The Impact of poor glycaemic control on the prevalence of erectile dysfunction in men with type 2 Diabetes Mellitus: A Systematic Review.

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Abstract:

BACKGROUND: The importance of poor glycaemic control as an indicator of reduced erectile function in diabetic men is still unclear. Several studies have demonstrated a significant correlation, however, some studies show only a borderline or no correlation between the two. In our review, we aim to clearly determine the impact of poor glycaemic control on the prevalence of erectile dysfunction (ED) in men with type 2 diabetes mellitus (DM), as well as the impact of other possible risk factors on the prevalence of ED.

METHODS: The databases Embase, Medline, Global health and PsychINFO were systematically searched for relevant research to identify the studies that evaluated the association between poor glycaemic control and the prevalence of ED in men with type 2 DM.

RESULTS: Five cross sectional studies involving 3299 patients were included. The findings pointed to a positive association between ED and glycaemic control. Three studies showed a significant positive association, while one study showed only a weak correlation and one study showed borderline significance. Patients' age, DM duration, peripheral neuropathy and body mass index had positive association with ED. However, smoking and hypertension was not associated with ED in most included studies. Physical activity had a protective effect against ED.

CONCLUSION: We may conclude that the risk of ED is higher in type 2 diabetic men with poor glycaemic control than those with good control.

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Introduction:

Erectile dysfunction (ED) is defined as the inability to achieve and/or maintain penile erection sufficient for satisfactory sexual intercourse(1). ED is a common problem in men with a history of diabetes mellitus (DM)(2). The prevalence of ED among patients with history of type 1 and/or type 2 DM in the literature varies from 35% to 90%(3-12). Literature including patients with history of type 2 DM only shows the prevalence of ED severity, by international index of erectile function (IIEF), as 73.10%(10), 86.10%(11) and 90%(12).

Diabetic men have almost a three-fold higher probability to develop ED compared to non-diabetic(13); they are also prone for the onset of ED to occur 10 to 15 years earlier than in non-diabetic men(13). ED in diabetic men has also been shown to be more severe and associated with a poorer quality of life(14). It is less responsive to medical treatment compared to non-diabetic men with ED(15). However, It is still unclear whether ED in diabetic men is a consequence only of hyperglycaemia and microvascular complications, or a collection of risk factors, as the patients often present with other ED risk factors, such as cardiovascular diseases, hypertension, smoking and obesity at the same time(16).

The importance of poor glycaemic control as an indicator of reduced erectile function in diabetic men is still unclear. Several studies have demonstrated a significant correlation between the two (11, 17-21), however, some studies have been mixed as to whether there is a statistically significant correlation between ED and poor glycaemic control, showing only a borderline (8, 22, 23) or no correlation at all (24-26). The inconsistency in the literature means that further studies are needed to clarify a causal link between prolonged hyperglycaemia and ED. This disparity between studies may be the result of the sample sizes used, and multivariate strategies used to analyse the data.

In our review, we aim to clearly determine the impact of poor glycaemic control on the prevalence of ED in men with type 2 DM, as well as the impact of other possible risk factors, such as duration of DM, patients' age, hypertension and cigarette smoking on the prevalence of ED.

Methods:

The databases Embase classic+Embase from 1947, Global health from 1973, Ovid Medline from 1946 and PsychINFO from 1967, were searched for relevant studies in June 2014 using the keywords: (Diabetes Mellitus **OR** diabetes mellitus type2 **OR** DM2 **OR** T2DM **OR** insulin resistance) **AND** (erectile dysfunction **OR** sexual dysfunction **OR** impotence) **AND** glycaemic control.

In consultation with the research team, we considered any observational study at any clinical settings that explored the Impact of glycaemic control level on the prevalence of ED in men with type 2 DM. The inclusion criteria for the participants were: any patient with type 2 DM, aged between 27 to 85 years. The primary outcome must include: glycaemic control which was measured by glycosylated haemoglobin (HBA1c) and diagnosis of ED was done by using the international index of erectile function (IIEF-5). We defined poor glycaemic control as HBA1c more than 7% (53 mmol\mol) and ED if IIEF-5 equal to or less than 21 (27). Our secondary outcomes were: the impact

of other possible risk factors on the prevalence of ED for men with T2DM e.g. duration of DM, patients' age, hypertension and smoking. Searching was restricted to articles in English language.

Two reviewers (TB and SH) performed the search and reviewed the results. The duplicate studies were removed using EndNote. During the initial review for titles and abstracts, studies that did not meet our criteria were excluded. If the reviewers were uncertain about certain studies during the initial review, then full text article was assessed. Independently, two reviewers (TB and SH) assessed all relevant studies, disagreement had been resolved by discussion and external opinion had been requested if needed.

Two reviewers (TB and SS) independently assessed the included studies for quality. Full critical appraisal was done for each study, by using Newcastle Ottawa quality assessment tool for cohort studies; checklists were adapted to be applied for cross sectional studies(28). Items reviewed included representativeness of the sample; sample size; response rate; validity of measurement tool, if validated and if non-validated; study controls for the most important factor and additional factors; assessment of the outcome; and statistical test used.

After the data extraction form was developed, two reviewers (TB and SS) independently extracted the data from included studies on the prevalence of ED among type 2 DM and the correlation between glycaemic control and other risk factors with ED. P values were used for the magnitude of the effect.

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Results:

Our electronic search identified 379 studies (Fig.1 PRISMA flow chart), of which 68 duplicated studies were excluded. An additional 289 studies were excluded after title and abstract review as they did not meet our inclusion criteria, leaving 22 studies; of these 22 studies, 17 studies were further excluded on reviewing their full text. The main reasons for exclusion were that Type 1 diabetic patients were included and some studies did not measure the association between the ED prevalence and glycaemic control.

We found one additional study El-Sakka et al (11) through bibliography hand searches; also one study Goyal, A. et al(29) was excluded because the author did not respond to our query about the assessment of DM control. Five studies were finally included in this systematic review (8, 11, 17, 20, 23); they were all of cross sectional design. Table 1 summarize the characteristics and the main findings of the 5 included studies and table 2 present their quality assessment.

Studies included were published between 2000 and 2010. Total sample size was 3299 patients; they were conducted in the USA (78 participants), Italy (555 participants), Korea (1312 participants), Taiwan (792 participants) and Saudi Arabia (562 participants). Mean age ± SD were 62 ± 12.3 years(17), 57.9 ± 6.9 years(20), 53.8 ± 6.65 years(8), 65.6 ± 13.2 years(23) and 53.7 ± 10.8 years(11). Mean HBA1c ± SD were 8.1 ± 1.9 % (17), 8.4 ± 1.3 % (20), 7.9 ± 1.83 % (8), 8.2 ± 2.0 % (23) and there was no data from El-Sakka et al.(11). Mean DM duration were 4.9 ± 1.5 years(20), 9.0 ± 7.5 years(23), 10.8 ± 7.5 years(11), median DM duration was 6 years(8) and there was no data from June H. Romeo et al.(17). Regarding all degrees of ED, the prevalence were 60%(20), 65.4%(8), 83.6%(23), 86.1%(11) and data not shown in one study June H. Romeo et al.(17).

The highest score of quality assessment is 9 points and the lowest score is 7 points, which demonstrate a good quality of included studies.

The findings generally pointed to a positive association between ED and glycaemic control. 3 studies showed a significant positive association (11, 17, 20), while one study showed only a weak correlation(8) and one study showed a borderline significant association(23).

