

Arthritis in Type 2 Diabetes Mellitus

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Abstract: Objectives: Estimating the possible causes of arthropathies in patients with type 2 diabetes mellitus attending outpatient clinics of internal medicine department at Menoufia university hospital. **Background:** Diabetes mellitus (DM) is a chronic disease and has become one of the main threats to human health in recent decades. Diabetes worldwide was estimated at between 151 million and 171 million in the year 2000 and, it is estimated that this number will triple by 2050. Uncontrolled diabetes with increased blood glucose is strongly correlated to causing long-term microvascular and macrovascular complications, such as nephropathy, neuropathy, retinopathy, muscular dystrophy and atherosclerosis. Rheumatological diseases are now common, which have an increased prevalence in diabetic population. **Patients & Methods:** The study include 90 patients, Patients divided into 3 groups **group 1:** 30 patients with type 2 diabetes mellitus without arthropathy, **group 2:** 30 patients with type 2 diabetes mellitus with arthropathy and **group 3:** 30 patients not diabetics with arthropathy. All the patients were subjected to the following: History taking with general, rheumatological and neurological clinical examinations, The following laboratory tests were done for all the patient: Randum blood sugar, Glycated hemoglobin(HbA1c), Erythrocyte sedimentation rate (ESR), Rheumatoid factor (RF) in the serum, using the latex fixation test, Serum uric acid and Anti-nuclear antibody(ANA), also plain x-ray of affected joint were done for patients with arthropathy. **Results:** BMI was significantly higher among diabetic patients with arthropathy (33.64 ± 2.26). Regarding RBS, it was significantly higher among diabetic patients with arthropathy (288.10 ± 83.64). and diabetic patients without arthropathy (240.53 ± 51.37), Regarding HbA1C, it was significantly higher among diabetic patients with arthropathy (8.72 ± 1.09) and diabetic patients without arthropathy (7.39 ± 0.47). Regarding ESR, it was significantly higher among non diabetic patients (58.60 ± 27.29). Regarding serum uric acid, it was significantly higher among non diabetic patients (5.11 ± 1.18), no significant difference between the studied groups regarding CRP ($P > 0.05$), Regarding RF, it was significantly lower among diabetic patients with arthropathy. Regarding ANA, it was significantly lower among patients with arthropathy. **Conclusion and Recommendations:** Musculoskeletal complications are most commonly seen in patients with a long standing history of type 2 diabetes mellitus. Diabetes mellitus is associated with several musculoskeletal disorders. The incidence of diabetes mellitus and the life expectancy of the diabetic patient have both increased, resulting in increased prevalence and clinical importance of musculoskeletal alterations in diabetic subjects. The development of musculoskeletal disorders is dependent on age and the duration of diabetes mellitus. It has been difficult to show a direct correlation with the metabolic control of diabetes mellitus. Most of these disorders can be diagnosed clinically but some radiological examination may help, especially in differential diagnosis.

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1. Introduction:

Arthritis refers to many types; e.g rheumatic conditions, both inflammatory and non-inflammatory, affecting joints as well as surrounding structures and other tissues. Many of them are systemic diseases that can cause generalized problems and fatigue with the heart, lungs, skin, kidneys and other parts of the body.(1)

The common types of arthritis and related conditions: osteoarthritis, rheumatoid arthritis (RA), fibromyalgia, osteoporosis and gout. The major complaint by individuals who have arthritis is joint pain. Pain is often a constant and may be localized to the affected joint. The pain from arthritis is due to inflammation that occurs around the joint, damage to

the joint from disease, daily wear and tear of joint, muscle strains caused by forceful movements against stiff painful joints and fatigue. (2)

Diabetes mellitus (DM) is a chronic disease and has become one of the main threats to human health in recent decades. Diabetes worldwide was estimated at between 151 million and 171 million in the year 2000 and, it is estimated that this number will triple by 2050 (3).

Type 1 diabetes is characterized by beta-cell failure, partly due to autoimmune destruction (4) and Type 2 diabetes arises as a result of beta-cell failure combined with associated insulin resistance (5).

