Original Research Article

The association of adult male and female infertility with celiac disease patients in Yemen

Abstract

Celiac disease's potentially destructive effect on reproductive health is among the most vital matters associated with progress awareness. Men and women with unexplained infertility, women with recurrent abortions, intrauterine growth retardation, low birth weight babies and menstrual disorders are not often screened for celiac disease (CD) despite scientific studies that point to a correlation. The aims of the present study were to examine the evidence of the correlation between CD and infertility by measuring sex hormones in CD comparing healthy controls (HC).

The study was carried out in Autoimmune Unit, AL-Thowra Hospital Sana'a city, Yemen. The study included 32 CD patients, and 32 HC. Blood samples were collected then examined for sex hormones in both groups, also auto-immunological markers of CD; and biochemistry markers were completed for both groups.

All auto-immunological markers of CD were positive in all CD and negative in HC. There was highly significant low down level of the mean ± SD of sex hormones among male and female CD than HC: for male CD FSH=1.96±1.4 IU/ml vs 3.3±1.27 IU/ml of HC, LH=3.9±3.3 IU/ml vs 6.5±2.03 IU/ml of HC; and the testosterone=1.03±0.76 IU/ml, vs 3.8±1.4 IU/ml of HC. For CD females the mean ± SD of FSH, for CD females was 4.37±2.46 IU/ml vs 4.92±2.35 IU/ml of HC, Estradiol (40.7±30.8 IU/ml vs 7.1±76.66 IU/ml of HC), and Progestrone (1.2±1.15 IU/ml, vs 6.4±4.38 IU/ml of HC). In conclusion, there was significant association between CD and infertility among Yemeni CD patients in which it indicated by low sex hormones in CD patients.

Key words: celiac disease, infertility, sex hormones, Sana'a, Yemen

Introduction

Celiac Disease (CD) is an autoimmune condition activated by the ingestion of gluten, the protein fraction of wheat, barley and rye. As in other autoimmune diseases, celiac disease is the result of an immune response to self-antigens leading to tissue destruction and the auto antibodies production. [1] It is important to consider that not all gluten T-cell epitopes are equally immunogenic and that many parts of gluten do not stimulate CD4+ T cells. In HLA-DQ 2.5-positive individuals, T-cells response directed against α- and ω-gliadins are clearly immune-dominant. [2] Some gluten peptides efficiently elicit inflammatory T-cell responses whereas others do not. It is inclined by at least three factors knowing: (a) resistance to proteolytic degradation, (b) substrate affinity to TG2 and (c) specificity to bind HLA molecules.[3]

Celiac disease's potentially destructive result on reproductive health is among the most urgent matters associated with progress awareness. Men and women with unexplained infertility, women with recurrent abortions, intrauterine growth retardation, low birth weight babies and menstrual disorders are rarely screened for celiac disease despite scientific studies that specify a correlation.[4] Not less than ten percent of the reproductive age population in the developed and developing countries suffers from infertility.[5, 6] Infertility is normally diagnosed when people are incapable to regard after six-to-12 months without using birth control, depending on several factors, such as age. Women with recurrent spontaneous abortions are also considered infertile.[7] In an attempt to have children, couples seek various treatments, such as surgery or artificial insemination. The average couple spends about $10,000 per attempt on Assisted Reproductive Technology (ART). On the

other hand, nearly one third of all pregnancy losses are the result of undiagnosed, and/or treatable diseases.[8] The aims of this study were to determine the relationship between infertility among Yemeni CD, by estimating the level of female/male sex hormones in CD comparing with their level in HC.

Subjects and methods

Study area and Study population

This cross-sectional study was conducted among 32 CD patients whom diagnosed from patients attending Autoimmune Unit, AL-Thowra Hospital Sana'a city, Yemen, starting in June and ending in August 2017. All CD and HC were older than 14 years. Also the study included 32 HC selected from community resembling cases in sex, age group and socioeconomic status. Blood samples were collected from both groups then investigated for sex hormones, auto-immunological markers of CD; and biochemistry markers.

