are generated by the enzymatic processing of type II and type I collagens, respectively, which is a result of induced cellular responses. Furthermore, it has been shown that adult articular cartilage ERs can be activated and can thereby induce the production of extracellular matrix molecules (eg, proteoglycans and collagens).[82,83] This is in line with the findings from the Women's Health Initiative, which showed that women taking estrogen with more than 80% compliance had a 50% reduction in total joint replacements.[84]

The effect of estrogen deficiency on cartilage has been shown in several animal studies. Ovariectomized sheep showed loss of articular cartilage integrity—although no major pathological changes were observed—at 12-month follow-up.[85] However, the cartilage of ovariectomized cynomolgus monkeys showed histopathological features caused by estrogen deficiency.[86] Ovariectomy of rats led to similar results.[87,88] Analysis of the knees of ovariectomized rats showed an elevated expression of several tissue-degrading protease and proinflammatory cytokines compared with controls.[89] This pattern was supported by Claassen et al,[90] who showed that estradiol could suppress the expression of the same degrading proteinases in cultured osteoarthritic chondrocytes. Furthermore, estradiol was able to protect chondrocytes from oxidative damage. A plethora of evidence suggests a positive effect of estrogen on joint biology that most probably results in direct effects on bone, muscle, and synovium, which, in combination, improve joint health.

Not only circulating estradiol is important for the regulation of metabolic homeostasis. The local conversion of androgenic precursors as testosterone into estradiol by aromatase and the paracrine/intracrine action of estradiol may even be more important. Being bone-forming cells, both osteoblasts and chondrocytes express high levels of aromatase; however, none of these cells are capable of converting cholesterol into C19 and are therefore dependent on, for example, a source of testosterone.[91] The aromatase KO mice ArKO are characterized by a metabolic phenotype, loss of bone mass in both sexes, and metabolic syndrome with insulin resistance, truncal obesity, and hepatic steatosis.[92] Although truncal fat deposition was significantly higher in KO mice, body weight was stable, indicating that musculoskeletal mass decreased. The mice had three times higher levels of circulating leptin and had hyperinsulinemia.[92] This suggests that estradiol plays a pivotal role in the regulation of metabolic homeostasis and skeletal health. Many, but not all, aspects of this mice phenotype are also present in ER^{-} KO and $ER^{-/-}$ KO mice,[93] further supporting the notion that estradiol is important.

Here we have discussed the effect of estrogen on cartilage and bone, but it is well known that estrogen also has substantial effects on muscle weakness and loss. In summary, the pleiotropic actions of estrogen on multiple tissues may attenuate some of the effects of metabolic syndrome, which may have positive effects on the whole-tissue pathophysiology of the joint, directly on the cell types involved and through secondary actions on the regulation of systemic hormone levels—the missing link.

Lesson learned from thyroid hormones

Another group of important regulatory hormones are the thyroid hormones. The importance of local thyroid hormone availability in the etiology of symptomatic OA has been revealed through the Genetics, Osteoarthritis, and Progression study, a genomewide linkage study. This and other studies of patients with OA found that the *DIO2* (deiodinase, iodothyronine, type 2 [D2]) gene was associated with OA. In a follow-up study including a meta-analysis of 5,000 women, genetic variation in the *DIO3* gene encoding type 3 (D3), which depletes active sources of thyroid, provided evidence for protective association. D2, together with its counterpart D3, is critical for maintaining the availability of the intracellular active thyroid hormone 3,3′,5-triiodothyronine (T3) in specific tissues, including joint tissues. In cartilage, the intracellular bioavailability of T3 stimulates chondrocyte differentiation and induces hypertrophy of chondrocytes, initiating terminal differentiation and calcification. Variation in the *DIO2* gene also showed associations with human height, stressing that skeletal development and growth may be involved in OA susceptibility in this study. A follow-up study investigated whether *DIO2* genotypes could contribute to nonoptimal joint geometry and subsequent predisposition to OA. The results suggested that genetic variation in *DIO2* increases the vulnerability of cartilage to nonoptimal bone shapes rather than directly influencing the formation of these shapes.

Pathophysiologically, D2 and D3, as key regulators of local T3 availability, may contribute to OA development in different ways. In articular cartilage, recuperating D2 activity at an older age or during OA development may affect the propensity of articular chondrocytes to become hypertrophic, a feature similar to that of chondrocytes residing in the growth plate. As such, chondrocyte hypertrophy debilitates cartilage viability by a switched expression of bone-specific collagens, which initiates calcification of the matrix and up-regulation of cartilage-specific proteolytic enzymes known to be detrimental to articular cartilage. It has been shown that there is an extensive up-regulation of *DIO2* expression in OA cartilage as compared with non-OA cartilage.[94,95] It is unclear whether this up-regulation reflects the underlying disease pathway or merely reflects the ongoing OA process. Finally, OA is characterized by the formation of bony enlargements at the edges of bones (called osteophytes), a process characterized by endochondral ossification.

