Novel Techniques in Arthritis & Bone Research
ISSN: 2575-8888

Juniper Publishers
key to the Researchers

Case Report
Volume 3 Issue 3 - November 2018
DOI: 10.19080/NTAB.2018.03.555611

Nov Tech Arthritis Bone Res

The Role of Thyroid Hormones on Management of Cartilaginous Joint Disorders

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Submission: November 02, 2018; **Published:** November 14, 2018

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Abstract

The purpose of the present research is to demonstrate the involvement of thyroid hormones and function on orthopaedic health, particularly focusing on the management of cartilaginous joint disorders. There is more than sufficient evidence in the literature suggesting that fluctuations in levels of thyroid hormones, that is, deficiency as well as excess, can lead to a wide array of complications and even the manifestation of systemic diseases. Several studies demonstrate the indispensable biological value of thyroid hormones and their role in diverse mammalian target tissues, especially in skeletal cells and chondrocytes. The investigations discussed in this article also shine light on cellular and molecular mechanisms of hormonal regulation, interaction and even thread further into the genetic perspective behind the metabolic processes. It is also well known that thyroid hormone receptors TRα1 and TRβ1 are both expressed in the skeleton, growth plate chondrocytes, bone marrow, osteoblasts and even stromal cells; deiodinase type 3 is expressed in all skeletal cells, further suggesting their relevance in human health. Inregards to thyroidal hormone impact on cartilage, appreciable studies evaluate the potential of parathyroid hormones in stimulating chondrocytes, ultimately suggesting that timing and duration of hormone application are vital, as chondrocytes seem to require time to adapt and respond to hormonal stimuli. Alternative approaches indicate that the implementation of small doses of dietary iodine in individuals with deficits in concentration of this micronutrient show significant changes and can be helpful in regulating thyroid status.

Keywords: Thyroid Hormones; Osteoarthritis; Metabolism; Cartilage; Bone

Introduction

When it comes to musculoskeletal disorders, osteoarthritis (OA) is the most frequent and age-related degenerative joint disorder, typically characterized by degeneration of articular joint cartilage. Conventional methods for managing OA such as non-steroidal anti-inflammatory drugs (NSAIDS) may intervene in common symptoms such as joint pain, stiffness and limited function, but does not reverse the disease process itself [1]. Obesity is known to be a risk factor for knee osteoarthritis (KOA) while age remains the major risk factor for the occurrence of OA, even though all of the exact mechanisms by which age is involved in the etiology of OA have not been completely elucidated yet [2]. The pathological changes associated with the progression of OA usually encompass biomechanical forces as well as multiple autocrine, paracrine and endocrine cellular events which all contribute to dysregulation of tissue homeostasis within the affected joint [3]. Thyroid hormones drive many complex actions in almost all tissues during the developmental stages in life, from childhood to adulthood. The skeleton is an important target tissue of triiodothyronine, the active form of the thyroid hormone (T3) and can illustrate the cellular and molecular processes that occur as a response from thyroid hormones. However, the mechanism of action of these hormones in bone and cartilage, specifically, continue to be studied for further clarification [4]. There is evidence in the literature, particularly in vitro studies, indicating that progenitor cells and immature chondrocytes are the major T3 target cells [5], which brings attention to thyroid hormones and their diverse physiological effects on the human body, motivating investigation of the possible ways for them to assist in the management of cartilaginous joint disorders.

Regulation of Thyroid Hormones: The hormones secreted by the thyroid gland are important regulators of endochondral ossification [6]. The thyroid gland is responsible for the

production of the pro-hormone tetraiodothyronine (T4) but also produces smaller amounts of its active form T3. The majority of circulating levels of T3 is obtained through metabolized T4, where an outer-ring iodine atom is removed by enzymatic activity of the either type 1 or type 2 iodothyronine deiodinase enzyme (Dio1, Dio 2), a process which occurs mainly in the liver and kidney [7]. The hypothalamic-pituitary-thyroid (HPT) axis detects the concentration of circulating thyroid hormones the physiological status of the thyroid gland is controlled by a negative feedback regulation of thyrotropin-releasing hormone (TRH) in the hypothalamus, whereas the synthesis and secretion of thyroid-stimulating hormone (TSH) takes place in the anterior pituitary gland [8]. It is estimated that more than 95% of circulating thyroid hormones are bound to plasma proteins, which leaves the remaining portion of free hormones T4 and T3 representing biologically available and active fraction. T4 and T3 can interact with peripheral target cells via specific cell membrane transporter proteins. Several transporters have already been largely identified, such as monocarboxylate transporters (MCT) 8 and 10, organic acid transporter protein-1c1 (OATP1c1) as well as non-specific L-type amino acid transporters (LATs) 1 and 2 [9]. Once these hormones penetrate the target cell they are metabolized further, where type 2 deiodinase (Dio2) comes into play by catalysing the conversion of T4 to T3 by removal of an outer-ring iodine, therefore activating T4. The type 3 deiodinase (Dio3) inactivates both T4 and T3 by removing a 5-iodine atom [10]. Elaborating these concepts further, intracellular concentration of T3 is then determined by the relative tissue activities of deiodinase enzymes, which provides a pre-receptor control mechanism regulating the availability of the active form of the hormone to the cell nucleus.

