Review Article

Increased risk of diabetes in inflammatory orthopedics diseases

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Abstract: Diabetes is one of most common chronic disease in modern society and the affected population is excepted to be 592 million by 2035. Inflammation was an established mechanism in the in the pathogenesis of diabetes and associated complications. Diabetes can increase the occurrence and deteriorate various diseases in orthopedics, such as osteoarthritis (OA) and osteomyelitis, which had been thoroughly investigated. On the other hand, inflammatory diseases are also common in orthopedics, such as inflammatory arthritis, OA and osteomyelitis. But whether patients with inflammation related diseases in orthopedics have higher risk for diabetes is seldom investigated. Here we reviewed studies concerning the risk of diabetes in various inflammation related diseases in orthopedics and intended to rise the attention of higher risk of diabetes in various arthritis and osteomyelitis.

Keywords: Diabetes; risk; rheumatoid arthritis (RA); osteoarthritis (OA); osteomyelitis

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Introduction

Type 2 diabetes (T2DM) is a common metabolic disorder caused by insulin resistance (IR), obesity, physical inactivity and β-cell dysfunction (1,2). The prevalence of T2DM substantially increased in recent years. In Asian population, more than 110 million individuals were living with diabetes, with a disproportionate burden among the young and middle aged in 2007 (2). In 2010, the prevalence of T2DM had reached 11.6% in China, which indicating that 113.9 million people aged 18 years or older suffering from T2DM (3). The prevalence of the disease is expected to rise to 592 million by 2035 (4). T2DM leads to a heavy health burden on people and healthcare system (5,6).

T2DM was characterized by defect in insulin secretion and reduced response to insulin-stimulated glucose uptake and oxidative stress, glucotoxicity, lipotoxicity and endoplasmic reticulum stress all contributed to its pathogenesis (7,8). All of these mechanisms were related to inflammatory responses (9). In pancreatic islets, free fatty acids (FFA) was able to activate Toll-like receptor 2 (TLR2) and TLR4 and translocate nuclear factor κB (NF-κB) to release of inflammatory cytokines and chemokine such as tumor necrosis factor (TNF), interleukin-1β (IL-1β) and IL-8 (10). Also, increased demand for insulin was an induction of endoplasmic reticulum stress, which activated the inflammasome (11). Similar alterations have been observed in liver, muscle and other insulin-sensitive tissues. Inflammation was an established mechanism in the in the pathogenesis of T2DM and associated complications (4).

Chronic inflammatory diseases, such as rheumatoid arthritis (RA), ankylosing spondylitis (AS), osteoarthritis (OA) and osteomyelitis, were common inflammatory conditions in orthopedics. In T2DM patients, 10–20% of patients with diabetes-related foot ulcers suffered from osteomyelitis (12). Various studies indicated that diabetes was able to increase the severity of inflammatory response in arthritis and osteomyelitis (13-18). However, only a few studies concern the risk of diabetes in patients suffering arthritis and osteomyelitis.

Here, we reviewed the risk of diabetes in different chronic inflammatory diseases in orthopedics and intended to raise the attention of higher risk of diabetes in various arthritis and osteomyelitis.

Risk of diabetes in inflammatory arthritis

Inflammatory arthritic diseases are a serious of autoimmune disorders where the host immune system invades self-defense mechanism and results in degeneration of the normal immune response and inflammation. RA, psoriatic arthritis (PsA) and AS are typical inflammatory arthritic diseases (19). RA is a major inflammatory disorder with the prevalence of 0.5–1% in the world population (20).

Risk of diabetes in RA

RA is associated with increased cardiovascular morbidity and mortality (21-23), which is resulted in the interactions among RA-related inflammatory activity, medications and traditional cardiovascular disease risk factors (24,25). Among these risk factors, T2DM is one of the most important (26,27).