As with other hormones, the pleiotropic features of T3 in target tissues should be taken into account. For example, T3 is also known as an important regulator of energy expenditure in infants, a process in which D2 is again an important enzyme

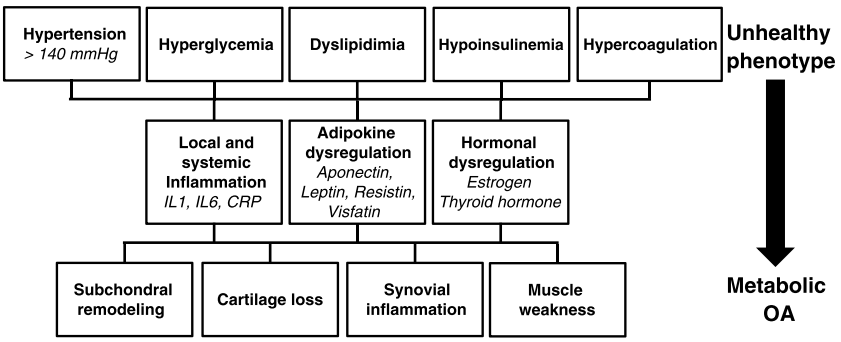

FIG. 3. An unhealthy phenotype (ie, metabolic dysfunction) may drive OA, resulting in metabolic OA. Metabolic syndrome is associated with hypertension, hyperglycemia, dyslipidemia, hypoinsulinemia, and hypercoagulation. Each of these conditions contributes to local and systemic inflammation, as well as hormonal and adipokine dysregulation, which can both induce subchondral bone remodeling, cartilage degradation, and synovial inflammation. IL, interleukin; CRP, C-reactive protein; OA, osteoarthritis.

determining bioavailability within brown adipose tissues. Recently in adult humans, depots of brown adipose tissue surrounding supraclavicular regions have been identified, indicating its physiological relevance at later ages.[96-98] Especially in older people, the amount of brown adipose tissue was inversely correlated with BMI and indexes of metabolic disease, suggesting a potential role of brown adipose tissue in adult human (fat) metabolism.[99,100] In brown adipose tissue, stimulation of β3-adrenergic receptors leads to increased intracellular concentration of T3 by means of D2; T3 in turn stimulates the transcription of UCP1, which causes leakage of protons from the inner membrane of the mitochondria, hence dissipating energy in the form of heat.

D2 deficiency, as a key regulator of intracellular T3 bioavailability, may predispose to the incidence of OA via several mechanisms. It may affect the processes of hypertrophy and cartilage calcification (affecting joint shape and local biomechanical stress) or, later in life, affect OA cartilage via its influence on the phenotypic stability of chondrocytes, the basal aspects of metabolism, or both.

CONCLUSIONS

In the present review, we have focused on a few systemic factors and hormones that directly or indirectly affect joint health, with a primary focus on cartilage, which might be considered as the surrogate endpoint tissue. We give examples of hormones and factors that should be investigated more in the context of OA and whole-joint pathology. Figure 3 summarizes the discussion, however, in a rather simplistic way. There is no doubt that each of the pathways involving multiple tissues is quite complex, and each is worthy of a systematic review. Although cartilage and bone OA pathogenesis has been thoroughly investigated, less is known about the involvement of muscle in OA. More than a few studies show that muscle tone is important for joint stability; however, little is known about muscle weakness (eg, sarcopenia) and its impact on the development and progression of OA. This leads to speculation that another subtype of OA is part of the frailty syndrome. Thus, it seems timely to revisit the traditional risk factors for OA and possibly to include levels of systemic hormones (in part defined as a subset of metabolic syndrome) in this list of risk factors for OA. These systemic factors are directly or indirectly regulated by metabolic status but, more importantly, have pleiotropic effects, which means that they are part of a delicate and balanced system that ensures tissue homeostasis. Whether these factors would be targets for intervention in metabolic OA is yet to be investigated.

Considerable evidence supports that systemic factors play a vital role in the development of OA; however, it can be debated whether these are initiators, drivers, or both. These systemic factors are regulated by an unhealthy metabolic phenotype (eg, altered insulin sensitivity, changes in lipid and thyroid metabolism) that is in part caused by the presence of metabolic syndrome.

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