Influence of metabolic dysregulation in pre ulcerative phase of diabetic foot

Article · October 2012

CITATIONS
4

READS
48

1 author:

Brankica Krstevska
Ss. Cyril and Methodius University in Skopje
81 PUBLICATIONS **317** CITATIONS

SEE PROFILE

Influence of metabolic dysregulation in pre ulcerative phase of diabetic foot

Authors: Ahmeti I[1], Bogoev M[1], Petrovski G[1], Milenkovic T[1], Krstevska B[1], Taravari A[2]

The Journal of Diabetic Foot Complications, 2012; Volume 4, Issue 1, No. 2, Pages 6-12

Abstract:

Aim. To estimate the impact of metabolic disturbances in type 2 diabetic patients (T2DM) – glucose regulation, obesity, dyslipidemia, hypertension and risk for ulceration in the preulcerative phase of the diabetic foot syndrome (DFS).

Materials and methods. In this prospective study 100 T2DM patients were evaluated for 1 year. The following parameters were estimated: duration, smoking habits, BMI, BP, HbA1c, TG, HDL, LDL, fundoscopy and measurements for risk score of DFS. Groups were stratified according to measurements : 0 – low risk, 1 – medium risk, 2- high risk, and 3 – very high risk.

Results. Out of 100 patients, 53% were female and 47% male. Mean duration of T2DM was 10.47 ± 4.77 years. Diabetes duration up to 10 years included 52% of subjects and 48 % had a duration of more than 10 years. Forty-three percent were smokers , of which 77.4% were male and 22.6% female. Results of measurements for risk score stratifications are in visit 1 (V1): score 0 - 29 %, score 1 – 35%, score 2-18% and score 3 – 18% and after 12 months in visit 2 (V2) score 0- 17 %, score 1 – 39%, score 2-19% and score 3 – 25%. BMI was recorded as follows: normal (18 -25 kg/m2) 14%, overweight (25-30 kg/m2) 71% and obese (>30 kg/m2) 15% of patients. Mean HbA1c in V1 according the risk score is: 0 - =7.6%, 1- 7.9%, 2 – 8.5% and 3- 8.2% (p<0,005), and in V2: score 0- 7.26%, score 1-7.46%, score 2-7.54% and score 3-7.54%. Systolic BP categorical scores were measured: score 0 – 136 mmHg, 1 – 142 mmHg, 2 – 145 mmHg, 3 – 142 mmHg. Mean levels of TG scores were: 0-1.97 mmol/L, 1- 2.37 mmol/L, 2- 2.3 mmol/L, 3- 2.6 mmol/L. Mean levels of HDL: 0 – 1.06 mmol/L, 1 – 1.02 mmol/L, 2 – 0.97 mmol/L, 3 – 1,00 mmol/L. Mean levels of LDL: 0 – 3.69 mmol/L, 1 – 4.27 mmol/L, 2 – 4.05 mmol/L 3 – 4.09 mmol/L. Diabetic retinopathy (DR) in V1 was present with 68% - 53% non proliferative and 15% proliferative. In V2, DR was present in 72% of which 51% was non-proliferative and 21% proliferative.

Conclusion: Suboptimal management of T2DM – high HbA1c, high BP, High TG and high LDL, are multiple factors for early appearance of DFS and have the impact of early progression from low to high score for foot ulceration. In T2DM, patients with duration more than 10 years , HbA1c>8%, TG>2.2 mmol/L, HDL<1.04 mmol/L , LDL>4 mmol/L have a high risk (2) or very high risk (3) score for ulceration.

