Insulin Resistance in firstborn offspring of mother who developed diabetes later in fourth decade: Are both related to possible maternal malnutrition?

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ABSTRACT

Back grounds and Aims: Diabetes mellitus is increasing each day. We aimed to study the insulin resistance (IR) in the offspring of people with diabetes and its relation with lifestyle and clinical factors.

Methods: This is a cross sectional study of IR in offspring over the age of 18 years and having parents with diabetes. Participants already diagnosed as having diabetes, suffering from any illness or using drugs that may have altered blood sugar levels were excluded. A fasting blood sample was taken for blood glucose and serum insulin level and IR was calculated using homeostatic model assessment for IR (HOMA –IR).

Results: Forty nine participants volunteered for the study of which 24.5% were found to have IR, the cut off value of HOMA –IR being 2.48. As compared to the later born offspring, the firstborn were six times more at risk for IR (Odds ratio 6.25, P value 0.015) and after adjustment for BMI, it was seven times (Odds ratio 7.29 , P value 0.011). IR was more in offspring with maternal diabetes than with paternal one. The mean age of diagnosis of diabetes in mothers having firstborn offspring with IR was 38.5 years as compared to 48.2 years of those having firstborn offspring without IR.

Conclusion: Higher risk of IR seen in the firstborn offspring whose mother later developed diabetes at fourth decade indicate the probability of relation of both conditions with possible maternal malnutrition during the first pregnancy. Further larger studies are required focusing on these aspects.

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BACKGROUND

The incidence and prevalence of Type 2 Diabetes Mellitus (T2DM) is increasing day by day in epidemic magnitude worldwide affecting millions of people. A field survey done in Nepal showed the prevalence of diabetes mellitus and impaired glycaemia to be around 14.6% and 9.1% respectively for people above the age of 20 years in the urban population. In this study, the urban prevalence of diabetes is six times more than that of rural population.[1]

Similarly, a clustered-sampled population-based study of the urban areas of Nepal was conducted between 2001 to 2002. In that study the prevalence of diabetes (known and newly diagnosed), IGT and impaired fasting glycaemia (IFG) were 19.0%, 10.6% and 9.9%, respectively in individuals aged ≥40 years.[2]

Finding a high insulin resistance(IR) in an off spring of a parent or parents with diabetes mellitus may lead to early awareness

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to a possibility of developing diabetes many years later and thus making timely preventional steps possible .

Data from USA suggests that children with a positive family history of T2DM are more at risk of developing insulin resistance .[3,4] A study done in India in normoglycemic offspring of T2DM patients using homeostatic model assessment for insulin resistance (HOMA-IR)also found that these off springs had higher BMI , plasma insulin levels as compared to controls.[5] A study done by Upadhyaya et al to find the prevalence of diabetes in first degree relatives of people with diabetes in Western Nepal found that the prevalence was about 17.33%.[6] As Nepal is also vulnerable to this epidemic non communicable disease , a study like this will help to forecast the magnitude of the disease burden for the future and will help in making strategies to prevent the increase in incidence of the disease as well. This study was conducted with such aim as data regarding this is very scarce in Nepal.

METHODOLOGY

This is cross-sectional observational study conducted in 2013. Off springs over the age of 18 years with parents having T2DM coming to Bir Hospital and surrounding local health service providing centers were invited to participate in the study. Written consent was obtained from all participants and the research was approved by Institutional Review Board of National Academy Medical Sciences, Kathmandu, Nepal. Participants already diagnosed as having diabetes, suffering from any illness or using any drugs (eg. steroids) that may alter blood sugar levels were excluded from the study.

The participants underwent an interview and a questionnaire was filled up with details of occupation, physical exercise, eating habits, relevant family history , order of birth etc . Each participant underwent physical examination with measurement of blood pressure (after resting for 5 minutes) , height , weight . All participants had undergone an overnight fast and blood samples were taken in fasting conditions the next morning. Cold chain and storage facilities for blood samples for laboratory analysis were maintained as per requirements.

Fasting plasma glucose (FPG) was measured using enzymatic glucose oxidase peroxidase method and insulin was measured using commercial ELISA kits.

Insulin resistance was calculated from FPG and serum insulin values using the formula for HOMA-IR. The HOMA is a method used to quantify insulin resistance and beta-cell function and the method was first described under the name HOMA by Matthews et al. in 1985.[7]

HOMA is found to be a simple and reliable tool for epidemiological purposes of assessing insulin sensitivity [8] and studies have demonstrated its usefulness in monitoring treatment efficacy in T2DM [9] including those taking sulphonylureas or diet alone.[10]

In this study, we had divided the Body Mass Index (BMI) as Normal : 18.0-22.9 kg/m^2, Overweight: 23.0-24.9 kg/m^2, Obesity: ≥25 kg/m^2 which is recommended for this region.[11,12]

Participant's weight was taken to the nearest 100 gm, while wearing light clothing.

