Original Article

The Relationship between Family History and C-peptide Level in Type2 Diabetic Patients

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Summary:

Background: Family history of type 2 diabetes is a major risk factor for type 2 diabetes. Type 2 diabetes is characterized by progressive β-cell dysfunction; many investigators have used C peptide levels as a biomarker of β-cell function.

Objective: the current study was design to investigate the impact of family history on biochemical characteristics (c-peptide, HbA1c, lipid profile, insulin secretion, insulin sensitivity and insulin resistance.

Subjects and methods: three hundreds patients (152 males 148 females) with type 2 DM were enrolled in this study; and two hundreds individual serves as a control groups (103 male 97 female). The following clinical characteristics were reported: age, sex, waist circumference WC, systolic blood pressure SBP, diastolic blood pressure DBP, family history, body mass index BMI, laboratory analyses included serum c-peptide, blood glycosylated hemoglobin (HbA1c) assay, lipid profile which included serum cholesterol, serum triglyceride(TG), serum low density lipoprotein cholesterol (LDL) and serum high density lipoprotein-cholesterol (HDL). Insulin secretion, sensitivity and resistance were calculated from fasting serum glucose (FSG) (mg/dl) and C-peptide (ng/ml) values by homeostasis model assessment (HOMA).The statistical analysis was done by SPSS (statistical packagefor social sciences- version 17).

Result: Statistically was observed that highly significant increase in serum C-peptide in patients compared to control group (3.85±1.02 vs 1.53±0.24 $p<0.01$).The patients with a family history of type 2 diabetes mellitus had longer diabetes duration, heavier weight, higher levels of TG, LDL-cholesterol, and lowered age, HDL-cholesterol than those without a family history . Also, the presence of a family history of diabetes was associated with lower levels of fasting plasma C-peptide (3.01± 1.78 vs 4.95±1.82, $p<0.05$). Serum C-peptide had a significant negative correlation with family history and duration of diabetes. Furthermore, C-peptide was inversely correlated with HbA1c, and insulin sensitivity (HOMA-S). On the other hand, C-peptide correlated positively with BMI, DBP, LDL-cholesterol, TG, insulin resistance HOMA-IR, and insulin secretion HOMA-B. As well as, C-peptide did not show significant correlation with age, FSG, and TC. When the multiple linear analysis was executed with C-peptide as dependent variable with other independent variable (BMI, duration, family history, HOMA-IR, HOMA-S, and HOMA-B) there were significant result with this variables. The person correlation analyses to identify the parameters that most closely related with diabetic duration according to family history of diabetes; which showed that diabetic duration had a significant negative correlation with C-peptide, and HOMA-B only in patients with family history of Type2 DM (-0.126, and -0.229) respectively.

Conclusion: the current study suggested that subjects with a family history of diabetes mellitus are predisposed to develop this disease earlier. Although, serum C-peptide increased significantly in diabetics group compared with controls, and C-peptide decreased in patients with family history of diabetes. In addition, the results showed that family history of type2 diabetic patients is thought to have a deep impact on duration of the disease, lipid profile, insulin resistance, insulin sensitivity, and this may lead to higher prevalence of diabetic complication compared to patients without family history. These results support the necessity of earlier screening for diabetes in family members of T2DM patients and prevention the complications of the disease.

Key word: family history, c-peptide, lipide profile, insulin resistance.

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Introduction:

Type 2 diabetes is a common metabolic disorder characterized by insulin resistance and β-cell dysfunction[1], β-cell function may have a crucial role in the progression and development of type 2 diabetes. Both β-cell dysfunction and insulin resistance are considerable phenotypic heterogeneity among individuals[2,3].Numerous studies on etiological factors of type 2 diabetes have been conducted; in particular, the genetic factor is c secretion defect[4], insulin resistance[5,6], or both which are related to early onset of the disease[7,8]. onsidered to be important in relation to insulin Therefore studies, on family history of diabetes are necessary to determine the genetic factors of type 2 diabetes mellitus (DM) and to establish the effective preventive measure for high risk group[9].A number of studies