Uncontrolled diabetes with increased blood glucose is strongly correlated to causing long-term

microvascular and macrovascular complications, such as nephropathy, neuropathy, retinopathy, muscular dystrophy and atherosclerosis. DM and arthritis share some risk factors including age and obesity.)6) The mechanism of this comorbidity remains uncertain; these co-occurring conditions have been associated with a significant reduction in quality of life and increased risk for other severe complications. Understanding the extent to which arthritis produces activity limitation among adults with DM will help raise awareness of the conjoint burden of these two diseases as well as the need of efforts to promote the benefits of physical activity in managing DM and arthritis. A recent most study in USA among adults with DM, the unadjusted prevalence of arthritis was 48.1% (9.6 million) and 55.0% (5.3 million), respectively. After adjusting for other characteristics, the prevalence ratios of arthritis and of arthritis-attributable activity limitation (AAAL) among arthritic adults with versus without DM (95% CI) were 1.44 (1.35 - 1.52) and 1.21 (1.15 - 1.28), respectively. From various arthritic and rheumatological manifestations, shoulder hand syndrome (SHS), diabetic hand syndrome (DHS), diffuse idiopathic skeletal hyperostosis (DISH) and neuroarthropathy are characteristically associated with DM. Rheumatological diseases are now common, which have an increased prevalence in the diabetic population.)7). All these have a severe clinical course in the diabetic population.)8)

2. Patients and Methods:

The study include 90 patients, They were randomly recruited from outpatient clinics of Internal Medicine department at Menoufia university hospital from June 2014 to December 2014, all groups were of almost same age and distribution of male and female. The studied patients were aged from 37 to 67 years. The disease duration ranged from 7 to 15 years, they divided into three groups: 30 patients with type 2 diabetes mellitus without arthropathy (twenty one males and nine females), 30 patients with type 2 diabetes mellitus with arthropathy (twenty two males and eight females) and 30 patients not diabetics with arthropathy(fifteen males and fifteen females).

All the patients were subjected to the following: History taking with general, rheumatological and neurological clinical examinations according to standardized rheumatological and neurological sheets. Plain x-ray of affected joint were done for patients with arthropathy. The following laboratory tests were done for all the patients: Randum blood sugar, Glycated hemoglobin (HbA1c), Erythrocyte sedimentation rate (ESR), Rheumatoid factor (RF) in the serum, using the latex fixation test, Serum uric acid and Anti-nuclear antibody (ANA).

Results were statistically analyzed by statistical package SPSS version 20. Two types of statistics were done; Descriptive: e.g. percentage (%), mean and standard deviation SD and Analytical:- One way ANOVA (F test): A one-way analysis of variance (ANOVA) is a single test used to collectively indicate the presence of any significant difference between several groups for a normally distributed quantitative variable. Kruskal -Wallis test: It is the non-parametric version of ANOVA it is used to collectively indicate the presence of any significant difference between several groups for a not normally distributed quantitative variable. Post hoc test: is used after one way ANOVA (F test) or Kruskal -Wallis test to show any significant difference between the individual groups. Chi-Squared (χ^2): It is used to compare between two groups or more regarding one qualitative variable. Fisher's exact test: It is used to compare between two groups regarding one qualitative variable in a 2x2 contingency table when the count of any of the expected cells less than 5. *P* value: Significant difference if $P < 0.05$, non-significant difference if $P > 0.05$. and highly significant difference if $P < 0.001$.

3. Results:

The studied groups underwent Randum blood sugar, Glycated hemoglobin(HbA1c), Erythrocyte sedimentation rate (ESR), Rheumatoid factor (RF) in the serum, using the latex fixation test, Serum uric acid and Anti-nuclear antibody(ANA).All patients were matched in terms of age, sex, BMI, HbA1c, ESR, RF and ANA.

Comparing the studied groups as regard age and sex, there was no significant difference ($P > 0.05$) (Table1).

