Assessment of Pancreatic Beta-Cell Function and the Ovarian Function in A sample of Type 1 Iraqi Diabetic Women

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Abstracts

Objective: The study was designed to correlate the residual beta cell secretary capacity with the ovarian function in Iraqi diabetic women.

Setting: Department of physiology, Medical College of Al-Mustansiriyah University in cooperation with the Iraqi National Diabetes Center (NDC) of Al- Mustansiriyah University in Baghdad from November 2004 till November 2005.

Outcomes measures: Residual Beta cell function was estimated by measuring C-peptide level by radioimmunoassay technique while ovarian function was estimated by measuring serum levels of FSH, LH, Progesterone and Estrogen using enzymatic Link Fluorescent assay technique.

Results: Data showed that the C-peptide level in type 1 diabetic subjects was significantly lower than the control subjects ($p < 0.0001$).C-peptide was significantly correlated to glycemic control expressed by HbA1c while it was not significantly correlated with fasting plasma glucose.

Also C-peptide showed no significant correlation with the, FSH, LH, progesterone, and estradiol levels in diabetic subjects and the healthy control group.

Conclusions: The present data reflects the deleterious effect of beta cell secretary capacity dysfunction on hyperglycemia and emphasizes that this decrease in beta cell capacity had no effect on ovarian function except for Progesterone.

Keywords: C-peptide, FSH, LH, progesterone, estradiol.

Introduction

C-peptide levels can serve as a valuable index for insulin secretion. Thus, low C-peptide levels are to be expected where insulin secretion is diminished, as in insulin-dependent diabetics, or suppressed, as a normal response to exogenous insulin .As insulin assay cannot be used to distinguish endogenous from exogenous insulin [1].

C-peptide measurement have been used to yield information on the natural history of insulin dependent diabetes, to indirectly monitor insulin secretion in the presence of anti-insulin antibodies, and help to settle an appropriate course of treatment [2,3,4,5].

The half-life of C-peptide in plasma has been estimated as approximately 30 minutes compared to approximately 5 minutes for insulin. So C-peptide measurement is easier and more informative. C-peptide level is a measure of B-cell secretary capacity in basal state and after stimulation [6, 2, 5].

It has been shown that serum C-peptide concentration in normal subjects after oral glucose tolerance test (OGTT), gives a more uniform response pattern than does insulin concentration. They attributed this finding in part to variation in insulin uptake and degradation by the liver [7].

Diabetes mellitus, both in Type 1 and Type 2 can cause various endocrine disorders by affecting the secretion, metabolism, clearance or bioavailability of hormones. Diabetes has many effects on the hypothalamo–pituitary– gonadal axis, including impaired gonadotropin release, which may be due to abnormal generation of gonadotropin–releasing hormone (GnRH) pulses in the hypothalamus [8].

In girls, Type 1 DM can delay menarche & diabetic women have anovulatory cycles, with oligo – or amenorrhea. Uncontrolled insulin–deficient diabetes can profoundly disturb gonadotropin secretion in humans and other species. Most diabetic women with amenorrhea or oligomenorrhea have anovulation with low or normal basal gonadotropin levels despite low estrogen levels [9, 10].

The age of menarche amongst women who developed Type 1 DM before the age of 10 years may be delayed by a year compared with non-diabetic controls, and the overall prevalence of menstrual disturbances (oligomenorrhea and secondary amenorrhea) is increased [11,12].

Amenorrheic diabetic women have fewer luteinizing hormone (LH) pulses and secretory episodes than normal women, and the responses of LH to exogenous GnRH have been reported to be normal or decreased. It is therefore possible that the GnRH pulse–generator is compromised, rather than primary pituitary dysfunction being responsible in these women [13].

Serum follicular–stimulating hormone (FSH) levels are usually normal.

Raised LH / FSH ratios are observed, with a high incidence of polycystic ovarian changes diagnosed by ovarian ultrasound [12, 14].

Improving glycemic control in a group of Type 1 DM women with hypogonadotrohpic secondary amenorrhea neither restored normal menstruation nor improved basal or GnRH–stimulated LH levels [10].

About 40 % of diabetic women treated with insulin did show some change in insulin requirements around the time of menstruation. Patterns vary from one individual to another, the more common being a modest increase in insulin requirement for the first 2 days or so of menstruation [15].

About 10 % of diabetic women experience a decrease in insulin requirements just before and on first day of menstruation, and increase at midcycle, and this can be difficult to manage, particularly if their cycles irregular [16] .

The aim of this study is to find any correlation between the degree of reduction in beta cell secretary capacity and the hormonal levels of both the ovaries and pituitary hormones in Type 1 Iraqi diabetic women at the reproductive age.

Subjects & methods

Sixty types 1 Iraqi diabetic woman with a mean age of 30.38 ± 6.2 years were enrolled in this study in comparison to 60 healthy women of matched age (30.47±6.5 years) and with normal oral glucose tolerance test as a control group. The duration of diabetes was 10.66+ 4.27 years.

