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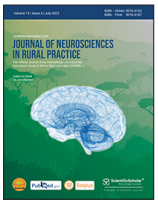

*Original Article*

# Type 2 diabetes mellitus, physical activity, and neuromusculoskeletal complications

Debasish Jena[1], Jagannatha Sahoo[1], Apurba Barman[1], Kishore Kumar Behera[2], Souvik Bhattacharjee[1], Sanyal Kumar[3]

Departments of [1]Physical Medicine and Rehabilitation and [2]Endocrinology, All India Institute of Medical Sciences, Bhubaneswar Odisha, [3]Department of Physical Medicine and Rehabilitation, ESIC Medical College and Hospital, Patna, Bihar, India.

## ABSTRACT

**Objectives:** The objectives of the study were to investigate the neuromusculoskeletal complications of Type 2 diabetes mellitus (T2DM) and their associated factors, including the level of physical activity (PA) and clinicodemographic characteristics.

**Materials and Methods:** In this cross-sectional analysis, we included 370 participants diagnosed with T2DM for no <1 year who satisfied the inclusion and exclusion criteria. Demographic and clinical characteristics were noted and a thorough clinical examination was performed on all the participants. International PA Questionnaire-Short Form was used to evaluate the level of PA of the participants. The continuous data is presented as mean ± SD and the categorical data is presented as the number of participants (n) and percentage (%). A logistic regression model was used to investigate the predictors for the prevalence of the complications.

**Results:** The mean duration of T2DM was 7.32 ± 5.53 years and the mean hemoglobin A1C (HbA1c) level (%) was 8.16±1.67. A majority of the participants were having uncontrolled diabetes with an HbA1c level ≥7.5% ($n$ = 190; 51.35%). The level of PA was low in a substantial proportion of the participants ($n$ = 276; 74.59%). A total of 162 (43.78%) participants were diagnosed with neuromusculoskeletal complications. Low back pain was the most common complication and degenerative disk disease was the most common diagnosis overall. Longer duration of diabetes, poor glycemic control, and low PA were associated with the prevalence of neuromusculoskeletal complications ($P < 0.05$).

**Conclusion:** Neuromusculoskeletal complications of T2DM are common and can result in significant disability in this population. Low PA is very common among T2DM patients and an important contributor to the development of complications. Health-care providers should consider PA an integral component of the management protocol for T2DM patients.

**Keywords:** Diabetes mellitus, Diabetic neuropathies, Rehabilitation, Orthopedics, Pain, Peripheral neuropathy

## INTRODUCTION

Diabetes mellitus (DM) has become a leading public health problem over recent years. Type 2 diabetes mellitus (T2DM) is the most common type (over 90%) of diabetes worldwide. According to the International Diabetes Federation, Diabetes Atlas (2021), there are an estimated 537 million adults (aged 20–79 years) who are presently living with diabetes representing 10.5% of the population in this age group. It is being postulated further that, by the year 2030, this number will rise to 643 million (11.3%) and 783 million (12.2%) by 2045.[1] Furthermore, the increase in numbers is predicted to be maximal in low- and middle-income countries. Rapid transition in socioeconomic conditions due to increased urbanization and industrialization is the main reason for the expected diabetes pandemic in the recent future. Other factors may include a surge in population, early detection due to improved health-care facilities, adaptation of a more sedentary lifestyle because of rapid technological advancement, unhealthy eating habits, and increased prevalence of obesity.[2]

The complications arising from longstanding T2DM can affect almost all systems of the human body and preferentially affect the kidneys, heart, eyes, nerves, and musculoskeletal (MSK) system.[3,4] MSK complications and neuropathies are widely prevalent among patients with T2DM and most of them are linked to a prolonged duration of diabetes and inadequate glycemic control.[5,6] Some of these complications are unique to diabetes and others are more prevalent in diabetics compared to the general population. Although MSK complications are seldom considered life threatening, they can cause significant disability and affect the quality of

***Corresponding author:** Debasish Jena, Department of Physical Medicine and Rehabilitation, All India Institute of Medical Sciences, Bhubaneswar, Odisha, India. debasish.mbbs@gmail.com

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life. Optimal care of diabetics should include prevention and management of such complications.

Physical activity (PA) is defined as the continuous bodily movements through the contraction of skeletal muscle that increases energy expenditure in daily life. This includes different activities that are conducted in both occupational and leisure time such as working at a desk, walking, cooking, washing, and sports.[7] Low PA is viewed as an important risk factor for the occurrence of diabetes-related complications. PA is known to improve glycemic control and reduce the incidence of cardiovascular and other complications in T2DM patients. A study reported that only 28.2% of patients with diabetes in the United States attained the recommended level of PA.[8] The PA level among the T2DM patients of the Indian population remains unclear! In addition, the prevalence of nerve and MSK complications in the T2DM population has been investigated in lesser detail and their association with PA has not been reported so far. Therefore, we aim for an explicit evaluation of the prevalence of such complications and their predictive factors.