Sample size

The sample size of our study was determined by Epi-Info version 7. For the population of Sana'a city (2,000,000) and expected frequency of 2% of CD in Yemen (CD in Middle East 2% according to Rostam. et al. [9] with acceptable margin of error equal to 3.5%, at least 32 CD patients and 32 healthy controls in confidence level equal to 95% for 2 clusters were needed.

Data collection

All participants gave oral consent, completed a questionnaire, and had blood drawn for sex hormones, auto-immunological markers of CD; and biochemistry markers testing. The questionnaire covered demographic data, body mass index for CD and HC and illness information for CD patients.

Laboratory methods

Ten ml whole blood was collected by vein puncture; then sera were separated and tested for the auto-immunological markers of CD including of tTG IgA, tTG IgG, AGA IgA, AGA IgG and EME; male hormones and female hormones; and plasma triglycerides, total cholesterol, HDL-cholesterol and LDL-cholesterol. The testes reagents porches from well known sources and procedures for every test were done according to the manufacturer's direction. For autoimmune markers the source was EUROIMMUN, GERMANY for Anti-tissue Transglutaminase ELISA (IgA, and G) , for Anti-Endomysial Antibody (EMA) was ImmuGlo (GERMANY). The sources for sex hormones; and plasma triglycerides, total cholesterol, HDL- cholesterol and LDL-cholesterol, was Roche diagnostics, Germany.

Results

There was significant different between the mean ±SD of male sex hormones of celiac patients group comparing with healthy controls in which very low values recorded in CD patients. The mean ±SD of FSH for CD patients was 1.96 ± 1.4 IU/ml, lower than 3.3±1.27 IU/ml of healthy controls, and LH for CD patients was 3.9 ±3.3 IU/ml, lower than 6.5±2.03 of healthy controls. The mean ±SD of testosterone for CD patients was 1.03± 0.76 IU/ml, lower than 3.8± 1.4IU/ml of healthy controls. The variations were highly significant in which P values were less than 0.05 for all results (table 1). There was significant different between the mean ±SD of Estradiol and progesterone hormones of celiac patients group comparing with healthy controls in which very low values recorded in CD patients, while no difference occurred for FSH. The mean ±SD of FSH for female CD patients was 4.37 ± 2.46 IU/ml, roughly similar to 4.92±2.35 IU/ml of healthy controls, while Estradiol for female CD patients was 40.7 ±30.8 IU/ml, lower than 137.1±76.66 IU/ml of female healthy controls (3.4-folds). The mean ±SD of progesterone for female CD patients was 1.2±1.15 IU/ml, lower than 6.4± 4.38 IU/ml of female healthy controls (4-folds). The variations were highly significant in which P values were less than 0.05 for all results (table 2).

Discussion

When we compared between the serum level of sex hormones among our CD females as shown in table 2, there was no difference in the mean ± SD of FSH for CD females (4.37±2.46 IU/ml) comparing with (4.92±2.35 IU/ml) of the healthy control females. However, there was highly significant low level of estradiol in CD patient group in which the mean ± SD Was 40.7±30.8 IU/ml while for healthy controls estradiol was 137.1±76.66 IU/ml. Furthermore, there was highly significant low level of progestrone in CD patient group in which the mean ±SD Was 1.2±1.15 IU/ml while for healthy controls it was 6.4±4.38 IU/ml. Our previous results confirmed the negative effect in fertility of CD in female CD patients. It is recognized that while infertility in 27 % of infertile couples is the result of ovulation disorders and 25 % the result of identified male disorders, 17% of couples remain infertile for unexplained reasons which might be CD is one of them.[10] Pellicano *et al*.[11] have found the rate of celiac disease to be 2.5 to 3.5 times greater in women with unexplained infertility than in women with normal fertility. The possible relationship between proper nutrition in females and the capacity to regard is an additional worthy note. It has been recommended that positive energy balance, as well as increased fat storage in females as a result of proper nutrition, produces an environment within the reproductive system that enhances a female's potential to consider. A range of ovarian function has been proposed, signifying that ovarian function and associated fruitfulness may be subject to minor alters in energetic environment, creating changes below the "clinical horizon" of menstruation. The rates of ovarian steroid genesis in women with positive energy stabilities are significantly higher than in those in negative energy stabilities who are subject to follicular suppression.[10,12] Malnutrition and its resulting symptoms most commonly present in undiagnosed females with celiac disease. This sign can directly compromise the potential and ability to picture due to a negative energy balance and the decreased ability to maintain fat storage in distress females. Those females with undiagnosed celiac disease and who do not follow a gluten-free diet may intensify unfavorable conditions for conception within the body and, more specifically, within the reproductive system.[13]