In 2006, researchers enrolled 28,208 RA patients to compare the risk factors between patients and controls and found the prevalence ratio of T2DM was 1.4 in RA patients compared with controls (28). However, following studies investigating DM prevalence in RA had inconsistent results. Simard *et al.* examined the cross-sectional association between prevalent RA and diabetes among US civilians older than 60 years (n=5,302) but found no evidence of association between prevalent RA and diabetes in subjects aged over 60 years (29). With the help of electronic medical records database of the UK general population from 1986 to 2010, researchers found that the incidence rate for diabetes was 6.3 case per 1,000 person-years in patients with RA and the hazard ratio (HR) for diabetes after matched for age and sex was 1.12. However, the HR was attenuated after adjusting for age, sex, BMI, smoking and alcohol (14) and with further adjustment for baseline glucocorticoid (GC) use and co-morbidities, the HR was 0.94 (0.84–1.06).

Concerning the inconsistent results above, not only the inflammatory activity in RA, but also some RA medications could impact glucose metabolism, IR and consequently DM development.

GC is one of the most common medications in the treatment of RA due to its strong anti-inflammatory actions. However, GC can result in IR and hyperglycemia and in a duration-dependent and dose-dependent manner (30). Movahedi *et al.* assessed the risk of T2DM associated with the duration, dosage and time of GC usage in RA patients by using UK primary care database (CPRD) and US National Data Bank for Rheumatic Diseases (NDB). The HR was 1.30 and 1.61 in current users compared with nonusers in CPRD and NDB, respectively. The risk increased with GC dosage and duration but doses taken >6 months previously did not influence current risk (30). Ozen *et al.* conducted an investigation of the impact of DMARD and statin treatments on the incident of T2DM (31). By analyzing RA patients in NDB who were without T2DM at baseline and followed up from 2000 through 2014, researchers found that adjusted HR for DM were 1.31 for GC and 1.56 for statins while other synthetic/biological DMARDs were not associated with any risk change.

There are several mechanisms how GC increase the risk of diabetes. First, GCs can induce peripheral IR by impairing insulin signaling, which results in reduced glucose disposal and augmented endogenous glucose production. Second, GCs can promote abdominal obesity, elevate plasma fatty acids and triglycerides, and suppress osteocalcin synthesis in bone tissue. Third, pancreatic β-cells undergo several morphofunctional adaptations that result in hyperinsulinemia and failure of β-cells to compensate for this situation favors glucose homeostasis disruption, which can result in hyperglycemia (32).

Alternatively, hydroxychloroquine (HCQ) (33-35), methotrexate (MTX) (36) and TNF inhibitors (TNFi) (37,38) have been shown to favorably alter glucose metabolism. Large epidemiological studies showed decreased risk of new-onset DM with HCQ in RA (39,40). A total of 121,280 participants diagnosed with RA were enrolled to investigate the risk of newly recorded DM and multivariate adjusted analysis indicated the HR for T2DM were 0.62 for TNF inhibitors, 0.77 for MTX, and 0.54 for HCQ compared with other DMARDS (39). From the study of Ozen, the adjusted HR for DM was 0.67 for HCQ, 0.52 for abatacept (compared with MTX monotherapy). Also, concomitant use of GC did not alter DM risk reduction with HCQ (HR =0.69) (31). In patients with both RA and T2DM, the reduction in glycosylated hemoglobin (HbA1c) among patients taking HCQ was 0.54% greater than those taking MTX after fully adjusted analysis (36). Further studies support the potential benefit of HCQ in attenuating the risk of diabetes in RA patients (40,41).

HCQ reduced diabetes risk by improving insulin sensitivity and pancreatic β-cell functions (42,43), which

may be independent of anti-inflammatory actions. In healthy individuals, the improvement in insulin sensitivity has been reported after HCQ treatment for 8 weeks (42,43). Furthermore, inflammatory cytokines in RA, particularly TNF-α and IL-6 were associated with IR and increased adiposity by triggering key steps in the insulin signaling pathways (44,45). In non-diabetic individuals, HCQ improved the adiponectin levels without significant change in serum inflammatory cytokines (TNF-α, IL-6) (43).