In El-Sakka et al.(11), there was a higher likelihood of 12.2 times of patients with poor glycaemic control to suffer ED as compared to their counterparts with good glycaemic control. In the study by June H. Romeo et al.(17), the researchers showed that HBA1c was an independent predictor of EF score (P <0.001). In F Giugliano et al.(20), there was a higher average level of HBA1c in diabetic men with ED than in those who don't have ED (8.7±1.0% vs 7.9±0.9%, P = 0.01). Meanwhile, in the largest study, N. H. Cho et al.(8), the data from 1312 Korean men with type 2 DM, after using multivariate logistic regression to recognize independent risk factors for all types of ED, there was only a weak independent connection with the occurrence of diabetic-related ED was shown by HBA1c (P 0.092). In Chih-Chen Lu et al.(23), men suffering from ED had significantly higher average HBA1c level compared to those not suffering from ED in the youthful age group (8.8 ± 2.2 vs 7.9 ± 2.0%, p < 0.0009), however, no significant difference in mean HBA1c level between men with ED and those not suffering among the older age group (8.0 ± 1.8% vs 8.1 ± 2.0%, P= 0.63). There was also a significant higher mean HBA1c level in those with severe ED than in those with no sever ED among the youth (9.6 ± 2.3 vs 8.3 ± 2.1%, p= 0.0002), while mean HBA1c level did not showed significant difference between those with severe ED and those who didn't have among the older generation (8.0 ± 1.9 vs 8.0 ± 1.7%, p = 0.99).

Patients' age, DM duration, peripheral neuropathy and body mass index had positive association with ED. However, smoking and hypertension was not associated with ED in most included studies. Physical activity had a protective effect against ED.

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Discussion:

Penile erection is defined as the result of smooth muscle relaxation in the cavernous body and associated blood vessels (30). Nitric oxide (NO) plays a major role in this process as it is one of the most important endogenous smooth muscle relaxants. For chronic hyperglycaemia and insulin resistant in diabetic patients, endothelial dysfunction is manifested as a decreased level of NO, leading to insufficient smooth muscle relaxation.

The correlation between glycaemic control and ED:

In our systematic review, we identified 5 cross-sectional studies that examined the association between the glycaemic control (measured by HBA1c) and ED (measured by IIEF-5) among type 2 diabetic men. 60% of included studies (June H. Romeo et al.(17), F Giugliano et al.(20) and El-Sakka et al.(11)) suggested that poor glycaemic control is positively associated with ED in type 2 diabetics as the mean HBA1c was found to be higher among those with ED than those without ED. In the literature, other studies had also shown positive correlation between poor glycaemic control and ED among Diabetic patients (18).

Chih-Chen Lu et al.(23) showed a significant positive association between ED and glycaemic control in a younger age group (≤60 years), but not in an older age group (>60 years). Also in the same study, odds ratio of ED for different risk factors, after adjustment for duration of DM and age, showed that the HBA1c level was significantly associated with ED risk (P 0.034). However, Thomas GN et al (22); study has shown that patients diagnosed with ED are mostly older and the commonness of the ED condition increased with age. Cho NH et al.(8) showed a weak relationship between HBA1c level and diabetes related ED when using a multiple logistic regression analysis to identify risk factors for all types of ED. However, in the same study, Classifying the patients based on the level of ED showed the connection between the severity of ED to HBA1c was significant (P <0.001).

Several studies had demonstrated an insignificant correlation between glycaemic control and ED in diabetic men (24-26).

In terms of severe (complete) ED, N. H. Cho et al.(8) showed a significant positive correlation between complete ED with patients who were on insulin and patients with either macrovascular disease or neuropathy. However, complete ED was not significantly associated to either smoking status or hypertension. On the other hand, patients who were on diet only had rates of complete ED 0.59 times of those on other treatments, also patients who exercised regularly and those who consumed alcohol had a lower rate of complete ED than sedentary patients and those of alcohol abstainers, respectively.

Chih-Chen Lu et al.(23) showed a significant positive association between severe ED with HBA1c, DM duration and hypertension among a young age group (≤60 years), while only age was a significant independent risk factor for severe ED among an older age group (>60 years).

In summary, we may conclude that the risk of ED is higher in type 2 diabetic men with poor glycaemic control than those with good control. Since 3 studies showed that there were positive association between the two and the other two studies showed some correlation.

Risk factors for ED:

Four of the included studies (8, 11, 20, 23) highlighted that the prevalence of ED was mainly attributable to patients' age and the duration of diabetes. This positive association was confirmed by additional study (31). Only one study June H. Romeo et al.(17) showed that both subjects age and DM duration were not associated with ED prevalence.

Two studies June H. Romeo et al.(17) and N. H. Cho et al.(8) examined the peripheral neuropathy and the correlation with ED, both studies showed significant positive association. This was consistent with previous reports (32, 33).

Two studies, F Giugliano et al.(20) and El-Sakka et al.(11), examined the correlation between body mass index and ED; both studies confirmed a significant association with ED. Similar finding was reported by Esposito K et al (34).

F Giugliano et al.(20) is the only study that examined metabolic syndrome, waist hip ratio and depression and their correlation with ED; all of these factors were positively associated with ED prevalence.

Hypertension was examined in 3 studies, F Giugliano et al.(20), N. H. Cho et al.(8) and Chih-Chen Lu et al.(23), only one study F Giugliano et al.(20) showed a positive association, while other 2 studies did not show any association with ED. Previous evidence support the result of Giugliano et al study (35).

Cigarette smoking was examined in 4 studies F Giugliano et al.(20), N. H. Cho et al.(8) , Chih-Chen Lu et al.(23)and El-Sakka et al.(11), only one of these studies showed a significant correlation between smoking and prevalence of ED, El-Sakka et al.(11). A systematic review of observational studies came to a conclusion that ED risk is higher in current and former users of smoking than in those who never smoke, and smoking cessation may lead to lower risk of ED than current smoking (36).

Dyslipidaemia was examined in F Giugliano et al.(20) and Chih-Chen Lu et al.(23), one study F Giugliano et al.(20) showed a positive association and the other study Chih-Chen Lu et al.(23) did not show that.

In N. H. Cho et al.(8), stratifying of the patients according to ED status (normal, mild, moderate and complete), showed a significant trend connecting the severity of ED to the duration of alcohol consumption ($P < 0.001$), but similarly using multivariate regression analysis independent predictors for all types of ED: alcohol consumption ($P < 0.05$) and exercise ($P < 0.01$) were negative independent risk factors of ED. Additional study F Giugliano et al. showed that physical activity protected against ED. An assessment of the association between ED and physical activity was performed in population based studies with meta-analysis, higher physical activity was seen to lower the risk of ED (37). In Look AHEAD (action for health in diabetes) (31), cardiorespiratory fitness was found to protect ED among the 373 men with diabetes aged 45-75 years. Further study De Berardis et al(4), measured quality of life in diabetic men with ED, showed that exercise can help prevent ED.

A systematic review of the association between ED and cardiovascular disease(38), has shown that ED could be a possible sign of systematic endothelial dysfunction. ED usually occurs before CVD and could therefore be attributed to as an early sign of symptomatic CVD.

Limitation of studies:

Included studies had some limitations, for example; there were considerable differences in study settings, sample size and in adjustment of confounding factors. Romeo et al study(17) had the lowest sample size (78 participants). The description of the sampling strategy was not mentioned in El-Sakka Al et al study(11). In both studies there were no descriptions of the response rate. However, there were similarities of included studies in the term of study design since all included studies are cross sectional studies and they all used IIEF-5 for the determination of ED and HBA1c to evaluate the glycaemic control level.

Conclusion:

We may conclude that the risk of ED is higher in type 2 diabetic men with poor glycaemic control than those with good control. Also, an increase in patients age, DM duration, BMI and peripheral neuropathy existence can increase the risk of ED among diabetic men.

This will raise the importance of early screening of ED among diabetic men and the importance of HBA1c control as there is supporting evidence for the reduction of DM complications. We therefore recommend the incorporation of early ED screening for all diabetic men alongside the screening of neuropathy, retinopathy and nephropathy which are already endorsed by all existing guidelines.

