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Beta Cell Function and Insulin Resistance in Nondiabetic, Prediabetic and Diabetic in a Subset of Obese Pakistani Population

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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ABSTRACT

Objective: To compare insulin resistance and beta-cell function in nondiabetic, prediabetic, and diabetic subjects in a subset of obese Pakistani population.
Materials and Methods: Two hundred and ten obese subjects underwent anthropometric measurements. After overnight fasting for 8 hours, 6 cc blood was drawn for fasting blood glucose level, fasting insulin level. Blood glucose samples were taken after drinking 75 gm glucose in 260 ml water. HOMA IR and HOMA BETA% were calculated by the formula. Subjects were divided into obese nondiabetic, obese prediabetic and obese diabetic according to WHO criteria.
Results: Out of 210 obese subjects, 53 (25.2%) were males and 157 (74.8%) were females. The mean BMI was 32.39±5.21. Mean abdominal circumference was 102.78±10.16. There were 101(48%) obese nondiabetic, 51(24%) were found to be obese prediabetic, 58(28%) were found to be obese diabetic. Mean insulin resistance in obese nondiabetic subjects was 2.8 ±3.7, in prediabetic 8.5± 12.3, in diabetic was 17.7±24.6. Mean HOMA beta was 245.3±267.4 in obese

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nondiabetic subjects, 290.5±298.4 in prediabetic, and 16.6±57 in diabetic.
Conclusion: There was a significantly increased incidence of prediabetes and diabetes in obese subjects. Prediabetic and diabetic subjects were found to have marked insulin resistance. Beta-cell function was markedly reduced in diabetic subjects having a family history of diabetes, emphasizing the genetic predisposition to develop beta-cell exhaustion.

Keywords: Beta-cell function; insulin resistance; obese prediabetes; obese diabetes.

1. INTRODUCTION

There is an increasing prevalence of diabetes in Pakistan over the past twenty years. In 2017 there were 27.4 million subjects with diabetes in Pakistan [1]. Similarly, there is an increased prevalence of obesity in Pakistan which is because of the increased sedentary lifestyle and rapid urbanization [2]. Pathophysiology of diabetes includes ongoing beta cell dysfunction as well as insulin resistance but which mechanism proceeds is still debatable [3]. Loss of Beta-cell function and mass both seem important in the development of diabetes. Glucose carries the main drive on beta cells and persistent hyperglycemia can exhaust the beta cells resulting in diabetes [4]. Obesity is considered to be an insulin-resistant state [5]. An ongoing chronic inflammatory state exists in obesity as the adipocyte secretes several inflammatory cytokines which creates an insulin-resistant state [6]. Different studies in young [7] and adults [8] are present in literature discussing the beta-cell function and insulin resistance in diabetes but in this study, only obese subjects have been selected. The objective is to investigate obese subjects in a subgroup of Pakistani subjects, for insulin resistance and beta-cell function in obese nondiabetic, prediabetic, and diabetic subjects, to see the influence of both of these mechanisms in prediabetes and diabetes in the presence of obesity.

1.1 Objective

To compare insulin resistance and beta-cell function in nondiabetic, prediabetic, and diabetic subjects in a subset of the obese Pakistani population.

2. MATERIALS AND METHODS

Brochures and banners were distributed in the vicinity of civil hospital Karachi, asking only obese subjects to participate in the study. Two hundred and ten obese subjects were selected after taking informed consent. Their anthropometric measurements, weight in kg, height in m2, abdominal girth in cm were taken. Their BMI was calculated by the formula weight (kg) /height (m2). Obesity was defined as a BMI of at least 30 kg/m2, according to the 1997 WHO criterion. Subjects were then called after overnight fasting for 8 hours and 6 cc blood was drawn for fasting blood glucose level and fasting insulin level. Subjects were then given 75 gm glucose in 260 ml water to drink and then a blood sample was taken for oral glucose tolerance test. Subjects were divided into obese nondiabetic, obese prediabetic and obese diabetic on the results of glucose tolerance test according to WHO criteria.

Diabetes mellitus was defined as a fasting plasma glucose (FPG) of at least 7.0 mmol/L, a 2-hour postprandial glucose loading plasma glucose level of at least 11.1 mmol/L, using the WHO 1999 criterion . For prediabetes defined by impaired fasting glucose (IFG) 5.6-6.9mmol/L, impaired glucose tolerance (IGT) 2 hours of postprandial glucose of 7.8 -11.0 mmol/L were identified.

HOMA IR and HOMA BETA% were calculated by the formula (fasting insulin x fasting glucose / 22.5) and (20x fasting insulin/ fasting glucose – 3.5) respectively.

