Introduction

The global health care burden of Type 2 Diabetes Mellitus (T2DM) as estimated by the International Diabetes Federation (IDF) is expected to exponentially increase to 10.4% by 2040. This estimation puts a spotlight on the risk for the development of secondary complications related to Type 2 Diabetes mellitus[1] [2]. Among the various secondary complication, Diabetic peripheral neuropathy (DPN) accounts for 3/4th of the total number [3] which is experienced as sensory-motor deficits. The sensory deficits implicate as loss of sensations of pain, pinprick, temperature, proprioception, vibration along with "pins and needles", "burning" and "electric shocks". The motor deficits present as an alteration in muscle structure, functional strength, and joint stiffness. An escalation of these severe sensory-motor deficits of diabetic neuropathy results in impaired gait, balance, and postural sway, which leads to an inability to perform various activities of daily living, thereby increasing the risk of falls. [4–6]

Recent evidence suggests a 17-fold rise in the risk of falls among the DPN individuals as compared to healthy elders. [7] Similar findings on fall risk due to balance deficits show a 36% rise among Type 2 Diabetes Mellitus without neuropathy and 53% with neuropathy.[8]

The consequences of fall not only include physical effects but also functional, social, and cognitive effects forming a vicious cycle. This leads to mild to severe fear for activity participation, resulting in deconditioning, social isolation, contributing to fall of risk, and reduced Quality of Life. [9–11]

The IDF interventional guidelines recommend the use of both pharmacological and nonpharmacological measures for fall prevention with exercises as a primary choice. [12] A study by Mendes R et al 2015 on exercise prescriptions for T2DM suggests the incorporation of an individualized aerobic, resistance, and flexibility program. [13] However the study of Kim et al. 2015 emphasis the role of educational interventions with a multifactorial approach for fall prevention. [14]

There exists an underlying difference between diabetes with neuropathy and without neuropathy owing to the additional sensory-motor deficits. Thus exercise guidelines targeting only diabetic population or older adults cannot be replicated for those with Type 2 diabetes with neuropathy. Thus the current review aims to determine the effect of multifactorial balance rehabilitation strategies on Quality of Life, fall risk, and balance on Type 2 Diabetes Mellitus with neuropathy.

METHODS

Registration

PROSPERO Reference ID: CRD42020161868

Search strategy

Review was conducted following PRISMA guidelines. Two independent reviewers searched the following six databases: Pub Med, Scopus, Web of Science, Cumulative Index to Nursing and Allied Health Literature (CINAHL), COCHRANE central, Embase. The databases were searched from the beginning years of the database up to 25th November 2019. We updated the search on 15th March 2020. Principal keywords for search stratagem were diabetic peripheral neuropathy, balance rehabilitation strategies, balance, fall risk, and Quality of Life. MeSH terms were used to search these keywords. Boolean operators "OR" and "AND" were used to create the combined search strategy. (Supplementary file 1)

Study selection:

Search from all the database was imported to online Rayyan software. Two reviewers (G.G and S.B) independently resolved the duplicates and screened the titles and abstracts. The selected articles were downloaded, read, and evaluated by the reviewers separately. In case of conflict third independent reviewer (A.G) was contacted to resolve the disagreement. The reference list of the included articles was screened to identify any other relevant study.

Eligibility criteria:

Only randomized controlled trials (RCTs) with balance rehabilitation strategies as an intervention on diabetic neuropathy population were included. For the present review, operational definition of balance rehabilitation strategies covers all the physiotherapeutic exercises (proprioceptive exercises, aerobic exercises, strength exercises, visual training, task training, gait training, weight shifting, or transfer exercises) aiming to improve balance or fall risk or Quality of Life in diabetic neuropathy. RCTs with interventions out of the scope of the operational definition of balance rehabilitation strategies were excluded. All types of study settings were included. The review compares the effect of balance rehabilitation strategy with standard diabetic care, diabetic self-care education, or no treatment. Outcome measures related to balance, fall risk, and Quality of Life were considered for this review.

Method of Data collection

Data regarding study population, size, design, type of interventions, duration, outcome measures, and study results were noted down and managed on an excel sheet. (Supplementary file 2)

Estimation of risk of bias (ROB) in included studies

The modified Cochrane Collaboration ROB tool was used to detect the quality of evidence. It was decided independently by the reviewer's judgment (G.G, S.B) and any agreement dispute was resolute by the third reviewer (A.G). Each study was assessed on five criterions (selection, performance, attrition, reporting, and other bias). Each criterion of ROB was classified as having low, high, or unclear risk. Later the overall ROB for each study was assessed and they were categorized into good, fair, and poor studies. If study met all ROB criteria (all low ROB) then the study was categorized as a good quality study, if the study had one high ROB or two unclear ROB and outcome of the study are unlikely to be biased it was rated as a fair quality study, if the outcome of the study were likely to be biased then the study was categorized as poor quality. Also if more than two criteria were high ROB or unclear then the study was rated poor-quality. [15]

