ORIGINAL ARTICLE

Anthropometric Measurements and their Association with Glycemic Parameters and Sex Hormones in Male Offspring of Type 2 Diabetic Parents

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ABSTRACT

Aim: To evaluate the association between body mass index, waist circumference and serum levels of insulin and insulin resistance and sex hormones levels in male offspring of type 2 diabetic parents.

Methods: This cross-sectional, analytical study comprised of 80 subjects, 40 non-diabetic males (20-30 years of age) of single type-2 diabetic parents and 40 age matched healthy male controls without a family history of diabetes. For each participant, detailed medical history and clinical examination was performed. Fasting serum glucose, insulin, total testosterone, and sex hormone binding globulin levels were measured using standard kits. BMI and insulin resistance index were calculated. For data analysis, groups of young adults were matched using valid criteria for significance of difference.

Results: Significantly higher values of body mass index (BMI) and waist circumference (WC), serum insulin and insulin resistance were observed in offspring of type 2 diabetics. On other hand mean sex hormone binding globulin levels were significantly low and an inverse correlation was found between serum SHBG and fasting blood glucose, serum insulin, insulin resistance, BMI and WC in study subjects.

Conclusion: Offspring of type 2 diabetics with higher BMI and WC may exhibit hyperinsulinemia and lower levels of SHBG. Thus, higher levels of BMI and WC and their inverse correlation with SHBG and resultant hyperglycemic changes may predict the possible development of diabetes mellitus in offspring of type 2 diabetics.

Keywords: BMI, WC, Sex Hormone Binding Globulin (SHBG), Insulin resistance, Type 2 diabetes

INTRODUCTION

The incidence of type 2 diabetes mellitus (DM) is rising rapidly, threatening to reduce life expectancy around the globe. The International Diabetes Federation (IDF) has estimated that, by 2040, 642 million people may be affected by the disease[1]. Accurate figures for prevalence of DM in Pakistan are not available, though several studies have reported that, prevalence of DM in Pakistan varies between 2.5% to 6.9%[2,3]. Thus, pre-DM screening is a critical issue. Recent research has shown that, insulin resistance (IR) is one of key indicators for development of diabetes and offspring of type 2 diabetics are more prone to develop the disease, but exact mechanism is not known[4]. Numerous studies have shown that the incidence of IR in elderly ranges from 35% to 50%[5]. Homeostasis model assessment of IR (HOMA-IR) which is convenient, trusted, and cost-effective clamp was preferred in this study over hyperinsulinemic normal blood glucose clamp being expensive, aggressive, time-consuming and not much convenient for large-scale researches[6]. Although the exact cause of IR is still unknown, it has a close correlation with obesity[7]. Obesity can be defined by measuring the individual's body mass index (BMI) by dividing his or her weight by the square of height (kg/m^2). There is increasing evidence that fat distribution, especially in the abdominal area, is correlated with the most severe state of IR[8,9]. Waist circumference (WC) is defined by the IDF as one of the criteria for abdominal obesity[10]. Additionally, as an endocrine organ, adipose tissue can secrete free fatty acids and adipocytokines such as tumor necrosis factor-alpha (TNF-α) and leptin, which can interfere with the insulin-signaling system and induce IR[11].

It has also been expressed that low plasma SHBG and serum testosterone are strongly associated and predict the onset of type 2 diabetes[12]. SHBG plays an important role in regulating the free sex hormones levels and helps in cellular uptake of the hormones[13]. However, any significant association has not been found between testosterone levels and insulin resistance. A strong correlation between SHBG, (which strongly binds and transports testosterone in the circulation) and insulin resistance, central body fat and dyslipidemia has been observed in type 2 diabetics[4].

Data is scarce regarding the relationship between BMI, WC, IR and SHBG and potential risk of development of type 2 DM particularly in offspring of type 2 diabetics. The aim of this study was to investigate the association between BMI, WC, IR and possible role of SHBG in development of IR among children of type 2 diabetics.