All women were tested for FSH and estradiol at midcycle while LH and progesterone were tested at 21st day of the menstrual cycle using the enzyme link fluorescent assay technique (ELISA).

Glycemic control was assessed using fasting plasma glucose and glycated hemoglobin as indicators. The residual beta cell secretary capacity was estimated by using the radioimmunoassay technique (RIA) for C-peptide measurements.

All diabetic women were attending the National Diabetic Center and all were with normal renal and hepatic function, the gynecological and ultrasonic examinations were performed by specialists.

Results

Sixty healthy women represent the control group. All the studied parameters are shown in table 1. The values are expressed as mean ± S.D with the range of each parameter is shown also.

There was no significant correlation between C-peptide and all other parameters in the control group as shown in table 2.

Table 1: The tested parameters of the control group (anthropometric and hormonal levels).

Tested Parameters	Mean ± S.D n = 60	Range
Age (years)	30.47 ± 6.58	16 – 42
B M I kg/m²	26.06 ± 2.55	20.14 – 29.5
F P G mg/dl	88.03 ± 6.34	74 – 105
$HbA_{\square c}$ %	4.87 ± 0.34	4.2 – 5.6
Menarche (ys.)	13.03 ± 1.25	11 – 15
C-peptide (pm/L)	686.8 ± 225.9	380 – 1148
F S H mlU/ml	5.15 ± 2.19	1.8 – 11.1
L H mlU/ml	11.8 ± 8.1	3.2 – 29.8
E2II pg/ml	164.4 ± 59.4	84.6 – 350
Progesterone ng/ml	12.4 ± 3.6	3.6 – 20.8

Table 2: The correlation between C-peptide and all parameters in the control group.

Tested parameters	Control n = 60 C-peptide pm/L	
	r – value	P – value
Age (ys.)	- 0.27	0.14
Menarche (ys.)	- 0.25	0.28
F P G mg/dl	0.04	0.83
$HbA_{\square c}$ %	- 0.28	0.12
FSH mlU/ml	0.04	0.82
LH mlU/ml	- 0.18	0.34
E2II pg/ml	- 0.31	0.09
PRG ng/ml	- 0.04	0.8
B M I kg/m^2	- 0.01	0.95

Type 1 D.M. subjects

Table 3 showed that there was no difference between this group and the control group concerning age and BMI.

The FPG 192.7 ± 87 mg/dl and $HbA_{\square c}$ (8.83 ± 2%) in this group were significantly higher than the control group (FPG: 88.03 ± 6.34 mg/dl and $HbA_{\square c}$: 4.87 ± 0.34%) (P-value < 0.0001). Also, the mean age at menarche was statistically higher in type 1 diabetic women compared with non diabetic women (14.06 ± 1.42 ys., 13.03 ± 1.25 ys.) respectively (P – value < 0.002).

Table 4 showed the C-peptide and hormonal assay levels of FSH, LH, E2II and Progesterone measured in the control subjects and type 1 diabetic woman.

The C-peptide was significantly lower in type 1 D.M. (103.5 ± 123.3 pm/L) than in the healthy women (686.8 ± 225.9 pm/L) (P–value < 0.0001).

Also Progesterone level was significantly lower in type 1 D.M. women (7.73 ± 6.04 ng/ml) than the control subjects (12.4 ± 3.6 ng/ml) (P – value < 0.0001).

FSH, LH, and E2II showed no significant difference between diabetic and the healthy women, (Table 4).

Table 5 showed that there was no significant correlation between C-peptide and all parameters in type 1 D.M. subjects except for $HbA_{\square c}$ (P – value < 0.0001).

Table 3: The tested parameters for type 1 D.M. patients compared with control subjects.

Tested parameters	Control n = 60 Mean ± S.D	Type 1 n = 60 Mean ± S.D	P – value
Age (ys.)	30.47 ± 6.58	30.31 ± 6.92	0.922
B M I kg/m^2	26.06 ± 2.55	25.02 ± 3.15	0.129
F P G mg/dl	88.03 ± 6.34	192.76 ± 87	0.0001*
$HbA_{\square c}$ %	4.87 ± 0.34	8.83 ± 2	0.0001*
Menarche (ys.)	13.03 ± 1.25	14.06 ± 1.42	0.002*

* P – value < 0.05

Table 4: The tested hormonal parameters and C-peptide levels for type 1 D.M. patients compared with control subjects.