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References:

1. NIH Consensus Conference. Impotence. NIH Consensus Development Panel on Impotence. JAMA. 1993;270(1):83-90.
2. Burke JP, Jacobson DJ, McGree ME, Nehra A, Roberts RO, Girman CJ, et al. Diabetes and sexual dysfunction: results from the Olmsted County study of urinary symptoms and health status among men. J Urol. 2007;177(4):1438-42.
3. McCulloch DK, Campbell IW, Wu FC, Prescott RJ, Clarke BF. The prevalence of diabetic impotence. Diabetologia. 1980;18(4):279-83.
4. De Berardis G, Franciosi M, Belfiglio M, Di Nardo B, Greenfield S, Kaplan SH, et al. Erectile dysfunction and quality of life in type 2 diabetic patients: a serious problem too often overlooked. Diabetes Care. 2002;25(2):284-91.
5. Fedele D, Coscelli C, Santeusanio F, Bortolotti A, Chatenoud L, Colli E, et al. Erectile dysfunction in diabetic subjects in Italy. Gruppo Italiano Studio Deficit Erettile nei Diabetici. Diabetes Care. 1998;21(11):1973-7.
6. Bacon CG, Hu FB, Giovannucci E, Glasser DB, Mittleman MA, Rimm EB. Association of type and duration of diabetes with erectile dysfunction in a large cohort of men. Diabetes Care. 2002;25(8):1458-63.
7. Siu SC, Lo SK, Wong KW, Ip KM, Wong YS. Prevalence of and risk factors for erectile dysfunction in Hong Kong diabetic patients. Diabet Med. 2001;18(9):732-8.
8. Cho NH, Ahn CW, Park JY, Ahn TY, Lee HW, Park TS, et al. Prevalence of erectile dysfunction in Korean men with Type 2 diabetes mellitus. Diabet Med. 2006;23(2):198-203.
9. Giuliano FA, Leriche A, Jaudinot EO, de Gendre AS. Prevalence of erectile dysfunction among 7689 patients with diabetes or hypertension, or both. Urology. 2004;64(6):1196-201.
10. Malavige LS, Jayaratne SD, Kathriarachchi ST, Sivayogan S, Fernando DJ, Levy JC. Erectile dysfunction among men with diabetes is strongly associated with premature ejaculation and reduced libido. J Sex Med. 2008;5(9):2125-34.
11. El-Sakka AI, Tayeb KA. Erectile dysfunction risk factors in noninsulin dependent diabetic Saudi patients. J Urol. 2003;169(3):1043-7.
12. Sasaki H, Yamasaki H, Ogawa K, Nanjo K, Kawamori R, Iwamoto Y, et al. Prevalence and risk factors for erectile dysfunction in Japanese diabetics. Diabetes Res Clin Pract. 2005;70(1):81-9.
13. Feldman HA, Goldstein I, Hatzichristou DG, Krane RJ, McKinlay JB. Impotence and its medical and psychosocial correlates: results of the Massachusetts Male Aging Study. J Urol. 1994;151(1):54-61.
14. Penson DF, Latini DM, Lubeck DP, Wallace KL, Henning JM, Lue TF, et al. Do impotent men with diabetes have more severe erectile dysfunction and worse quality of life than the general population of impotent patients? Results from the Exploratory Comprehensive Evaluation of Erectile Dysfunction (ExCEED) database. Diabetes Care. 2003;26(4):1093-9.
15. Goldstein I, Lue TF, Padma-Nathan H, Rosen RC, Steers WD, Wicker PA. Oral sildenafil in the treatment of erectile dysfunction. Sildenafil Study Group. N Engl J Med. 1998;338(20):1397-404.
16. Lewis RW, Fugl-Meyer KS, Corona G, Hayes RD, Laumann EO, Moreira ED, et al. Definitions/epidemiology/risk factors for sexual dysfunction. J Sex Med. 2010;7(4 Pt 2):1598-607.
17. Romeo JH, Seftel AD, Madhun ZT, Aron DC. Sexual function in men with diabetes type 2: association with glycemic control. J Urol. 2000;163(3):788-91.
18. Roth A, Kalter-Leibovici O, Kerbis Y, Tenenbaum-Koren E, Chen J, Sobol T, et al. Prevalence and risk factors for erectile dysfunction in men with diabetes, hypertension, or both diseases: a community survey among 1,412 Israeli men. Clin Cardiol. 2003;26(1):25-30.
19. Matfin G, Jawa A, Fonseca VA. Erectile dysfunction: interrelationship with the metabolic syndrome. Curr Diab Rep. 2005;5(1):64-9.
20. Giugliano F, Maiorino M, Bellastella G, Gicchino M, Giugliano D, Esposito K. Determinants of erectile dysfunction in type 2 diabetes. Int J Impot Res. 2010;22(3):204-9.

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21. De Angelis L, Marfella MA, Siniscalchi M, Marino L, Nappo F, Giugliano F, et al. Erectile and endothelial dysfunction in Type II diabetes: a possible link. Diabetologia. 2001;44(9):1155-60.
22. Thomas GN, Tomlinson B, Abdullah AS, Yeung VT, Chan JC, Wong KS. Association of erectile dysfunction with cardiovascular risk factors and increasing existing vascular disease in male chinese type 2 diabetic patients. Diabetes Care. 2005;28(8):2051-3.
23. Lu CC, Jiann BP, Sun CC, Lam HC, Chu CH, Lee JK. Association of glycemic control with risk of erectile dysfunction in men with type 2 diabetes. J Sex Med. 2009;6(6):1719-28.
24. Al-Hunayan A, Al-Mutar M, Kehinde EO, Thalib L, Al-Ghorory M. The prevalence and predictors of erectile dysfunction in men with newly diagnosed with type 2 diabetes mellitus. BJU Int. 2007;99(1):130-4.
25. Zheng H, Fan W, Li G, Tam T. Predictors for erectile dysfunction among diabetics. Diabetes Res Clin Pract. 2006;71(3):313-9.
26. Shiri R, Ansari M, Falah Hassani K. Association between comorbidity and erectile dysfunction in patients with diabetes. Int J Impot Res. 2006;18(4):348-53.
27. Rosen RC, Cappelleri JC, Smith MD, Lipsky J, Peña BM. Development and evaluation of an abridged, 5-item version of the International Index of Erectile Function (IIEF-5) as a diagnostic tool for erectile dysfunction. Int J Impot Res. 1999;11(6):319-26.
28. Herzog R, Álvarez-Pasquin MJ, Díaz C, Del Barrio JL, Estrada JM, Gil Á. Are healthcare workers' intentions to vaccinate related to their knowledge, beliefs and attitudes? A systematic review. BMC Public Health. 2013;13:154.
29. Goyal A, Singh P, Ahuja A. Prevalence and Severity of Erectile Dysfunction as Assessed by IIEF-5 in North Indian Type 2 Diabetic Males and Its Correlation with Variables. J Clin Diagn Res. 2013;7(12):2936-8.
30. Gratzke C, Angulo J, Chitaley K, Dai YT, Kim NN, Paick JS, et al. Anatomy, physiology, and pathophysiology of erectile dysfunction. J Sex Med. 2010;7(1 Pt 2):445-75.
31. Wing RR, Rosen RC, Fava JL, Bahnson J, Brancati F, Gendrano Iii IN, et al. Effects of weight loss intervention on erectile function in older men with type 2 diabetes in the Look AHEAD trial. J Sex Med. 2010;7(1 Pt 1):156-65.
32. Hecht MJ, Neundörfer B, Kiesewetter F, Hilz MJ. Neuropathy is a major contributing factor to diabetic erectile dysfunction. Neurol Res. 2001;23(6):651-4.
33. Ledda A. Diabetes, hypertension and erectile dysfunction. Curr Med Res Opin. 2000;16 Suppl 1:s17-20.
34. Esposito K, Giugliano F, Ciotola M, De Sio M, D'Armiento M, Giugliano D. Obesity and sexual dysfunction, male and female. Int J Impot Res. 2008;20(4):358-65.
35. Seftel AD, Sun P, Swindle R. The prevalence of hypertension, hyperlipidemia, diabetes mellitus and depression in men with erectile dysfunction. J Urol. 2004;171(6 Pt 1):2341-5.
36. Cao S, Yin X, Wang Y, Zhou H, Song F, Lu Z. Smoking and risk of erectile dysfunction: systematic review of observational studies with meta-analysis. PLoS One. 2013;8(4):e60443.
37. Cheng JY, Ng EM, Ko JS, Chen RY. Physical activity and erectile dysfunction: meta-analysis of population-based studies. Int J Impot Res. 2007;19(3):245-52.
38. Gandaglia G, Briganti A, Jackson G, Kloner RA, Montorsi F, Montorsi P, et al. A systematic review of the association between erectile dysfunction and cardiovascular disease. Eur Urol. 2014;65(5):968-78.