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have accounted on the impact of family history (FH) of type 2 DM on the clinical characteristics of these patients[10,11]; but few studies have assessed the effects of FH of DM on residual β-cell function. C-peptide is a hormonally active peptide[12], Patients with diabetes can lead relatively normal lives when treated with the hormone insulin, a report done by Ido et al[13] suggests that these complications might be alleviated by the simultaneous administration of C-peptide, a protein fragment cleaved from insulin during its synthesis; C-peptide is made when proinsulin is splited into two different sites to form active insulin and C-peptide. They are splited before proinsulin is released from endocytic vesicles within the pancreas one C-peptide for each insulin molecule[14]; C-peptide is secreted in equimolar amounts along with insulin and is not extracted by the liver; the clearance rates of C-peptide are constant over the range of C-peptide levels. Thus, in practice, C-peptide levels have been used as an indirect measurement of β-cell function [15-17].However, many researchers have supposed that a family history of diabetes has influence on the metabolic aspects of patients; the current study was designed to examine the impact of family history of diabetes on some biochemical characteristics of DM (c-peptide, HbA1c, lipid profile, insulin secretion, insulin sensitivity and insulin resistance).

Patients and Methods:

A total of 500 subjects were examined in this study including 300(152 male, and 148 female) type 2diabetes mellitus patients, who were referred to the national diabetes center, AL- Mustansirya University, and 200 healthy individuals who served as a control group (103 male, and 97 female).Medical history was taken by personal interviewing .exclusion was made for those who had a concurrent acute illness or another major systemic disease. Also patient who were taking lipid lowering agents or were smokers were excluded as well as those who had evidence of ischemic heart disease or ischemic stroke. All subjects were matched with age, and BMI. Weight and height were measured in indoor clothing without shoes; and the body mass index BMI was calculated as weight (kg)/height^2 (m^2). Waist circumferences (WC) were measured in a horizontal plane midway between the inferior margin of the ribs and the superior border of the iliac crest. Blood pressure (systolic SBP and diastolic DBP) was measured twice on the right arm using standard mercury sphygmomanometer while the patient was sitting after resting for 10 min. Blood samples were taken after overnight fasting; serum was separated, store at -80 ^{0}C, and were analyzed at later time. Laboratory evaluations consisted of measuring glycemic control including (fasting serum glucose (FSG), glycated hemoglobin (HbA_{1c}), lipid profile [total cholesterol (TC), triglycerides (TG), high density lipoprotein (HDL), and low density lipoprotein (LDL)], c-peptide, insulin sensitivity and insulin resistance. Hemoglobin A_{1c} program intended for the determination of Glycated hemoglobin ($A1_c$) in human depended on high performance liquid chromatography and who supplied by Variant Company, USA. Glucose level was determined using kits supplied by spinracte, Spain. Total cholesterol TC, Triglycerides, High density lipoprotein (HDL) was determined using kits from (biomaghreb, France). Low density lipoprotein (LDL) was calculated mathematically using the Friedwald formula.

C-peptide assay: the serum c-peptide was measured by immunoradiometric assay (IRMA) technique; IMMUNOTECH s.r.o kit was supplied from Germany. Insulin secretion, sensitivity and resistance were calculated from FSG (mg/dl) and C-peptide (ng/ml) values by homeostasis model assessment (HOMA) using HOMA-CIGMA software (HOMA2 calculator program)[18].The homeostasis model assessment (HOMA) estimate steady state beta cell function (B%) and insulin sensitivity (S%), as percentages of a normal reference population. The HOMA Calculator has been a tool for assessing the insulin sensitivity (S %) and beta cell function (B %), for professionals in the health care field. This program can assist you in managing Type 2 diabetes, but not by replacing a formal medical assessment.

Statistical analysis:

Data were analyzed using the computer facility with available statistical packages of SPSS 17.0 (statistical packages for social sciences-version 17.0).Data was presented in simple measure of number, mean, SD and the parametric statistical tests were used namely student t-test for independent samples was used to test the difference in mean between two groups. P-value less than 0.05 was used as the level of significant, and P-value less than 0.01 was used as the level of a highly significant. Pearson correlations coefficient were used to analyze the relationship between variables, which is significant at the 0.05 level (2-tailed). Multiple linear regression analyses were conducted to determine association between fasting serum C-peptide level and a family history of type 2 diabetes mellitus. Statistical analysis was performed after adjustment for confounding variables.

