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Effects of varying levels of gonadotropins and estrogen in adolescent females having type 1 diabetes with their impact on health-related quality of life in Karachi Pakistan

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Abstract: The purpose of this study is to evaluate quality of life, the gonadotropins and estrogen levels in type 1 diabetic adolescent females. This cross-sectional study was conducted at Baqai Institute of Diabetology and Endocrinology (BIDE). The Diabetes quality of life for youth questionnaire (DQOLY) was used to evaluate quality of life. FSH was found to be significantly lower in Type 1 Diabetes. HbA1c had a significant inverse moderate correlation with FSH(-0.300*).In Type 1 Diabetes, FSH had a positive moderate correlation with LH(0.415*), (P-value<0.05). LH and estradiol levels were almost similar in both groups. Overall mean percentage score of DQOLY questionnaire for Type 1 Diabetes was 26.94±1.36. Low QOL score was observed on the basis of impact on activities. Adolescent females with Type 1 Diabetes were found to be shorter and underweight than non-diabetic adolescent females. Lower height and weight of the diabetes as compared to controls cannot be attributed to only metabolic control, suggesting other mechanisms for short stature. Control on metabolism has always been the target for diabetes treatment for ensuring the improved prognosis of disease but also for the quality of life in Type 1 diabetes.

Keywords: Type 1 diabetes, gonadotropins, estrogen, diabetes quality of life for youth.

INTRODUCTION

Living & dealing with Type 1 Diabetes (T1D) is cost effective & intensive course. self-management on daily basis involves frequent blood glucose monitoring and insulin adjustments, administration, physical activity, nutrition, stress & illness (Hilliard *et al*, 2018).

Diabetes also disturbs human physiology thereby affecting pubertal development and growth along with metabolic instability (López-Bastida, 2019). Poor glycemic control has also known to be associated with menstrual irregularities in Type 1 Diabetes; however, the physiological mechanisms leading to these reproductive changes are poorly understood (Karlamangla, Burnett-Bowie & Crandall, 2018).Type 1 Diabetic adolescent girls exhibit premature ovarian aging, disruption of the hypothalamic-pituitary-ovarian (HPO) axis, higher ovarian autoantibody levels, and higher frequency of polycystic ovarian syndrome and ovarian hyperandrogenism (Karlamangla, Burnett-Bowie & Crandall, 2018). Mild hypoestrogenism in adolescents with Type 1 Diabetes is also common due to an imbalance in various serum estrogens, its metabolites and/or other modulating factors of estrogen (Mahmoodzadeh, Shokoufeh; Dworatzek, Elke, 2019).

Hence, significant stress exists in the adolescent females and their family due to these abnormalities (Hagger *et al*, 2018, Askari *et al*, (2020).

Although intensive glycemic control has reduced the incidence of these complications, the majority of patients with T1D are still prone to these challenges. Major research efforts are needed to achieve early diagnosis, preserve ovarian function and develop better treatment options to improve the quality of life and prognosis of those affected. Hence, we aim to evaluate the Gonadotropins and Estradiol profile in adolescent's female with T1D & their QoL.

MATERIALS AND METHODS

The cross-sectional study was conducted at Baqai Institute of Diabetology and Endocrinology (BIDE), a tertiary care unit in Karachi, Pakistan from January 2019 to December 2019 after the approval given by the ethics committee of Baqai Medical University with reference letter No. BMU-EC/2018-03; Dated 4th October 2018. The study collected data from 109 subjects, which included 54 cases and 55 controls, after the written and verbal consent. Patients below 15 year of age, their consent was obtained from their parents. The sample size for this study was calculated by using the Fleiss method with continuity correction. Adolescent females with age between 13-19 years were recruited. Subjects with

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pregnancy, known case of PCOs and with any chronic illness were excluded.

Sample collection

Blood samples were collected for the assessment of HbA1c, FSH, LH and Estradiol during follicular phase of menstrual cycle after taking a detailed menstrual history.

Biochemical Analysis

HbA1c was measured by high-performance liquid chromatography (HPLC) (Tsai, Shou-Ai, 2018). Serum Estrogen, LH and FSH were estimated by using Immuno-enzymatic assay (ELISA) DR-200Bs Microplate Reader of Diatek (USA) was calibrated by the given calibrators of respective kit. Quality controls were checked according to recommended application protocol by Diatek.