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Fig.1 Flow chart showing search findings

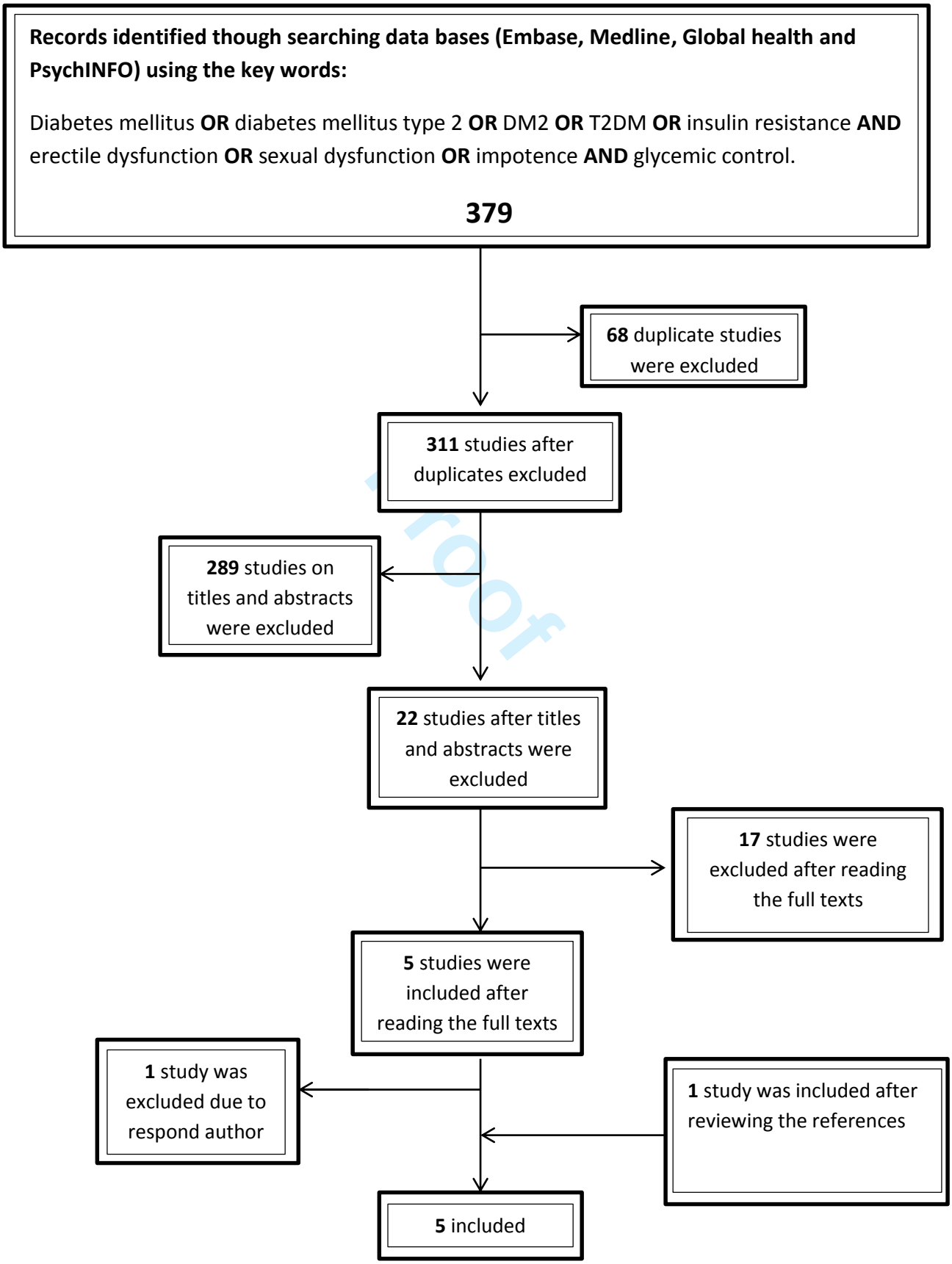

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Table 1: Data extracted from articles:

Study	Objective of study	Sample characteristics	Outcomes	Confounders included
Sexual Function In Men With Diabetes Type2 : Association With Glycemic Control **June H. Romeo et al (17)** Cross sectional study, Ohio	To evaluate the association of glycemic control with ED in men with type 2 DM	-Total study population 78 -Mean age 62.0 ± 12.3 years (38-82) -Mean HBA1c 8.1% ± 1.9% (5.2-15.6) -Mean EF score 16.6 ± 5.9 (5-23)	**-After EF scores were stratified by the level of glycemic control :** **-Mean EF score decreased as HBA1c increased (analysis of variance P= 0.002)** **-After Bivariate analysis to examine the correlation of ED with subject characteristics:** **There was a significant correlation of HBA1c with neuropathy but NOT with participant age, duration of DM or some medication use(data not shown)** **-Multivariate analysis showed that HBA1c was an independent predictor of EF score (P <0.001) even after adjusting for peripheral neuropathy, which was also an independent predictor (P= 0.023)** **-When subject age and DM duration were included in multivariate models, only HBA1c and neuropathy were significant independent predictors of EF score**	**-HBA1c** -Age -DM duration -Peripheral neuropathy -Some medications
Determinants Of Erectile Dysfunction In Type 2 Diabetes **F Giugliano et al (21)** Cross sectional study, Naples	To evaluate the prevalence and correlates of ED in a population of diabetic men	-Total study population 555 -All ED 333 (60%) -Mild (9%) -Mild to moderate (11.2%) -Moderate (16.9%) -Sever (22.9%) -Mean age 57.9 ± 6.9 years (35-70) -Mean HBA1c	**Contribution of different risk factors to risk of ED in the diabetic population (based on multivariate logistic regression):** 1-**Age** (OR 1.10) 95% CI 1.05-1.15 (P 0.001) 2-**DM duration** (OR 1.05) 95% CI 1.01-1.10 (P 0.01) 3-**HBA1c** (OR 1.18) 95% CI 1.02-1.37 (P 0.03) 4-**MS** (OR 2.08) 95% CI 1.17-3.26 (P 0.01)	**-HBA1c** -Age -DM duration -Metabolic syndrome -BMI -WHR -HTN -DLD -Cigarette Smoking -Physical activity -Depression

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(Italy)		8.4% ± 1.3% -Mean DM duration 4.9 ± 1.5 years	5-**BMI** (OR 1.03) 95% CI 1.00-1.07 (P 0.04) 6-**WHR** (OR 1.04) 95% CI 1.01-1.08 (P 0.03) 7-**HTN** (OR 1.34) 95% CI 1.08-2.03 (P 0.02) 8-**DLD** (OR 1.23) 95% CI 1.04-1.49 (P 0.01) 9-**Cigarette smoking**: a-**past** (OR 1.15) 95% CI 0.86-1.98 (P 0.56) not significant b-**current** (OR 1.36) 95% CI 0.81-2.09 (P 0.35) not significant 10-**Physical activity** (OR 0.90) 95% CI 0.77-0.98 (P 0.04) **protective of ED** 11-**Depression** (OR 1.09) 95% CI 1.02-1.19 (P 0.03) **The mean HBA1c level was significantly higher in diabetic patients with ED than those without ED (8.7±1.0% vs 7.9±0.9%, P = 0.01).**	
Prevalence Of Erectile Dysfunction In Korean Men With Type 2 DM **N. H. Cho et al (8)** Cross sectional study, May2002 to March2003, Korea	To investigate the prevalence and risk factors for developing ED in 1312 Korean men with diabetes	-Total study population 1312 -All ED 858 (65.4%) -Mild (20.1%) -Moderate (19.5) -Complete (25.8%) -Mean age 53.8 ± 6.65 years (40-64) -Mean HBA1c 7.9% ± 1.83% -Median DM duration 6 years (range 1-43)	**When the subjects were stratified according to ED status (Normal, mild, moderate and complete), there were significant trends relating the severity of ED to:** 1-Age (P <0.001) 2-DM duration (P <0.001) 3-Fasting glucose (P <0.05) 4-HBA1c (P <0.001) 5-Duration of alcohol consumption (P <0.001) -**No significant differences were observed in Blood Pressure or Duration of smoking** **Other risk factors for ED were examined:** 1-Subjects who exercised regularly	**-HBA1c** -Age -DM duration -HTN -Smoking -Neuropathy -Use of insulin -Macrovascular disease -Alcohol consumption -Exercise

