

Original Research Article

Management of diabetes and arthritis –A systematic review

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Abstract

Purpose: Diabetes is a metabolic syndrome with reported musculoskeletal effects. This systemic review aimed to identify a relationship between diabetes and arthritis; disease-related risk factors, the effect of diet in disease management and the effect of anti-arthritic drugs on diabetes treatment.

Methods: This study analysed 20 articles identified and selected according to the study criteria. PRISMA guidelines were used for identification and screening of literature. Data search covered several primary databases, including Pubmed, Wiley library, Scopus, Clinical Trial Registry, etc.

Results: The study findings suggest a significant correlation between diabetes and arthritis. Obesity, impaired glucose tolerance (MS components), vascular cell adhesion molecule 1 (VCAM-1) hypertension and dyslipidemia are the most common risk factors leading to disease progression. Omega -3-fatty acid showed no protective effect on disease condition.

Conclusion: The findings indicate that anti-tumor necrosis factor (Tnf)- α , disease modifying anti-rheumatic drugs, and Interleukin receptors antagonist improved the efficacy of diabetic medication and maintained blood sugar levels. However, Tnf- α reduced glucose intolerance, and therefore, its therapeutic use in conjunction with diabetic medications should be limited.

Keywords: Diabetes, Arthritis, Risk factors, Diet, Pathogenesis, Disease progression, Medication

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INTRODUCTION

The prevalence and incidence of diabetes mellitus is steadily increasing over past few decades. The global burden of diabetes is 422 million approximately in 2014, then 108 million in 1980 [1]. Diabetes Mellitus (DM) is a metabolic disease which involves many physiological organs and primarily characterized by elevated levels of blood sugar [2]. The disease presented in two forms, type1 DM and type2 DM.

Type 1 diabetes is insulin-dependent diabetes commonly diagnosed among children and young adults. The exact cause for type 1 diabetes is still unknown however it is believed that genetic and environmental factors play vital role in disease development and progression. In contrast autoimmune response on β -cells of pancreas are responsible for development Type 2 DM. Type 2 diabetes is usually developed among middle aged and older adult population [3].

DIABETES AND ARTHRITIS

The patient with diabetes mellitus suffers with the associated myriad musculoskeletal conditions. Diabetes had reported linked to musculoskeletal changes with symptoms such as joint pain and stiffness and this can severely affect the feet and mobility of the patient. People with diabetes are twice more likely to develop arthritis, indicating strong association between diabetes and arthritis [2]. However, there are many forms of arthritis including osteoarthritis, rheumatoid arthritis, gout and juvenile arthritis, yet with the limited literature it is difficult to establish a relationship with all the forms. The prevalence of arthritis is approximately 52.0 % among adults with diabetes [3].

Type 2 DM and rheumatoid arthritis (RA)

Rheumatoid arthritis (RA) is a chronic disease characterized by systemic inflammation, persistent synovitis, and the presence of auto-antibodies. Elevated Inflammatory mediators were in patients with type 2 diabetes years before the clinical onset of RA, thus suggesting a vital role of diabetes in the pathogenesis of RA. Literature also reported that RA patients' were 50 % more likely to develop type 2 diabetes as compared with non-RA. Attaining sedentary lifestyle because of RA pain further increases the risk for type 2 diabetes mellitus [7].

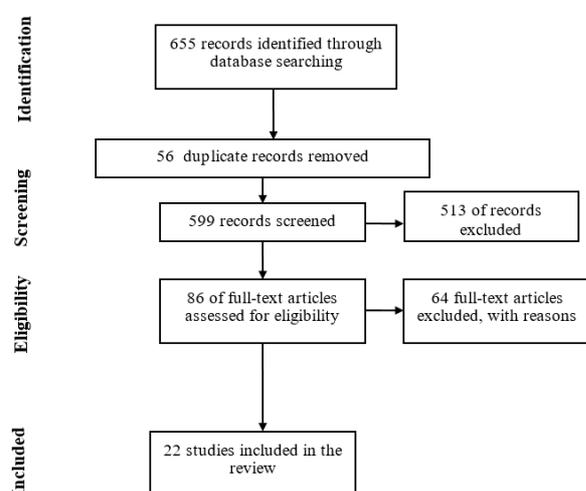


Figure 1: PRISMA flow-chart

Impact of diabetes, obesity and MS on OA

Osteoarthritis (OA) is the most common type of rheumatic disease and a leading cause of disability among patients. Literature suggested that > 10 % of the world population has confirmed diagnosis of OA. Severe joint pain limits patients' mobility with disease progression. Recently, OA has been recognized as a