Assessment of Quality of life for youth

A validated Questionnaire, DQOLY for the evaluation of T1D in adolescents was used (Hilliard *et al*, 2020). That questionnaire comprised of 22-item to estimate problems in 6 dimensions. The answers were coded as 0, never; 1, sometimes 2, regularly 3, often & 4, all the time. Data was calculated by adding the codes of 22 responses. Unrefined codes ranged from 0 to 88. A score of 0 represented the likelihood while 88 represented the worst possible QoL. Saima Askari and her colleagues presented Questionnaire in English language and it was modified for females and various studies have already been conducted by using the same questionnaire (Askari *et al*, 2020).

STATISTICAL ANALYSIS

Statistical analyses were performed using Statistical Package for Social Sciences (SPSS) version 20 and excel version 16. Normality of the data was check by Shapiro-Wilk Test. Student's T-test, Mann Whitney U test and Chi squared tests to determine the association between variables. Spearman correlation analysis was used to examine the relationship of HbA1c, FSH, LH and Estradiol with each other. Linear regression was used to find the associated factors of QoL and glycemic control at <0.05 P-value.

RESULTS

One hundred & nine females were enrolled in this study, out of which 54(49.5%) were Type 1 Diabetic patients and 55(50.5%) were non-Diabetes Mellitus (non-DM) individuals after the evaluation of HbA1c test. table 1 presented the comparison of baseline parameters between T1D subjects and non-DM subjects. The mean age and height of T1D subjects was significantly lower than non-DM subjects (15.65±2.36 vs 16.78±2.29 years; P-value <0.05) and (152.87±5.48 vs 158.35±4.26 cm; P-value <0.0001) respectively. Whereas, Type 1 Diabetic subjects had significantly higher body mass index than non-Diabetes Mellitus subjects (21.14±3.53 vs 18.85±2.07 kg/m^2; P-value <0.05) (table 1).

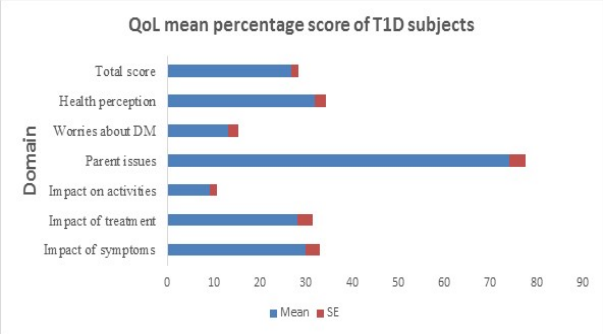

Fig. 1: QoL mean percentage score of T1D subjects.

Mean HbA1c level was significantly high in T1D subjects than non-DM subjects (10.21±2.78 vs 5.57±0.34, P-value <0.0001** (table 1).

It was observed that FSH was found to be significantly lower in Type 1 Diabetic subjects as compared to non-Diabetes Mellitus individuals while levels of LH and estradiol were almost similar in both groups (P-value >0.05) while (table 1).

Results revealed that HbA1c had a significant inverse moderate correlation with FSH. Whereas, in diabetic subjects, FSH had a positive moderate correlation with LH (P-value <0.05)(table 2).

Linear regression model showed that HbA1c level, FSH, LH and estradiol did not significantly affect the Quality of Life (QoL) of T1D subjects (table 3). Though high HbA1c level was significantly associated with low level of FSH (P value 0.006*) but no significant association of HbA1c was found with LH and estradiol among studied subjects (table 4).

Overall mean percentage score of QoL was 26.94±1.36. Maximally reported adverse impact was related to parent's issues i.e. (mean ± SE: 74.07±3.56), followed by health perception (mean ± SE: 31.94±2.51) and impact of symptoms (mean ± SE: 29.94±3.05). Additionally, good QoL score was observed on the basis of impact on activities (mean ± SE: 26.94±1.36) (fig. 1).

DISCUSSION

We evaluated levels of Gonadotropins and Estradiol in female adolescents with T1D and its impact on Quality of Life (QoL) on the patients. Our results observed that the mean age and height of T1D subjects was significantly lower than non-DM subjects that is consistent with other study which also found that children with T1D were shorter and underweight than age matched controls, though children who received intensive insulin therapy were less affected than those in the conventional regime, although the difference was not statistically significant. (Ahmed *et al*, 2020).