Results:

The clinical and biochemical characteristics of patients and controls were presented in Table1, which showed that patients and controls were matched with age, sex, waist circumference WC, and BMI. There was a highly significant increased in serum C-peptide in patients compared to control group (3.85±1.02 ng/ml vs 1.53±0.24 ng/ml $p<0.01$). Moreover, there were a significant increased in serum fasting glucose, HbA1c, triglycerides TG, LDL-cholesterol, and HOMA-IR in diabetic patients compared to control group (210.1± 75.84 mg/dl vs 95.25±19.18 mg/dl, $p<0.01$; 8.17 ± 2.06% vs 5.19 ±0.89% $p<0.01$; 176.08±50.7 mg/dl vs 127.88 ±15.34 mg/dl $p<0.01$; 125.13±21.45 mg/dl vs 90.3± 20.34 mg/dl, $p<0.05$;

5.37 ±1.03 vs 2.01± 0.27, p<0.01) respectively. While, there were a highly significant decreased in HOMA-S, and HOMA-B in diabetic patients compared to control group (35.34±12.41 vs 8010.81±42., p<0.01; and 59.88±19.67 vs 10570.1±37., p<0.01) respectively. But, there were no significant differences in SBP, DBP, TC, and HDL between the two groups.

Table 2 summarized the general characteristics of the patients group according to the presence of diabetic family history; which showed that the patients with a family history of type 2 diabetes mellitus had longer diabetes duration, heaver weight, higher levels of TG, LDL-cholesterol, and lowered age, HDL-cholesterol than those without a family history (11.8 ± 4.8 vs 8.4 ± 3.2 yrs, p<0.01; 79.28 ± 13.8 vs 73.50 ± 11.2 kg, p<0.05; 190.98 ±60.7 vs 167.88 ±66.34 mg/dl, p<0.05; 125.7±31.45 vs 123.57± 33.34 mg/dl, p<0.05; 49.98±10.03 vs 52.1 ±11.22 yrs, p<0.01;40.83 ±4.43 vs 42.03±3.32 mg/dl, p<0.05) respectively. Also, the presence of a family history of diabetes was associated with lower levels of fasting plasma C-peptide (3.01± 1.78 vs 4.95±1.82, p<0.05). Patients with a family history showed a higher insulin resistance (HOMA-IR) and lowered insulin sensitivity (HOMA-S) as measured by HOMA-2 calculator (6.98 ±2.03 vs 3.01± 0.27, p<0.01; 32.01±10.31 vs 40.89 ± 14.34; p<0.05). In the other hand there were no differences in age, body mass index, waist circumference, SBP, DBP, fasting blood glucose, HbA1c, TC, and HOMA-B between the two groups. Pearson correlation analysis was used to identify the parameters that most closely related to serum C-peptide as shown in Table3; which showed that serum C-peptide had a significant negative correlation with family history and duration of diabetes (r= -0.103, and r=-0.106; p<0.05) respectively. Furthermore, C-peptide was significantly negatively correlated with HbA1c, and insulin sensitivity (HOMA-S) (r= -0.114, p<0.05; and r=-0.676, p<0.01) correspondingly. On the other hand, C-peptide significantly posatively correlated with BMI, DBP, LDL-cholesterol, TG, HOMA-IR, and HOMA-B (r= 0.204, p<0.01; r= 0.106, p<0.05; r=0.127, p<0.05; r=0.349, p<0.01; r=0.209, p<0.01, r= 0.662, p<0.01) respectively. As well as, C-peptide did not show significant (P<0.05) correlation with age, FSG, and TC.Table4 showed multiple linear regression analyses with C-peptide as the dependent variable with other variables as independent; and the result showed significant relation between C-peptide and some independent variable (BMI, duration, family history, HOMA-IR, HOMA-S, and HOMA-B. Table5 showed the person correlation analyses to identify the parameters that most closely related with diabetic duration according to family history of diabetes; which showed that diabetic duration had a significant negative correlation with C-peptide, and HOMA-B only in patients with family history of Type2 DM (-0.126, and -0.229) respectively.