GRADE evaluation

GRADE system was used to examine the quality of evidence. It also helped to summarize the recommendations. [16] GRADE evidence profile (www.gradeworkinggroup.org) with GRADEpro GDT online service was prepared to assess the quality of evidence. Any disagreements between the reviewers (G.G and M.H) were resolute by a third reviewer (A.G)

Data synthesis

A meta-analysis of pooled data using a random-effect model was done by Cochran review manager software version 5.3. More than 50% of the variance in I^2 was considered heterogeneity. Standard deviations and mean differences values were pooled for synthesizing meta-analysis results. We conducted the narrative analysis whenever data cannot be pooled due to the varied use of outcome measures.

RESULTS

Study selection

A total of 2371 citations appeared in the search, after duplicate removal, title, and abstract screening; full-text screening for 54 articles was done. Seven RCTs were included for final narrative synthesis and meta-analysis. (Figure 1) Out of these seven RCT's:

- Only one study was eligible for the narrative synthesis of Quality of Life.
- Due to the varied use of outcome measures of all seven RCT's were assessed for the narrative synthesis of balance and fall risk.
- Four RCTs observing the Berg Balance Scale, Functional Reach Test, Timed Up-Go test, and One-Leg Stance as their balance and fall risk outcome measures were included for meta-analysis.

Risk of Bias (ROB):

In the present review, two included studies were of good quality, four were fair quality and one included study was poor quality. Participant blinding (performance bias) and allocation concealment (selection bias) were the two primary biases seen in the included studies. (Figure 2)

The GRADE quality of evidence for Quality of Life was moderate. Evidence for balance and fall risk (BBS, FRT, and TUG) was very low and for the one-leg stance, it varied from moderate to very low. (Table 2)

Study Characteristics

Participants:

Seven RCTs with a total of 418 participants aged 30 years and above were included for the review. [17–23] Due to an inconsistent pattern of reporting, diabetic duration, and glycemic parameters could not be summarized for the present review. (Table 3)

Intervention:

Multi-factorial Balance rehabilitation strategies: Multifactorial nature of balance rehabilitation was not studied in any of the included RCT. Balance rehabilitation strategies in two of the included studies comprised of balance exercises along with lower limb strengthening exercises. Another included study combined the balance exercises with health care education while the other study combined the balance exercises with gait training. Two studies evaluated multi-sensory exercises and one RCT evaluated the effect of task-oriented balance training. (Table 3)

Control group interventions included standard medical care or diabetic self-care education or traditional balance exercises or no treatment. (Table 3)

Description of outcome measures

Quality of Life: Out of seven included studies only one study by Venkatraman et al 2019 measured Quality of life in their outcome measures. It was measured by the EQ-5D-5L index score and SF36v2.

Balance and fall risk: All the seven included RCTs measured the balance and fall risk in their outcome measures. Wide verities of outcome measures were used in the included studies. List of various balance and fall risk outcome measures included were Berg Balance Scale (BBS), Functional Reach Test (FRT), Timed Up and Go Test (TUG), one leg stance (OLS)/unipedal stance, Activity Specific Balance Confidence scale (ABC), Fall Efficacy Scale- International (FES-I), Romberg's test, Performance-Oriented Mobility Assessment (POMA), backward release test, postural assessment, proprioceptive, outdoor gait assessment via gyroscope, dynamic balance test on a 5m beam, static balance test via Biodex Balance System and tandem stance time. Thus there was only a small similarity of balance outcome measures in the included studies.

Effects of balance rehabilitation strategies:

Narrative synthesis: Effect of the balance rehabilitation strategies on Quality of Life:

Only one RCT evaluated the effect of a balance exercise intervention on QoL. Eight weeks of lower limb strengthening and balance training once weekly was given. The study utilized two generic QoL tools; the EQ-5D-5L index as a primary outcome and SF-36v2 as its secondary outcome measure. On comparing EQ-5D-5L outcome measure over 6 months it showed a non-significant difference (mean difference-0.02 [95% CI 0.01, 0.06]; p= 0.175). Domain wise analysis of SF36v2 showed that the intervention group showed improvement in body pain (mean difference 5.14 [95% CI 2.05, 8.23]; p= 0.001) and in general health but improvements in general health was not statistically significant (mean difference 2.36 [95% CI -0.28, 4.99]; p= 0.080)

Meta-analysis: Effect of balance rehabilitation strategies on balance and fall risk measures:

The balance and fall risk was measured by all seven RCTs but as the outcome measures were not consistently studied in most of the RCTs; they did not qualify for meta-analysis. Only four (BBS, FRT, TUG, and OLS) balance and fall risk outcomes measures were synthesized using meta-analysis.