## MATERIALS AND METHODS

This cross-sectional study was carried out in a tertiary care teaching hospital between July 2021 and December 2021 and a total of 370 participants were included in the study. Sample size was determined using the standard method according to the study by Mathew *et al*.[9] Consecutive T2DM patients referred from the endocrinology department of our institute to physical medicine and rehabilitation (PMR) outpatient facility were screened for the study. Participants were included if they had a history of T2DM for no less than one year. Diagnosis of T2DM was done according to the World Health Organization (WHO) as a fasting plasma glucose level of ≥126 mg/dl (7.0 mmol/l).[10] Patients were excluded if they were diagnosed with Type 1 DM, rheumatic diseases and other inflammatory arthritis, other metabolic diseases, primary disorders of the MSK, and/or nervous system. In addition, we also excluded patients who were unwilling to participate and had cognitive dysfunction or a serious illness that prevented participation in the study. Ethical clearance was obtained from the Institutional Ethics Committee (reference number: T/IM-NF/PMR/21/16). All participants signed an informed written consent that was approved by the committee. This study adheres to the Strengthening the Reporting of Observational Studies in Epidemiology guidelines (supplemental checklist, supplemental digital content 1).

For all included participants, we recorded certain demographic parameters including age (years), gender, and body mass index (BMI; kg/m$^2$). Furthermore, we also noted clinical parameters that included duration of T2DM (years), the (HbA1c; %) level, antidiabetic treatments (oral hypoglycemic drugs; OHAs, insulin, or no treatment), and the level of PA. BMI was classified according to the 2000 WHO criteria.[11] Diabetes was considered controlled if the HbA1c level was <7.5% and uncontrolled if ≥7.5%. The PA level was evaluated with the International PA Questionnaire-Short Form (IPAQ-SF). It is a 9-item scale that records activities of four intensity levels: (1) Sitting, (2) walking, (3) moderate-intensity activity (e.g., leisure cycling), and (4) vigorous-intensity activity (e.g., aerobics) and includes a "last 7-day recall" version for PA surveillance studies.[12] PA was reported in three categories including low, moderate, and high PA levels. All assessments were carried out by a single observer and participants were assisted in understanding the questionnaire, if required.

A detailed assessment of each participant was done by a single PMR resident including a targeted history taking, thorough MSK, and peripheral nervous system examination. Routine blood investigations (and radiological investigations if needed) were performed for all participants. All investigations were performed in standardized laboratories of our institution. Electrodiagnostic studies including the nerve conduction study and electromyography were conducted, wherever indicated. All diagnoses were confirmed by a PMR specialist with more than 10 years of experience.

The statistical analysis was conducted using the IBM Statistical Package for the Social Sciences, version 20.0. The continuous data are presented as mean ± SD and the categorical data are presented as the number of participants (n) and percentage (%). A binary logistic regression analysis was conducted to recognize the predictors of the complications. The significance level was expressed as *P*-value and $P < 0.05$ was considered statistically significant. Logistic regression, randomization, and odds ratio were used to control for the confounders.

## RESULTS

We screened a total of 430 patients with T2DM for this study. Twenty-eight patients were having the duration of diabetes for <1 year. Twenty-one patients were having other conditions including thyroid disorders, osteoporosis, hypovitaminosis D, and cognitive dysfunction, and 11 patients did not agree to participate. After excluding the above patients, a total of 370 participants were included in the final analysis [Figure 1]. The mean age was 53.60 ± 9.27 years with most of them aged more than 50 years ($n$ = 237; 64.05%) and a male gender ($n$ = 244; 70.54%). The mean BMI was 25.76 ± 2.91 kg/m$^2$ with 37.03% ($n$ = 137) of the participants falling in either the overweight or obese category. The mean diabetes duration was 7.32 ± 5.53 years and the mean HbA1c level (%) was 8.16 ± 1.67. A majority of the participants were having uncontrolled diabetes with an HbA1c level ≥7.5% ($n$ = 190; 51.35%). A substantial proportion of the participants were