Key words: Metabolic dysregulation, diabetic foot, preulcerative phase

Abbreviations: BMI (Body mass index), BP (Blood pressure), HbA1c (Glycosylated Hemoglobin A1c), TG (Tryglicerides), HDL (High density lipoprotein), LDL (Low density lipoprotein), ABI (Ankle brachial index)

Corresponding author:

Ass. Dr Irfan Ahmeti
University Clinic of Endocrinology, Diabetes and metabolic disorders, Skopje, Macedonia

Email: *iahmeti@yahoo.com*
irfana@endocrinology.org.mk

Affiliations:

1. University Clinic of Endocrinology, diabetes and metabolic disorders, Skopje. Macedonia

2. University Clinic of Neurology, Skopje. Macedonia

Introduction

Diabetes is a chronic metabolic disease characterized by micro and macro vascular complications. With a global prevalence of 5-6%, the number of people with diabetes in the world according to the International Diabetes Federation (IDF) is 285 million and by the year 2030 is expected to be 438 million.[1] Also, with the growth in prevalence of diabetes and with the longer life expectancies, the number of chronic diabetes complications also grows. One of the parameters for good glucose regulation, according IDF recommendations, is HbA1c<7% which delays chronic complications and prevents comorbidity, invalidity and mortality. Concurrently, it is necessary to prevent risk factors such as dyslipidemia, high blood pressure, and smoking, all of which are responsible for atherogenesis of blood vessels. Unfortunately, it is extremely difficult to stop the progression of chronic diabetes complications. Over the course of time they become the main problem in the treatment of diabetes and are responsible for deterioration of quality of life. Macro vascular complications such as coronary artery disease (CAD), cerebrovascular disease (CVD) and peripheral artery disease (PAD) are 2-4 times more frequent in people with diabetes. Micro vascular complications, diabetic retinopathy, nephropathy and neuropathy are also 2-4 times more common in diabetic persons.

Diabetic foot syndrome (DFS) is a complex heterogenic disorder that affects 15 -20% of people with type 2 diabetes (T2DM) and is responsible for most of the amputations in developed countries[2]. DFS consists of clinical manifestations as well as neurological, vascular and immunological impairments characterized by different aetiologies and pathologic mechanisms. T2DM patients have a 25 times higher risk of lower extremity amputation than general population.[3] In a global perspective, 70% of all non traumatic amputations are due to diabetes. Distal peripheral neuropathy (DPN) has been estimated to be present in 50%, while PAD affects 40%. [4] These two conditions frequently are present together in DFS. The importance of measurements of associated risk factors in DFS is to prevent ulcerations and amputations. These measurements for practical and clinical use are categorized in three phases: 1- pre ulcerative, 2- ulcerative and 3- post ulcerative phase. In the pre ulcerative phase, the focus is to identify risk factors, to quantify with a risk score, and finally, to plan for preventive interventions. Evaluation of risk score has the purpose of classifying the risk for diabetic foot ulceration (DFU). According to the International Consensus Group on the Diabetic Foot (ICGDF), the risk score for ulceration is classified in 4 groups: 0- low risk (no neuropathy), 1- medium (neuropathy, no deformity, no PAD), 2 – high (neuropathy, PAD and/or deformity) and 3 – very high risk (previous ulcer or amputation). Its purpose is to prevent and appropriately delay progression from one phase to other phases of diabetic foot disease.[4]

The aims of the current study were (1) to estimate the impact of metabolic effects in type 2 diabetic patients in the pre ulcerative phase according to risk score and (2) to calculate the prevalence of DFS in the pre ulcerative phase in hospitalized patients.

Material and Methods

This is a prospective, observational study that included 100 T2DM patients hospitalized at the University Clinic of Endocrinology - Skopje. Inclusion criteria were: type 2 DM after 1 year of diagnosis, and both male and female between 35-75 years of age. Exclusion criteria were: neuropathy of non diabetic aetiology, use of drugs for neuropathy, ABI>1.3 (Monckeberg's sclerosis), and persons aged >75 years. According to duration of T2DM, patients were divided into 3 groups: up to 5 years, between 5-10 years and more than 10 years.