A meta-analysis of Berg Balance Scale as an outcome measure:

A meta-analysis of three RCTs with a total of 135 participants showed balance rehabilitation has no effect as compared to control or diabetic education (self-care or foot care) or standard care. (MD 1.45, 95% CI -0.47, 3.38; p =0.14; I^2= 59%) (Supplementary file 3)

A meta-analysis of Functional Reach Measure as an outcome measure:

A meta-analysis of four RCTs with total 233 participants on FRT as an outcome showed balance rehabilitation was effective compared to control or diabetic education (self-care or foot care) or standard care (MD 3.82, 95% CI 0.82, 3.83; P=0.01; I^2= 72%) (Supplementary file 3)

A meta-analysis of Timed Up and Go Test as an outcome measure:

A meta-analysis of five RCTs with a total of 326 participants on TUG as an outcome showed balance rehabilitation was effective compared to control or diabetic education (self-care/ foot care) or standard care (MD -1.41, 95% CI -2.14, -0.69; P=0.0001; I^2= 50%) (Supplementary file 3)

A meta-analysis of one leg balance Test as an outcome measure:

Meta-analysis of two RCTs with total of 75 participants on OLS/ unipedal stance under four testing conditions (right and left eyes open and closed) showed balance rehabilitation was effective compared to control or diabetic education (self care or foot care) or standard care{Right EO (MD 7.86, 95% CI 1.97, 13.94, ; $p<0.009$; I^2= 34%), Left EO (MD 6.14 , 95% CI 2.64,9.64 ; $p<0.0006$; I^2= 1%), right EC (MD 2.45, 95% CI 0.61, 4.28; $p<0.009$; I^2= 56%), Left EC (MD 1.80, 95% CI 0.86, 2.75, ; $p<0.0002$; I^2= 0%). Though Robin L Kruse et al 2010 observed a one-leg stance test in their study, it was not included for the present meta-analysis as separate data for right and left side of the leg was not available. (Supplementary file 3)

Narrative synthesis: Effect of balance rehabilitation strategies on balance and fall risk:

Out of seven included RCTs; five RCTs were included for narrative synthesis. In all the five studies fall risk was the indirect interpretation of balance. One study reported that after 8 weeks of supervised intervention, postural assessment, and proprioception significantly improved in intervention groups.[18] One study measured Balance confidence via Activities-Specific Balance Confidence (ABC) scale, reported improvement after eight weeks as well as at six months follow up.[21] With twelve months follow up of leg strengthening and balance exercise intervention another study did not report any improvement in patient's balance confidence with fall efficacy scale (FES). Kruse et al 2010 also measured the one-leg stance time as a balance outcome measure and reported no significant difference between the groups except under the eyes-closed condition. The author did not report the detailed procedure of a one-leg stance (OLS) test mentioning on which leg the participants performed the test; hence OLS data is not included for meta-analysis in the present review. [22] Malik et al 2016 observed a backward release test (reactive balance) and Romberg's test (static balance) as an outcome measure of their study with 8 weeks of task-oriented training but possibly due to selective reporting bias the results of these outcomes were not addressed in their results.[19] Another study measured the effect of 12 weeks of intervention by the wide range of balance and fall risk outcome measures (POMA, Outdoor gait assessment, dynamic balance test, static balance test by Biodex USA and FES-I) reported that in comparison with the control group intervention group increased their habitual speed of walking by 0.15 m/s ($p<0.001$). Also, they reported significant improvement in dynamic balance (time to walk over beam), POMA (balance and gait measures), postural sway on biodex, and balance confidence (FES-I). [21]

Discussion:

The review focused on the effect of multifactorial balance rehabilitation strategies on Quality of Life, fall risk, and balance in diabetic neuropathy. Rehabilitation guidelines are available for Type 2 Diabetes Mellitus but when it progresses to diabetic neuropathy, the added deficits and complications require detailed exercise recommendations, were not well explored. [24–26] We observed that included studies used varied balance and fall risk outcome measures hence all the outcome measures could not be pooled for meta-analysis. Meta-analyses were performed for berg balance scale, timed up and go test, functional reach test, and one-leg stand test. For the rest of the outcome measures on fall risk, balance, and Quality of Life, a narrative synthesis was done.

