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ASSOCIATION BETWEEN TYPE 2 DIABETES AND DIFFERENT POORLY CONTROLLED FACTORS

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Abstract

The main objective of this study is to show the association between diabetic complications and different factors poorly controlled. The factors are body mass index (BMI), systolic blood pressure (SBP), diastolic blood pressure (DBP), age, gender, duration of diabetes, hypertension, coronary heart disease (CHD), smoking, nephropathy, retinopathy, neuropathy, cataract, insulin, oral drugs, exercise and metformin. The forest plot has been drawn to display the counts, risk estimates and their associated confidence intervals. Random effects model has been used to combine the data. Heterogeneity among studies is assessed using the Q statistic and I^2 index. In Bangladesh Institute of Research and Rehabilitation for Diabetes, Endocrine and Metabolic Disorders (BIRDEM) data, BMI, gender, duration of diabetes, retinopathy, insulin, oral drugs, metformin, and adherence to exercise have shown significant result. In diabetology data (a dataset of six studies worldwide), BMI, age, gender, hypertension, CHD, neuropathy, retinopathy, nephropathy, oral drugs and adherence to exercise have also shown significant result. BMI, age, gender, retinopathy, use of insulin, oral drugs and physical exercise are found to be significantly different for these two sets of data.

Key words: Type 2 diabetes, Poorly controlled factors, Diabetic complications, Meta-analysis.

Introduction

Diabetes mellitus is one of the most common chronic diseases in nearly all countries. It continues to increase in numbers. It is also a global healthcare challenge, both in industrialized and developing nations. Estimates of future prevalence indicate that diabetes is reaching epidemic proportions worldwide, with between 5 and 10% of the world population affected.

In December 2006, the world's governments unanimously passed a United Nations Resolution on diabetes, recognizing that diabetes is a chronic, debilitating and costly disease and agreed to act on diabetes prevention, treatment and care. That Resolution was spearheaded by the International Diabetes Federation and is the mandate for the Federation's Strategic Plan 2010-2012 and beyond.

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More than 300 million people have diabetes representing 6% of the world's adult population and the number is increasing fast everywhere. An additional seven million people are developing the disease each year. By 2025, the federation estimates that 380 million people will have diabetes, with the greatest burden falling on low and middle-income countries. It is causing premature death in both children and adults. The cost of diabetes is challenging the health systems even in the wealthiest countries. In low-income countries, it threatens to reverse health and economic progress made towards the Millennium Development Goals. In most cases diabetes can be prevented, and where it cannot be prevented, it can be treated so lives can be saved and those affected can continue their lives uninterrupted.

Materials and Methods

Data Description and Management: Data of 2724 diabetes patients were collected retrospectively from BIRDEM, Bangladesh. It is a full follow up data. Patients are entered in the study from January to December in 1984 and observed them till 1998. For the study purpose last observation of each patient was considered. From the record sheet of BIRDEM few variables were selected for the study purpose such as age, sex, height, weight, SBP, DBP, duration of diabetes, blood glucose level, diabetic complications, hypertension and treatments of diabetes. In diabetic complications, CHD, nephropathy, retinopathy and cataract are considered as complicating factors. Insulin, oral drugs, physical exercise, metformin etc are considered as treatment factors.

The variables BMI, SBP, DBP, height, weight are considered as continuous variables Age, gender, smoking habit, duration of diabetes, hypertension, nephropathy, retinopathy, neuropathy, insulin, physical exercise, oral drugs, blood glucose level are considered as binary variables. Age is categorized as two groups as, age <60 and ≥ 60 years. Duration of diabetes is categorized into two groups as duration <5 years and duration ≥ 5 years. Hypertension is categorized as two groups as hypertensive patient (both systolic and diastolic pressure above 140 and 90 respectively) and non hypertensive patient (systolic or diastolic pressure below 140 or 90 respectively). In this study, blood glucose level is the dependent variable of interest. Complications are observed in two groups based on blood glucose level (HbA_1c). When $HbA_1c \geq 7$, they are considered as poorly controlled group and when $HbA_1c < 7$, they were considered as controlled group.