Cellular Interaction - Thyroid Hormone Receptors: The cellular interaction between thyroid hormones and its target cells occur due to the presence of the thyroid hormone receptors (TRs) TRα1, TRβ1 and TRβ2, which bind ligand with high affinity, acting as hormone-inducible transcription factors which subsequently regulate the expression of specific genes in response to T3 interaction. The TRα1 and TRβ1 isoforms are found in almost all tissue types albeit in different concentrations that vary with distinct stages of biological development as well as age, whereas TRβ2 expression, however, is known to be exclusively pertinent to the hypothalamus and the pituitary [11-12]. The TRs are present in the nucleus even if there is no bound hormone but in cases where there is positive regulation of genes in response to T3, the free TRs bind co-repressor to repress target gene transcription [13]. Once T3 is bound, the co-repressor is released and co-activator proteins are recruited to allow hormone-dependent activation of gene expression initiation in T3-responsive cells. In overview, the pre-receptor control mechanism of T3 availability in combination with the diversity of TR expression creates a sophisticated mechanism which regulates temporal and spatial responses to thyroid hormones in key biological tissues during early developmental stages as well as in adulthood [13].

Target Cells: As previously introduced, T3 interacts with a diversity of target cells and tissues, including the skeleton and cartilaginous structures, which makes it a vital biological agent for the developmental processes. MCT10 seems to be largely expressed in the growth plate while MCT8 remains widely expressed in chondrocytes, osteoblasts and osteoclasts. LAT1 and LAT2 transporter proteins have also been identified in skeletal tissue. OATP1C1 mRNA, however, is neither expressed in bone nor cartilage [14-15]. Thyroid hormone is also metabolized by skeletal cells and despite the fact that Dio1 is not expressed in cartilage or bone, Dio2 is expressed in osteoblasts only, while Dio3 is found in all skeletal cells [16-19]. Regarding receptor expression, TRα1 and TRβ1 are both expressed in the skeleton, but quantitative RT-PCR shows that TRα1 is expressed about 10 times greater than TRβ1 [20]. Both of these receptors are present in growth plate chondrocytes, bone marrow, osteoblasts and even stromal cells, but it is not known for certain whether these are expressed in osteoclasts or osteocytes, two important skeletal cell types that participate in environmental stimuli transduction and communication, endocrine and paracrine signalling and, ultimately, dictate bone resorption as is the case with osteoclasts, or bone formation, a property displayed by osteocytes. These observations therefore show that the skeleton is a great T3 target tissue throughout life since it encompasses many of the factors involved in the regulation of T3, such as hormone transporters, TRs and deiodinase enzymes (to either activate or inactivate the hormone), all of which are present in cartilage and bone.

Thyroid Hormone Effects on Cartilage: Investigations on the effects of thyroid hormones in cartilage and bone are relatively new and undergoing expansion in order to allow researchers to understand broader pathophysiological consequences of the thyroid hormone action. As OA puts patients under great debilitation, there has been great motivation in the field of cartilage developmental biology to identity new suitable stimuli and application in the self-assembling process towards the amelioration of biomechanical properties and function of articular joints. To clarify, during skeletal development, T3, T4 and parathyroid hormone (PTH) from the parathyroid glands regulate the phenotype of growth plate chondrocytes and also the progression of cartilage growth during endochondral calcification [21]. PTH maintains the proliferative pool of chondrocytes in the epiphyseal growth plate while T3 promotes the transition from the proliferative phase to chondrocyte hypertrophy. While the roles of PTH, T3 and T4 have been extensively analysed, many studies attempt to discuss their effects on articular cartilage chondrocytes and their ability to restore degenerated cartilage. Studies using PTH 1-34 (PTH fragment 1-34), a parathyroid hormone analogue, explored its potential therapeutic effects on promoting cartilage matrix synthesis [22-25]. Results concluded that this hormone analogue can reduce collagen type X deposition and recover glycosaminoglycan (GAG) and collagen type II levels. Additionally, PTH 1-34 also improved gross morphology and histological appearance of repair cartilage. Overall, by showing a reduction in hypertrophic markers and supporting articular cartilage phenotype, these investigations alike indicate that articular chondrocytes can respond to PTH, which would imply