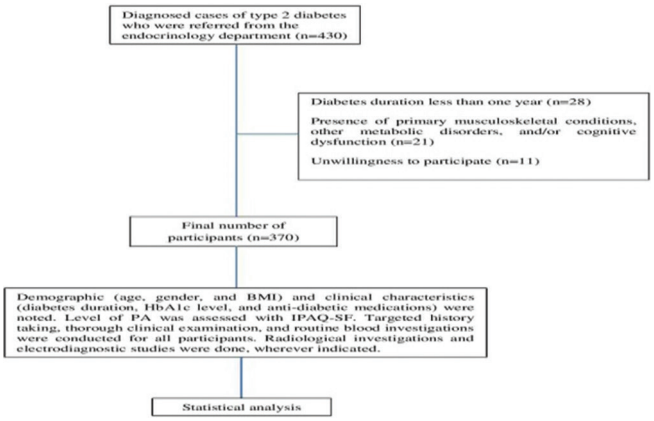


**Figure 1:** Participant flow diagram.

taking OHAs only (*n* = 307; 82.97%) and only 11.35% of the patients were on insulin with or without OHAs. On the assessment of the level of PA with IPAQ-SF, a considerable proportion of the participants (*n* = 276; 74.59%) displayed low PA. Among the participants with moderate-to-high PA (*n* = 94), walking was the most commonly practiced PA (*n* = 75; 79.79%) followed by cycling (*n* = 14; 14.89%). Furthermore, the proportion of men with moderate-to-high PA (*n* = 68; 72.34%) was higher compared to that of women (*n* = 26; 27.66%). The baseline characteristics of the participants are summarized in [Table 1].

Nerve and MSK complications were found in a significant percentage of participants (*n* = 162; 43.78%). The mean duration since the onset of these complications was 6.27 ± 5.39 years. Low back pain (LBP) was the most frequent reported symptom (*n* = 52; 14.05%). Other complications in descending order of the prevalence were shoulder pain, neck pain, knee pain, hand and wrist complications, foot complications, diabetic neuropathy, polyarthralgia, and elbow pain. Degenerative disk disease was the predominant cause of LBP and the most common diagnosis overall. The most common cause of shoulder pain was periarthritis shoulder followed by rotator cuff pathology. Similar to LBP, degenerative disk disease was also the most common diagnosis among patients with neck pain. The most common diagnosis among the patients with knee pain, hand and wrist complications, and foot complications were osteoarthritis knee, carpal tunnel syndrome, and diabetic foot, respectively. Finally, distal symmetrical sensorimotor polyneuropathy (DSPN) was the most common type of neuropathy reported. The detailed prevalence of nerve and MSK complications is summarized in [Table 2]. On logistic regression analysis, poor glycemic control (HbA1c ≥7.5%), longer duration of diabetes (≥7 years), and low PA were found to be associated with the prevalence of complications ($P < 0.05$). Low PA with an odds ratio of 2.99 was having the strongest association with the prevalence of neuromusculoskeletal complications [Table 3].

**Table 1:** Descriptive characteristics of participants (*n*=370).

| | |
|---|---|
| Age (years) | |
| Mean | 53.60±9.27 |
| <50 | 133 (35.95) |
| ≥50 | 237 (64.05) |
| Gender | |
| Male | 244 (70.54) |
| Female | 126 (34.05) |
| BMI (kg/m$^2$) | |
| Mean | 25.76±2.91 |
| <25 | 233 (62.97) |
| ≥25 | 137 (37.03) |
| Characteristics of T2DM | |
| Duration (years) | |
| Mean | 7.32±5.53 |
| <7 | 227 (61.35) |
| ≥7 | 143 (38.65) |
| HbA1c (%) | |
| Mean | 8.16±1.67 |
| <7.5 | 180 (48.65) |
| ≥7.5 | 190 (51.35) |
| Medications | |
| OHA | 307 (82.97) |
| Insulin±OHA | 42 (11.35) |
| No drugs | 21 (5.66) |
| Physical activity level* | |
| Low | 276 (74.59) |
| Moderate | 68 (18.38) |
| High | 26 (7.03) |

Data are presented as mean±SD or n (%) BMI: Body mass index, T2DM: Type 2 diabetes mellitus, HbA1c: Hemoglobin A1c, OHA: Oral hypoglycemic agent *categorized according to the International Physical Activity Questionnaire Short Form (IPAQ-Short Form)

## DISCUSSION

There have been numerous researches on the MSK complications of DM, but there is significant heterogeneity in the methodology and the type of diabetes included in the study has not been mentioned by many authors.[13] In addition, most of the studies have either focused only on hand and shoulder complication or lack a detailed evaluation of the complications.[13] Furthermore, the association between PA and the prevalence of complications has not been established so far! Finally, the prevalence of these complications in the developing countries has not been reported in detail.