Once we compared between the serum level of sex hormones among males as shown in table 1, there is highly significant low down level of sex hormones among male CD patient group in which the Mean±SD of FSH was 1.96±1.4 IU/ml while for healthy controls FSH was 3.3±1.27 IU/ml. As well, there is highly significant low down level of LH in CD patient group in which the Mean±SD of LH was 3.9±3.3 IU/ml whereas for healthy controls LH was 6.5±2.03 IU/ml. What's more there is highly significant low down level of testosterone in CD patient group in which the Mean±SD of the testosterone hormone was 1.03±0.76 IU/ml, at the same time as for healthy controls testosterone was 3.8±1.4 IU/ml higher than that of CD group. Our prior results confirmed the destructive effect in fertility of CD in male patients. It is recognized that men also suffer from infertility stemming from undiagnosed celiac disease.[10, 13] Affected males show a picture of tissue resistance to androgens. The increases of follicle-stimulating hormone and prolactin may indicate an imbalance at hypothalamus-pituitary level.[14] Hypogonadism is a known factor in male infertility and has been found in 7% of celiac males in one survey. Endocrine dysfunction unaccompanied by other features of hypogonadism was found commonly and 19% of male celiac were infertile.[14] Moreover, it is well-known that improvement in semen quality and successful pregnancy in previously infertile women is associated with gluten removal by their male partners. The majority outstanding endocrine findings in a study of 41 newly diagnosed men with celiac disease was increased plasma testosterone and free testosterone index, reduced dihydrotestosterone (testosterone's potent peripheral metabolite), and elevated serum luteinizing hormone, a pattern of abnormalities indicative of androgen resistance. When jejunal morphology

improved, hormone levels restored to normal.[12,13] These higher rates of infertility among victims of celiac disease, in addition to improvement associated with the gluten-free diet, point out the value of celiac-related antibody testing in couples, both the male and female partners with unexplained infertility.[12]

Conclusions

The current study is the first study of celiac disease and its association with infertility among Yemeni, the CD appear to be relatively common in Yemen. There was low level of male and female sex hormones in CD patients , comparing with normal level in Yemeni healthy adults which indicate infertility negative effect of CD.

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Conflicts of Interest

The authors would like to clear that No conflict of interest associated with this work.

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Table 1: The mean ±SD of male sex hormones markers namely FSH, LH and testosterone of celiac patients group comparing with values of control group.

Hormones	**Celiac disease Group (n = 10) The mean ±SD/IU/ml**	**Control Group (n = 10) The mean ±SD**	**P-value**
FSH IU/ml	1.96± 1.4	3.3± 1.27***	0.001
LH IU/ml	3.9±3.3	6.5±2.03***	0.0001
Testosterone IU/ml	1.03±0.76	3.8±1.41***	0.01

Data are expressed as means ± SD, vs. control (*p < 0.05, **p < 0.01, ***p < 0.0001)

Table 2: The mean ±SD of female sex hormones markers namely FSH, ESTRADIOL, and progesterone of celiac patients group comparing with values of control group.

Hormones	**Celiac disease Group (n = 22)**	**Control Group (n = 22)**	**P-value**
FSH IU/ml	4.37±2.46	4.92± 2.35***	0.0001
ESTRADIOL IU/ml	40.7±30.8	137.1±76.66***	0.0001
PROGESTRONE IU/ml	1.2±1.15	6.4±4.38***	0.0001

Data are expressed as means ± SD, vs. control (*p < 0.05, **p < 0.01, ***p < 0.0001)