Table 1: Comparison of basic characteristics, glycatedhemoglobin, FSH, LH and Estradiol between non-DM and T1D subjects

Parameters	Non-DM	T1D	P-value
N	55	54	-
Age (years)	16.78±2.29	15.65±2.36	0.019*
Weight (kg)	47.37±6.26	49.33±8.19	0.163
Height (cm)	158.35±4.26	152.87±5.48	<0.0001**
Body mass index (kg/m^2)	18.85±2.07	21.14±3.53	<0.0001**
HbA1c (%)	5.57±0.34	10.21±2.78	<0.0001**
FSH (mIU/ml)	6.14±3.98	4.05±1.88	0.001*
LH (mIU/ml)	7.11±5.65	8.46±6.13	0.234
Estradiol (pg/ml)	85±808	3.2±120	0.924

Table 2: Correlation of HbA1c, FSH, LH and Estradiol

Overall (n=109)				
	HbA1c	FSH	LH	Estradiol
HbA1c	1	-0.300*	0.035	-0.043
FSH	-	1	0.164	0.119
LH	-	-	1	0.115
Estradiol	-	-	-	1
T1D subjects (n=54)				
	HbA1c	FSH	LH	Estradiol
HbA1c	1	-0.025	-0.097	-0.067
FSH	-	1	0.415*	0.178
LH	-	-	1	0.16
Estradiol	-	-	-	1
Non-DM subjects (n=55)				
	HbA1c	FSH	LH	Estradiol
HbA1c	1	-0.108	-0.135	-0.023
FSH	-	1	0.137	0.118
LH	-	-	1	0.051
Estradiol	-	-	-	1

Table 3: Linear regression analysis expressing association of QoL, hormonal levels and HbA1c among T1D subjects

Parameters	Standardized Coefficients (β)	P-value
FSH	0.032	0.838
LH	0.029	0.851
Estradiol	0.035	0.807
HbA1c	0.221	0.109

Table 4: Linear regression analysis expressing association of HbA1c and hormonal levels among T1D subjects

Parameters	Standardized Coefficients (β)	P-value
FSH	-0.27	0.006*
LH	0.082	0.393
Estradiol	-0.021	0.828

We found that the levels of LH and Estradiol were almost similar in both groups while FSH was found to be significantly lower in T1D subjects as compared to non-DM subjects. Agnieszka Zachurzok *et al*., also found no significant differences in examined hormonal profile in relation with LH and Estradiol between girls with T1D and healthy controls. They found LH levels as well as LH/FSH ratio in diabetic girls not significantly lower than in healthy controls (Coons & Shubrook, 2021).

A significant adverse impact on QoL score in one-fourth of adolescents with T1D in current study. Our studies revealed overall mean percentage score of QoL as 26.94±1.36. Findings are positively associated to the

previous studies who (Kent & Quinn, 2018, Kumar *et al*, 2020). noted mean DAWN QOL score 29.3. Among the sub domains, the adverse impact was related to the parent's issues i.e. (mean ± SE: 74.07±3.56), followed by health perception (mean ± SE: 31.94±2.51) and impact of symptoms (mean±SE: 29.94±3.05). This outcome correlates with the younger age of children as they were more conscious and possessive about their healthy life style and less worried about inadequacies that execute by diabetes.

The treatment of diabetes focuses mainly on metabolic control to not only determine the evolutionary pattern of the disease but also ensure a higher QoL. The mechanism behind children's metabolic control ability deteriorations is due to hormonal changes similar to psychological & behavioral factors (Janez *et al*, 2020). A contemporary cohort study of 2602 diabetic patients with an average age of 13 years showed that poor metabolic management assessed by HbA1c measurement is associated with poor QoL (Yang, Yang & Li, 2021). However, other study (Parviainen, *et al*, 2020) had not established a connection between HbA1c and QoL, or detected an inverse association.

In other observation, adolescents with a delayed diagnosis of DM had worse HRQOL. The correlation between the happiness of young people and the longer duration of disease indicates the deterioration of QoL (Lukács, 2018).

CONCLUSION

Type 1 Diabetic subjects were shorter and underweight than non-Diabetes Mellitus adolescents. Gonadotropins were found to be similar in both groups while only FSH was found to be lower in T1D subjects. This study can enable researchers to evaluate the levels of gonadotropins and estradiol in T1D girls and facilitate clinicians to take necessary measures for early intervention and better treatment globally for planning, which can enable the patients to sustain their normal reproductive functioning.

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