The results of our study show a prevalence of nerve and MSK complications in 43.78% of participants with T2DM for at least 1 year duration. This finding complies with some past studies investigating MSK complications in DM.[9,14,15] The demographic and diabetes characteristics are also similar to a few past reports.[16,17] Furthermore, our results showed the association of the duration of diabetes and poor glycemic control with the prevalence of the complications, which is similar to the results of different past studies.[5,6] Previously,

the female gender has also been linked with the prevalence of MSK complications but our study did not reveal any gender association! The most plausible explanation for this may be the predominance of the male population included in this study. The PA level was found to be low in a huge proportion of participants (74.59%) and was the strongest predictor of the complications. In the developing countries, several factors may act as contributors to the low PA in diabetic population. This may include but is not limited to, physical concerns, lack of awareness about the benefits of PA (including lack of emphasis by health-care providers), beliefs, and barriers including cultural and external barriers to carrying out exercises.[17,18]

**Table 2:** Distribution of nerve and musculoskeletal complications among the participants ($n$ = 370)*.

| | |
|---|---|
| Low back pain | 52 (14.05) |
| Degenerative disk disease | 35 (9.46) |
| Lumbar spinal stenosis | 21 (5.68) |
| Spondylolisthesis | 9 (2.43) |
| Others | 11 (2.97) |
| Shoulder pain | 41 (11.08) |
| Periarthritis shoulder | 27 (7.30) |
| Rotator cuff pathology | 11 (2.97) |
| AC joint arthropathy | 7 (1.89) |
| Others | 9 (2.43) |
| Neck pain | 26 (7.03) |
| Degenerative disk disease | 19 (5.13) |
| Spinal canal stenosis | 10 (2.70) |
| Others | 8 (2.16) |
| Knee pain | 25 (6.76) |
| Osteoarthritis knee | 21 (5.68) |
| Pes anserinus bursitis | 7 (1.89) |
| Others | 10 (2.70) |
| Hand and wrist complications | 20 (5.40) |
| Carpal tunnel syndrome | 11 (2.97) |
| Flexor tenosynovitis | 9 (2.43) |
| De Quervain's tenosynovitis | 7 (1.89) |
| Dupuytren's contracture | 5 (1.35) |
| Diabetic cheiroarthropathy | 4 (1.08) |
| Others | 5 (1.35) |
| Foot complications | 25 (6.76) |
| Diabetic foot | 15 (4.05) |
| Plantar fasciitis | 9 (2.43) |
| Others | 6 (1.62) |
| Diabetic polyneuropathy | 13 (3.51) |
| Distal symmetrical polyneuropathy | 8 (2.16) |
| Mononeuropathy | 5 (1.08) |
| Polyarthralgia | 8 (2.16) |
| Elbow pain | 3 (0.81) |
| Lateral and medial epicondylosis | 3 (0.81) |

Data are presented as n (%); *more than 1 complication may coexist

PA plays a crucial role in the prevention and management of T2DM and associated health problems through a multitude of mechanisms. In T2DM patients, regular aerobic exercises alone or in combination with resistance exercises are known to improve insulin sensitivity, glycemic control, body composition, waist circumference, lipid profile, HbA1c levels, cardiorespiratory function, nerve function, quality of life, and modulate inflammatory cytokine levels. In addition, resistance training also improves triacylglycerol levels and augments GLUT-4 translocation in skeletal muscles. Several studies have reported that a combined aerobic and resistant training might be the most efficient exercise regimen to improve lipid profile and glycemic control in T2DM patients.[19] The American College of Sports Medicine and the American Diabetes Association (ADA) have recommended at least 150 min/week of moderate (50–70% of an individual's maximum heart rate) to vigorous (>70% of an individual's maximum heart rate) PA for T2DM patients.[20] Furthermore, the ADA has recommended that diabetic patients should be encouraged to decrease their sedentary time and avoid sitting for more than 90 min.[21] For optimal management of diabetes, all health-care professionals should consider prescribing a structured exercise program besides dietary advice and medications.