Three studies are used to perform meta-analysis technique such as first quartile, second quartile and third quartile from this data set. First quartile study considered patients who entered in the study between January 1 to April 30 (1984-1998). Second quartile study considered patients who entered in the study during May 1 to August 31 (1984-1998). Third quartile study considered patients who entered in the study between September 1 to December 31 (1984-1998). For each of the study the last follow up of each patient is considered.

To make comparison between these two sets of BIRDEM and Diabetology (Hassan 2011) the data are considered as two subgroups. BIRDEM data consists of first quartile, second quartile and third quartile study data. Diabetology data consists of the eleven studies worldwide. In this paper it has been shown how diabetic complications are associated with different covariates. To observe the association six independent studies are considered. These studies are made from follow up data set that was collected from BIRDEM hospital and each of the study considered the last follow up of each patient. Here every two month is treated as individual study.

All studies conducted on people with type 2 diabetes irrespective of region or languages are included. This includes case control, cohort and cross-sectional studies which make an attempt to address the factors, responsible for poor control of diabetes. The studies conduct on people with type 1 and gestational diabetes are excluded. For analysis purpose different statistical software are used, such as R meta package, SPSS and Excel.

Statistical Analysis: Meta-analyses have been performed using odds ratios (ORs) for binary outcomes and weighted mean differences (WMDs) for continuous outcome measures. A slightly amended estimator of OR was used to avoid the computation of reciprocal of zeros among observed values/counts in the calculation of the original OR. Random effects model, developed by using the inverse variance weighted method approach has been used to combine the data. Heterogeneity among studies is assessed using the Q statistic, (Cochran 1954) and I^2 index (Higgins and Thompson 2002). If the observed value of Z is larger than the critical value at a given significant level, in this case 0.05, we conclude that the outcome variable is statistically significant. For the computations of the confidence intervals estimates of mean and standard deviation are required. However, some of the published clinical trials did not report the mean and standard deviation, but rather reported the size of the trial, the median and range. Funnel plots are synthesized in order to determine the presence of publication bias in the meta-analysis. Both total sample size and precision (1/standard error) were plotted against the treatment effects- OR for the dichotomous variables and WMD for continuous variables (Sutton *et al*. 2000). All estimates are obtained using computer programs written in statistical program R. All plots are obtained using the 'meta' package in R.

Results and Discussion

In this section the association of different factors and poor control group of complications has been presented. For BIRDEM data, the factors are BMI, SBP, DBP, age, gender, duration of diabetes, hypertension, coronary heart disease (CHD), nephropathy, retinopathy, cataract, insulin, oral drugs, exercise and metformin. The result of test of heterogeneity, overall effect of each factors and the percentage of real heterogeneity of this data set are also presented. These results have been shown by the forest plot. For each of the factor results are represented in individual Tables.

For BMI and complications in Table 1, the Z-value of overall effect of BMI is 2.91 and p-value 0.003. At 5% level of significance this test is significant. Hence, it may be concluded that there is a difference in mean BMI of poorly controlled and well controlled diabetes.

The combined SMD is 0.13 and its confidence interval 0.04 to 0.22. 95% confidence interval around this estimate is not reasonably wide, indicating no uncertainty in the pooled result. According to the Cohens rules of thumb SMD less than 0.2, so it indicates very small effect on blood glucose level.

Table 1. Association between BMI and Complications.