At enrolment (visit 1 – V1) each patient underwent history and physical examination, laboratory investigations, (glycaemia with Glucose Analyser 2 - Beckman, and HbA1c ion changing chromatography, Drew), CBC (complete blood count), and Lipid profile. Evaluation of measurements in the pre-ulcerative phase of the DFS is done at the diabetic foot outpatient clinic and patients are grouped according their risk score for ulceration. According to these results, a plan for preventive intervention was developed including the frequency of visits. Ophthalmologic control was also performed for each patient at the ophthalmologic outpatient clinic. After 12 months (V2), metabolic parameters and measurements of DFS were done. Progression from low to high risk score was also registered.

Measurements of DFS in the preulcerative phase were systematically classified according the International Consensus on the Diabetic Foot (ICGDF).

Results

The group of 100 patients with T2DM had an average age of 60 ± 8 years (35-75). Risk score stratification for age was: for score 0 – 53.8 yrs, score 1- 59.5 yr, score 2- 64.7yr, and score 3- 63.3 years. From these results it can be seen that there is statistical significance between the risk factor age and risk score for ulceration. (p=0.04). Distribution of sex was 53% female and 47% male: Kruskal-Wallis test for gender shows that male patients have a higher risk score for ulceration than females (X2 = 8.232, df=3. p<0.05). Average duration of T2DM was10.47 ± 4.77 years. The risk score in the pre ulcerative phase of DF is strongly associated with the duration of diabetes (Kruskal-Wallis test: X2= 8.930, df = 3, p<0.05).

In this study, there was not a statistically significant association between smoking and risk score for ulceration, probably because of a small number of patients who were smokers (p=0.595). Of a total 45% of participants who were smokers, 77.4% of these were men and 22.6% women. BMI in the examined group was 27.61 ± 3.22 kg/m2. Results did not show a statistical significance for BMI between score groups at risk for foot ulceration, although in all groups the patients were overweight (BMI> 25). The BMI of participants was as follows: normal (18 -25 kg/m2)14%, overweight (25-30 kg/m2) 71% , and obese (>30 kg/m2) 15% of patients.

Systolic blood pressure on average was more than 130 mmHg, but did not show statistically significant differences between risk score groups in V1 (p=0.190) (see Figure 1) and V2 (p=0.453).

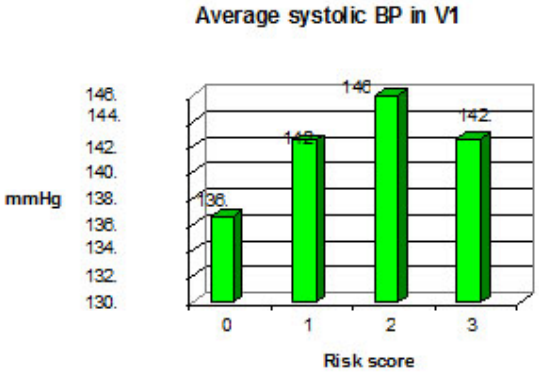

Figure 1: Average systolic BP in the risk score groups of DFS at visit 1 (V1)

The analysis of the test values of HbA1c, showed statistically significant differences between scores groups in V1 (X2= 8.653, df = 3, p = 0.034). There were 18% of the total number of patients with HbA1c <7%, 43% had HbA1c 7-8%, and 49% of patients had HbA1c> 8%. After 12 months (V2), because of small differences in average HbA1c between groups, there was no statistical significance between groups and HbA1c score (V2 : X2 = 2.178, df = 3, p = 0.53). *(Table 1)*

Table 1. Mean HbA1c in the pre ulcerative phase of DFS (Kruskal Wallis test)

REPORT						
V1T HbA1c	P=0.03			V2 HbA1c		P=0.53
V1Score risk	Mean	N	Std. Dev.	Mean	N	Std. Dev.
0-absent/minimal	7.61	29	1.03	7.25	17	.41
1-medium	8.00	34	1.21	7.46	39	.56
2- high	8.42	19	1.32	7.54	19	.70
3-very high	8.18	18	1.39	7.54	25	.58
Total	8.00	100	1.23	7.46	100	.57