metabolic disease linked to metabolic syndrome. Evidence also reported the contribution of OA in the development of type 2 diabetes through complex processes involving metabolic syndrome, physical inactivity, and muscle weakness. High frequency of Osteoarthritis among diabetic patients' showed a positive association in-between the diseases [8]. There are several theories suggesting the possible pathogenesis of arthritis in diabetic patients like; a harmful role of excess glucose accumulation through advanced glycation end products (AGEs), oxidative stress and proliferation of systemic inflammation. Risk factors like hypertension, dyslipidemia, pulmonary diseases, depression, psychotic disorders and impaired glucose tolerance are considered factors responsible for the disease development [9,10]. Diabetes and Osteoarthritis frequently coexist due to sharing of common risk factors; age, and obesity [11]. Current available literature to establish relationship of arthritis among diabetic population reported contradiction in the conclusions drawn on the effect of diabetes on arthritis and presence of confounding risk factors & also treatment variability for both diabetes and arthritis. This systematic review managed to reach a consensus on the relationship in-between arthritis and the diabetes and also addresses the discrepancies in the earlier reports.

Diabetes and gout psoriatic arthritis

Gout is characterized as extreme arthritis pain and the elevated uric acid blood levels. Particularly in western countries gout is commonly found among middle aged population. Gout also poses a risk for cardiovascular complications including hypertension, obesity, the metabolic syndrome and premature mortality. Higher serum uric acid levels are reported to be a risk factor of diabetes development particularly among women. A study conducted in Canada found higher prevalence of DM in patients with Psoriatic Arthritis [12].

METHODS

Search subjects

This study searched the literature on the basis of required criteria as; pathogenesis of arthritis among diabetic patients, the progression rate of arthritis among patient of diabetes and various risk factors associated with it. Complications related to diet & least mobility in diabetic patients and also its effects on arthritis. Treatment options and related consequences specific to diabetes mellitus only.

Search eligibility criteria

This systemic review specifically focused on studies fulfilled the eligibility criteria; published in-between 2001-2017 and should be written in the English language only. A systematic review and meta-analyses on arthritis among diabetic patients but did not limit our article search to specific type of arthritis. Primarily literature search focused on original research article reported the disease progression and/or development either arthritis-to-diabetes or vice versa.

Search keywords

Different keywords were used for literature search; 'arthritis', 'type 1 diabetes', 'type 2 diabetes', 'mobility', 'gout', 'psoriatic arthritis', 'diet', 'treatment options', 'risk factors', 'consequences' and 'complications related to diabetes'.

Primary search

Different databases and individual journal websites, like Pubmed, Research Gate, Google Scholar, Wiley Online Library, New England Journal of Medicine, Rheumatology, Journal of Medical Case Reports, Clinical Geriatric Medicines, Handbook Experimental Pharmacology, Annals of Rheumatology Disorders, Osteoarthritis and Cartilage, Caspian Journal of Internal Medicines and British Medical Journal were used for primary search.

Secondary search

Once the primary search was completed secondary search was made by using the references of articles that were identified earlier. Primary screening of the articles was mainly focused on the screening of titles and abstracts. Articles that passed through primary screening were critically appraised for the inclusion in the study analysis.

RESULTS AND DISCUSSION

A total of 22 articles matched the aforementioned criteria and were included for study analysis. Out of 22 studies, 8 studies assessed the association of Arthritis and Diabetes Mellitus and/or glycaemia or Metabolic syndrome (MetS); 5 showed a significant association in their conclusions whereas 3 studies displayed no association. Four studies showed various risk factors, obesity, hypertension, glucose intolerance, vascular cell adhesion molecule-

1(VCAM-1) and dyslipidemia associated with patients suffering from diabetes and arthritis. One study reported no specific effect of diet on either diabetic or arthritis patients'. Nine studies found that the drugs used in the treatment of arthritis like anti-tumor necrosis factor α , interleukin-1 receptor antagonists and disease modifying anti-rheumatics were also effective in diabetes management (Table 1 and Table 2).

