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ORIGINAL ARTICLE

Gender as a threat for type 2 diabetes mellitus: Elevated fasting glucose, insulin, and HOMA-IR levels in females.

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ABSTRACT… Objective: The research aimed to compare serum levels of fasting plasma glucose, 2hrpp, fasting insulin, Homeostasis Model Assessment of Insulin Resistance (HOMA-IR), and waist-to-height ratio in individuals with a diabetic background. **Study Design:** Cross-sectional Observational draft. **Setting:** District Headquarters Hospital, Gujranwala. **Period:** December 22, 2020, to December 22, 2022. **Material & Methods:** Overall, 80 healthy participants, 20-50 years old, were recruited and graded into two groups based on gender. Group A comprised males, and Group B comprised females. All participants demonstrated normal glucose tolerance centered on the oral glucose tolerance test. **Results:** Females exhibited significantly higher mean levels of fasting plasma glucose (p=0.01), fasting plasma insulin (p=0.004), and Homeostasis Model Assessment of Insulin Resistance (p=0.007) compared to males. Homeostasis Model Assessment of Insulin Resistance and waist-to-height ratio exhibited a positive correlation (p=0.001). **Conclusion:** Females with a positive family history may present an amplified threat of Type 2 Diabetes Mellitus.

Key words: Homeostasis Model Assessment Index, Irreversible Risk Factor, Type 2 Diabetes Mellitus, Women.

INTRODUCTION

The terrifying rise in the incidence of Type 2 diabetes mellitus (T2DM) has raised concerns among researchers worldwide. T2DM affects approximately one out of every eleven individuals globally, with Asia experiencing a significant burden of the disease.[1] South Asians are particularly vulnerable to T2DM due to dual mechanisms. Firstly, they exhibit reduced insulin secretion and impaired insulin action on its goals such as the liver, muscle, and adipocytes, which can be attributed to evolutionary factors. Additionally, sedentary lifestyles prevalent in this population exacerbate the problem.[2] Furthermore, females have been found to be more prone to developing T2DM due to factors related to body composition and fat accumulation.[3] In Pakistan, approximately 17% of the population is affected by T2DM, and limited access to medical care, coupled with financial constraints, further complicates the management of the disease.[4]

It is noteworthy that the regression from pre-diabetes to normal glucose levels occurs more frequently than the progression to T2DM.[5] Individuals with diabetic background have a 30-70% higher chance of having it, often accompanied by metabolic inflexibility, characterized by increased abdominal adipocyte size and decreased basal energy consumption.[6] Maternal history of T2DM has been associated with adipocyte hypertrophy and increased lipid catabolism.[7] When both parents are affected, the subsequent generation inevitably experiences impaired residual beta-cell function.[8] Moreover, diabetic females tend to have shorter lifespans and are more susceptible to cardiovascular complications and disturbed lipid metabolism.[9]

While Family History (FH) is documented as a non-modifiable aspect for T2DM, the inclusion of female gender in this list remains a topic of investigation. This research targets to address

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this hiatus by judging the metabolic status of Normal Glucose Tolerant (NGT) females and males in terms of fasting plasma glucose (FPG), 2-hour postprandial (2hrpp) glucose levels, fasting plasma insulin (FPI), insulin resistance using the HOMA-IR model, and waist-to-height ratio (WHtR). Additionally, it aims to evaluate the correlations between gender, FPG, 2hrpp glucose levels, FPI, HOMA-IR, and WHtR in individuals with and without diabetic lineage.

MATERIAL & METHODS

This comparative investigation employed a convenient sampling technique to recruit participants. The sample size was determined by the standard sample size formula.[9] The calculated sample size in each group was 15, but to ensure the validity of the research, the sample size was amplified to 40 participants respectively.

Initially, a diabetes screening camp was organized in the outpatient department of the District Headquarters Hospital, Gujranwala. Individuals with acute illness at the time of the research, known cases of type 1 insulin-dependent diabetes mellitus, cardiovascular, cerebrovascular, and peripheral arterial disease, hypertension, chronic renal illness, malignancy, bone disease, and pregnancy were excluded from the study based on their medical history.

Healthy individuals were randomly selected to participate in an Oral Glucose Tolerance Test (OGTT) for diabetes screening. A total of 80 individuals were evaluated by obtaining their family histories (maternal, paternal, or both) and conducting anthropometric dimensions, including height and waist circumference, using stereotyped practices. An approval was acquired from all members in printed form.