Examination of the lipid profile in the group of patients at risk for ulceration did not show statistical significance in the results of TG, LDL and HDL cholesterol between the risk scores. However, patients in V1 had a higher average TG than those in V2. *(Table 2)*

Table 2. Average TG in V1 and V2. Kruskal Wallis test: no statistically significant difference in the distribution of frequencies of patients with TG in different score groups

REPORT						
V1TG	P=0.49			V2 TG		P=0.16
V1Score risk	Mean	N	Std. Dev.	Mean	N	Std. Dev.
0-absent/minimal	1.96	29	.53	1.92	17	.38
1-medium	2.36	34	1.29	2.08	39	.41
2- high	2.30	19	.72	1.98	19	.38
3-very high	2.62	18	2.01	2.23	25	.65
Total	2.28	100	1.22	2.07	100	.48

The frequency of patients with TG <2.2 mmol / L in patients with risk score 0 and 1 is 47%, while it is 21% for risk score groups 2 and 3. Patients with values of TG> 2.2 mmol / L were distributed in the risk score groups equally.

LDL cholesterol was higher in groups with score 1, 2 and 3 (LDL> 4 mmol / L).

Values of HDL cholesterol did not differ by group risk score although a somewhat lower value is noted in group 2 and 3.

However, differences between negative and positive Wilcoxon rank test shows statistically significant differences between risk score groups V1 and V2 (for TG p=0.011, For LDL p<0.001 and for HDL p=0.013). Values are decreased on average 0.2 mmol / L from V1 to V2 for TG, for LDL 0.5 mmol / L and are increased for HDL by 0.03 mmol / L.

In this group of patients, diabetic retinopathy was present with 68% - 53% having non-proliferative and 15% proliferative retinopathy. By risk score at visit 1 retinopathy was present as follows: score 0 – 15% non-proliferative and 0% proliferative, score 1- 18% non-proliferative and 1% proliferative, score 2 -11% non-proliferative and 6% proliferative, and score 3 - 9% non-proliferative and 8% proliferative. After 12 months (V2) diabetic retinopathy was present in 72% of which 51% was non-proliferative and 21% proliferative. In scored groups diabetic retinopathy was present at V2 as follows: score 0 – 6% non-proliferative and 0% proliferative, score 1 - 22% non-proliferative and 3% proliferative, score 2 - 10% non-proliferative and 7% proliferative, and score 3 - 13% non-proliferative and 11% proliferative.

Discussion

Suboptimal metabolic control of diabetes is associated with the progression of chronic macro- and microvascular complications. The impact of poor glucose control, dyslipidaemia, hypertension, smoking, and duration of diabetes is associated with chronic complications of diabetes. In our population, diabetic foot syndrome - preulcerative phase was represented in 61.7% of participants. The risk score in V1 was: score 0- 29%, score 1- 34%, score 2- 19%, score 3- 18%, while in V2: the risk score was 0- 17%, risk 1- 39%, risk 2- 19%, and risk 3- 25%. The prevalence and incidence of risk score for ulceration in Mexican Americans in a cohort study amounted to: risk 0 - 58.6%, risk level 1 - 5.9%, risk level 2- 24.7%, risk level 3 - 10.8%. [5] Diabetes is the leading cause of neuropathy in the Western world. Data from the U.S shows that ten to seventy percent of patients with diabetes have some form of peripheral neuropathy.[6] Distal sensory polyneuropathy in our study group was present 58% in V1 and 68% in V2 as established by history, and testing with monofilament and tuning fork.