3. RESULTS

Out of 210 obese subjects, 53 (25.2%) were males and 157 (74.8%) were females. The mean age in females was 42.49± 10.78 years. The mean age of males was 41.057±13.42 years. The mean BMI in both genders was 32.39±5.21. Mean abdominal circumference was 102.78±10.16. Based on the glucose tolerance test there were 101(48%) obese nondiabetes, 51(24%) were found to have prediabetes, 58(28%) were found to have diabetes. Mean insulin resistance in obese nondiabetes subjects was 2.8 ±3.7, in prediabetes 8.5± 12.3, in diabetes was 17.7±24.6. Mean HOMA beta was 245.3±267.4 in obese nondiabetes subjects,

290.5±298.4 in obese prediabetes, and 16.6±57 in obese diabetes. Insulin resistance and beta-cell function in the three groups are shown in Table 1.

Increased Insulin resistance was found in 137 (65.2%) of the participants. Insulin was 21.5 folds higher among participants with diabetes (OR = 21.46 95% CI: 7.20 – 63.95, P < 0.001). The risk of increased insulin resistance among individuals with prediabetes was 10 times greater than those who did not observe the same (Table 2). Diabetes mounted the risk almost twice in comparison of prediabetes (OR = 9.99, 95% CI: 4.09 – 24.39, P < 0.001).

A Decrease in HOMA beta was found in 89 (42.4%) of the participants. HOMA beta was 29.4 folds less among participants with diabetes (OR = 29.4, 95% CI: 11.2 – 77.1, P < 0.001). The risk of HOMA beta decrease among individuals reporting prediabetes was not observed (OR = 01.3, 95% CI: 0.59 – 2.77, P = 0.53) (Table 3). So there is a significant decrease in beta-cell function in diabetic subjects as compared to prediabetes. Out of 52 diabetic subjects with decreased beta-cell function, 37 (71.2%) p-value = 0.00 had a family history of diabetes.

Overall family history of diabetes was positive in 108(51.4%) subjects. Among the 58 diabetic subjects 39 (67.2%) p-value 0.018 had a positive family history of diabetes, so genetic predisposition of diabetes may account for the greater decrease of beta-cell function.

4. DISCUSSION

In obesity, there is ongoing low-grade inflammation [9]. Excess adipose tissue in obesity is the major source of inflammation as there is infiltration of macrophages which results in the release of various cytokines creating

Table 1. Beta-cell function and insulin resistance in the three study groups

Obese subjects (n=210)		HOMA BETA[a]	Insulin Resistance[b]
Diabetes (n=58)	Mean[a,b] (SD)	16.6*(57)	17.7*(24.6)
	95% C.I	(-41.1,74.3)	(14.2,21.30)
Prediabetes (n=51)	Mean[a,b] (SD)	290.5(298.4)	8.5(12.3)
	95% C.I	(230.1,351)	(4.7,12.2)
Nondiabetes (n=101)	Mean[a,b] (SD)	245.3(267.4)	2.8(3.7)
	95% C.I	(201.4,289.3)	(0.2,5.4)

a- Adjusted mean using covariate insulin resistance
b- Adjusted mean using covariate BETA
^Post Hoc test (Bonferroni test)
**Sig at 0.017, Comparing three groups with normal*

Table 2. Relationship of three study groups with Insulin Resistance

Obese Groups	Insulin Resistance		Univariable Analysis	
	Normal (n = 73)	Increased (n = 137)	OR (95% CI)	P-value
Diabetes (n = 58)	4 (06.9%)	54 (93.1%)	21.46 (7.20 - 63.95)	<0.001**
Prediabetes (n = 51)	7 (13.7%)	44 (86.3%)	9.99 (4.09 - 24.39)	<0.001**
Nondiabetes (n = 101)	62 (61.4%)	39 (38.6%)	1	
**Significant at 1%				

Table 3. Relationship of three study groups with HOMABETA

Obese Groups	HOMA BETA		Univariable Analysis	
	> = 100 (n = 121)	< 100 (n = 89)	OR (95% CI)	P-value
Diabetes (n = 58)	6 (10.3%)	52 (89.7%)	29.4 (11.2 – 77.1)	<0.001**
Prediabetes (n = 51)	37 (72.5%)	14 (27.5%)	01.3 (0.59 – 2.77)	0.53
Nondiabetes (n = 101)	78 (77.2%)	23 (22.8%)	1	
**Significant at 1%				