Apart from the risk of T2DM, RA is associated with increased risk of type 1 diabetes (T1DM). In a recent meta-analysis, the pooled risk estimate of 11 case-control studies showed a statistically significant increased risk of DM prevalence among RA individuals (T1DM, OR =4.87; T2DM, OR =1.41) (46). However, the mechanism underling the occurrence of T1DM in RA patients is different from that in T2DM. Both RA and T1DM are two autoimmune disorders that have been reported to co-occur in the same subjects and sharing of disease susceptibility loci is an accepted mechanism. Single-nucleotide polymorphisms such as SKAP2/rs7804356, GLIS3/rs7020673, PRKCQ/DKFZp667F0711/rs947474, GSDMB/rs2290400, BACH2/rs11755527, C6orf173/rs9388489, and DLK1/rs941576 are potential loci (47). Also, the involvement of oxidative stress may trigger genetically controlled autoimmunity to reactive oxygen species (ROS)—collagen type II (CII) and explain the association between T1DM and RA (48).

Risk of diabetes in psoriatic and psoriasis arthritis

Apart from RA, psoriatic (PsA) and psoriasis arthritis (PsO) were also common chronic, inflammatory arthritis. Nas *et al.* examined the association between PsA and its comorbid conditions. When compared with RA, PsA had relatively lower frequency of comorbidities like diabetes mellitus, hypertension and cataract/glaucoma surgery (49). Based on the CPRD database, researchers found that patients with severe PsO had significantly higher rates of diabetes (HR =1.23) compared with mild PsO (50). Radner *et al.* compared the incidence of cardiovascular risk factors of diabetes, hypertension, hyperlipidemia and obesity in patients with PsA, PsO and RA. The prevalence for diabetes was 6.2%, 6.3% and 7.8% in RA, PsO, and PsA, respectively. Incidence rates per 1,000 patient-years during follow-up for RA, PsO, and PsA cohorts for diabetes were 10.6, 13.0, and 14.7. The prevalence of hypertension, hyperlipidemia and obesity had similar trend in this cohort (51).

Risk of diabetes in AS

AS is a chronic inflammatory disease of the axial skeleton with approximately 0.2–0.9% of the general populations affected (52,53). Previous studies have suggested that patients with AS exhibit increased cardiovascular mortality and morbidity (54,55) and cerebrovascular diseases, such as stroke, were more common in patients with AS (28). IR and following diabetes may make contribution to it. However, the research concerning the relationship between AS and T2DM was few. Brophy *et al.* included 1,686 AS patients and 1,206,621 controls and found the prevalence of diabetes and hypertension, but not hyperlipidemia/hypercholesterolemia, were higher in AS (56). Using the Taiwan National Health Insurance data (57), researchers found that the risk of T2DM in the AS patients in Taiwan was 17.4% higher than that in the general population. Compared with non-AS cohort, the incidence of T2DM was 1.17-fold higher in the AS cohort (11.5 *vs.* 13.5, per 1,000 person-years), with an adjusted HR of 1.16 (58). Furthermore, the incidence of T2DM in women with AS was higher than that in men with AS (14.8 *vs.* 12.3 per 1,000 person-years).

Risk of diabetes in OA

OA is the most frequent musculoskeletal disease in subjects over 65 years old (59) and leads to functional decline and loss in quality of life (60). OA is characterized by joint pain, tenderness, stiffness, crepitus, limitation of movement, variable degrees of local inflammation and occasional effusion and in clinical practice (61). In a cross-sectional study of 543 primary care patients over 65 years old, 47.3% had OA and 14.2% had diabetes (62). The prevalence of OA in diabetes patients was 2-fold greater in those without diabetes, even after controlling for OA risk factors (63). A bundle of factors made contribution to OA pathophysiology in diabetes, including pro-inflammatory cytokines and adipokines, abnormal metabolites, acute phase proteins, vitamin D deficiency, and deregulated microRNAs (64). Diabetes was an independent risk factor for OA (65,66).