Out of four fall risk and balance outcome measures (BBS, FRT, TUG, and OLS) meta-analysis of three (FRT, TUG, and OLS) shows positive therapeutic effects of balance rehabilitation on fall risk and balance. Though there are no previous meta-analysis recommendations available, our results are in line with previous narrative synthesis conducted on the heterogenic neuropathy population. [27,28]

A possible explanation for BBS to show no treatment effect could be that BBS assessment covers more aspects (control of centre of gravity, lower limb strength, gaze stabilization, use of proprioceptive inputs, flexibility of upper, lower body and trunk) of balance than the other three tests. As compared to BBS, TUG mainly focuses on functional mobility, FRT focuses on limits of stability and one-leg stance tests the balancing ability in a reduced base of support condition. Hence to get significant treatment effect on BBS assessment, balance rehabilitation needs to covers mores aspects of balance mechanism. Thus the difference in the results of the treatment effect could be due to different assessment nature of outcome measures.

The study by Venkatraman et al. 2019, included for the narrative synthesis of Quality of Life, reported no overall effect on Health-related Quality of Life (HRQoL) with 8 weeks of balance exercises. Although subgroup analysis showed that improvement in functional measures (timed up and go, five-time sit to stand and balance confidence) is associated with improvement in EQ 5D 5L index scores. The author concluded that to achieve meaningful changes in Quality of Life in diabetic neuropathy, exercises must be more vigorous and training must be given for a longer period. Due to lack of literature on DPN population, we cannot be conclusive about these findings but two large RCT's conducted on the diabetic population without neuropathy also reported similar observations that exercises have beneficial effects over QoL in diabetic population but the intervention must have high volume and must be given for longer duration (9 to 12 months) for it to show significant changes.[29,30] As diabetic neuropathy population has various added deficits it may require even more time to achieve the statistically or clinically significant changes in QoL

Study limitations

The inclusion of only English language articles was one of the limitations of the review.

Clinical implications:

Based on the review we found there is a dearth of evidence on a multifactorial balance rehabilitation program. There is a need for high-quality RCT on a multifactorial balance rehabilitation program in diabetic neuropathy. This will benefit people living with diabetic neuropathy for management of fall risk, balance and improve overall Quality of Life.

CONCLUSION:

The present systematic review suggests that strategies specific/ targeting to balance have a positive effect on balance issues and fall risk in diabetic neuropathy. There is not sufficient data available to conclude the effect of multifactorial balance rehabilitation strategies on Quality of Life in diabetic neuropathy.

DECLARATION

ETHICS STATEMENT:

The present study was a meta-analysis, which did not involve human participants and/or animals. Besides, no informed consent was needed for the meta-analysis.

FUNDING:

This systematic review did not receive financial support from any funding agencies.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

AUTHOR CONTRIBUTION

A.G designed the study and led the study design. G.G and S.B. identified and acquired reports of trials and extracted data. G.G. and R.S. performed all data analyses, checked for statistical inconsistency, and interpreted data. A.G., G.G., R.S., S.B., N.R., and M.H. contributed to data interpretation. G.G., N. R., and A.G. drafted the report, and all other authors (R.S., S.B., and M.H.) critically reviewed the report. A.G. and G.G. are the guarantors of this work and, as such, had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis

ACKNOWLEDGMENT:

Authors would wish to acknowledge the Centre for Diabetic Foot Care and Research, MCHP, MAHE, Manipal for providing all the technical and logistical support during the review process.

REFERENCES:

[1] Zheng Y, Ley SH, Hu FB. Global aetiology and epidemiology of type 2 diabetes mellitus and its complications. Nat Rev Endocrinol 2018;14:88–98. https://doi.org/10.1038/nrendo.2017.151.

[2] International Diabetes Federation. IDF Diabetes Atlas Eighth edition 2017. 2017. https://doi.org/http://dx.doi. org/10.1016/S0140-6736(16)31679-8.

[3] Juster-Switlyk K, Smith AG. Updates in diabetic peripheral neuropathy. F1000Research 2016;5:738. https://doi.org/10.12688/f1000research.7898.1.

[4] Mustapa A, Justine M, Mohd Mustafah N, Jamil N, Manaf H. Postural Control and Gait Performance in the Diabetic Peripheral Neuropathy: A Systematic Review. Biomed Res Int 2016;2016. https://doi.org/10.1155/2016/9305025.

[5] Almurdhi MM, Brown SJ, Bowling FL, Boulton AJM, Jeziorska M, Malik RA, et al. Altered walking strategy and increased unsteadiness in participants with impaired glucose tolerance and Type 2 diabetes relates to small-fibre neuropathy but not vitamin D deficiency. Diabet Med 2017;34:839–45. https://doi.org/10.1111/dme.13316.

[6] Priya TMV, Rajarajeswari A, Sivakumar R. Effectiveness of training on postural stablity in mild to moderate diabetic neuropathy patients. Indian J Public Heal Res Dev

2019;10:780–5. https://doi.org/10.5958/0976-5506.2019.01985.5.