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in its application towards a regenerative approach in damaged articular cartilage, as is the case with OA, for example. Many studies demonstrate the beneficial effects of thyroid hormones on increasing the biochemical content of cells, more specifically, enhancing the collagen production in cultured chondrocytes. Other studies, however, aim to evaluate the potential of thyroid hormones to enhance the functional properties of articular chondrocytes, which remains somewhat understudied.

A two-phase study led by Lee and colleagues in 2015 [26] aimed to evaluate the effects of PTH, T3 and T4 thyroid hormones on generating mechanically functional tissues using an in vitro model of scaffold-free engineered neocartilage. During phase 1 each hormone was administered at an early (week 1) or late (week 3) point of neocartilage formation, which remained in culture for 4 weeks. It occurred that the early administration of T3 significantly improved the biochemical and mechanical properties of cartilage and it was therefore carried on to phase 2. The second phase of the study consisted in applying PTH after T3 to modulate the hypertrophic response generated by T3. The results showed that T3 applied in week 1 induced 4.0 and 3.1-fold increase in neocartilage compressive and tensile stiffness, respectively, confirming the hypothesis that thyroid hormone application to articular chondrocytes in an in vitro model of scaffold-free cartilage formation induces matrix maturation as well as the improvement of matrix mechanical properties. Secondly, the use of T3 caused a 2.2- and 1.5-fold increase in collagen and GAG content, respectively. sequential administration of PTH reduced hypertrophic marker collagen X expression but still maintained the functional properties elicited by T3, confirming the second hypothesis that sequential administration of PTH does in fact decrease the T3-induced hypertrophic marker expression. To reiterate, this study provides yet another example demonstrating the significant impacts of thyroid hormones on cartilage, at least in vitro, where T3 elicits the most significant increase in functional properties, as well as the fact that chondrocytes do respond quite well to T3, T4 and PTH.

A preclinical study performed in 2011 investigated the effects of the transient activation of PTH/PTH-related peptide (PTHrP) signalling in the repair of 5-mm-diameter full-thickness defects of articular cartilage in rabbits. The authors mechanically induced cartilage defects in the femoral trochlea of male adolescent Japanese white rabbits using a hand-drill and later administered recombinant human PTH (1-84) into the joint cavity continuously or intermittently for 2 weeks following the injury induction. The reparative tissues were examined for gross morphology by histological observation and via immunohistochemistry for the detection of type II collagen expression at 2, 4 and 8 weeks. Additionally, double immunostaining analysis was also employed for the PTH/PTHrP receptor and proliferating cell nuclear antigen (PCNA) in tissues that underwent regeneration. It was found that cartilage formation occurred at 4 weeks in both continuous and intermittent PTH-treated defects. At 8 weeks post-trauma, in the intermittently treated defects category, the regenerated cartilage covered the defects and the original bone-articular cartilage junction was restored. Conversely, in the continuously treated group, the defects were covered with either fibrous or fibrocartilaginous tissue. In addition, PCNA and PTH/PTHrP receptor-double positive mesenchymal cells displayed significant increase in both continuous and intermittent PTH-treatment of defects at 2 weeks following the induced trauma. These findings indicate that the transient activation and release from PTH/PTHrP signalling during the early stages of the cartilage repair process facilitates the promotion of regenerative chondrogenesis in full-thickness articular cartilage defects. Collectively, it appears that timing and duration of hormone application are vital, as chondrocytes seem to require time to adapt and respond to hormonal stimuli.

A Genetic Perspective on Osteoarthritis and Thyroid Signalling: There is much evidence in the scientific literature illustrating the involvement of deiodinase genes in the pathogenesis of OA. A genome-wide association study (GWAS) of siblings with generalized OA detected a nonsynonymous coding variant (rs225014; T92A) which identified the DIO2 gene as a disease-susceptibility locus [1]. Replication studies identified a correlation between symptomatic OA and a DIO2 haplotype containing a minor allele of rs225014 and a major allele of rs12885300, thus reinforcing the speculation on the susceptibility of disease [27]. Data further suggested that the expression of the rs225014 allele may be greater than that of the protective allele in osteoarthritic cartilage from heterozygous patients, an observation that may be attributed to epigenetic modifications. Additionally, elevated levels of DIO2 mRNA and protein expression have been identified by quantitative RT-PCR as well as immunohistochemical examination of late-stage osteoarthritic cartilage [28-30]. The rs12885300 DIO2 polymorphism also seems to affect the correlation between hip shape and OA susceptibility by increasing vulnerability of articular cartilage to abnormal hip morphology, for example [31]. Studies in transgenic rats overexpressing human DIO2 in chondrocytes revealed that the animals suffered increased risk of OA development after provocation surgery. Furthermore, a meta-analysis of genes involved in the regulation of thyroid hormone metabolism and T3 effects on chondrocytes proposed the role of DIO3 as a disease-modifying locus in OA.