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			had rate of complete ED 0.62 times those of alcohol abstainers or sedentary subjects (95% CI 0.44-0.89, P < 0.01) 2-Subjects who consumed alcohol had rate of complete ED 0.49 times the same comparison above (95% CI 0.36-0.66, P < 0.001) 3-Subjects who were on insulin treatment 6.1 times more likely to have complete ED than non-insulin users (95% CI 3.2-11.4, P<0.001) 4-Subjects who were on diet therapy alone had rates of complete ED only 0.59 times of those receiving the other treatments (95% CI 0.36-0.95, P<0.001) 5-Subjects with either neuropathy or macrovascular disease were, respectively, 1.8 times (95% CI 1.11-2.9, P<0.05) and 3.5 times (95% CI 1.14-10.6, P<0.05) as likely to have complete ED as those subjects without such complications 6-Complete ED was not significantly related to either HTN or smoking status **When multiple logistic regression analysis was used to identify significant independent risk factors for <u>ALL</u> type of ED:** 1-Age (P <0.001) 2-DM duration (P <0.005) 3-Neuropathy (P <0.05) 4-Use of insulin (P <0.001) 5-Macrovascular complications (P 0.038) Were independent **<u>POSITIVE</u>** risk factors for all types of ED. **<u>BUT</u>**, **Alcohol consumption**(P <0.05) and **Exercise**(P <0.01) were	

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			independent **NEGATIVE** risk factors. **Moreover, HBA1c showed only WEAK (or NO) independent relationship with the development of diabetic-related ED (P 0.092).** **-When we analyzed the data further using complete ED as the dependent variable, those variables also showed independent relationship with all types of ED with EXEPTION of neuropathy.**	
Association Of Glycemic Control With Risk Of Erectile Dysfunction In Men With Type 2 Diabetes **Chih-Chen Lu et al (20)** Cross sectional study, Jan2004 – May 2006, Taiwan	To evaluate the association of glycemic control with risk of ED in type 2 diabetics	-Total study population 792 -All ED 662 (83.6%) -Mild 123 (15.5%) -Mild to moderate 133 (16.8%) -Moderate 64 (8.1%) -Sever 342 (43.2%) -Mean age 65.6 ± 13.2 (27-85) -Mean duration of DM 9.0 ± 7.5 (1-39) -Mean HBA1c 8.2% ± 2.0% (4.3-17.5)	**The prevalence of ED was POSITIVELY correlated with subjects age and duration of diabetes (P 0.000)** **Higher HBA1c level was associated with a higher risk of ED with borderline significant (P=0.059)** **-The ORs of ED for risk factors(HBA1c, HTN, DLD and cigarette smoking) after adjusted for age and DM duration:** **ONLY HBA1c level was significantly associated with ED risk (P 0.034)** **-The prevalence of ED was 66.7% in younger group, and 93.1% in the older group (p = 0.000)** **-Those with ED had a significantly higher mean HBA1c level than those without ED in younger group (8.8 ± 2.2 vs 7.9 ± 2.0%, p < 0.0009)** **-There was no significant difference in mean HBA1c level between those with or without ED in the older group (8.0 ± 1.8 vs 8.1 ± 2.0%, P= 0.63)** -**When multivariate logistic regression was used for the contribution of risk factors to risk of ED:** **1-in young group (≤ 60):**	**-HBA1c** -Age -DM duration -HTN -DLD -Cigarette Smoking

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			a-Age OR 1.06 (95% CI 1.02-1.10) P 0.002 b-DM duration OR 1.06(95% CI 1.001-1.12) P 0.045 c-HBA1c OR 1.21 (95% CI 1.06-1.39) P 0.004 were **significant** independent risk factors for ED **2-in old group (> 60):** a-**Age** OR 1.07 (95% CI 1.02-1.13) P 0.009 b-**DM duration** OR 1.07 (95% CI 1.01-1.14) P 0.019 were **significant** independent risk factors for ED **-The mean HBA1c level was significantly higher in those with sever ED than those without sever ED among the younger group (9.6 ± 2.3 vs 8.3 ± 2.1%, p= 0.0002)** **-The mean HBA1c level did not show significant difference between those with sever ED and those without among the older group (8.0 ± 1.9 vs 8.0 ± 1.7%, p = 0.99)** **-Contribution of HBA1c and other risk factors to risk of SEVER ED based on multivariate logistic regression:** **1-in young group:** a-**DM duration** OR 1.09 (95% CI 1.03-1.16) P 0.003 b-**HBA1c** OR 1.27 (95% CI 1.09-1.49) P 0.003 c-**HTN** OR 2.68 (95% CI 0.64-1.53) P 0.015 **were significantly independent risk factors for SEVER ED compared with normal, mild or moderate ED**	

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			2-in old group: **ONLY Age** OR 1.08 (95% CI 1.05-1.11) P 0.000 **was significant independent risk factors for SEVER ED compared to normal, mild or moderate ED.**	
Erectile Dysfunction Risk Factors In Noninsulin Dependent Diabetic Saudi Patients **El-Sakka AI et al (11)** Cross Sectional Study, Saudi Arabia	To assess the prevalence of and analyze risk factors for ED in patients with noninsulin dependent diabetes in Makkah, Saudi Arabia	-Total study population 562 -All ED (86.1%) -Mild (7.7%) -Moderate (29.4%) -Sever (49.1%) -Mean age 53.7 ± 10.8 years (27-85) -Mean DM duration 10.8 ± 7.5 years (1 - 40)	-The prevalence of ED increased with **age**, in younger than 50 years the prevalence was 25% and in 50 years or older the prevalence was 75%. Men without ED 70% were younger and 30% were older than 50 years (P = 0.0001) -**Patents with a greater than 10 years history of DM** were 3 times as likely to report ED as those with a history of less than 5 years (P = 0.0001). -Patients with **poor glycaemic control** were 12.2 times as likely to report ED as those with good glycaemic control **The prevalence of ED was significantly associated with:** **1-poor glycaemic control** (P = 0.0001). **2-increased body mass index** (P = 0.0001). **3-a history of smoking** (P = 0.0001). **4-the duration of smoking** (P = 0.003). **5-the number of cigarettes daily** (P = 0.0001). **6-Some DM treatment** (P = 0.0001)	**-HBA1c** -Age -DM duration -BMI -Smoking -DM treatments

Table 1 Characteristics and main findings of included studies

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Summary:

The importance of poor glycaemic control as an indicator of reduced erectile function in diabetic men is still unclear. Several studies have demonstrated a significant correlation, however, some studies show only a borderline or no correlation between the two. In our review, we aim to clearly determine the impact of poor glycaemic control on the prevalence of erectile dysfunction (ED) in men with type 2 diabetes mellitus (DM), as well as the impact of other possible risk factors on the prevalence of ED.

The databases Embase, Medline, Global health and PsychINFO were systematically searched for relevant research to identify the studies that evaluated the association between poor glycaemic control and the prevalence of ED in men with type 2 DM.

Five cross sectional studies involving 3299 patients were included. The findings pointed to a positive association between ED and glycaemic control. Three studies showed a significant positive association, while one study showed only a weak correlation and one study showed borderline significance. Patients' age, DM duration, peripheral neuropathy and body mass index had positive association with ED. However, smoking and hypertension was not associated with ED in most included studies. Physical activity had a protective effect against ED.

We may conclude that the risk of ED is higher in type 2 diabetic men with poor glycaemic control than those with good control.

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Introduction:

Erectile dysfunction (ED) is defined as the inability to achieve and/or maintain penile erection sufficient for satisfactory sexual intercourse(1). ED is a common problem in men with a history of diabetes mellitus (DM)(2). The prevalence of ED among patients with history of type 1 or type 2 DM in the literature varies from 35% to 90% (3). Some of the studies in the literature included only men suffering from type 2 DM, who were evaluated for ED and its severity by international index of erectile function (IIEF), the prevalence of ED were 73.10%(4), 86.10%(5) and 90%(6).