Despite the frequent occurrence of OA in people with diabetes, little is known about the impact of OA on the occurrence of diabetes and its complications. OA caused joint pain, stiffness, and reduced range of motion, which result in fatigue, depressed mood and functional limitations, including difficulty walking (67).

In people with hip and knee OA, difficulty walking has been independently linked with higher risk for all-cause

death and cardiovascular events (68). Moreover, receipt of hip or knee joint replacement surgery reduced these risks (69), suggesting a direct relationship between difficulty walking and cardiovascular morbidity in patients with OA. However, the relationship between OA and the risk of diabetes was seldom investigated.

In Canadian Rheumatology Association 2017 Annual Meeting, Prof. Kendzerska presented the newest data on the relationship between OA and diabetes a population cohort. In this study, 16,362 subjects who were over 55 years old and absent of diabetes were enrolled from 1996–1998 and followed them to 2014. A total of 1,637 subjects suffered from OA in hip, 2,431 subjects suffered from OA in knee while there were 3,539 subjects developed into diabetes in the whole period of study. After adjusted for baseline age, gender, income, body mass index, history of hypertension and cardiovascular diseases, the risk for diabetes were significantly increased in subjects with OA. HR for OA in hip and knee were 1.25 and 1.16, respectively. However, this relationship disappeared after further adjusted for difficulty walking. Hence, researchers stated that the risk of diabetes was significantly increased in patients with OA, and this was mainly caused by the difficulty in walking.

Besides the study on the risk of diabetes in OA patients, the group also investigated the potential impact of OA-related pain and disability on diabetes outcomes. In the subjects with hip and knee OA from population cohort above (n=2,225), one in six reported a diabetes diagnosis. In subjects with both diabetes and OA, baseline difficulty walking was a predictor of risk for diabetes complications. Greater baseline difficulty walking was associated with shorter time to the first diabetes-specific complication (adjusted HR per unit increase in difficulty walking score was 1.24). After controlled for risk factors for diabetes complications, cardiovascular events and for other conditions that may affect mobility, those findings were still robust (70). OA-related difficulty walking exacerbated the accumulation of advanced glycation end products, dyslipidemia, hyperglycemia and systemic inflammation (71), and increasing risk for diabetes complications. Hence, researchers suggested that difficulty walking in people with diabetes may be a modifiable risk factor for complications.

Difficulty walking and accompanied obesity is an explanation for the increased risk of in OA (72). In the past few decades, the diabetes mellitus incidence have doubled, with an increasing number of T2DM cases (73). The level of FFA is elevated in obesity and FFA mediate many metabolic dysfunctions, especially IR (74). Elevated FFA is associated with both peripheral glucose uptake, hepatic gluconeogenesis and impaired glucose tolerance (75). Long-term lipid overload can result in the accumulation of lipids (such as triglyceride) in insulin responsive tissue and promote the lipotoxicity in cells (76).

Risk of diabetes in osteomyelitis

Chronic osteomyelitis (COM) is a chronic infection-inflammation status and is a common complication of T2DM (77). Osteomyelitis occurs in approximately 10–20% of patients with diabetes-related foot ulcers (12). Since chronic inflammation is a well-known risk factor for T2DM, COM is excepted to increase the risk of T2DM. However, only one study concerned the influence of COM on the risk of developing T2DM.

Using a retrospective cohort study from the Taiwan National Health Insurance Database (NHIRD) from 1997 to 2010, Lin *et al.* identified 20,641 patients with COM and 82,564 age- and sex-matched controls for comparison. The incidence of T2DM in COM patients was 1.6-fold higher than in controls (29.1 *vs.* 18.2 per 10,000 person-years) (78). The COM patients exhibited a higher diabetes risk (adjusted HR =1.64) after controlled the baseline and comorbidities. Also, an increased risk of T2DM in COM patients with comorbidities (adjusted HR =1.70) was observed when compared with that of their non-COM counterparts. Younger and higher income patients exhibited a higher COM-to-reference incidence rate ratio for T2DM compared with that of their counterparts.