[7] Vinik AI, Camacho P, Reddy S, Valencia WM, Trence D, Matsumoto AM, et al. Aging, Diabetes, and Falls. Endocr Pract 2017;23:1120–42. https://doi.org/10.4158/EP171794.RA.

[8] Timar B, Timar R, Gaiță L, Oancea C, Levai C, Lungeanu D. The Impact of Diabetic Neuropathy on Balance and on the Risk of Falls in Patients with Type 2 Diabetes Mellitus: A Cross-Sectional Study. PLoS One 2016;11:e0154654. https://doi.org/10.1371/journal.pone.0154654.

[9] Tander B, Atmaca A, Ulus Y, Tura Ç, Akyol Y, Kuru Ö. Balance performance and fear of falling in older patients with diabetics: a comparative study with non-diabetic elderly. Turk J Phys Med Rehab 2016;62:314–22. https://doi.org/10.5606/tftrd.2016.77861.

[10] Pin S, Spini D. Impact of falling on social participation and social support trajectories in a middle-aged and elderly European sample. SSM - Popul Heal 2016;2:382–9. https://doi.org/10.1016/j.ssmph.2016.05.004.

[11] Atler KE, Schmid AA, Klinedinst TC, Grimm LA, Marchant TP, Marchant DR, et al. The Relationship between Quality of Life, Activity and Participation among People with Type 2 Diabetes Mellitus. Occup Ther Heal Care 2018;32:341–62. https://doi.org/10.1080/07380577.2018.1522017.

[12] International Diabetes Federation. IDF Clinical Practice Recommendations for managing Type 2 Diabetes in Primary Care International Diabetes Federation - 2017. 2017.

[13] Mendes R, Sousa N, Almeida A, Subtil P, Guedes-Marques F, Reis VM, et al. Exercise prescription for patients with type 2 diabetes - A synthesis of international recommendations: Narrative review. Br J Sports Med 2016;50:1379–81. https://doi.org/10.1136/bjsports-2015-094895.

[14] Kim EJ, Arai H, Chan P, Chen LK, Hill KD, Kong B, et al. Strategies on fall prevention for older people living in the community: A report from a round-table meeting in IAGG 2013. J Clin Gerontol Geriatr 2015;6:39–44. https://doi.org/10.1016/j.jcgg.2015.02.004.

[15] Higgins JP, Savović J, Page MJ, Elbers RG, Sterne JA. Assessing risk of bias in a randomized trial. 2019. https://doi.org/10.1002/9781119536604.ch8.

[16] Granholm A, Alhazzani W, Møller MH. Use of the GRADE approach in systematic reviews and guidelines. Br J Anaesth 2019;123:554–9. https://doi.org/10.1016/j.bja.2019.08.015.

[17] Majeed Kutty NA, Majida NAL. Effects of Multisensory Training on Balance and Gait in Persons with Type 2 Diabetes: A Randomised Controlled Trial. Disabil CBR Incl Dev 2013;24:79. https://doi.org/10.5463/dcid.v24i2.206.

[18] Ahmad I, Noohu MM, Verma S, Singla D, Hussain ME. Effect of sensorimotor training on balance measures and proprioception among middle and older age adults with diabetic peripheral neuropathy. Gait Posture 2019;74:114–20.

https://doi.org/10.1016/j.gaitpost.2019.08.018.

[19] Ghazal J, Malik AN, Amjad I. Task oriented training improves the balance outcome and reducing fall risk in diabetic population. Pakistan J Med Sci 2016;32:983–7. https://doi.org/10.12669/pjms.324.10092.

[20] Song CH, Petrofsky JS, Lee SW, Lee KJ, Yim JE. Effects of an Exercise Program on Balance and Trunk Proprioception in Older Adults with Diabetic Neuropathies. Diabetes Technol Ther 2011;13:803–11. https://doi.org/10.1089/dia.2011.0036.

[21] Allet L, Armand S, Bie RA De, Golay A. The gait and balance of patients with diabetes can be improved : a randomised controlled trial 2010:458–66. https://doi.org/10.1007/s00125-009-1592-4.

[22] Kruse RL, Lemaster JW, Madsen RW. Fall and Balance Outcomes After an Intervention to Promote Leg Strength, Balance, and Walking in People With Diabetic Peripheral Neuropathy: “Feet First” Randomized Controlled Trial. Phys Ther 2010;90:1568–79.

[23] Venkataraman K, Tai BC, Khoo EYH, Tavintharan S, Chandran K, Hwang SW, et al. Short-term strength and balance training does not improve quality of life but improves functional status in individuals with diabetic peripheral neuropathy: a randomised controlled trial. Diabetologia 2019;62:2200–10. https://doi.org/10.1007/s00125-019-04979-7.