Diabetic men have almost a three-fold higher probability to develop ED compared to non-diabetic(7); they are also prone for the onset of ED to occur 10 to 15 years earlier than in non-diabetic men(7). ED in diabetic men has also been shown to be more severe and associated with a poorer quality of life(8). It is less responsive to medical treatment compared to non-diabetic men with ED(9). It is still unclear whether ED in diabetic men is a consequence only of hyperglycaemia and microvascular complications, or a collection of risk factors, as the patients often present with other ED risk factors, such as cardiovascular diseases, hypertension, smoking and obesity at the same time(10). Also, It is unclear if the correction of glucose control in poorly controlled diabetics have a positive effect on ED. However, the correction of glucose control in poorly controlled diabetics had no significant effect on cardiovascular or micro-vascular complications (11).

The importance of poor glycaemic control as an indicator of reduced erectile function in diabetic men is still unclear. Several studies have demonstrated a significant correlation between the two (5, 12-16), however, some studies have been mixed as to whether there is a statistically significant correlation between ED and poor glycaemic control, showing only a borderline (17-19) or no correlation at all (20-22). The inconsistency in the literature means that further studies are needed to clarify a causal link between prolonged hyperglycaemia and ED. This disparity between studies may be the result of the sample sizes used, and multivariate strategies used to analyse the data.

In our review, we aim to clearly determine the impact of poor glycaemic control on the prevalence of ED in men with type 2 DM, as well as the impact of other possible risk factors, such as duration of DM, patients' age, hypertension and cigarette smoking on the prevalence of ED.

Methods:

The databases Embase classic+Embase from 1947, Global health from 1973, Ovid Medline from 1946 and PsychINFO from 1967, were searched for relevant studies in June 2014 using the keywords: (Diabetes Mellitus **OR** diabetes mellitus type2 **OR** DM2 **OR** T2DM **OR** insulin resistance) **AND** (erectile dysfunction **OR** sexual dysfunction **OR** impotence) **AND** glycaemic control.

In consultation with the research team, we considered any observational study at any clinical settings that explored the Impact of glycaemic control level on the prevalence of ED in men with type 2 DM. The inclusion criteria for the participants were: any patient with type 2 DM, aged between 27 to 85 years. The primary outcome must include: glycaemic control which was measured by glycosylated haemoglobin (HBA1c) and diagnosis of ED was done by using the international index of erectile function (IIEF-5). We defined poor glycaemic control as HBA1c more than 7% (53

mmol\mol) and ED if IIEF-5 equal to or less than 21 (23). Our secondary outcomes were: the impact of other possible risk factors on the prevalence of ED for men with T2DM e.g. duration of DM, patients' age, hypertension and smoking. Searching was restricted to articles in English language.

Two reviewers (TB and SH) performed the search and reviewed the results. The duplicate studies were removed using EndNote. During the initial review for titles and abstracts, studies that did not meet our criteria were excluded. If the reviewers were uncertain about certain studies during the initial review, then full text article was assessed. Independently, two reviewers (TB and SH) assessed all relevant studies, disagreement had been resolved by discussion and external opinion had been requested if needed.

Two reviewers (TB and SS) independently assessed the included studies for quality. Full critical appraisal was done for each study, by using Newcastle Ottawa quality assessment tool for cohort studies; checklists were adapted to be applied for cross sectional studies(24). Items reviewed included representativeness of the sample; sample size; response rate; validity of measurement tool, if validated and if non-validated; study controls for the most important factor and additional factors; assessment of the outcome; and statistical test used.

After the data extraction form was developed, two reviewers (TB and SS) independently extracted the data from included studies on the prevalence of ED among type 2 DM and the correlation between glycaemic control and other risk factors with ED. P values were used for the magnitude of the effect.

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Results:

Our electronic search identified 379 studies (Fig.1 PRISMA flow chart), of which 68 duplicated studies were excluded. An additional 289 studies were excluded after title and abstract review as they did not meet our inclusion criteria, leaving 22 studies; of these 22 studies, 17 studies were further excluded on reviewing their full text. The main reasons for exclusion were that Type 1 diabetic patients were included and some studies did not measure the association between the ED prevalence and glycaemic control.

We found one additional study El-Sakka et al (5) through bibliography hand searches; also one study Goyal, A. et al(25) was excluded because the author did not respond to our query about the assessment of DM control. Five studies were finally included in this systematic review (5, 12, 15, 18, 19); they were all of cross sectional design. Table 1 summarize the characteristics and the main findings of the 5 included studies and table 2 present their quality assessment.

Studies included were published between 2000 and 2010. Total sample size was 3299 patients; they were conducted in the USA (78 participants), Italy (555 participants), Korea (1312 participants), Taiwan (792 participants) and Saudi Arabia (562 participants). Mean age ± SD were 62 ± 12.3 years(12), 57.9 ± 6.9 years(15), 53.8 ± 6.65 years(18), 65.6 ± 13.2 years(19) and 53.7 ± 10.8 years(5). Mean HBA1c ± SD were 8.1 ± 1.9 % (12), 8.4 ± 1.3 % (15), 7.9 ± 1.83 % (18), 8.2 ± 2.0 % (19) and there was no data from El-Sakka et al.(5). Mean DM duration were 4.9 ± 1.5 years(15), 9.0 ± 7.5 years(19), 10.8 ± 7.5 years(5), median DM duration was 6 years(18) and there was no data from June H. Romeo

et al.(12). Regarding all degrees of ED, the prevalence were 60%(15), 65.4%(18), 83.6%(19), 86.1%(5) and data not shown in one study June H. Romeo et al.(12).

The highest score of quality assessment is 9 points and the lowest score is 7 points, which demonstrate a good quality of included studies.

The findings generally pointed to a positive association between ED and glycaemic control. 3 studies showed a significant positive association (5, 12, 15), while one study showed only a weak correlation(18) and one study showed a borderline significant association(19).

In El-Sakka et al.(5), there was a higher likelihood of 12.2 times of patients with poor glycaemic control to suffer ED as compared to their counterparts with good glycaemic control. In the study by June H. Romeo et al.(12), the researchers showed that HBA1c was an independent predictor of EF score (P <0.001). In F Giugliano et al.(15), there was a higher average level of HBA1c in diabetic men with ED than in those who don't have ED (8.7±1.0% vs 7.9±0.9%, P = 0.01). Meanwhile, in the largest study, N. H. Cho et al.(18), the data from 1312 Korean men with type 2 DM, after using multivariate logistic regression to recognize independent risk factors for all types of ED, there was only a weak independent connection with the occurrence of diabetic-related ED was shown by HBA1c (P 0.092). In Chih-Chen Lu et al.(19), men suffering from ED had significantly higher average HBA1c level compared to those not suffering from ED in the youthful age group (8.8 ± 2.2 vs 7.9 ± 2.0%, p < 0.0009), however, no significant difference in mean HBA1c level between men with ED and those not suffering among the older age group (8.0 ± 1.8% vs 8.1 ± 2.0%, P= 0.63). There was also a significant higher mean HBA1c level in those with severe ED than in those with no sever ED among the youth (9.6 ± 2.3 vs 8.3 ± 2.1%, p= 0.0002), while mean HBA1c level did not showed significant difference between those with severe ED and those who didn't have among the older generation (8.0 ± 1.9 vs 8.0 ± 1.7%, p = 0.99).

Patients' age, DM duration, peripheral neuropathy and body mass index had positive association with ED. However, smoking and hypertension was not associated with ED in most included studies. Physical activity had a protective effect against ED.

Discussion:

Penile erection is defined as the result of smooth muscle relaxation in the cavernous body and associated blood vessels (26). Nitric oxide (NO) plays a major role in this process as it is one of the most important endogenous smooth muscle relaxants. For chronic hyperglycaemia and insulin resistant in diabetic patients, endothelial dysfunction is manifested as a decreased level of NO, leading to insufficient smooth muscle relaxation. Alternatively, diabetes is known to cause vascular, neuropathic and psychological disturbances which contribute to erectile dysfunction by different mechanisms (3).