Height was measured in centimeters (cm) using a stadiometer. Waist circumference (WC) was evaluated with a metal tape on individuals standing erect, with their abdomen relaxed, between the lower costal margin and the iliac crest. The waist-to-height ratio (WHtR) was determined by dividing WC (cm) by height (cm). A cut-off value of 0.5 is generally recognized for central obesity in adults.[10]

After an overnight fast, three to five milliliters (ml) of blood were drawn from the antecubital vein of each subject in an aseptic environment to assess glucose and insulin levels. The blood was drawn into 5 ml vacutainer tubes and left to coagulate for 30 minutes. Serum was then aliquoted into Eppendorf tubes after centrifugation. Serum samples were kept at -40°C until further use. Following the administration of 75g of oral glucose, blood samples (3 ml) were obtained again after 120 minutes to measure the 2-hour postprandial glucose level by glucose oxidase method.

Fasting serum insulin levels were quantified via an enzyme-linked immunosorbent assay (ELISA) kit (Amgenix International Inc., San Jose, CA, USA) and a CODA automated EIA immunoassay analyzer (Bio-Rad Laboratories, Hercules, CA, USA). The insulin in the test serum was coupled with enzymes and solid-phase antibodies following the sandwich ELISA test principle. Insulin Resistance was assessed using the HOMA-IR (Homeostasis Model Assessment of Insulin Resistance) formula: [(Fasting insulin * Fasting glucose) / 22.5].[11]

Permission to conduct the research was obtained from the institutional review board (UHS/Education/126-21/676) of the University of Health Sciences, Lahore, in harmony with the Helsinki Declaration.

Statistical Analysis

The collected data was submitted and explored by SPSS (Statistical Package for Social Sciences) version 25 and Graph Pad Prism 9.11. The normality was probed by the Shapiro-Wilk test. The statistics were stratified based on gender. For normally distributed data, an independent sample t-test was operated to assess variables between the two groups. For non-normally distributed data, the Mann-Whitney U test was applied. Mean ± SD and median (IQR) were calculated for quantitative variables, namely HOMA-IR and WHtR, depending on the normality of the data. Frequency and percentage were calculated for qualitative variables. Spearman's correlation analysis was implemented to observe the correlations among HOMA-IR and WHtR.

RESULTS

Participant Characteristics

- The study included a total of 80 participants, with 47 males and 33 females (Figure-1).
- All participants were confirmed to have normal glucose tolerance through the oral glucose tolerance test (OGTT).
- The assessed parameters for all participants included age, gender, family history, parental history, WC, height, WHtR, FPG, 2 hr pp, FPI, and HOMA-IR.

Comparison of Anthropometric Characteristics

- Anthropometric data was stratified by gender to assess the effect of these parameters.

Independent t-test and Mann-Whitney test disclosed significant differences in age and height between males and females (Table-I).

Parameters	Males n=47	Females n=33	P-Value*
Age (years)	28(15)	34(10)	0.01*
WC (cm)	92±12.8	95±22.9	0.46
Height (cm)	70(8)	162(18)	0.0001*
WHtR	0.54±0.07	0.6±0.16	0.05

The unpaired t-test was used to evaluate the p-value. Mann Whitney U test was used to evaluate the p-value where data were not normally distributed. Group A = NGT Males. Group B= NGT Females. "n" represents the number of cases in each group.

Table-I. Comparison of anthropometric parameters in both groups

Comparison of Biochemical Characteristics

- Mann-Whitney test results showed significant differences in FPG, 2 hr pp, FPI and HOMA-IR among males and females (Table-II). Females had significantly greater means of FPG, 2-hr pp, FPI, and HOMA-IR (Figure-1, Figure-2, and Figure-3).

Parameters	Males n=47	Females n=33	P-Value*
FPS (mg/dl)	75.4±7.6	80±7.4	0.01*
2hpp(mg/dl)	101(15)	104 (25)	0.04*
Insulin(Mu/L)	9.6(9.8)	15.3(20.7)	0.004*
HOMA -IR	1.8(1.7)	3.9(4.5)	0.007*

The unpaired t-test was used to evaluate the p-value. Mann Whitney U test was used to evaluate p-value where data were not normally distributed. Group A = NGT Males. Group B= NGT Females. "n" represents the number of cases in each group.