RESEARCH DESIGN AND METHODS

This was a cross-sectional, analytical study, conducted in the Department of Physiology, University of Health Sciences, Lahore, in collaboration with diabetes clinic of CMH, Muzaffarabad and AJK Medical College, Muzaffarabad, between March and August 2017. The study was approved by the Ethical committee and Advance Studies and Research Board of the University of Health Sciences, Lahore. All participants provided written informed consent before enrolling in the study. A total of 80 non-diabetic, healthy male subjects between 20-30 years of age were included in this study. The study population was divided into two groups of forty subjects each. The control group consisted of offspring of both non-diabetes parents having no history of any metabolic disease. The controls were recruited from different colleges, universities and

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institutions. The study group consisted of offspring having one of the parents suffering from type 2 diabetes. The subjects were recruited from diabetes clinics of public-sector hospitals. Subjects with endocrine abnormalities were excluded from the study. Each participant completed a questionnaire during a face-to-face interview. The questionnaire included the individual's personal information, medical history, demographic information, family history of diabetes, concomitance medication as well as their life style characteristics e.g. physicalactivity, dietary habits, smoking and economic status. All subjects underwent a complete physical examination that included, recording of pulse, systemic arterial blood pressure (BP), temperature, and systemic examination. Anthropometric measurements were taken, and blood sampling was performed.

Anthropometric and Biochemical Analysis

Height (cm) and body weight (kg) were measured by standard procedure and BMI was calculated as weight divided by the square of height (kg/m2). Waist circumference (WC) was measured using a flexible measuring tape in the horizontal position, in the middle between 12th rib and iliac crest at the level of umbilicus during mid-inspiratory phase with the subject breathing normally. Systemic arterial blood pressure was measured, in sitting position, using an automated sphygmomanometer placed on the participant's right arm. The lowest of 3 readings was recorded, using an appropriate cuff size. The first and fifth krotokoff sound was recorded as systolic and diastolic B.P respectively. Five ml of venous blood from each subject was drawn between 08:00 to 10:00AM after an overnight fasting of 8-12 hours. Two ml of the sample was added toan ethylene demine tetra acetic acid (EDTA) tube for glucose estimation. Fastingserum glucose levels were determined within 24 hours of sample collection. Three ml of the blood sample were added in plain serum tubes and were centrifuged immediately at a speed of 5000 revolution per minute (rpm) for 10 minutes. Following centrifugation, the samples were aliquot and stored immediately at- 4 C for biochemical analysis.

Fasting plasma glucose (FPG) level were assayed by a glucose oxidize method using commercial reagent (Linear Chroma Spain) using humastar-180 chemistry analyzer (Human, Wiesbaden, Germany). Serum insulin was measured by a commercially available ELISA kit (Aesku, Diagnostics) with an automated EIA analyzer (code; Bio-Redlaboratories Hercules CA, USA). IR was determined by HOMA and calculated using FPG and fasting insulin levels for each participant, using the following formula: HOMA-IR=fasting glucose (mmol/L)×fasting insulin (mU/mL)/22.5. Reference range for insulin resistance (HOMA-IR) was considered to be >2.5.

Serum total testosterone was measured by chemiluminescent enzyme immunometeric assay with the help of VITROS ECIQ immunodiagnostic system. Serum SHBG concentrations were measured by enzyme- linked immunosorbent assay technique (ELISA) using commercially available kit (Diagnostic System Laboratories Hercules CA, USA).

Statistical analysis: For data analysis, SPSS version 19 was used. Values are expressed as a percentage of each group or as mean+SD unless otherwise stated. Comparisons between groups were made using a student's t-test. Results were considered statistically significant at $p<0.05$. Shapirwilk test was applied to check the normality of the data. The p- value of all quantitative variables was <0.05, indicating that the data follows normal distribution and so appropriate statically tests have been applied.