The correlation between glycaemic control and ED:

In our systematic review, we identified 5 cross-sectional studies that examined the association between the glycaemic control (measured by HBA1c) and ED (measured by IIEF-5) among type 2 diabetic men. 60% of included studies (June H. Romeo et al.(12), F Giugliano et al.(15) and El-Sakka

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et al.(5)) suggested that poor glycaemic control is positively associated with ED in type 2 diabetics as the mean HBA1c was found to be higher among those with ED than those without ED. In the literature, other studies had also shown positive correlation between poor glycaemic control and ED among Diabetic patients (13).

Chih-Chen Lu et al.(19) showed a significant positive association between ED and glycaemic control in a younger age group (≤60 years), but not in an older age group (>60 years). Also in the same study, odds ratio of ED for different risk factors, after adjustment for duration of DM and age, showed that the HBA1c level was significantly associated with ED risk (P 0.034). However, Thomas GN et al (17); study has shown that patients diagnosed with ED are mostly older and the commonness of the ED condition increased with age. Cho NH et al.(18) showed a weak relationship between HBA1c level and diabetes related ED when using a multiple logistic regression analysis to identify risk factors for all types of ED. However, in the same study, Classifying the patients based on the level of ED showed the connection between the severity of ED to HBA1c was significant (P <0.001).

Several studies had demonstrated an insignificant correlation between glycaemic control and ED in diabetic men (20-22).

In terms of severe (complete) ED, N. H. Cho et al.(18) showed a significant positive correlation between complete ED with patients who were on insulin and patients with either macrovascular disease or neuropathy. However, complete ED was not significantly associated to either smoking status or hypertension. On the other hand, patients who were on diet only had rates of complete ED 0.59 times of those on other treatments, also patients who exercised regularly and those who consumed alcohol had a lower rate of complete ED than sedentary patients and those of alcohol abstainers, respectively.

Chih-Chen Lu et al.(19) showed a significant positive association between severe ED with HBA1c, DM duration and hypertension among a young age group (≤60 years), while only age was a significant independent risk factor for severe ED among an older age group (>60 years).

In summary, we may conclude that the risk of ED is higher in type 2 diabetic men with poor glycaemic control than those with good control. Since 3 studies showed that there were positive association between the two and the other two studies showed some correlation.

Risk factors for ED:

Four of the included studies (5, 15, 18) highlighted that the prevalence of ED was mainly attributable to patients' age and the duration of diabetes. This positive association was confirmed by additional study (27). Only one study June H. Romeo et al.(12) showed that both subjects age and DM duration were not associated with ED prevalence.

Two studies June H. Romeo et al.(12) and N. H. Cho et al.(18) examined the peripheral neuropathy and the correlation with ED, both studies showed significant positive association. This was consistent with previous reports (28, 29).

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Two studies, F Giugliano et al.(15) and El-Sakka et al.(5), examined the correlation between body mass index and ED; both studies confirmed a significant association with ED. Similar finding was reported by Esposito K et al (30).

F Giugliano et al.(15) is the only study that examined metabolic syndrome, waist hip ratio and depression and their correlation with ED; all of these factors were positively associated with ED prevalence.

Hypertension was examined in 3 studies, F Giugliano et al.(15), N. H. Cho et al.(18) and Chih-Chen Lu et al.(19), only one study F Giugliano et al.(15) showed a positive association, while other 2 studies did not show any association with ED. Previous evidence support the result of Giugliano et al study (31).

Cigarette smoking was examined in 4 studies F Giugliano et al.(15), N. H. Cho et al.(18) , Chih-Chen Lu et al.(19)and El-Sakka et al.(5), only one of these studies showed a significant correlation between smoking and prevalence of ED, El-Sakka et al.(5). A systematic review of observational studies came to a conclusion that ED risk is higher in current and former users of smoking than in those who never smoke, and smoking cessation may lead to lower risk of ED than current smoking (32).

Dyslipidaemia was examined in F Giugliano et al.(15) and Chih-Chen Lu et al.(19), one study F Giugliano et al.(15) showed a positive association and the other study Chih-Chen Lu et al.(19) did not show that.

In N. H. Cho et al.(18), stratifying of the patients according to ED status (normal, mild, moderate and complete), showed a significant trend connecting the severity of ED to the duration of alcohol consumption ($P < 0.001$), but similarly using multivariate regression analysis independent predictors for all types of ED: alcohol consumption ($P < 0.05$) and exercise ($P < 0.01$) were negative independent risk factors of ED. Additional study F Giugliano et al. showed that physical activity protected against ED. An assessment of the association between ED and physical activity was performed in population based studies with meta-analysis, higher physical activity was seen to lower the risk of ED (33). In Look AHEAD (action for health in diabetes) (27), cardiorespiratory fitness was found to protect ED among the 373 men with diabetes aged 45-75 years. Further study De Berardis et al(34), measured quality of life in diabetic men with ED, showed that exercise can help prevent ED.

A systematic review of the association between ED and cardiovascular disease(35), has shown that ED could be a possible sign of systematic endothelial dysfunction. ED usually occurs before CVD and could therefore be attributed to as an early sign of symptomatic CVD.

Limitation of studies:

Included studies had some limitations, for example; there were considerable differences in study settings, sample size and in adjustment of confounding factors. Romeo et al study(12) had the lowest sample size (78 participants). The description of the sampling strategy was not mentioned in El-Sakka Al et al study(5). In both studies there were no descriptions of the response rate. However, there were similarities of included studies in the term of study design since all included studies are

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cross sectional studies and they all used IIEF-5 for the determination of ED and HBA1c to evaluate the glycaemic control level.

Conclusion:

We may conclude that the risk of ED is higher in type 2 diabetic men with poor glycaemic control than those with good control. Also, an increase in patients age, DM duration, BMI and peripheral neuropathy existence can increase the risk of ED among diabetic men.

This will raise the importance of early screening of ED among diabetic men and the importance of HBA1c control as there is supporting evidence for the reduction of DM complications. We therefore recommend the incorporation of early ED screening for all diabetic men alongside the screening of neuropathy, retinopathy and nephropathy which are already endorsed by all existing guidelines.

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References:

1. NIH Consensus Conference. Impotence. NIH Consensus Development Panel on Impotence. JAMA. 1993 Jul;270(1):83-90. PubMed PMID: 8510302. eng.
2. Burke JP, Jacobson DJ, McGree ME, Nehra A, Roberts RO, Girman CJ, et al. Diabetes and sexual dysfunction: results from the Olmsted County study of urinary symptoms and health status among men. J Urol. 2007 Apr;177(4):1438-42. PubMed PMID: 17382749. eng.
3. Malavige LS, Levy JC. Erectile dysfunction in diabetes mellitus. J Sex Med. 2009 May;6(5):1232-47. PubMed PMID: 19210706. eng.
4. Malavige LS, Jayaratne SD, Kathriarachchi ST, Sivayogan S, Fernando DJ, Levy JC. Erectile dysfunction among men with diabetes is strongly associated with premature ejaculation and reduced libido. J Sex Med. 2008 Sep;5(9):2125-34. PubMed PMID: 18624974. eng.
5. El-Sakka AI, Tayeb KA. Erectile dysfunction risk factors in noninsulin dependent diabetic Saudi patients. J Urol. 2003 Mar;169(3):1043-7. PubMed PMID: 12576842. eng.
6. Sasaki H, Yamasaki H, Ogawa K, Nanjo K, Kawamori R, Iwamoto Y, et al. Prevalence and risk factors for erectile dysfunction in Japanese diabetics. Diabetes Res Clin Pract. 2005 Oct;70(1):81-9. PubMed PMID: 16126126. eng.
7. Feldman HA, Goldstein I, Hatzichristou DG, Krane RJ, McKinlay JB. Impotence and its medical and psychosocial correlates: results of the Massachusetts Male Aging Study. J Urol. 1994 Jan;151(1):54-61. PubMed PMID: 8254833. eng.
8. Penson DF, Latini DM, Lubeck DP, Wallace KL, Henning JM, Lue TF, et al. Do impotent men with diabetes have more severe erectile dysfunction and worse quality of life than the general population of impotent patients? Results from the Exploratory Comprehensive Evaluation of Erectile Dysfunction (ExCEED) database. Diabetes Care. 2003 Apr;26(4):1093-9. PubMed PMID: 12663579. eng.
9. Goldstein I, Lue TF, Padma-Nathan H, Rosen RC, Steers WD, Wicker PA. Oral sildenafil in the treatment of erectile dysfunction. Sildenafil Study Group. N Engl J Med. 1998 May;338(20):1397-404. PubMed PMID: 9580646. eng.
10. Lewis RW, Fugl-Meyer KS, Corona G, Hayes RD, Laumann EO, Moreira ED, et al. Definitions/epidemiology/risk factors for sexual dysfunction. J Sex Med. 2010 Apr;7(4 Pt 2):1598-607. PubMed PMID: 20388160. eng.
11. Duckworth W, Abraira C, Moritz T, Reda D, Emanuele N, Reaven PD, et al. Glucose control and vascular complications in veterans with type 2 diabetes. N Engl J Med. 2009 Jan;360(2):129-39. PubMed PMID: 19092145. eng.
12. Romeo JH, Seftel AD, Madhun ZT, Aron DC. Sexual function in men with diabetes type 2: association with glycemic control. J Urol. 2000 Mar;163(3):788-91. PubMed PMID: 10687978. eng.
13. Roth A, Kalter-Leibovici O, Kerbis Y, Tenenbaum-Koren E, Chen J, Sobol T, et al. Prevalence and risk factors for erectile dysfunction in men with diabetes, hypertension, or both diseases: a community survey among 1,412 Israeli men. Clin Cardiol. 2003 Jan;26(1):25-30. PubMed PMID: 12539809. eng.
14. Matfin G, Jawa A, Fonseca VA. Erectile dysfunction: interrelationship with the metabolic syndrome. Curr Diab Rep. 2005 Feb;5(1):64-9. PubMed PMID: 15663920. eng.
15. Giugliano F, Maiorino M, Bellastella G, Gicchino M, Giugliano D, Esposito K. Determinants of erectile dysfunction in type 2 diabetes. Int J Impot Res. 2010 2010 May-Jun;22(3):204-9. PubMed PMID: 20147958. eng.
16. De Angelis L, Marfella MA, Siniscalchi M, Marino L, Nappo F, Giugliano F, et al. Erectile and endothelial dysfunction in Type II diabetes: a possible link. Diabetologia. 2001 Sep;44(9):1155-60. PubMed PMID: 11596671. eng.
17. Thomas GN, Tomlinson B, Abdullah AS, Yeung VT, Chan JC, Wong KS. Association of erectile dysfunction with cardiovascular risk factors and increasing existing vascular disease in male chinese type 2 diabetic patients. Diabetes Care. 2005 Aug;28(8):2051-3. PubMed PMID: 16043759. eng.

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18. Cho NH, Ahn CW, Park JY, Ahn TY, Lee HW, Park TS, et al. Prevalence of erectile dysfunction in Korean men with Type 2 diabetes mellitus. Diabet Med. 2006 Feb;23(2):198-203. PubMed PMID: 16433719. eng.
19. Lu CC, Jiann BP, Sun CC, Lam HC, Chu CH, Lee JK. Association of glycemic control with risk of erectile dysfunction in men with type 2 diabetes. J Sex Med. 2009 Jun;6(6):1719-28. PubMed PMID: 19473477. eng.
20. Al-Hunayan A, Al-Mutar M, Kehinde EO, Thalib L, Al-Ghorory M. The prevalence and predictors of erectile dysfunction in men with newly diagnosed with type 2 diabetes mellitus. BJU Int. 2007 Jan;99(1):130-4. PubMed PMID: 17026597. eng.
21. Zheng H, Fan W, Li G, Tam T. Predictors for erectile dysfunction among diabetics. Diabetes Res Clin Pract. 2006 Mar;71(3):313-9. PubMed PMID: 16174541. eng.
22. Shiri R, Ansari M, Falah Hassani K. Association between comorbidity and erectile dysfunction in patients with diabetes. Int J Impot Res. 2006 2006 Jul-Aug;18(4):348-53. PubMed PMID: 16307007. eng.
23. Rosen RC, Cappelleri JC, Smith MD, Lipsky J, Peña BM. Development and evaluation of an abridged, 5-item version of the International Index of Erectile Function (IIEF-5) as a diagnostic tool for erectile dysfunction. Int J Impot Res. 1999 Dec;11(6):319-26. PubMed PMID: 10637462. eng.
24. Herzog R, Álvarez-Pasquin MJ, Díaz C, Del Barrio JL, Estrada JM, Gil Á. Are healthcare workers' intentions to vaccinate related to their knowledge, beliefs and attitudes? A systematic review. BMC Public Health. 2013;13:154. PubMed PMID: 23421987. Pubmed Central PMCID: PMC3602084. eng.
25. Goyal A, Singh P, Ahuja A. Prevalence and Severity of Erectile Dysfunction as Assessed by IIEF-5 in North Indian Type 2 Diabetic Males and Its Correlation with Variables. Journal of Clinical and Diagnostic Research JCDR. 2013 Dec;7(12):2936-8. PubMed PMID: 24551679. Pubmed Central PMCID: PMC3919388. English.
26. Gratzke C, Angulo J, Chitaley K, Dai YT, Kim NN, Paick JS, et al. Anatomy, physiology, and pathophysiology of erectile dysfunction. J Sex Med. 2010 Jan;7(1 Pt 2):445-75. PubMed PMID: 20092448. eng.
27. Wing RR, Rosen RC, Fava JL, Bahnson J, Brancati F, Gendrano Iii IN, et al. Effects of weight loss intervention on erectile function in older men with type 2 diabetes in the Look AHEAD trial. J Sex Med. 2010 Jan;7(1 Pt 1):156-65. PubMed PMID: 19694925. eng.
28. Hecht MJ, Neundörfer B, Kiesewetter F, Hilz MJ. Neuropathy is a major contributing factor to diabetic erectile dysfunction. Neurol Res. 2001 Sep;23(6):651-4. PubMed PMID: 11547937. eng.
29. Ledda A. Diabetes, hypertension and erectile dysfunction. Curr Med Res Opin. 2000;16 Suppl 1:s17-20. PubMed PMID: 11329816. eng.
30. Esposito K, Giugliano F, Ciotola M, De Sio M, D'Armiento M, Giugliano D. Obesity and sexual dysfunction, male and female. Int J Impot Res. 2008 2008 Jul-Aug;20(4):358-65. PubMed PMID: 18401349. eng.
31. Seftel AD, Sun P, Swindle R. The prevalence of hypertension, hyperlipidemia, diabetes mellitus and depression in men with erectile dysfunction. J Urol. 2004 Jun;171(6 Pt 1):2341-5. PubMed PMID: 15126817. eng.
32. Cao S, Yin X, Wang Y, Zhou H, Song F, Lu Z. Smoking and risk of erectile dysfunction: systematic review of observational studies with meta-analysis. PLoS One. 2013;8(4):e60443. PubMed PMID: 23573257. Pubmed Central PMCID: PMC3616119. eng.
33. Cheng JY, Ng EM, Ko JS, Chen RY. Physical activity and erectile dysfunction: meta-analysis of population-based studies. Int J Impot Res. 2007 2007 May-Jun;19(3):245-52. PubMed PMID: 16929337. eng.
34. De Berardis G, Franciosi M, Belfiglio M, Di Nardo B, Greenfield S, Kaplan SH, et al. Erectile dysfunction and quality of life in type 2 diabetic patients: a serious problem too often overlooked. Diabetes Care. 2002 Feb;25(2):284-91. PubMed PMID: 11815497. eng.

For Proof

35. Gandaglia G, Briganti A, Jackson G, Kloner RA, Montorsi F, Montorsi P, et al. A systematic review of the association between erectile dysfunction and cardiovascular disease. Eur Urol. 2014 May;65(5):968-78. PubMed PMID: 24011423. eng.

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