A FPG value of less than 5.6 mmol/L was considered as having normal fasting glucose tolerance.[13]

For insulin resistance cut off value, it has been found to be different in different study populations and most studies have used a cut off value of 75th percentile above which is considered as abnormal.[14] Similarly, in our study too , we have used a cut off value from the 75th percentile of the insulin resistance values.

Data was analyzed using SPSS version 17.0 and independent t tests, using bivariate analysis with chi square test (exact test where applicable). A P value of <0.05 was considered as statistically significant.

RESULTS

A total of 55 participants volunteered to take part in the study out of which 49 participants fulfilled the inclusion criteria and were included in the study. There were 29 male participants and 20 female participants in the study. In this study of 49 participants when the cut off value of 2.48 (75th percentile) was taken, 12 participants were found to have insulin resistance that is almost one fourth of the participants.

The measurement of fasting serum insulin was significantly greater in the IR group than in the Non-IR group. There were no significant difference between age , BMI , blood pressure and FPG among the two groups (Table 1) .

Table1. Baseline characteristics of participants with and without insulin resistance

	Non insulin resistant (n=38)	Insulin Resistant (n=12)	P value
	Mean (SD)	Mean (SD)	
Age (yrs)	30.00(9.42)	28.50(7.66)	0.620
BMI Kg/m^2	24.40(4.05)	26.94(3.84)	0.062
Systolic BP (mm/Hg)	109.95(9.27)	114.33(10.26)	0.171
Diastolic BP (mm/Hg)	69.68(8.16)	71.50(8.40)	0.507
Fasting plasma blood glucose (mmol/L)	4.44(0.41)	4.43(0.24)	0.922
Serum Insulin level(µU/ml)	7.18(2.62)	21.84(9.16)	<0.001

Students had significantly lower BMI as compared to the non student group but such differences were not observed for FPG, serum insulin and insulin resistance (Table 2).

Table 2. Mean values of various parameters in different subgroups

	BMI Mean(SD)	FPG Mean(SD) mmol/L	Insulin Mean(SD) µU/ml	Insulin Resistance Mean(SD)
First born	26.01 (5.00)	4.43(0.36)	13.84(10.64)	2.72(2.04)
Non First born	24.29 (3.20)	4.44(0.40)	8.46(4.34)	1.66(0.85)
P value	0.149	0.874	0.038	0.035
Maternal DM	25.19(4.65)	4.47(0.29)	12.01(7.62)	2.39(1.50)
Paternal DM	23.90(3.21)	4.48(0.48)	9.61(8.35)	1.85(1.45)
P value	0.346	0.949	0.369	0.270
Single parent DM	24.45(3.95)	4.47(0.40)	10.78(7.98)	2.11(1.48)
Double parent DM	26.62(4.28)	4.32(0.30)	10.71(8.65)	2.13(1.83)
P value	0.102	0.227	0.981	0.970
Male offspring	24.66(3.76)	4.47(0.41)	11.05(8.96)	2.16(1.66)
Female offspring	25.55(4.62)	4.38(0.33)	10.36(6.76)	2.05(1.44)
P value	0.465	0.422	0.772	0.821
Smokers	24.52(3.12)	4.31(0.36)	16.69(13.84)	3.15(2.43)
Non smokers	24.97(4.22)	4.45(0.38)	9.69(6.64)	1.92(1.34)
P value	0.803	0.395	0.044	0.068
Exercise	25.23(4.10)	4.37(0.24)	9.68(5.02)	1.90(1.03)
No Exercise	24.96(4.17)	4.36 (0.38)	11.12(8.86)	2.19(1.70)
P value	0.842	0.464	0.596	0.580
Age up to 35	23.94(3.37)	4.46(0.38)	11.17(8.76)	2.19(1.68)
Age more than 35	28.77(4.38)	4.36(0.38)	9.37(5.00)	1.85(1.06)
P value	0.000	0.486	0.519	0.531
≥3 Meals out of home/wk	24.24(3.60)	4.45(0.42)	11.30(9.07)	2.21(1.72)
<3 Meals out of home/wk	26.38(4.58)	4.40(0.31)	9.84(6.07)	1.95(1.24)
P value	0.079	0.662	0.546	0.567
Having motorized Vehicle	25.37 (3.42)	4.57(0.41)	13.33(9.85)	2.64(1.85)
No motorized vehicle	24.64(4.83)	4.28(0.27)	7.87(3.88)	1.53(0.82)
P value	0.550	0.007	0.014	0.009
Student	22.34(3.01)	4.27 (0.28)	10.33 (7.60)	2.00(1.61)
Non student	26.10(4.03)	4.50 (0.39)	10.94(8.34)	2.16 (1.55)
P value	0.003	0.057	0.813	0.750
Sendentary Life ≥ 5 hrs day	25.31(4.55)	4.41(0.24)	13.73(7.46)	2.70(1.48)
Sendentary Life < 5 hrs day	24.91(3.99)	4.45(0.42)	9.58(8.09)	1.88(1.54)
P value	0.765	0.745	0.105	0.094