BMI was significantly higher among patients with arthropathy (33.64 ± 2.26) than both of patients without arthropathy (24.25 ± 1.91) and non diabetic patients (24.66 ± 2.12) ($P < 0.001$) (Table2), Regarding RBS, it was significantly higher among patients with arthropathy (288.10 ± 83.64) than both of patients without arthropathy (240.53 ± 51.37) and non diabetic patients (107.70 ± 20.50) ($P < 0.001$). Also it was significantly higher among patients without arthropathy (240.53 ± 51.37) than non diabetic patients (107.70 ± 20.50) ($P < 0.001$), Regarding HbA1C, it was significantly higher among patients with arthropathy (8.72 ± 1.09) than both of patients without arthropathy (7.39 ± 0.47) and non diabetic patients (6.06 ± 0.21) ($P < 0.001$). Also it was significantly higher among diabetic patients without arthropathy (7.39 ± 0.47) than non diabetic patients (6.06 ± 0.21) ($P < 0.001$), Regarding ESR, it was significantly higher among non diabetic patients (58.60 ± 27.29) than both of diabetic patients with arthropathy (36.10 ± 24.14) and diabetic patients without arthropathy (34.43 ± 28.36) (P

<0.001), Regarding serum uric acid, it was significantly higher among non diabetic patients (5.11 ± 1.18) than both of diabetic patients with arthropathy (4.99 ± 0.93) and diabetic patients without arthropathy (4.88 ± 1.0) ($P = 0.689$)(Table3), no significant difference between the studied groups regarding CRP ($P > 0.05$) (table4), Regarding RF, it was significantly lower among patients with

arthropathy (0.0%) than both of patients without arthropathy (20.0%) and non diabetic patients (33.3%) ($P = 0.0101$ & 0.001 respectively)(Table5). Regarding ANA, it was significantly lower among patients with arthropathy (0.0%) than both of patients without arthropathy (30.0%) and non diabetic patients (23.3%) ($P = 0.001$ & 0.011 respectively)(Table6).

Table (1): Distribution of the studied groups regarding their age and sex:

	Groups						Test	P-value
	Diabetic							
	With arthropathy ^(I) (N=30)		Without arthropathy ^(II) (N=30)		non diabetic patients ^(III) (N=30)			
	no	%	no	%	no	%		
Age							F=1.1259	I vs. II=0.634
Mean \pm SD	50.06 \pm 6.99		51.03 \pm 8.77		7.53 \pm 7.64		P=0.209	I vs. III=0.214 II vs. III=0.087
Sex							$\chi^2=0.08$	I vs. II=0.774
Male	21	70.0	22	73.3	15	50.0	$\chi^2=2.50$	I vs. III=0.114
Female	9	30.0	8	26.7	15	50.0	$\chi^2=3.45$	II vs. III=0.063

Table (2): Statistical comparison of BMI between studied groups:

	Groups			F test	Post hoc value
	Diabetic				
	With arthropathy ^(I) (N=30)	Without arthropathy ^(II) (N=30)	non diabetic patients ^(III) (N=30)		
	Mean \pm SD	Mean \pm SD	Mean \pm SD		
BMI	33.64 \pm 2.26	24.25 \pm 1.91	24.66 \pm 2.12	189.90 P<0.001(HS)	I vs. II<0.001 I vs. III<0.001 II vs. III=0.450

Table (3): Statistical comparison of lab investigations between studied groups:

	Groups			Test	Post hoc value
	Diabetic				
	With arthropathy ^(I) (N=30)	Without arthropathy ^(II) (N=30)	non diabetic patients ^(III) (N=30)		
	Mean \pm SD	Mean \pm SD	Mean \pm SD		
RBS	288.10 \pm 83.64	240.53 \pm 51.37	107.70 \pm 20.50	F=133.51 P<0.001(HS)	I vs. II=0.001 I vs. III<0.001 II vs. III<0.001
HbA1c	8.72 \pm 1.09	7.39 \pm 0.47	6.06 \pm 0.21	F=108.49 P<0.001(HS)	I vs. II<0.001 I vs. III<0.001 II vs. III<0.001
ESR	36.10 \pm 24.14	34.43 \pm 28.36	58.60 \pm 27.29	Kruskal-Wallis 16.83 P<0.001(HS)	I vs. II=0.705 I vs. III=0.002 II vs. III<0.001
Uric acid	4.99 \pm 0.93	4.88 \pm 1.0	5.11 \pm 1.18	F=0.37 P=0.689	I vs. II=0.694 I vs. III=0.640 II vs. III=0.390