an insulin-resistant state [10]. The pathophysiology of diabetes includes both insulin resistance and beta-cell dysfunction [11]. According to Cerf ME [12], in healthy population beta-cell dysfunction rather than insulin resistance plays a pivotal role in the development of diabetes, as many genes involved in the regulation of cell replication or regeneration have been identified. This observation emphasizes inherited abnormalities of beta-cell function or mass for developing diabetes. Similarly, Ashcroft and Rorsman [13] describe beta-cell dysfunction as the main determinant of diabetes and insulin resistance to play an added role with it. A study conducted on the postmortem and surgical pancreas provides an important clue in the pathogenesis of beta-cell failure in type 2 diabetes [14]. In this study, not only beta-cell volume but also markers of beta-cell proliferation and apoptosis were studied. They found that in subjects with impaired fasting sugar and diabetes obese subjects, there was 40% and 63% respectively loss of beta-cell volume compared to the controls. In comparison to normal lean subjects, lean diabetic subjects had a 41% loss of beta-cell volume. This reduced volume was more because of apoptosis rather than reduced beta-cell proliferation. So according to them, beta-cell mass reduction starts at an impaired fasting glucose state.

This study focuses on obese subjects with normal glucose levels, impaired glucose levels, and diabetics, to see the beta-cell function as estimated by HOMA B and insulin resistance in all the obese three groups. Moreover, to observe which of these two factors are more pronounced in prediabetes and diabetes.

Mean beta-cell function in both obese nondiabetes subjects and obese prediabetes was increased and were not statistically different although insulin resistance showed a fourfold increase in obese prediabetes as compared to normal obese subjects. This highlights the fact that insulin resistance plays an important role in obesity, predisposing to prediabetes. At this stage, the insulin secretion was very high HOMA B 245.3%, indeed more than normal obese subjects who also had increased insulin secretion but with euglycemia. This observation is very important, indicating a very high beta-cell secretion of insulin to maintain normoglycemic state start in obese nondiabetes subjects. So obesity itself imposes a burden on beta cells of the pancreas to secrete more insulin to maintain a normal glycemic state. This may be either because of high caloric intake or they may be genetically predisposed, which needs further studies. In contrast in obese diabetic subjects having markedly increased insulin resistance, the insulin secretion is drastically decreased. This observation can be explained by the fact the continuous burden on beta-cell starting in obesity at a normal glycemic level ultimately leads to severe beta-cell exhaustion resulting in diabetes.

Beta-cell function was a thirtyfold decrease in diabetic subjects which was not seen in both obese prediabetes and obese nondiabetes subjects and around 71% of these diabetic subjects had a family history of diabetes. So, genetic factors seem to play an important role in predisposing these individuals to develop diabetes. Similarly, a study conducted in Singapore also emphasized the risk of developing diabetes and decreased beta-cell function in subjects having diabetes in the family.

All the subjects in this study were obese with increased abdominal circumference, which is an indirect but important parameter to access visceral obesity [15]. In visceral fat tissue, there is an ongoing lipolytic activity going on which releases important cytokines like TNF and IL6, which creates an insulin-resistant state [16]. So the main focus should be to manage obesity to decrease this ongoing inflammatory response. This can be achieved with regular exercise programs which may although not reduce weight but creates a healthy environment in the body by decreasing the release of cytokines [17]. Also drugs like glitazones, metformin are found to be beneficial in obesity thus decreasing the risk to develop diabetes [18,19]. Increased secretion of insulin by the beta cells was seen in normoglycemic subjects as well as prediabetes, so weight reduction should be targeted which may reduce the drive on beta cells.

The limitations of this study are the small sample size. Based on this study there is a need of controlling obesity at all age groups by health education programs, magazines, and seminars to the community that can fight this morbid condition and thus help in reducing the health budget being spend not just on diabetes but other conditions like ischemic heart disease, hypertension, etc.

5. CONCLUSION

In this subgroup of obese subjects all with central obesity, there was a significantly increased

incidence of prediabetes and diabetes. Insulin resistance was increased in all three groups but more in prediabetes and diabetes. Beta-cell function was markedly reduced in diabetic subjects and particularly in subjects having a family history of diabetes.

Although this finding emphasizes the genetic predisposition to develop beta-cell exhaustion in diabetes the increased insulin resistance cannot be ignored. Prediabetic subjects although insulin-resistant had significant beta-cell secretion which may be one of the factors which can lead to beta-cell exhaustion leading to diabetes. Measures at prediabetes should be taken to decrease insulin resistance and beta-cell exhaustion by healthy and low caloric meals, reducing weight, and avoiding insulin secretagogues which may reduce the chance to develop diabetes.

ETHICAL APPROVAL

After approval from the institutional review board (DUHS), data collection was started.

CONSENT

As per international standard or university standard, patient's written consent has been collected and preserved by the author(s).

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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