Study	Poor control		Control		Standardize mean Difference, Fixed, 95% C.I	Standardize mean Difference, Fixed, 95% C.I
	No	Mean (S.D.)	No	Mean (S.D.)		
BMI						
First Quartile	815	23.19	264	22.90		0.08(-0.05
Second Quartile	730	(3.63)	185	(3.32)		to 0.25)
Third Quartile	756	23.51	174	22.70		0.21(0.05 to
		(3.85)		(3.31)		0.37)
Total	2301	23.50	623	23.07		0.11(-0.04
		(3.76)		(3.46)		to 0.28)
					-0.3 -0.2 -0.1 0 0.1 0.2 0.3	0.13(0.04 to 0.22)
Test for Heterogeneity: Q=1.58, p-value=0.45, $I^2 = 0\%$						
Test for overall effect: Z=2.91, p-value=0.003						

The test statistic value of heterogeneity, Q is 1.58. It is compared to a chi-squared distribution with 2 (k-1) degrees of freedom, which gives a p-value which is highly insignificant (p-0.45). Hence, it is concluded that between studies heterogeneity is insignificant, implying that the variability between study estimates is too tiny to assume that they are estimating the different underlying treatment. The I^2 statistic is 0% which implies that real heterogeneity is 0% to the total variance across the observed effect estimate.

From the results presented in Table 2, it is apparent that the z-value of overall effect of gender is 4.91 and p-value 0.0003 for gender and complications. At 5% level of significance this test is highly significant. Hence there is an association between gender and complications. That is male patient have better diabetes control as compared to females. The combined odds ratio is 0.60 and its confidence interval is 0.19 to 0.73. 95% CI around this estimate is not reasonably wide, indicating no uncertainty in the pooled result. The test statistic value of heterogeneity is 2.83. It is compared to a chi-squared distribution on 2 (k-1) degrees of freedom, which gives an insignificant p-value (p=0.24). That means the variability between study estimates is negligible. The I^2 statistic was 29.37% which implies that real heterogeneity was 29.37% to the total variance across the observed effect estimate.

Table 2. Association between Gender and Complications.

Study	Poor control		Control		Odds ratio, I, Fixed, 95% CI	Odds ratio, I, Fixed, 95% CI
	Male	Female	Male	Female		
Gender (Female)						
	530	285	201	63		0.58 (0.42
First	480	250	133	52		to 0.80)
Quartile	489	267	138	36		0.75 (0.53
Second						to 1.07)
Quartile	1499	802	472	151		0.48 (0.32
Third						to 0.71)
Quartile						
					0.5 1 2	0.60 (0.49
Total						to 0.73)
Events						
Test for Heterogeneity: Q=2.83, p-value=0.24, $I^2 = 29.37\%$						
Test for overall effect: Z=4.91, p-value = 0.0003						

For duration of diabetes and complications, the heterogeneity statistic is highly insignificant (Q=1.75, df = 2, p-value 0.42). The I^2 statistic is 0% which implies that real heterogeneity is 0% to the total variance across the observed effect estimate. The test value of overall effect of duration of diabetes is 5.17 and p-value 0.001. At 5% level of significance this test is highly significant. Hence there is an association between duration of diabetes and complications. Therefore it is concluded that less than 5 years durable diabetic patients have better diabetes control as compared to greater than 5 years durable diabetic patients. The combined odds ratio is 0.60 and its confidence interval is 0.50 to 0.72. 95% CI around this estimate is not reasonably wide, indicating no uncertainty in the pooled result (Table 3).

Table 3. Association between Duration of diabetes and Complications for BIRDEM data.

Study	Poor control		Control		Odds ratio, I, Fixed, 95% CI	Odds ratio, I, Fixed, 95% CI
	Duration < 5	Duration ≥ 5	Duration < 5	Duration ≥ 5		
Duration of diabetics (≥5 years)	216	599	90	174		0.70 (0.52 to 0.94)
First Quartile	184	546	68	116		0.58 (0.41 to 0.82)
Second Quartile	154	602	58	117		0.51 (0.36 to 0.73)
Third Quartile	554	1747	216	407		0.60 (0.50 to 0.72)
Total Events					0.5 1 2	
Test for Heterogeneity: Q=1.75, p-value=0.41, $I^2 = 0\%$						
Test for overall effect: Z=5.17, p-value=0.0001						

For retinopathy and complications, the test statistic value of Q statistic is 0.32, df = 2, p-value =0.32, which is highly insignificant (Table 4). The Z-value of overall effect of retinopathy is 1.94 and p-value 0.05. At 5% level of significance this test is significant. Hence, there is an association between retinopathy and complications. The combined odds ratio is 0.42 and its confidence interval 0.17 to 1.02. It is concluded that presence of retinopathy problem is the factor associated with poor control of diabetes. 95% CI around this estimate is not reasonably wide, indicating no uncertainty in the pooled result.