Peripheral arterial disease in different studies have differing prevalences, and ranges between 22-73%. Prompers et al. (2008) in the EURODIALE study, found a 49% prevalence of PAD in patients with the diabetic foot syndrome.[7] In our study, PAD was present in 41.7% of patients with T2 DM. Out of 100 T2DM patients, critical limb ischemia (ABI<0,6) was found in 8.3% and ABI 0.9-0.6 was measured in 31.4% PAD when measured by ABI in V1 is registered in 41.7% and in V2 in 46% - ABI 0.9-0.6 in 35%, and ABI<0.6 in 11%.

The average duration of diabetes in our patients with diabetic foot syndrome was 10.47 years (*8.6 years in score 0 and 12.6 years in score 3*). This confirms the fact that with longer duration of diabetes, patients develop a higher risk score for foot ulceration. Duration of diabetes in patients investigated for diabetic peripheral neuropathy in the literature ranges from 8.4 to 12.49 years. [8] The patients in our study showed almost equal gender representation of men and women with DFS. Distribution by gender is 53% women and 47% males (Kruskal Wallis test X2 = 8.232, df = 3. p <0.05). The groups with risk score 3 show a higher percentage of DFS in men (13%) compared with women (5%). This difference is probably due to the greater number of male smokers in this risk group (77.4% of patients were men and 22.6% women of total smokers) and also probably due to lower ABI (<0.9) in the group with risk score 3, (72% male vs. 28% female in V1 and 64% male vs 36% female in V2). If we take into account the number of cigarettes smoked per day, it is evident that 90% of males and only10% of females smoked more than 15 cigarettes / day. Gender distribution was similar to that found in the literature for diabetic neuropathy, 47.8% men and 52.2 % women. [9]

BMI showed no statistical significance in the pre ulcerative phase risk score groups (p> 0.05), although the 2008 study of Pinzur et al. shows that morbidly obese patients are much more likely to develop diabetic foot ulcers than non-obese patients. [10]

Systolic BP on average was more than 130 mmHg, but did not show statistical significance between risk score groups in V1 (p=0.190) and V2 (p=0.453). Differences in negative and positive Wilcoxon signed Ranks Test showed that there was statistical significance in risk score groups V1 (140 mmHg) and V2 (134 mmHg) for the risk factor systolic BP (p<0.01). In the UKPDS study, Stratton et al. conclude that each 10 mmHg decrease in updated mean systolic BP was associated with reduction in risk of 12% for any complication related to diabetes.[11] In visit 1 we note that HbA1c has statistical significance with the risk score in the pre ulcerative phase of DFS. At visit 1, those with HbA1c> 8% included 49% of our patients. After 12 months, at visit 2, there was no significant difference between groups, although in V2 we noted a decrease in HbA1c by 0.54% compared to risk score groups in V1. This suggests that improvements in HbA1c from V1 to V2 do not prevent progression of risk for foot ulceration for a period of 12 months.

Callaghan et al (2011) in the DISTANCE study concluded that hypertriglyceridemia is a significant risk factor for LEA in diabetic patients.[12] In our study, values of TG, LDL and HDL cholesterol did not show statistical significance for DFS in the pre ulcerative phase for this period of 12 months, although a value of TG <2.2 mmol / L is common in patients with risk score 0 and 1 (47%), while for risk score 2 and 3 it is much less frequent at only 21%. Patients with values of TG> 2.2 mmol / L are noted in the risk score groups equally. LDL cholesterol is higher in groups 1, 2, and 3, (LDL> 4 mmol / L). Values of HDL cholesterol did not differ by risk score groups although somewhat lower values are noted in group 2 and 3.

However, differences between negative and positive Wilcoxon ranking test shows statistical significance between risk score groups in V1 and V2 (for TG p=0.011, for LDL p=0.000 and for HDL p=0.013). TG values are decreased approximately 0.2 mmol/L from V1 to V2, for LDL 0.5 mmol / L and for HDL they are increased 0.03 mmol/L.