In this study as we compared insulin resistance among offspring having mother vs father with T2DM , there is more insulin resistance in offspring with maternal diabetes however there is not much difference in insulin resistance between having single parent with T2DM and both parents with T2DM.

As shown in Table 3, a comparative analysis was done between possible risk factors in insulin resistant and non insulin resistant groups and it was observed to have statistically significant risk factors in birth order (p value 0.010), sedentary life as denoted of having ≥5 hours/day screen time (p value 0.024).

Table 3. Comparison between possible risk factors in insulin resistant and non insulin resistant groups

		Insulin resistance n =12 (%)	Noninsulin resistance n = 37 (%)	P value
History of parental DM	Single parent	9 (24.3)	28 (75.7)	0.962
	Both parents	3 (25.0)	9(75.0)	
History of DM in parents	father	3 (15.8)	16(84.2)	0.442
	mother	6(33.3)	12(66.7)	
	both	3(25.0)	9(75.0)	
Having motorized vechile for commuting	yes	9(34.6)	17 (65.4)	0.080
	no	3(13.0)	20(87.0)	
Doing physical exercise	yes	3 (25.0)	9 (75.0)	0.962
	no	9(24.3)	28(75.7)	
Occupation	student	3 (21.4)	11 (78.6)	0.753
	nonstudent	9 (25.7)	26 (74.3)	
Gender of offspring	male	8(27.6)	21(72.4)	0.788
	female	4 (20)	16 (80)	
Order of birth	First born	9 (42.9)	12(57.1)	0.010
	laterborn	3 (21.4)	25 (78.6)	
Sendentary life style	yes	7(50.0)	7(50.0)	0.024
	no	5(14.3)	30(85.7)	
Having more than 3 away from home meals	yes	8 (25.8)	23(74.2)	1.000
	no	4(22.2)	14(77.8)	
Smoking status	Current smoker	3 (50.0)	3 (50.0)	0.051
	Non smoker	8 (19)	34 (81.0)	
	Ex smoker	1(100.0)	0(0.0)	
BMI (Kg/m^2)	<22.9	1 (6.3)	15(93.8)	0.097
	23-24.9	3 (25.0)	9 (75.0)	
	≥25	8 (38.1)	13 (61.9)	

The mean age of diagnosis of T2DM in mothers having firstborn off spring with IR (not including participants with both parents with T2DM) was 38.5 years. This was lower than the mean age of diagnosis of T2DM in mothers having firstborn off spring without IR (48.2 years). Non of the participating offsprings' mothers had diabetes at the time of birth of the offspring.

In Table 4, we can see that with increasing BMI, there is also an

increase in fasting serum insulin levels and insulin resistance although statistically not significant however such trend was not observed for fasting blood glucose.

Table 4. Increase in insulin and insulin resistance with BMI

	BMI normal	n=16	BMI over-weight	n=12	BMI Obese	n=21	
	Mean	SD	Mean	SD	Mean	SD	p value
FBS (mmol/L)	4.22	0.22	4.63	0.29	4.48	0.45	0.010
Insulin (µU/mL)	8.99	8.94	10.00	8.45	12.56	7.10	0.390
Insulin resistance	1.67	1.56	2.07	1.76	2.48	1.41	0.296

Bivariate analysis with logistic regression was also done for insulin resistance and BMI and single or both parental history of DM. It showed that the first born child was six times at risk of becoming insulin resistant as compared to later born children (Odds ratio 6.25, 95% CI 1.43-27.37, P value 0.015) and the same risk factor hold true with adjustment for single or both parents with diabetes (Odds ratio 6.48 ,95% CI 1.45-28.99, P value 0.014).

After adjustment for BMI , the odds ratio for developing insulin resistance in the first born child increased to seven times that of a later born child (Odds ratio 7.29 , 95% CI 1.59-33.46, P value 0.011).