Studies have shown a positive association between DM and the prevalence of neck pain and LBP.[22] Some authors have also argued that DM and LBP may have a spurious association that can be attributed to confounding variables like obesity.[23] Our results suggested that LBP and neck pain are among the most prevalent MSK complications in T2DM

**Table 3:** Logistic regression analysis demonstrating the association of participant variables with the prevalence of the neuromusculoskeletal complications.

| Variable | Predictor | Coefficient | Standard error | *P*-value | Odds ratio | 95% confidence interval |
|---|---|---|---|---|---|---|
| Age (years) | ≥50 (vs. <50) | 0.1100 | 0.2478 | 0.6571 | 1.1163 | (0.6868; 1.8143) |
| Gender | Male (vs. female) | −0.2877 | 0.2462 | 0.2426 | 0.7500 | (0.4629; 1.2151) |
| BMI (kg/m2) | ≥25 (vs. <25) | 0.1595 | 0.2445 | 0.5141 | 1.1729 | (0.7264; 1.8939) |
| T2DM duration (years) | ≥7 (vs. <7) | 0.5666 | 0.2554 | 0.0265# | 1.7623 | (1.0683; 2.9071) |
| Antidiabetic medication | Insulin (vs. no insulin) | −0.0840 | 0.3659 | 0.8183 | 0.9194 | (0.4488; 1.8834) |
| HbA1C (%) | ≥7.5 (vs. 7.5) | 0.9722 | 0.2488 | 0.0001# | 2.6437 | (1.6235; 4.3049) |
| Physical activity | Low (vs. moderate and high) | 1.0944 | 0.2566 | 0.0000# | 2.9874 | (1.8067; 4.9397) |

patients. In a cross-sectional study conducted by Krein *et al*. on 993 diabetic patients, nearly 60% reported chronic pain, and back pain was the most prevalent pain symptom.[24] T2DM is known to increase the prevalence of back and neck pain by various mechanisms including intervertebral disk (IVD) degeneration, disk prolapse, and spinal canal stenosis. Won *et al*. reported that DM is associated with increased and premature apoptosis of the notochordal cells of the nucleus pulposus, leading to early degeneration of IVD.[25] Furthermore, it has also been proposed that increased blood glucose results in the formation of advanced glycation end products (AGEs) in the nucleus pulposus that accelerates the degeneration of IVD.[26-28] Nonetheless, the direct association of T2DM with LBP and neck pain remains unclear!

Our results also suggest that shoulder, hand, and knee complications are also common manifestations of T2DM. Of these, periarthritis shoulder, rotator cuff disease, osteoarthritis knee, carpal tunnel syndrome, and trigger finger are some of the commonly diagnosed conditions. The main pathophysiology underlying the development of these complications includes the faster rate of formation and accumulation of AGEs in collagen-rich tissues in T2DM patients compared to non-diabetics.[29-31] AGEs such as pentosidine and AGE receptors tend to accumulate more with a longer duration of disease and poor glycemic control. Their accumulation makes the tissue stiffer, thicker, weaker, and more vulnerable to injury.[32,33]

The most common type of neuropathy observed in this study was DSPN that is known as the most common type of diabetic neuropathy.[34] Long-standing hyperglycemia may lead to several metabolic derangements and microvessel alterations that can result in DSPN. These metabolic derangements may include but are not limited to accumulation of AGEs, increased oxidative stress, polyol shunting, accumulation of sorbitol and resultant osmolarity-associated nerve damage, and lipid abnormalities.[34] Other patterns of diabetic neuropathy include mononeuropathy, mononeuritis multiplex, diabetic autonomic neuropathy, cranial neuropathy, radiculoplexus neuropathy, and treatment-induced neuropathy.[35] Inadequate treatment may lead to severe disability through foot ulceration, muscle weakness, gait impairments, and amputation of extremities.

### Limitations

The main limitation of this study is the non-inclusion of a control population. Another important limitation is that we could not assess other known risk factors including smoking and the presence of other diabetes-associated complications. Nonetheless, the explicit evaluation of the prevalence of neuromusculoskeletal complications of T2DM and showing a strong association with low PA adds to the strength of our study. The generalizability of our finding is still questionable due to the geographical differences in the demographic characteristics, health awareness, and level of PA. The authors recommend further multicenter and well-designed studies evaluating the prevalence of such complications and their association with PA level.

## CONCLUSION

Persons with T2DM are at increased risk of developing nerve and MSK complications. Although certain complications including hand and shoulder complications, diabetic polyneuropathy, and diabetic foot are known to be the specific complications of DM, spinal pain remains the most commonly reported one. The prevalence of low PA can be very high among T2DM patients in the developing countries and can be a strong contributor to the development of these complications. Physical inactivity can further elevate hyperglycemia and bodyweight resulting in MSK pain. Therefore, health care workers and policy-makers should consider implementing a structured PA or exercise program while managing patients with T2DM.

### Declaration of patient consent

Institutional Review Board (IRB) permission obtained for the study.

### Financial support and sponsorship

Nil.

### Conflicts of interest

There are no conflicts of interest.

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