[24] Riandini T, Wee HL, Khoo EYH, Tai BC, Wang W, Koh GCH, et al. Functional status mediates the association between peripheral neuropathy and health-related quality of life in individuals with diabetes. Acta Diabetol 2018;55:155–64. https://doi.org/10.1007/s00592-017-1077-8.

[25] Chau RMW, Ng TKW, Kwan RLC, Choi C, Cheing GLY, Chau RMW, et al. Risk of fall for people with diabetes. Disabil Rehabil 2013;35:1975–80. https://doi.org/10.3109/09638288.2013.770079.

[26] Chapman A, Meyer C, Renehan E, Hill KD, Browning CJ. Exercise interventions for the improvement of falls-related outcomes among older adults with diabetes mellitus: A systematic review and meta-analyses. J Diabetes Complications 2017;31:631–45. https://doi.org/10.1016/j.jdiacomp.2016.09.015.

[27] Majeedkutty NA, Jabbar MA, Sreenivasulu S. Physical therapy for diabetic peripheral neuropathy: A narrative review. Disabil CBR Incl Dev 2019;30:112–25. https://doi.org/10.5463/dcid.v30i1.760.

[28] Streckmann F, Zopf EM, Lehmann HC, May K, Rizza J, Zimmer P, et al. Exercise intervention studies in patients with peripheral neuropathy: a systematic review. Sports Med 2014;44:1289–304. https://doi.org/10.1007/s40279-014-0207-5.

[29] Nicolucci A, Balducci S, Cardelli P, Cavallo S, Fallucca S, Bazuro A, et al. Relationship of exercise volume to improvements of quality of life with supervised exercise training in patients with type 2 diabetes in a randomised controlled trial: The Italian Diabetes and Exercise Study (IDES). Diabetologia 2012;55:579–88. https://doi.org/10.1007/s00125-011-2425-9.

[30] Myers VH, McVay MA, Brashear MM, Johannsen NM, Swift DL, Kramer K, et al. Exercise training and quality of life in individuals with type 2 diabetes. Diabetes Care 2013;36:1884–90. https://doi.org/10.2337/dc12-1153.

FIGURE LEGENDS

Fig 1: Flow diagram for the article selection and screening process according to PRISMA guidelines

Fig 2: Summary of Risk of bias based on authors' judgments about each ROB domain.

TABLE LEGENDS

Table 1: Inclusion and Exclusion criteria

Table 2: Grade evidence Profile and Summary of findings table

Table 3: Description of included studies

Table 1: Inclusion and Exclusion criteria

Criteria	Inclusion	Exclusion
Study design	RCTs	Non-RCT, case series, case reports, pre-post study design, conference presentations, review articles, and cross-sectional studies
Population	Type 2 Diabetes Mellitus with diabetic neuropathy	Type-I diabetes, gestational diabetes, or where the type of diabetes was not specified. Cause of neuropathy was other than Type 2 diabetes,
Intervention	Multifactorial Balance Rehabilitation strategies	Exercises delivered through Expensive sophisticated instruments (e.g.: isokinetic exerciser), electrotherapy (monotherapy, light therapy, vibrating insole), or alternative interventions (yoga, tai chi, acupressure, dance, etc.)
Comparison	Standard Diabetic Care/Diabetic Self Care Education /No Treatment	Pharmacological interventions, electrotherapy interventions
outcomes	Balance and/or QoL related outcomes	Outcomes not related to Balance and/or QoL related outcomes

Table 2: Grade evidence Profile and Summary of findings table

Question: Balance rehabilitation exercises compared to diabetic education/ self-care health education/ standard care or no treatment for diabetic neuropathy

Setting: out-patient/ rehab-clinic/ home exercises or combination of supervised exercises and home program

Certainty Assessment							**Number of patients**		**Effect**		**Certainty**	**Importance**
Number of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Balance rehabilitation exercises**	**diabetic education/ self-care health education/ standard care or no treatment**	**Relative (95% CI)**	**Absolute (95% CI)**		
Quality of Life (follow up: mean 8 weeks; assessed with: EQ-5D-5L index and SF-36v2)												
1	randomized trials	serious [a]	not serious	not serious	not serious	none	The overall study showed a non-significant difference between the groups, but the domain wise analysis of SF-36V2 showed improvement in the "body pain domain" with 8 weeks of once-weekly leg strengthening and balance training in DPN.				⊕⊕⊕◯ MODERATE	CRITICAL
Balance and Fall risk (follow up: mean 8-24 weeks; assessed with: Berg Balance Scale; Scale from- 0 to 56)												
3	randomised trials	very serious [b]	serious [c]	not serious	very serious [d]	none	68	67	-	MD **1.45 higher** (0.47 lower to 3.38 higher)	⊕◯◯◯ VERY LOW	IMPORTANT
Balance and Fall Risk (follow up: mean 8 weeks; assessed with: Functional Reach Test)												
5	randomised trials	very serious [e]	serious [c]	not serious	serious [f]	none	114	119	-	MD **3.82 higher** (0.82	⊕◯◯◯ VERY LOW	IMPORTANT