Table 4. Association between Retinopathy and Complications for BIRDEM data.

Study	Poor control		Control		Odds ratio, I, Fixed, 95% CI	Odds ratio, I, Fixed, 95% CI
	Yes	No	Yes	No		
Retinopathy (No)						
	2	813	3	261		0.21 (0.04 to 1.29)
First Quartile	8	722	2	183		1.01 (0.21 to 4.81)
Second Quartile	3	753	3	171		0.23 (0.05 to 1.13)
Third Quartile	13	2288	8	615		0.42 (0.17 to 1.02)
Total Events					0.1 0.5 1 2 10	
Test for Heterogeneity: Q=2.30, p-value=0.32, $I^2 = 13.35\%$						
Test for overall effect: Z=1.94, p-value =0.05						

As regard the insulin and complication, the test value of overall effect (Z) of insulin is 9.63 and p-value 0.0001 (Table 5). At 5% level of significance this test is highly significant. Hence, there is an association between insulin and complications. The combined odds ratio is 3.65 and its confidence interval ranged from 2.82 to 4.74. Hence insulin user patient have 3.65 times more control on diabetes complications as compared to poorly controlled patient. 95% CI around this estimate was not reasonably wide, indicating no uncertainty in the pooled result. The Q statistic was highly insignificant (Q=1.66, df=2, p-value=0.43). The I^2 statistic is 0% which implies that real heterogeneity was 0% to the total variance across the observed effect estimate.

Table 5. Association between Insulin and Complications for BIRDEM data.

Study	Poor control		Control		Odds ratio, I, Fixed, 95% CI	Odds ratio, I, Fixed, 95% CI
	Yes	No	Yes	No		
Insulin (No)						
First Quartile	270	545	32	233		3.74 (2.50 to 5.59)
Second Quartile	253	477	28	157		2.97 (1.93 to 4.57)
Third Quartile	221	535	14	160		4.72 (0.10 to 8.28)
Total Events	744	1557	73	550		3.65 (2.82 to 4.74)
Test for Heterogeneity: Q=1.66, p-value=0.43, $I^2 = 0\%$					0.2 0.5 1 2 5	
Test for overall effect: Z=9.63, p-value=0.0001						

For oral drugs and complications, the heterogeneity test is highly insignificant (Q=0.23, df=2, p-value=0.89). Hence, it is concluded that between studies heterogeneity is almost absent of this data set. The I^2 statistic is 0% which implies that real heterogeneity is 0% to the total variance across the observed effect estimate. The Z-value of overall effect of oral drugs is 4.25 and p-value 0.0001 (Table 6). At 5% level of significance this test is highly significant. Hence, there is an association between oral drugs and complications. The combined odds ratio is 1.54 and its CI=[1.26, 2.89]. It may be concluded that oral drugs user patients have 1.54 times more control on complications than poorly controlled patients. 95% CI around this estimate is not reasonably wide, indicating no uncertainty in the pooled result.

Table 6. Association between Oral Drugs and Complications for BIRDEM data.

Study	Poor control		Control		Odds ratio, I, Fixed, 95% CI	Odds ratio, I, Fixed, 95% CI
	Yes	No	Yes	No		
Oral drugs (No)						
First Quartile	285	530	68	196		1.55 (1.14 to 2.12)
Second Quartile	241	489	47	138		1.45 (1.00 to 2.08)
Third Quartile	270	486	44	130		1.64 (1.13 to 2.38)
Total Events	796	1505	159	464		1.54 (1.26 to 2.89)
Test for Heterogeneity: Q=0.23, p-value=0.89, $I^2 = 0\%$					0.5 1 2	
Test for overall effect: Z=4.25, p-value = 0.0001						