COM increased the risk of T2DM via following methods. First, proinflammatory cytokines, such as TNF-α, IL-1β and IL-6 increased markedly in the bone compartment of COM patients (79), which could block downstream insulin signaling, interrupt insulin action and contribute to preclinical stages of T2DM (80). Second, COM patients were immobile because of pain or difficulty in engaging in physical activity [25], where the lack of physical activity could increase the risks of obesity, metabolic syndrome, and T2DM. Third, COM patients needed to make frequent medical visits due to the relapse of COM, where blood glucose levels were frequently tested and increased the likelihood to detect T2DM.

Conclusions

Patients with inflammation related arthritis and osteomyelitis had higher risk for diabetes in various long follow-up

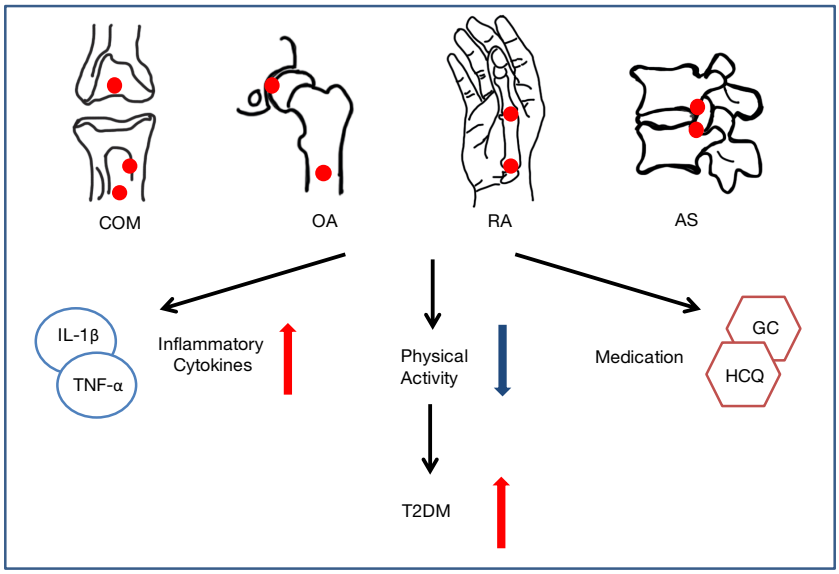

Figure 1 Possible mechanism in inflammatory orthopedics diseases which related to higher risk of type 2 diabetes. COM, chronic osteomyelitis; OA, osteoarthritis; RA, rheumatoid arthritis; AS, ankylosing spondylitis; IL-1β, interleukin-1β; TNF-α, tumor necrosis factor α; GC, glucocorticoid; HCQ, hydroxychloroquine; T2DM, type 2 diabetes.

cohorts. The causes were as follows (*Figure 1*): (I) Local and systemic increased of inflammatory cytokines, such as TNF-α and IL-6, which triggered key steps in the insulin signaling pathways and resulted in increased adiposity and IR. (II) The pain or difficulty avoided activities such as walking and immobile status increased the risk of obesity, diabetes and metabolic syndrome. (III) The medical treatment of arthritis and osteomyelitis can influence the glycometabolism and insulin pathways. For example, GC and statins increased the risk of diabetes while HCQ and MTX were protective medication of diabetes. The combination of different treatment in various arthritis and osteomyelitis lead to different results in the occurrence of diabetes. In conclusion, inflammation related arthritis and osteomyelitis had higher risk of diabetes according to present limited studies. Further studies are needed to verify the conclusion and investigated the mechanism underlining the association between chronic orthopedics diseases and diabetes.

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Footnote

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/amj.2017.05.25). Dr. Deng serves as an unpaid Section Editor of *AME Medical Journal*. The other authors have no conflicts of interest to declare.

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