										higher to 6.83 higher)		
Balance and Fall Risk (follow up: mean 6-24 weeks; assessed with: Timed Up & Go Test)												
6	randomised trials	serious [g]	serious [c]	not serious	serious [h]	none	163	163	-	MD **1.41 lower** (2.14 lower to 0.69 lower)	⊕◯◯◯ VERY LOW	IMPORTANT
Balance and Fall Risk (follow up: mean 8 weeks; assessed with: One Leg Stance (OLS) right eyes open)												
3	randomised trials	serious [i]	not serious [j]	not serious	serious [h]	none	39	36	-	MD **7.86 higher** (1.97 higher to 13.74 higher)	⊕⊕◯◯ LOW	IMPORTANT
Balance and Fall Risk (follow up: mean 8 weeks; assessed with: One Leg Stance (OLS) left eyes open)												
3	randomised trials	serious [i]	not serious	not serious	serious [h]	none	39	36	-	MD **6.14 higher** (2.64 higher to 9.64 higher)	⊕⊕◯◯ LOW	IMPORTANT
Balance and Fall Risk (follow up: mean 8 weeks; assessed with: One Leg Stance (OLS) right eyes closed)												
3	randomised trials	serious [i]	serious [c]	not serious	serious [h]	none	39	36	-	MD **2.45 higher** (0.61 higher to 4.28 higher)	⊕◯◯◯ VERY LOW	IMPORTANT
Balance and Fall risk (follow up: mean 8 weeks; assessed with: One Leg Stance (OLS) left eyes closed)												
3	randomised trials	serious [i]	not serious	not serious	not serious	none	39	36	-	MD **1.8 higher** (0.86 higher to 2.75 higher)	⊕⊕⊕◯ MODERATE	IMPORTANT

CI: Confidence interval; **MD:** Mean difference

Explanations

a. ROB was fair

b. Out of 3 included studies ROB for Malik et al 2016 was poor, Song et al 2011 was fair, hence marked very serious

c. heterogeneity is between 50% to 75 % i.e. moderate heterogeneity

d. CI of Kruse et al 2010 was large and crosses the clinical decision threshold. Also, the overall pooled effect of also crosses the clinical decision threshold.

e. out of 4 included studies Malik et al 2016 was poor, Song et al 2011, Ahmed et al2019 and Venkatraman et al2019 were fair, hence marked very serious

f. Though the overall pooled effect does not have wide CI, 2 of the included individual studies had wide CI crossing the clinical decision threshold

g. all the 5 included studies were at fair ROB according to the author's judgment, hence marked serious

h. Though the overall pooled effect does not have wide CI, one of the included individual studies had wide CI crossing the clinical decision threshold

i. Both the included studies of Ahmed et al 2019 and Song et al 2011 were at fair ROB, hence marked serious

j. Heterogeneity is between 25% to50% i.e. Low heterogeneity

Table 3: Description of included studies

Author	Journal & Year	Age (years)	Population	Study Design	Total Sample	No of Subjects Intervention Group	No of Subjects In Control	Intervention Group	Control Group	Duration	Outcome Measures Balance	Outcome Measures QOL
Ahmed et al	Gait & posture 2019	45-75	DPN	RCT	37	a) Less than 60 years: 8, b)more than 60 years: 12	a) Less than 60 years: 8, b) More than 60 years: 9	Sensory-motor training, Diabetic & Foot Care Education	Diabetic &Foot Care Education	8 weeks	FRT, TUG, OLS, Postural Assessment, Proprioception	Nil
Venkataraman et al	Diabetologia 2019	40-79	DPN	RCT	143	70	73	Balance retraining and strengthening interventions guided by a physiotherapist	Standard medical care	8 weeks	FRT, TUG, ABC	SF-36V2, EQ-5D-5L.
Malik et al	Pak J Med Sci 2016	30-70	DPN	RCT	18	8	10	Task-oriented training	Traditional balance training	8 weeks	FRT, BBS, Rhomberg's, Backward Release Test	Nil