RESULTS

Fig. 1 Correlation between Serum SHBG and BMI

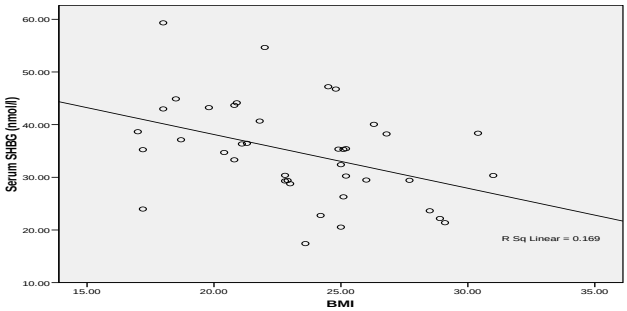


Fig. 2 Correlation between Serum SHBG And WC

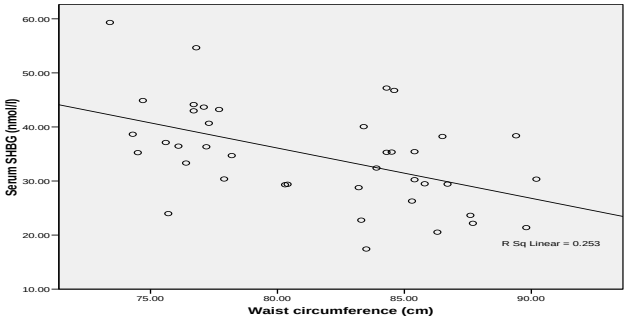
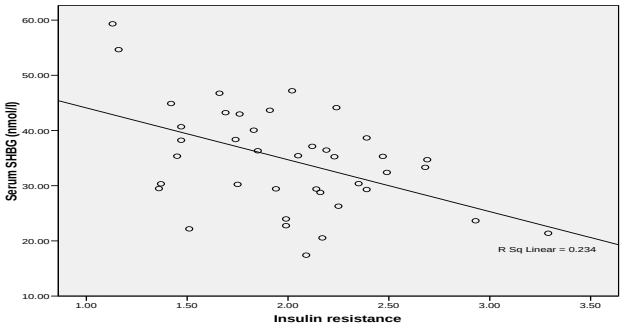


Fig. 3: Correlation between insulin resistance and serum SHBG



The study comprised of a total of 80 healthy male subjects, forming two groups; the control and the study group, each having 40 subjects. Table 1 summarizes the anthropometric and hormonal levels of control and study group (non-diabetic offspring of single diabetes parents). The mean±SD age of control and study groups was 22.45±2.25 and 24.23±2.65 years respectively. The mean±SD BMI of control group was 20.21±3.02Kg/m2 and of study group was 26.27+3.63 Kg/m^2. The difference in BMI for both group was statically significant ($p<0.003$). The mean±SD WC was 73.56±4.26 cm and 89.25±3.20 cm in control and study group respectively. The WC difference was statistically significant between both group; ($p<0.002$).

No significant difference was observed in mean±SD FPG concentration of control (4.25±0.72.mml/L) and study group (4.87±0.63mmol/L); ($p=0.375$). The mean±SD serum insulin concentration was 4.377±2.64uU/ml and

12.36±3.47uU/ml in control and study groups respectively and was significant in two groups: (p=0.003). The mean±SD serum IR was 0.72±0.33 and 1.98±0.57 in control and study groups respectively and was statistically significant between the two groups; (p=0.000).The mean±SD serum testosterone concentration was 20.46±5.15nmol/1 and 11.61±2.31nmol/1 in control and study groups respectively. The serum testosterone difference between two groups was statistically significant; p = 0.002. The difference of serum SHBG concentration in control and study groups was significant as p = 0.000. The mean±SD values for serum SHBG was 76.40±31.24nmol/l and 24.64±8.23nmol/l in control and study groups respectively.

Table 2 expresses Pearson's correlation analysis between different study markers. The analysis revealed that serum SHBG was correlated directly with serum testosterone (r=0.314, *p*=0.048) and an inverse correlation was found between serum SHBG and fasting blood glucose (=-0.314, *p*=0.049), serum insulin (r=-0.383, *p*=0.015), insulin resistance (r=- 0.484., *p*= 0.002), BMI (r=-0.412, *p*=0.008) and WC (r=-0.503, *p*=0.001). A positive correlation was observed between BMI and WC (r =0.953, p = 0.000).

Table 1: Anthropometric and hormonal assessments of control and study group

Parameters	Controls (n= 40) Mean±SD	Study subjects (n=40) Mean ± SD	P-value
Age (years)	22.45 ± 2.25	24.23 ± 2.65	0.346
BMI (kg/m^2)	20.21 ± 3.02	26.27 +3.63	0.003**
Waist circumference (cm)	73.56 ± 4.26	89.25 ± 3.20	0.002**
Fasting blood glucose(mmol/L)	4.25±0.72	4.87 ± 0.63	0.375
Fasting serum insulin(µU/ml)	4.377±2.64	12.36 ± 3.47	0.003**
Insulin resistance(HOMA-IR)	0.71 ± 0.33	1.98 ± 0.57	0.000**
Serum testosterone (nmol/l)	20.46 ± 5.15	11.61± 2.31	0.002**
Serum SHBG (nmol/l)	76.40 ± 31. 24	24.64 ± 8.23	0.000**

Table 2 Pearson's correlation analysis

Parameter	BMI		Waist		Glucose		Insulin		HOMA-IR		Testosterone		SHBG	
	r	P	r	p	r	p	r	p	r	p	r	p	r	p
Glucose	0.023	0.890	0.031	0.851	1	1	0.059	0.719	0.665	0.000**	-0.163	0.316	-0.314	0.049*
Insulin	-0.002	0.989	0.052	0.752	1	1	1	1	0.776	0.000**	-0.083	0.613	-0.383	0.015*
HOMA-IR	0.028	0.865	0.072	0.659	1	1	1	1	1	1	-0.176	0.276	-0.484	0.002**
SHBG	-0.412	0.008**	-0.503	0.001**	1	1	1	1	1	1	0.314	0.048*	1	1
Testosterone	-0.196	0.225	0.013	0.935	1	1	1	1	1	1	1	1	1	1
BMI	1	1	0.953	0.000**	1	1	1	1	1	1	1	1	1	1