In 2015, a forced-exercise model study involving murine subjects revealed that adult DIO2-deficient mice have normal articular cartilage and no features of spontaneous joint damage but display increased subchondral bone mineral content [32]. The authors observed that these mice were protected from articular cartilage damage upon excessive mechanical stress, in comparison to the unfavourable effect in wild-type cartilage homeostasis, pointing to DIO2 activity as a therapeutic target in OA. Some studies, however, demonstrate that DIO2 mRNA expression is not necessarily correlated with enzyme activity, a feature that may be attributed to the labile property of DIO2 protein, which means that it undergoes rapid degradation after exposure to high concentrations of T4 in a local feedback-loop

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fashion [33-34]. In contrast, other studies show DIO2 mRNA expression in rat articular cartilage and increased levels of DIO2 mRNA and protein in human articular cartilage from joints of individuals suffering from advanced OA stages. Despite different observations, it is still not entirely clear whether increased DIO2 expression represents a secondary response to joint destruction or whether it precedes cartilage damage, becoming a causative factor in disease progression.

Impaired Thyroid Function: After much discussion of the several possible effects of thyroid hormones on target tissues and structures, this section shines light on the major detrimental effects that may arise when the thyroid function is disrupted. ISTH is a great example to initiate discussion. The impaired sensitivity to thyroid hormone (ISTH), also known as syndrome of thyroid hormone resistance, is an inherited condition affecting 1 out of every 40,000 live births [35]. This condition is characterized by decreased tissue sensitivity to thyroid hormone action, usually arising as a consequence of germline mutations in the thyroid hormone receptor beta (THRB) gene [36,37]. This mutation renders the receptor less efficient where its binding affinity for thyroid hormones is lowered and, therefore, serum TSH levels remain non-suppressed despite elevated concentrations of thyroid hormones. Patients can display symptoms of either hyper- or hypothyroidism, and they usually exhibit elevated levels of thyroid hormone and normal or elevated TSH levels [38]. Variation of thyroid status can bring about serious consequences on patients suffering from hyper- or hypothyroidism. Previous investigations [39-40] have reported the effects of hypothyroidism on bone turnover via histomorphometry, which typically include reduced osteoblast activity, impaired osteoid apposition and a prolonged period of secondary bone mineralization. Low bone turnover state would remain parallel with the reduced osteoclast activity and bone resorption. As a result, there is a net increase in mineralization but no prominent change in bone volume, however, bone mass may be susceptible to increase due to an extended remodelling cycle [41]. Regarding hyperthyroidism, the major thyrotoxicosis effects on bone turnover are the elevation of biomarkers for bone formation and resorption, correlating with disease severity in men and pre- and postmenopausal women [42]. The treatment of thyrotoxicosis of premenopausal women in 2006, for example, resulted in a 4% increase in bone mineral density (BMD) within only 1 year [43]. There is also concern regarding fracture risks and dysregulated thyroid function. Large-scale cross-sectional population studies have identified a correlation between hypothyroidism and fracture. Patients with previous histories of hypothyroidism or elevated concentrations of TSH had a chance of about a 3-fold risk of fracture, lasting up to 10 years following diagnosis [44]. Other studies, however, indicate that there is a chance that overtreating patients with T4 may actually put some of them at a greater risk of vertebral fracture [45]. Undiagnosed hyperthyroidism can be an important contributor to secondary bone loss and osteoporosis in individuals with fractures and the presence of thyroid disease has been suggested to be a comorbidity factor, increasing 1- and 2-year mortality rates in the elderly population presenting hip fracture [46,47]. A cross-sectional study and 4 population studies were able to identify a connection between fracture and prior history of thyrotoxicosis but could not determine if reduced BMD or thyrotoxicosis were causally related to fracture risk. However, a study by Franklyn et al [48] identified an increased mortality ratio due to hip fracture in a follow-up population of patients treated with radioiodine for hyperthyroidism. Another cross-sectional study [49] pointed out a link between fracture and prior history of thyrotoxicosis in postmenopausal women. More recently, population studies have shown a reduced BMD and increased risk of fracture in postmenopausal women with thyrotoxicosis [50-51]. Regarding possible solutions to ameliorate thyroid function in patients, consideration has been given to administration of iodine dosage. Several studies indicate that iodine may influence thyroid hormone status. Reinhardt et al. [52] evaluated the effects of small doses of iodine on thyroid function and thyroid antibody levels in euthyroid patients with Hashimoto's thyroiditis who had mild dietary iodine deficiency. It was concluded that small amounts of supplementary iodine, 250 micrograms, caused slight but significant changes in thyroid hormone function in predisposed individuals, and in this particular instance it is suggested that iodine may have changed the natural course of autoimmune thyroiditis, resulting in a more rapid progression towards hypothyroidism. However, patients remained euthyroid and TBII negative after iodine was withdrawn. Another study [53] aimed to analyse the role of iodine supplementation in the development of postpartum thyroid dysfunction (PPTD) in a placebo-controlled, randomized double blind trial, performed in early pregnancy in a population of healthy pregnant Danish women with mild to moderate iodine deficiency, with no previous history of diagnosed thyroid disease. Measurements were based on Thyroid Peroxidase Antibody (TPO-Ab) levels. All participants received a daily vitamin and mineral tablet containing 150 µg iodine or no iodine. Nøhr et al. concluded that, in their study, administration of 150 µg of iodine during pregnancy and postpartum period to TPO-Ab positive women with mild to moderate iodine deficiency did not induce or worsen PPTD. Interestingly, the hypothyroid phase of PPTD tended to be less severe in women receiving iodine postpartum, which in this case indicated that supplementary administration of this chemical was a safe approach. Additionally, the study also serves as evidence that screening for TPO-Ab in early pregnancy can predict women at high risk of developing PPTD. On a different scenario, Gardner and colleagues [54] previously demonstrated the effects of low dose oral iodide supplementation on thyroid function in normal men. When implementing 500 µg of iodide per day they saw a significant increase in the serum TSH response to TRH, and the 1500 µg and 4500 µg larger doses per day resulted in increases in both basal and TRH-stimulated serum TSH concentrations. The authors propose that the synthesis of normal quantities of thyroid hormone depends on adequate dietary consumption of iodide; however, if ingested in excess, it may elicit inhibitory effects on thyroid function. They explain that these effects are mediated by two mechanisms, firstly the inhibition of iodide organification and subsequent decrease in thyroid hormone synthesis, and