From Table 7 it is evident that, the test value of overall effect of exercise is 2.88 and p-value 0.001. At 5% level of significance this test is highly significant. Hence, there is an association between exercise and complications. It is suggested that patients that continue exercise regularly have better diabetes control than the other treatment user patients (OR=0.56, CI=[0.36, 0.88]). 95% CI around this estimate was reasonably wide, indicating considerable uncertainty in the pooled result. The Q statistic value is 6.52. It is compared to a chi-squared distribution on 2 (k-1) degrees of freedom and p-value of this test is 0.03 which is highly significant. Hence, it may be concluded that between studies heterogeneity is almost present in this data set. The I^2 statistic is 69.32% which implies that real heterogeneity is 69.32% to the total variance across the observed effect estimate.

Table 7. Association between Physical Exercise and Complications for BIRDEM data.

Study	Poor control		Control		Odds ratio I, Random, 95% CI	Odds ratio, I, Random, 95% CI
	Yes	No	Yes	No		
Adherence to Exercise (No)						
First Quartile	24	774	15	245		0.51 (0.26 to 0.98)
Second	16	658	13	163		0.30 (0.14 to 0.65)
Quartile	25	684	3	160		1.95 (0.58 to 6.54)
Third Quartile	65	2116	31	568		0.56 (0.36 to 0.88)
Total Events						
Test for Heterogeneity: Q=6.52, p-value=0.03, $I^2 = 69.32\%$					0.2 0.5 1 2 5	
Test for overall effect: Z=2.88, p-value =0.001						

From the results on metformin and complications (Table 8) it is apparent that the Q statistic is 0.83, p-value = 0.65 which is highly insignificant. The Z-value of overall effect of metformin is 17.27 and p-value 0.0001. At 5% level of significant this test is highly significant. Hence, there is an association between metformin and complications. The combined odds ratio is 0.16 and its confidence interval ranged from 0.13 to 0.19. Hence it can be suggested that metformin user patients have better diabetes control than the other treatment user patients.

Table 8. Association between Metformin and Complications for BIRDEM data.

Study	Poor control		Control		Odds ratio, I, Fixed, 95% CI	Odds ratio, I, Fixed, 95% CI
	Yes	No	Yes	No		
Metformin (No)						
First Quartile	80	735	102	162		0.17 (0.12 to 0.24)
Second Quartile	70	660	75	110		0.16 (0.11 to 0.23)
Third Quartile	77	679	79	95		0.14 (0.09 to 0.20)
Total Events	227	2074	256	367		0.16 (0.13 to 0.19)
Test for Heterogeneity: Q=0.83, p-value=0.65, $I^2 = 0\%$ Test for overall effect: Z= 17.27, p-value= 0.0001					0.1 0.5 1 2	

In diabetology data, BMI, age, gender, hypertension, CHD, neuropathy, retinopathy, nephropathy, oral drugs, and adherence to exercise have shown significant result. Comparison of BIRDEM patients variable-wise with that of diabetology data, BMI, age, gender, retinopathy, using of insulin, oral drugs and physical exercise are found to be different in magnitude. This might be because of the diversity of the patients of Bangladesh with that of the patients worldwide.

In this study it is found that life style modification is one of the major determinants of diabetes control. Male elderly patients with more than 60 years of age with normal BMI have found to have better control on diabetes than female. Patients with less than 5 years of diabetes have fifty percent better control as compared to greater than 5 years of diabetes (OR=0.50). Patients who continue exercise regularly have better forty four percent less complications than the patients who are not accustom to physical exercise (OR=0.56).

Patients who use insulin have 3.65 times more control on diabetes complications as compared to poorly controlled patient (OR=3.65). Oral drugs user patients have 1.54 times more control on complications than poorly controlled patients (OR=1.54).

Metformin user patients have eighty four percent more control on diabetes complications than other treatment user patients (OR=0.16).

Presence of other diseases like coronary heart disease, neuropathy and retinopathy are associated with poor control of diabetes too. However, diabetic patients can live a better life maintaining a discipline life, regular physical activity and proper medication.

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