Association between DFS, risk score for foot ulceration and diabetic retinopathy is statistically significant. Groups with risk score 0 and 1 have more non-proliferative retinopathy and groups with score 2 and 3 have more proliferative retinopathy (Cross tabulation. Kruskal Wallis test p<0.01). Independent factors associated with retinopathy were duration of diabetes, systolic blood pressure, and HbA1c. The U.K. Prospective Diabetes Study showed a 34% reduction in the progression of retinopathy with tighter blood pressure control and glycemic control.[13]

Conclusion

Inadequate management of Type 2 diabetes – high HbA1c, high BP, High TG and high LDL, are multiple factors for early appearance of the DFS and had the impact of early progression from low to high score for foot ulceration.

The prevalence of diabetic foot syndrome DFS in the pre ulcerative phase is higher than in other studies probably because of our patient group (in-patients), and duration of diabetes more than 10 years, HbA1c>8%, TG>2,2 mmol/L, HDL<1,04 mmol/L , LDL>4 mmol/L. Our study has shown that such patients tend to have a high risk (score 2) or very high risk (score 3) for ulceration.

REFERENCES

1. http://atlas.idf-bxl.org/content/diabetes/

2. The International Consensus on the Diabetic Foot (IWGDF): The diabetic foot: a challenge for professionals and policymakers. Noordwijkerhout, the Netherlands. 2007

3. The International Consensus on the Diabetic Foot. Practical guidelines on the management and prevention of the diabetic foot. Noordwijkerhout, the Netherlands. 2007

4. Piagessi et al. Measurements in diabetic foot. Wounds. 2005;17(9):247-254. 2005 Health Management Publications, Inc.

5. Lavery LA, Armstrong DG, Wunderlich RP, Jeffrey T, Boulton AJM. Diabetic Foot Syndrome. Evaluating the prevalence and incidence of foot pathology in Mexican Americans and non-Hispanic whites from a diabetes disease management cohort. Diabetes Care May 2003 vol. 26 no. 5 1435-1438

6. (www.wrongdiagnosis.com/d/diabetic_neuropathy/prevalence.htm).

7. L. Prompers, N. Schaper, J. Apelqvist, M. Edmonds, E. Jude, D. Mauricio, L. Uccioli, V. Urbancic, K. Bakker, P. Holstein, A. Jirkovska, A. Piaggesi, G. Ragnarson-Tennvall, H. Reike, M. Spraul, K. Van Acker, J. Van Baal, F. Van Merode, I. Ferreira, and M. Huijberts. Prediction of outcome in individuals with diabetic foot ulcers: focus on the differences between individuals with and without peripheral arterial disease. The EURODIALE Study. Diabetologia. 2008 May; 51(5): 747–755.

8. Meijer J.W.G., van Sonderen E, Blaauwwiekel E.e., Smit A.J., Groothoff J.W, Eisma W.H, Links T.P. Diabetic neuropathy examination; a hierarchical Scoring system to diagnose distal polyneuropathy in diabetes. Diabetes Care 2000;23(6): 750-753

9. Fedele, D.; Giugliano, D. Peripheral diabetic neuropathy: Current recommendations and future prospects for its prevention and management. Drugs. SEP 1997;54(3):414-421.

10. Pinzur M, Freeland R, Juknelis D. The association between body mass index and foot disorders in diabetic patients. Foot Ankle Int. 2005 May; 26(5): 375-7

11. Irene M Stratton, Amanda I Adler, H Andrew W Neil, David R Matthews, Susan E Manley,Carole A Cull, David Hadden, Robert C Turner, Rury R Holman on behalf of the UK Prospective Diabetes Study. Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study. BMJ Aug 2000; Vol. 321.

12. Callaghan BC, Feldman E, Liu J, Kerber K, Pop-Busui R, Moffet H, Karter AJ. Tryglicerides and amputation risk in patients with diabetes: ten-year follow-up in the DISTANCE study. Diabetes Care. 2011 Mar;34(3):635-40. Epub 2011 Feb 1.

13. UK Prospective Diabetes Study (UKPDS) Group: Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 38. BMJ 317:703–713, 1998