Tested parameters	Control n = 60 Mean ± S.D	Type I n = 60 Mean ± S.D	P – value
C-peptide (pm/L)	686.8 ± 225.9	103.5 ± 123.3	0.0001*
FSH mlU/ml	5.15 ± 2.19	5.13 ± 3.31	0.98
LH mlU/ml	11.8 ± 8.1	12.39 ± 9.99	0.78
E2II pg/ml	164.4 ± 59.43	166.37 ± 103.3	0.33
PRG ng/ml	12.4 ± 3.6	7.73 ± 6.04	0.0001*

* **P – value < 0.05**

Table 5: The correlation between C-peptide and all parameters in the type 1 D.M. subjects.

Tested parameters	Type 1 n = 60 C-peptide pm/L	
	r – value	P – value
Age (ys.)	0.12	0.38
Duration (ys.)	- 0.18	0.19
Menarche (ys.)	- 0.26	0.06
F P G mg/dl	- 0.09	0.52
$HbA_{□c}$ %	-0.001	0.0001*
FSH mlU/ml	0.04	0.76
LH mlU/ml	- 0.02	0.86
E2II pg/ml	0.24	0.09
PRG ng/ml	0.17	0.23
B M I kg/m²	- 0.07	0.58
Regular mense	- 0.1	0.59

* **P – value < 0.05**

4- Discussion

The control group

In the present study, no significant correlation was found between C-peptide level and FPG, FSH, LH, E2II and PRG.

The basal serum C-peptide level in healthy women was found to be 686.8 ± 225.9 pmol/L (ranging from 380 to 1148 pmol/L). This figure is nearly compatible with the previous values reported by another similar Iraqi studies [17, 18].

No significant correlation was found between basal C-peptide level and FPG in our control subjects (r = 0.04, P = 0.833). These results are in agreement with Ludvigson and Heding [19], but disagree with Bonser and Webb [20] who found a very weak but significant correlation between the two parameters (r = 0.21, P < 0.001)

Type 1 D.M. group

The 60 diabetic women with duration of D.M. equals to 10.66 ± 7.24 years showed no significant difference when compared to the control group regarding BMI, while FPG, $HbA_{\square c}$ in this group were significantly higher than the control group (P – value < 0.001).

The C-peptide level also was significantly lower in type 1 D.M. than in the healthy women. These differences were explained by Atkinson to be attributed to cellular autoimmune destruction of the B-cells of the pancreas leading to insulin deficiency as the main pathophysiological cause of diabetes in type 1[21]. These results are identical to those reported by Hendrikon [22] and Heding [23]. Similar results were mentioned by Alsharify study [17] who showed that C-peptide level was significantly lower in type 1 D.M. subjects than the control healthy group in Iraqi population.

The mean age at menarche was statistically higher in type 1 diabetic women compared with non diabetic women (Table 3). This result is similar to that reported by Dorman, F. [24], and with Elsas et. *al* , [25] who found an about 1 – year delay in menarche with type 1 diabetes as well as a later menarche among those with an earlier age at onset of D.M. [26,27,28,29]. In contrast to the findings of Schriock et al, [30] for non registry cases, we noted that only cases with age of onset < 10 years had a later menarche. Griffin *et. al*, [31] stated that diabetes onset before puberty may disrupt the hypothalamic – pituitary – gonadal axis and / or cause weight loss, decreasing body fat important for menarche to occur.

A relationship between body weight, reproductive function, and gonadotropin secretion has been recognized for many years. Typically, women with low body weight have amenorrhea and functional GnRH deficiency resulting in low serum levels of LH and FSH. [32].

The present study showed that Progesterone level was significantly lower in type 1 D.M. than in the healthy women (Table 4), (P – value < 0.0001). Two possible causes may explain this low progesterone, menstrual cycle dysfunction and irregularity. First, in those diabetic women there may be either a decrease in hypothalamic drive or a decrease in count / quality of acolytes due to an increased rate of artesian, possibly through effects of insulin deficiency. Secondly, the hypothalamic – gonadotropin – releasing hormone (GnRH) pulse generator slows and thus decreasing luteinizing and follicle – stimulating hormone stimulation[31] and in particular, this may occur in women with poor glycemic control [33], and this explanation support our results which showed low progesterone in diabetic women to be associated with poor diabetic control. So low Progesterone may be present with low level of C-peptide.

The other hormones FSH, LH and E2II showed that there were no significant difference between type 1 diabetic patient and healthy women. Also there was no significant correlation found between C-peptide and all parameters measured in type 1 diabetic woman except between C-peptide and $HbA_{\square c}$, (P – value 0.0001). This above finding is in total agreement with the finding reported by Grajwer who stated that there is a positive correlation between C-peptide levels and the metabolic control of D.M. And this explains that the presence of residual beta cell secretory function can facilitate a better [35] control. [34]. And also in harmony with the finding of Sherwin and Feling, who stated that the stability of glycemic control is dependent on the amount of residual endogenous beta cell secretary activity present [35].

There was no similar study that measure C-peptide level, FSH, LH, E2II and PRG in diabetic women and correlated them together. So this is the first step in this long road hopping that more light will be shed on this interesting subject in future.

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