DISCUSSION

Present study, showed that young offspring of type 2 diabetics, had HOMA-IR value of1.98, which is close to cut-off values of 2.3 and 2.29 established in an earlier studies[1,15]. Our study results show that 2 obesity indices BMI, WCare significantly associated with IR in Pearson's analysis, indicating that higher BMI and WC may predict early onset of IR in study subjects. Similar findings were observed in another study, which revealed that higher value of BMI and WC had an important role in predicting IR than dyslipidemia, hypertension and other markers[16]. The cutoff values of BMI and WC to predict IR were 26.27kg/m2 and 89.25cm, respectively, which nearly meet the obesity criteria (BMI: 27kg/m2, WC: 90cm in males and 80cm in females) set by the Pakistan Ministry of Health. These results reinforce the relationship between IR and obesity, and suggest that overweight and obese persons should be made aware of the risk of IR and standardly screened for development of diabetes and other diseases in advance.

Previous studies have reported inconsistent association between the obesity index and IR and demonstrated that inclusion of body fat distribution score to the BMI can better predict onset of cardiac, diabetic and other diseases[17,18]. This highlights the importance of BMI and WC for predicting IR and is in line with our study findings. Another cross-sectional study showed that individuals with higher BMI, WC, and body fat mass had significantly higher HOMA-IR values[19]which isin accordance with our study results. In contrast, an African American population study[20], found that not alone BMI, WC, but addition of 3rd marker, BF% was the best predictor of IR. These studies suggest that IR may be influenced by ethnic background, age, and gender-related body composition. However, our study results strongly indicate the correlation between BMI and WC and IR in Asiansparticularly in middle-aged offspring of type2 diabetics.

Insulin resistance is probably, one of the most likely causative factors in the development of DM in the offspring of type 2 diabetics, but exact mechanism is still not fully explored. Insulin has a potent effect on steroid hormone metabolism and it has been shown that physiologic increase in serum insulin levels decrease serum androgens and SHBG levels[21]. In the present study, significantly lower levels of SHBG (p=0.001) in male offspring of type 2diabetics were found than controls. Moreover, strongly inverse correlation was seen between serum SHBG and IR (p=0.002). The correlation of IR with steroid hormones and transport proteins is expressedin many cross-sectional studies, proposing that pre-diabetic hyperinsulinemia might inhibit the production of SHBG[22].Serum SHBG concentration is regulated by plasma insulin or IR so elevated insulin levels orIR are correlated with lower SHBG levels[23]. These observations are quite similar to current study results, which also found highly significant inverse correlation between IR and SHBG; high serum insulin (hyperinsulinemia) and low SHBG. Birkeland et al also observed a strong direct correlation between insulinsensitivity and SHBG in men with type 2 DM[24].Our study results exhibited hyperinsulinemia, insulin resistance and significantly lower levels of SHBS in study subjects.

Moreover, an inverse correlation was found between serum SHBG and fasting blood glucose, serum insulin, insulin resistance, BMI and WC in study subjects. This strong correlation demonstrates that higher or above normal obesity indices like BMI and WC may predict IR and possible occurrence of diabetes in study subjects. Haffner et al also reported rather moreconsistent evidence of occurrence of DMs with higher insulin and low SHBG levels[25]. In addition, it is also reported that advanced techniques, like magnetic resonance imaging, dual-energy X-ray absorptiometry, and computed tomography only weakly predict IR. On other hand anthropometric measurements are better predictors of IR than advanced tools, which enlighten the importance of these simple, traditional measures.

Our study had a few limitations. First, being a cross-sectional study; the causal relationship between BMI, WC, IR and SHBG could not be well established. Secondly, it was a small scale study and a large scale study is needed to solidify the conclusions drawn in this study.

CONCLUSION

Our study concluded that in the offspring of type 2 diabetic parents, higher BMI and WC can strongly predict the onset of IR. There is a negative correlation between SHBG and IR in study subjects making the offspring more susceptible to develop diabetes. Individuals with family history of diabetes with high BMI or WC need to undergo lifestyle modifications and primary prevention of diabetes.

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