Table-II. Comparison of biochemical parameters in both groups

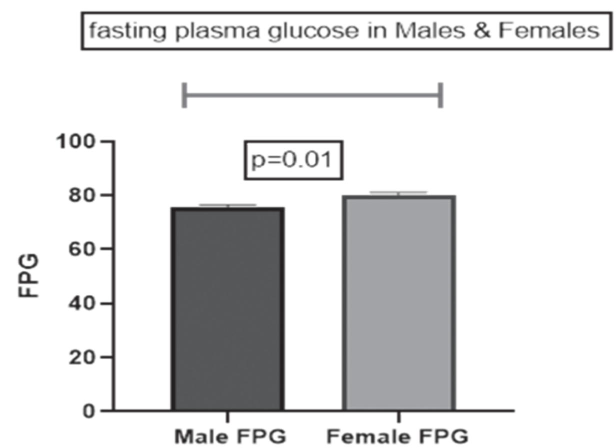

Figure-1. Females had significantly higher means of fasting plasma glucose than males

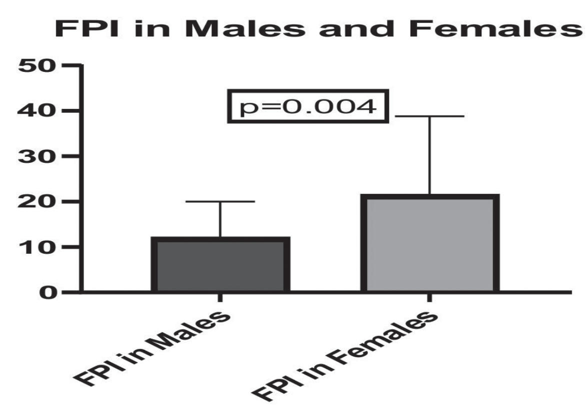

Figure-2. Females had significantly higher means of fasting plasma insulin than males

Correlation of HOMA-IR with Anthropometric and Biochemical Parameters

- Spearman's rho correlation analysis was conducted to examine the relationship between HOMA-IR and anthropometric and biochemical parameters.

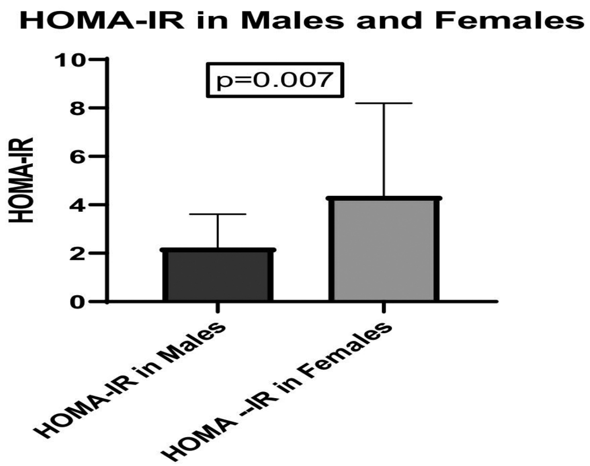

Figure-3. Females had significantly higher means of HOMA-IR than males

- HOMA-IR showed a positive and significant correlation with age (r=0.29, p=0.008, n=80), gender (r=0.304, n=80, p=0.006), WC (r=0.35, n=80, p=0.0001), WHtR (r=0.36, p=0.001, n=80), FPG (r=0.23, p=0.04, n=80), and FPI(r=0.987, n=80, p=<0.0001). These results indicate that elevated fasting plasma insulin levels are associated with higher HOMA-IR values (Table-III).
- The WHtR exhibited a positive and significant correlation with FPI (r=0.37, p=0.001, n=80) and HOMA-IR (r=0.36, p=0.001, n=80). This ratio was significantly correlated with age, WC, and FPI. It was inversely related to height (Table-III).
- Gender also showed positive correlations with FPG (r=0.3, p=0.01, n=80), 2-hr pp (r=0.23, p=0.04, n=80), FPI (r=0.302, p=0.004, n=80), and HOMA-IR (r=0.302, p=0.007, n=80).

DISCUSSION

The occurrence of T2DM is rising worldwide, particularly among women. This research directed to explore the association among gender and T2DM risk factors, shedding light on the unique challenges faced by women in terms of insulin resistance and central obesity.

Interestingly, our findings revealed a noticeable difference between male and female participants. Females had significantly higher average levels of FPG, FPI, WHtR, and HOMA-IR compared to males. This gender discrepancy aligns with previous studies suggesting that females are more susceptible to developing T2DM and metabolic disorder.[12] The preponderance of IR is 2.3 times more in female adults than in males in Brazil.[13]