Metabolic syndrome: a risk factor for osteoarthritis

MetS is a clustering of risk factors, including dyslipidemia, high blood pressure, impaired glucose tolerance, and abdominal obesity. Hypertension due to subchondral ischemia can cause diminished nutrients exchange into the bone tissues which further trigger bone remodeling leading to OA. On the other hand, hyperglycemic conditions, locally cause oxidative stress and the glycation metabolites can cause cartilage damage and systemically glucose accumulation can lead to low-grade systemic inflammation which can exacerbate OA. Obesity also contribute to the etiology of OA particularly due to high adipokines levels [13,14].

Vascular cell adhesion molecule (VCAM-1)

For the risk of hip and knee joint OA, vascular cell adhesion molecule (VCAM-1) is a strong and independent predictor [4]. Increased sVCAM-1 level were found in knee osteoarthritis among type 2 diabetic postmenopausal women in a study also showed inflammation and active cartilage damage. A positive correlation of hyperglycemia with VCAM-1 is present which is consistent with the hypothesis that high intracellular glucose concentration in diabetes promotes the formation of advanced glycation end products. AGE compounds interact with membrane receptors called RAGE present on chondrocytes and give rise to a cascade of events that promote release of pro-inflammatory factors such as TNF- α , and activate transcription factors such as Nf-kB, which in turn induces VCAM-1 and promotes inflammation and cartilage degradation [10-12].

Diabetes and arthritis are autoimmune disorders that share obesity and impaired glucose metabolism as risk factor, but may also have relationship through pathogenic mechanisms involving metabolic abnormalities and systemic inflammation [5]. Furthermore, there are pathophysiological evidences linking arthritis and diabetes like age, dyslipidemia and hypertension [6,7]. However, the association between Diabetes and arthritis needs to be further

assessed. This systemic review critically appraised the twenty studies included for analysis. Out of twenty studies, eight studies assessed the association of Arthritis and Diabetes Mellitus; five studies indicated a significant association in their conclusions [8-12]. Three studies displayed no association, they found overweight and inflammation as a cause for arthritis [13-15]. Obesity, hypertension and dyslipidemia and impaired glucose tolerance are major risk factors associated with progression of arthritis (MS components). Two studies found the accumulation of MS components is significantly related to the presence and joint space reduction of knee osteoarthritis [16,17]. In one study comorbid diseases reported to play an important role in predicting survival of primary hip and knee replacements in OA patients [18]. Omega-3-fatty acid had no effect on fasting blood sugar or glycosylated hemoglobin and on pain, swollen joint in arthritis patients' [19].

In summary, most studies found the direct association between diabetes and arthritis. There is a positive association found for risk factors like obesity, hypertension, glucose intolerance, vascular cell adhesion molecule-1 (VCAM-1) and dyslipidemia between diabetes and arthritis. Omega-3-fatty acid had no effect on diabetes and arthritis [10-13]. Different drugs used in the therapy of arthritis helps in reducing the risk of diabetes [10-12]. The relative side effects of these drugs were not found except for anti-tumor necrosis factor α which reported to cause glucose intolerance (Table 3 and Table 4).

There are arthritis drugs which have specific use in diabetes like anti-tumor necrosis factor α , interleukin-1 receptor antagonists (bDMARDs) and disease modifying anti-rheumatics (cDMARDs). The use of Anakinra (interleukin-1 receptor antagonist, bDMARDs) showed better glycemic control among diabetic patients in six months [20]. The use of Anti-TNF α (bDMARDs) was associated with 51 % reduction in risk of developing diabetes mellitus. It also causes overall reduction in the risk of type 2 DM and CVD in RA patients [21-24]. With the use of Infliximab (anti-TNF- α , bDMARDs) showed dramatic improvement in insulin resistance and sensitivity compare to conventional disease-modifying anti-rheumatic drugs (cDMARDs) [22].

A long-term positive effect of infliximab and etanercept (bDMARDs) on insulin resistance was also observed in RA patients. Patients with rheumatoid arthritis, use of hydroxychloroquine (cDMARDs) and abatacept (bDMARDs) was positively associated with a reduced risk of diabetes progression [22,23,25]. Hydroxychloroquine (cDMARDs) also optimized glycemic control in type 1 diabetic patient with subtle improvement in the lipid profiling [25].