Table (4): Statistical comparison of CRP between studied groups:

	Groups						χ^2	P-value
	Diabetic				non diabetic patients (III) (N=30)			
	With arthropathy ^(I) (N=30)		Without arthropathy ^(II) (N=30)					
	no	%	no	%	no	%		
CRP Positive	18	60.0	15	50.0	21	70.0	$\chi^2=0.60$	I vs. II=0.436
CRP Negative	12	40.0	15	50.0	9	30.0	$\chi^2=0.65$ $\chi^2=2.50$	I vs. III=0.417 II vs. III=0.114

Table (5): Statistical comparison of RF between studied groups:

	Groups						χ^2	P-value
	Diabetic				non diabetic patients (III) (N=30)			
	With arthropathy ^(I) (N=30)		Without arthropathy ^(II) (N=30)					
	no	%	no	%	no	%		
RF Positive	0	0.0	6	20.0	10	33.3	$\chi^2=6.66$	I vs. II=0.010(S)
RF Negative	30	100.0	24	80.0	20	66.7	$\chi^2=12.0$ $\chi^2=1.36$	I vs. III=0.001(S) II vs. III=0.243

Table (6): Statistical comparison of ANA between studied groups:

	Groups						χ^2	P-value
	Diabetic				non diabetic patients (III) (N=30)			
	With arthropathy ^(I) (N=30)		Without arthropathy ^(II) (N=30)					
	no	%	no	%	no	%		
ANA Positive	0	0.0	9	30.0	7	23.3	$\chi^2=10.58$ FE=7.92	I vs. II=0.001(S) I vs. III=0.011(S)
ANA Negative	30	100.0	21	70.0	23	76.7	$\chi^2=0.34$	II vs. III=0.559

4. Discussion:

Diabetes may affect the musculoskeletal system in a variety of ways. The metabolic perturbations in diabetes (including glycosylation of proteins; microvascular abnormalities with damage to blood vessels and nerves; and collagen accumulation in skin and periarticular structures) result in changes in the connective tissue. Musculoskeletal complications are most commonly seen in patients with a longstanding history of type 2 diabetes. Musculoskeletal disorder among the diabetic patient lead to pain, discomfort and disability. Moreover, the quality of life of the patient also alter for such consequence. The medical team should be implemented in order to enhance quality of care of the diabetic patient to resolve the musculoskeletal disorder.

It is generally accepted that diabetes control, monitored by American Diabetes Association recommended annual cholesterol and biannual hemoglobin A1C (A1c) testing, reduces macro- and microvascular complications, respectively. At the same time, the European League Against Rheumatism

(EULAR) recommends “annual cardiovascular risk assessment” for RA patients, which although not explicitly stated, would likely include screening and monitoring traditional cardiac risks, such as hyperlipidemia. Still, a 2011 report cited that only 32% of general practitioners recognized RA as an independent risk factor for CVD, despite growing evidence regarding the heightened risk of CVD associated with RA. (9)

The Centers for Disease Control and Prevention estimate that >26% of adults over 65 have diabetes mellitus (DM), and reports note that diabetes is a key mortality predictor in patients with rheumatoid arthritis (RA). Both RA and DM increase cardiovascular disease (CVD) risk; thus, the question of how comorbid RA impacts diabetes care merits consideration, but has received little prior attention. (10)

In large national cohort study of Medicare diabetes patients with and without RA, the comorbid presence of RA predicted lower rates of A1c testing, but slightly improved lipid testing, and was associated

with higher baseline CVD and diabetes microvascular complications. (10)