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secondly, there is inhibition of thyroglobulin proteolysis, resulting in decrease of thyroid hormone secretion. Overall, it seems that short-term iodide supplementation within the range of normal daily intake has small but significant anti-thyroid effect in normal men.

A clinical study in Denmark in 2006 [55] aimed to monitor the iodine fortification program initiated in 2000/2001 to rectify the iodine deficiency issue in the population. The results revealed prominent effects of even small differences in iodine intake level on the prevalence of nodules, goiter and thyroid dysfunction, for example. The authors concluded that there are a number of environmental factors, encompassing lifestyle habits, that may influence the epidemiology of thyroid disease, and relatively small differences of iodine intake of a population can exert pronounced effects on the occurrence of thyroid abnormalities. They further proposed that monitoring and adjustment of iodine consumption in a population is vital in order to optimize the approach, thus remaining a critical component of preventive medicine.

Conclusion

In summary, there seems to be a connection between normal thyroid function and management of articular joint status. In vitro studies demonstrate that thyroid hormones can convey beneficial effects by improving the biochemical content of cells, more specifically, enhancing the collagen production in cultured chondrocytes. Additional similar studies evaluate the potential PTH, T3 and T4 thyroid hormones on enhancing functional properties of chondrocytes. PTH/PTHrP signalling during the early stages of the cartilage repair process facilitates the promotion of regenerative chondrogenesis in full-thickness articular cartilage defects. The DIO2 gene was identified as a disease-susceptibility locus. Numerous studies found that iodine is important for thyroid status. Monitoring and adjustment of iodine intake is important to avoid the negative impacts on the musculoskeletal status, with particular regards to joint health and the locomotor apparatus as a whole.

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How to cite this article: Gabriel S S, Gabriel O M A, Silvia B C V, Stephany C H, Alex M, etc al. The Role of Thyroid Hormones on Management of Cartilaginous Joint Disorders. Nov Tech Arthritis Bone Res. 2018; 3(3): 555611. DOI: 10.19080/NTAB.2018.03.555611.

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