		Age	WC	Height	WHtR	FPG	2hrpp	FP1	HOMA-IR
Gender	r	0.277*	0.071	-0.4**	0.14	0.289**	0.229*	0.324	0.304**
	p	0.013	0.532	0.0001	0.217	0.01	0.043	0.004	0.006
Age	r		0.456**	0.0017	0.405**	0.14	0.014	0.306**	0.296**
	p		0.0001	0.884	0.0001	0.201	0.902	0.006	0.008
WC	r			-0.038	0.938	0.059	0.121	0.366	0.355**
	p			0.737	0.0001	0.603	0.288	0.001	0.001
Height	r				-0.336**	-0.09	-0.04	-0.15	-0.162
	p				0.002	0.09	0.673	0.196	0.154
WHtR	r					0.078	0.084	o.372**	0.364**
	p					0.493	0.461	0.001	0.0001
FPG	r						0.641**	0.093	0.229
	p						0.0001	0.416	0.042
2hrpp	r							0.016	0.121
	p							0.889	0.287
FPI	r								0.984**
	p								0.0001

*. Correlation is significant at the 0.05 level (2-tailed).
**. Correlation is significant at the 0.01 level (2-tailed).
A positive value of r represents direct co-relation and a negative value of r represents inverse correlation where applicable.

Table-III. Correlation of anthropometric and biochemical parameter in normal glucose tolerant males and females

Similar results were obtained in a 2020 European study, which found positive correlations between fasting plasma insulin, HOMA-IR, and WHtR[14] Higher HOMA-IR values also pose a greater risk of heart failure, even in non-diabetic individuals according to a study in Pakistan, although gender was not considered in their findings.[15] Another study examining fasting plasma triglyceride and HOMA-IR levels in subjects with and without diabetic background illustrated significantly greater IR and postprandial triglycerides in individuals with a diabetic background. However, this study did not focus on gender differences.[16]

This research strongly refutes the idea that gender plays no role in T2DM risk. The intricate hormonal dynamics experienced by women during various life stages, such as menstruation, menopause, and pregnancy, may influence their response to obesity markers and insulin resistance. Additionally, factors like stress management, dietary patterns, and metabolic processes uniquely shape women's predisposition to T2DM, setting them apart from men. These gender-specific complexities highlight the need for tailored interventions and preventive strategies to address the growing burden of T2DM in women. Interestingly, men tend to respond more favorably to exercise-based weight loss approaches, indicating potential gender-specific disparities in therapeutic interventions.[17] Such nuanced insights can pave the way for targeted interventions that take into account the diverse needs and characteristics of different genders.

While our study provides compelling evidence supporting gender as a threat for T2DM, it's worthy to acknowledge that conflicting results have been reported in other studies. For instance, research from Iran has suggested higher HOMA-IR values in males, challenging the conventional understanding.[18] Similarly, studies from Pakistan have reported no significant differences in HOMA-IR values between genders. These contrasting findings warrant further exploration to understand the complex interplay between gender and T2DM risk. Additionally, the impact of central obesity cannot be overstated. Accumulation of abdominal fat has detrimental effects on various cardio metabolic indices, including insulin resistance and dyslipidemia. In this regard, the WHtR is an effective screening device due to its simplicity, accuracy, and ability to account for gender and height differences. A WHtR value below 0.5 is indicative of reduced risk for cardiovascular disease and T2DM. Remarkably, our study supports previous research by demonstrating a positive association among HOMA-IR, WHtR, and FPI, emphasizing the clinical relevance of these measures.[19] The greater ranks of central and general obesity were coupled with an amplified peril of diabetic nephropathy in women with T2DM, while no significant association was detected in men.[20] Lean ladies tend to have better metabolic flexibility due to factors such as lower body fat, reduced inflammation, improved insulin sensitivity, and higher fitness levels.[21] In pediatric populations, the indicators of IR and obesity varies among boys and girls, influenced by biological and hormonal differences.[22] Girls who go through early puberty have higher levels of glucose and insulin in their blood, which can indicate potential difficulties in how their bodies process glucose. This may be a sign of poorer glucose metabolism, which can lead to diabetes.[23]

Given the challenges faced by the South Asian population, including low health literacy and limited healthcare resources, there is an urgent need to develop gender-specific screening programs for the prompt recognition of undiagnosed diabetes mellitus (UDM). These programs should be globally accepted and tailored to address the unique risks and needs of both men and women.[24] Further research should explore ethnic and genotypic factors, which may further elucidate the complex interactions between gender, genetics, and T2DM risk.

Although this study acknowledges certain drawbacks that should be tackled in forthcoming experiments, such as considering ethnic and genotypic factors specific to the Pakistani population and avoiding inherent bias in convenience sampling, it significantly contributes to the existing knowledge by establishing the female gender as a threat for Type 2 diabetes mellitus (T2DM). The findings underscore the importance of gender-specific approaches in the anticipation in T2DM.

CONCLUSION

This study concluded that females have significantly higher means of WHtR and HOMA-IR as compared to males. Furthermore, the HOMA-IR and WHtR were positively correlated with each other. In addition, WHtR was significantly associated with fasting plasma insulin.

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