These findings were consistent with our hypotheses drawn from the Piette and Kerr model theorizing that RA (a condition whose care is discordant from routine diabetes care) would predict less A1c testing. A1c testing is generally perceived as a diabetes care goal but not a RA priority, which might explain lower testing rates in patients who also have competing RA care needs. Lower A1c monitoring in diabetes patients with RA is a problem because poor glycemic control increases the same micro-vascular complications that were more prevalent in patients with RA. (11)

In this study, we show that long-standing type 2 diabetes is independently associated with advanced OA of knee and hip joints. This finding adds to the yet short list of risk predictors for OA established in prospective evaluations. After controlling the analysis for age, BMI, and other potential confounders, type 2 diabetes comprised a twofold risk of severe OA necessitating arthroplasty. (12)

The population-based design is a strength of this study, as well as its long term and complete follow-up and the use of joint failure necessitating arthroplasty as a hard end point. A further strength of our study is that the link between type 2 diabetes and OA was consistent when using three distinct approaches of OA ascertainment as follows: 1) joint failure as determined by arthroplasty; 2) signs and symptoms of OA as quantified by the WOMAC and KOOS scores; and 3) severity of joint changes as determined by musculoskeletal US. (13)

The link between obesity and OA is well-established and particularly supported by longitudinal data showing that obesity entails a higher risk for developing severe OA. Traditionally, mechanical factors have been considered to explain more rapid joint degeneration in obese individuals. However, this concept has been challenged by the link between obesity and OA in non weight-bearing joints, suggesting that metabolic changes directly enhance the risk of OA. Despite evidence from cross-sectional studies that OA is linked to the metabolic syndrome and higher blood glucose levels, no study addressed whether diabetes is in-dependently linked to OA and in particular whether such a link is independent of body weight. Our study shows that type 2 diabetes predicts severe OA independent of age, sex, and BMI and provides both longitudinal and cross-sectional evidence for an independent association between type 2 diabetes and OA. (14)

In population-based prospective study with an average of 12 years of follow-up, we found that the risk of diabetes was higher in persons with OA compared to those without OA, after adjusting for

confounding variables. The risk was significant in both younger and older women and in younger men, compared to their age-sex matched non-OA counterparts. We also observed that younger OA subjects who underwent TJR had a 37% higher risk of diabetes compared to non OA individuals. Older men with OA showed no significant increased risk of diabetes. (15)

In contrast, diabetes patients with RA were slightly more likely to receive LDL testing. Dual indications for lipid testing in those with both RA and diabetes accurately predicted a concordant motivation for athero-sclerosis prevention via LDL testing, per Piette and Kerr. Heightened LDL testing contrasts with our groups' prior reports of low lipid testing in RA patients, most likely reflecting that in the present study patients were selected for active diabetes, a disease in which lipid performance is routinely monitored and publically reported. The trend for slightly increased lipid testing noted here among diabetes patients with RA also may suggest growing awareness of CVD prevention needs in RA. (16)

Prior studies report higher morbidity and mortality among RA patients with diabetes, but to our knowledge no studies have reported heightened prevalence of microvascular complications in patients with comorbid diabetes and RA. We found that CVD, with the exception of MI, was more prevalent in patients with both diabetes and RA. The MI rate is consistent with other RA reports, including a Danish study showing similar MI rates in patients with RA, diabetes or both (17)

Strengths of this study include the use of a large, nationally representative sample of Medicare patients with diabetes and RA, and extensive demographic, comorbidity and utilization data. However, a few limitations should be noted. (18)

In light of reduced A1c testing in patients with comorbid RA and diabetes, and heightened microvascular and CVD risk, we urge providers to consider DM and RA as concordant risk factors. We recommend further research examining the interplay between RA and other comorbidities on care quality and outcomes for vascular-risk conditions. This research should examine more direct quality of care measures, including appropriateness of pharmacotherapy and prospective morbidity and mortality. Lastly, given observed lapses in process care measures, such as A1c testing for patients with both RA and diabetes, additional research should investigate optimal co-management or shared disease-management and prevention strategies among specialty and primary care providers. (19)