Song et al	Diabetes Technology & Therapeutics 2011	≥ 70	DPN	RCT	38	19	19	Balance Exercises	Health education	8 weeks	FRT, TUG, OLS, BBS	Nil
Kruse et al	Physical Therapy 2010	≥ 50	DPN	RCT	79	41	38	Part 1 leg strengthening and balance exercises,self-monitored walking program; part 2 telephone calls	8 visits by therapist for self-care in diabetes	12 months	BBS, OLS, TUG, FES-I	Nil
Majeed K et al	Disability, CBR & Inclusive Development2013	55-75	DPN	RCT	32	16	16	multisensory training and diabetic education	diabetic education	6 weeks	TUG, 6MWT	Nil
Allet et al	Diabetologia 2010	> 60	DPN	RCT	71	35	36	Gait and balance exercises	No treatment	12 weeks	POMA, Out Door Gait Assessment, Dynamic Balance Test, Static Bal Test ByBiodex	Nil

Fig 1: Flow diagram for the article selection and screening process according to PRISMA guidelines

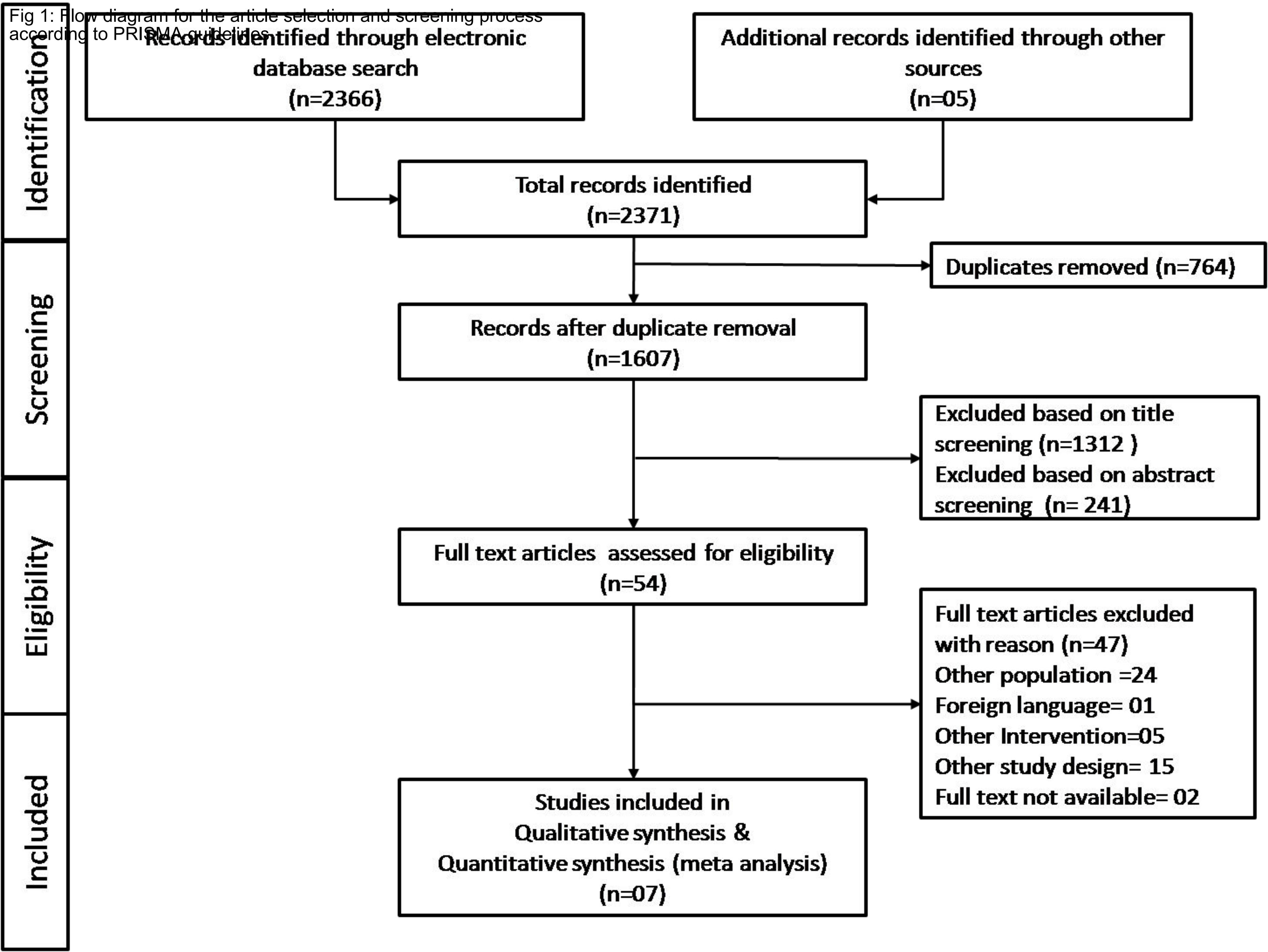

Fig 2: Summary of Risk of bias based on authors' judgments about each ROB domain.