CONCLUSION

The relative side effects of anti-rheumatic drugs were not found except for anti-TNF α which causes hypoglycemic attack without warning. Thus further clinical studies are required for finding out side effect of anti-arthritis drug that has specific use in diabetes mellitus.

Table 1: Musculoskeletal effects of diabetes mellitus and association

Conclusion	Article	Summary of findings
Positive association	[12]	Positive association for the musculoskeletal effect in diabetic patients
Positive association	[11]	High frequency of OA in patients with DM and positive association between both diseases.
Positive association	[8]	Positive association for rheumatoid arthritis patients suffering from diabetes
Positive association	[9]	Positive association for adults with diagnosed DM, nearly half also have diagnosed arthritis.
No association	[14]	RA <i>per se</i> is not associated with increased risk of T2DM
Positive association	[10]	Reports the evidence from clinic and laboratories that DM is implicated in disease development, severity and outcome for OA.
No association	[15]	The association between MetS and radiographic knee OA can be explained by an excessive weight but not by insulin resistance, key pathophysiology feature of MetS.
No association	[13]	MetS reported to be not significantly linked with hip OA. However in women, CRP was found to be linked with knee OA, when adjusted for age.

Table 2: Progression and association of arthritis among diabetes patients

Various risk factors/Predictors associated with it	Conclusion	Article	Summary of findings
Obesity, hypertension, and dyslipidemia	Positive association	[21]	Type 2 DM linked with joint space reduction in men with knee OA.
Overweight, hypertension, dyslipidemia and impaired glucose tolerance (MS components)	Positive association	[16]	The accumulation of MS components is significantly related to presence of KOA
Vascular cell adhesion molecule 1 (VCAM-1)	Positive association	[4]	VCAM-1 strongly linked and an independent predictor of the risk for hip and knee joint replacement due to OA
Cardiovascular diseases, hypertension, diabetes, cancer, pulmonary diseases, depression, psychotic disorders and neurodegenerative diseases	Positive association	[18]	An important role of co-existing diseases in predicting survival of primary hip and knee replacements emerged.

Table 3: Complications related to diet and least mobility with diabetes and arthritis

Diet	Conclusion	Articles	Summary of findings
Omega -3-fatty acid	No association	[19]	Omega -3-fatty acid had no effect on fasting blood sugar or glycosylated hemoglobin and on pain, swollen joint in arthritis patients

Table 4: Arthritic drugs and relative effect to diabetes and relative side effects

Drug	Use in Diabetes	Relative side effect	Articles
Anakinra (recombinant non-glycosylated human interleukin-1 receptor antagonist) (bDMARDs)	Better glycemic control in 6months	-----	[20]
Anti-Tumor Necrosis Factor α . (bDMARDs)	Anti-TNF use was associated with a 51 % reduction in risk of developing diabetes mellitus. It also causes overall reduction in the risk of type 2 DM and CVD in RA patients	Unstable DM-hypoglycemic attack without warning.	[21,23]
Disease-Modifying Anti-rheumatic Drugs (csDMARDs) & (bDMARDs)	Patients with RA, the adjusted risk of DM was lower for individuals starting a TNF inhibitor or hydroxychloroquine compared with the start other non-biologic DMARDs.	-----	[22]
Hydroxychloroquine (csDMARDs) and Abatacept (bDMARDs)	Helps in decreasing the risk of DM	-----	[24]
Hydroxychloroquine (csDMARDs)	Patients with rheumatoid arthritis using hydroxychloroquine reported to be at less risk to develop diabetes.	----	[23]
Infliximab (anti-TNF- α) (bDMARDs)	A long-term positive effect of infliximab and etanercept on insulin resistance in RA patients was noted.	----	[18]
Hydroxychloroquine (HCQ) (csDMARDs)	Glycemic control was optimized with the introduction of HCQ as treatment for type 1 diabetes.	----	[17]

DECLARATIONS

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Conflict of interest

No conflict of interest is associated with this work.

Authors' contribution

We declare that this work was done by the authors named in this article and all liabilities pertaining to claims relating to the content of this article will be borne by the authors. SWG & MIMA: Principal investigator and drafted the manuscript. HAZ & IAA: Content analysis. SAUR & SF: Literature search and revised manuscript. All authors read and approved the final manuscript.

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