Our findings support conceptualizing RA and diabetes on a concordant risk pathway to improve screening for complications and diabetes monitoring

performance in patients with RA. Lower rates of A1c monitoring, in particular, may offer a target for improving the higher-than-expected rates of microvascular complications observed in this study for RA patients with diabetes.(20)

The prevalence of arthritis was 52.0% among adults with diabetes. Also, the prevalence of physical inactivity was higher among adults with diabetes and arthritis (29.8%) compared with adults with diabetes alone. This finding held true for the state of Minnesota as well with higher prevalence of physical inactivity among adults with diabetes and arthritis (20.3%) in comparison with those without arthritis (16.0%). These results suggest that arthritis may be an under recognized barrier to being physically active for adults with arthritis and diabetes as well as, arthritis and HD. (21)

To assess insulin resistance in early untreated rheumatoid arthritis patients and its relation to the clinical, inflammatory and biochemical characteristics of these patients. Patients and methods: Sixty-six untreated rheumatoid arthritis (RA) patients with disease duration less than 1 year along with age and sex matched controls were studied. Disease activity score (DAS28) was used to assess disease activity. Plasma levels of C- reactive protein (CRP), glucose, insulin and complete lipid profile were measured. Insulin resistance (IR) was estimated by the homeostasis model assessment for insulin resistance (HOMA-IR).(22)

None of the studied RA patients in the current study was obese (BMI \geq 30), despite the marked inflammation encountered in them. This was in agreement with previous reports by other investigators.

In this regard, Rall and Roubenoff explained how RA patients with active disease often suffer from loss of body cell mass; a condition referred to as rheumatoid cachexia. It is related to inflammatory cytokine production and insulin resistance. However, patients with high disease activity had higher BMI as compared with patients with moderate disease activity and with controls. This may be related to increased prevalence of central obesity and metabolic syndrome among RA patients that was also found to be related to disease activity, circulating inflammatory cytokines and insulin resistance. (23)

In a recent study Mathew et al. showed that rheumatic-musculoskeletal disorders were predicted by both duration of T2DM and HbA1c. The different results may very well be caused by differences in the methodology leading to a focus on different musculoskeletal problems and the characteristics of the included patients, which in our study were characterized by lower HbA1c, higher age and longer duration of T2DM. (Dina Shahin *et al.*,2010)

Conclusions:

Diabetes mellitus is associated with several musculoskeletal disorders. The incidence of diabetes mellitus and the life expectancy of the diabetic patient have both increased, resulting in increased prevalence and clinical importance of musculoskeletal alterations in diabetic subjects. The development of musculoskeletal disorders is dependent on age and the duration of diabetes mellitus. It has been difficult to show a direct correlation with the metabolic control of diabetes mellitus. Most of these disorders can be diagnosed clinically but some radiological examination may help, especially in differential diagnosis.

Every diabetic patient has a risk of various bone and joint disorder in future life. Factors such as nerve damage (diabetic neuropathy), arterial disease and obesity may contribute to these problems. The complications of diabetes mellitus are numerous and include involvement of the musculoskeletal system.

Musculoskeletal disorders are common in type 2 diabetic subjects and examination particular regions of the hands, the joints, shoulders and feet, as well as the skeleton should be included in the evaluation of patients with diabetes mellitus.

Diabetic patients often suffer with many types of musculoskeletal problem like as shoulder pain, frozen shoulder, hand syndrome, back pain, neck pain, osteoarthritis, elbow pain, epicondylitis, carpal tunnel syndrome, Dequerven tenosynovities, leg and foot pain, amyotrophy etc. But they are not aware about these problems. This study aims to address these problems and design physiotherapy intervention for this diabetic patient with musculoskeletal problem.

This study also will be helpful in making physiotherapist to aware about the musculoskeletal problem of diabetic patient. This study might give a clear reflection of the prevalence of musculoskeletal problem arises among the patient with diabetes. Physiotherapy plays a vital role in the management of diabetic patient. So it will also be helpful for physiotherapist in working for delivering treatment service. This study will also be helpful for different organizations working for including physiotherapy service in their program for delivering a comprehensive treatment service. As a result patients would be more benefited.

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