DISCUSSION

The most notable finding in our study is that as compared to the later born offspring, the firstborn were six times more at risk for IR which was seven times after adjustment for BMI. IR was more associated in offspring with maternal diabetes and the mean age of diagnosis of diabetes in mothers having firstborn offspring with IR was 38.5 years as compared to 48.2 years of those having firstborn offspring without IR. As mentioned earlier none of the participating off springs' mothers had diabetes at the time of birth of the offspring. It indicates that the IR in the firstborn offspring was not related with maternal hyperglycemia during pregnancy. The mean age of onset of diabetes in mother is lower than that seen in industrialized countries.[15] Maternal malnutrition is a known risk factor of development of glucose intolerance in offspring. [16,17]After the birth of a child, the mothers are well fed and their nutritional status and body weight increases,[18] which decreases the risk of fetal malnutrition in the later pregnancies. The malnourished mothers themselves are at increased risk of development of diabetes if they gain excessive weight later.[17] The improved feeding may increase the BMI of the mother excessively increasing their risk of development of diabetes later in life .[18] On the basis of such prevalent social trends and observations it thus raises the possibility that whether the development of IR in the firstborn child and of early diabetes in the mother are both related to the maternal malnutrition from one generation to another . A review article by Sanchez-Muniz et al emphasized that proper nutrition since the onset of pregnancy is essential for fetal pancreatic growth and development required for optimum glucose homeostasis during fetal life as well as preventing or delaying the onset of T2DM in adulthood.[19]

The increased possibility of development of insulin resistance in offsprings of people with T2DM has been shown by several studies.[20-21] A study done by Preethi BL et al in Bangalore had compared insulin resistance in normoglycemic young adults and it was estimated by using physiological mathematical models like HOMA-IR, etc. and their formulas derived from Oral Glucose Tolerance Test (OGTT) .[20] The study showed that siblings of people with diabetes had higher insulin resistance values and lower insulin sensitivity values. Studies done by Osei K et al on first degree relatives of African American Type 2 Diabetes patients showed that the triad of decrease insulin secretion, insulin action, and glucose effectiveness antecede the development of diabetes in these individuals.[21] A cut off value of 75th percentile has been used for both IR and serum insulin values in epidemiological studies.[22] The cut off value for IR in our study is 2.48. The IR cut of values can vary among different ethnic groups, age groups and risk groups. For the research of Ascao and team [23] it was 2.6 and for the study done by Hydrie's team, it was 1.82. [22]

A cross-sectional study was done in Lahore, Pakistan in male offspring of parents having T2DM. In that study , the IR values for single parent with diabetes and both parents with diabetes were 2.4 and 3.17 respectively whereas in our study it was with IR 2.11 and 2.13 (P value 0.970) respectively.[24] In our study, there is more fasting insulin levels and IR in the first born offspring as compared to the later born offspring (IR 2.72 vs 1.67 , p value 0.035). This is similar to a research done by Ayyavoo A et al which showed comparatively reduced insulin sensitivity in the first born child despite being taller and slimmer.[25]

Active travel such as walking and bicycling to work has been associated with reduced cardiovascular risk in the Indian population.[26] In our study too those having their own motorized vehicle for daily commuting were also compared with those who do not have such vehicles and the mean value IR was statistically significant with 2.64 vs 1.53 p value 0.009 respectively. In our study, we can see that there is gradual increase in insulin resistance from normal weight (1.67) to

overweight (2.07) to obese (2.48) showing a proportional increase of insulin resistance with BMI . The results observed are statistically significant for firstborn child, sedentary life style, owning motorized vehicle for commuting reinforcing the theory that both family history , genetics and life style are contributing factors for the development of insulin resistance and future risk of T2DM.

Limitations of the study.

The sample size is relatively small. There is no comparision with euglycemic clamp. Participants did not undergo prandial blood sugar testing, HbA1C , or Oral Glucose Tolerance Test. Almost all participants had normal fasting blood glucose and normal blood pressure which helps to reduce the possibility of already having diabetes or impaired fasting glucose and the effect of hypertension on IR which strengthens the role of inheritance of other factors influencing IR. The research does not include healthy controls i.e., offspring of parents without diabetes, the addition of which could have made some contributors for IR more comparative. However the later born and non-IR firstborn offspring and their parents provided some comparative data. There is variance in IR according to age groups, ethnicity etc. and no well established cut off values of insulin resistance that may predict the likelihood of future diabetes development.

CONCLUSION

Higher risk of insulin resistance is seen in the firstborn offspring whose mother later developed diabetes at fourth decade indicates the possibility of relation of both conditions with maternal malnutrition during their first pregnancy. Further larger studies are required focusing on these aspects.

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