Table1. The general characteristics of patients and control

	G1:Patients	G2:Control
No.	**300**	**200**
Age, yrs	**50.9±10.28**	**50.3 ±10.01**
Sex (M:F)	**(152: 148)**	**(103: 97)**
Weight (kg)	**77.16±12.23**	**77.01 ±11.29**
BMI (kg/m²)	**28.52±6.63**	**28.08 ±5.98**
WC (cm)	**98 ± 3.3**	**99 ± 5.1**
SBP (mmHg)	**128.3±17.1**	**126 ± 16.89**
DBP (mmHg)	**78.3 ± 11.5**	**77.3 ± 11.01**
Duration (yrs)	**9.85 ±4.02**	**-------**
FSG (mg/dl)	**210.1± 75.84****	**95.25±19.18**
$HbA1_c$ %	**8.17 ± 2.06****	**5.19 ±0.89**
TC (mg/dl)	**203.45 ± 60.86**	**166.17± 15.34**
TG (mg/dl)	**176.08 ±50.7****	**127.88 ±15.34**
HDL-C (mg/dl)	**41.21 ±3.46**	**41.89 ± 3.34**
LDL-C (mg/dl)	**125.13±21.45***	**90.3± 20.34**
C-peptide (ng/ml)	**3.85±1.02****	**1.53±0.24**
HOMA-IR	**5.37 ±1.03****	**2.01± 0.27**
HOMA-S%	**35.34±12.41****	**8010،81±42،**
HOMA-B%	**59.88±19.67****	**10570،1±37،**

Data are mean ± SD, *P<0.05 was considered significant, and **P<0.01 is a highly significant.

Table2: the general clinical characteristics in patients according to Family history

	Patients	
	Family History (+)	**Family History (-)**
No.	**160**	**140**
Age, yrs	**49.98±10.03****	**52.1 ±11.22**
Sex (M:F)	**(81: 79)**	**(71: 69)**
Wight (kg)	**79.28 ± 13.8***	**73.50 ± 11.2**
BMI (kg/m²)	**28.9±7. 3**	**28.01 ±5.8**
WC (cm)	**98 ± 2.3**	**97 ± 3.01**
SBP (mmHg)	**128 ±16.01**	**128.8 ± 17. 9**
DBP (mmHg)	**78.1 ± 10.8**	**78.9 ± 11.21**
Duration (yrs)	**11.8 ± 4.8****	**8.4 ± 3.2**
FSG (mg/dl)	**210.1± 67.8**	**209±87.8**
$HbA1_c$ %	**8.13 ± 1.6**	**8.27 ±2.18**
TC (mg/dl)	**205.5 ± 65.86**	**200.3± 58.4**
TG (mg/dl)	**190.98 ±60.7***	**167.88 ±66.34**
HDL-C (mg/dl)	**40.83 ±4.43***	**42.03±3.32**
LDL-C (mg/dl)	**125.7±31.45***	**123.57± 33.34**
C-peptide (ng/ml)	**3.01± 1.78***	**4.95±1.82**
HOMA-IR	**6.98 ±2.03****	**3.01± 0.27**
HOMA-S	**32.01±10.31***	**40.89 ± 14.34**
HOMA-B	**58.86±13.56**	**60.66±174،**

Data are mean ± SD, *P<0.05 was considered significant, and **P<0.01 is a highly significant.

Table 3:-Correlations of C-peptide with other studied variables in patients

	C-peptide
Age	-0.093
Body mass index	0.204**
SBP	0.001
DBP	0.106*
Fasting blood glucose	-0.087
HbA1c	-0.114*
Total cholesterol	0.015
Triglycerides	0. 349**
HDL-cholesterol	-0.026
LDL-cholesterol	0.127*
Duration	-0.106*
Family history	-0.103*
HOMA-IR	0.209**
HOMA-S	-0.676**
HOMA-B	0.662**

* Correlation is significant at the 0.05 level
**Correlation is significant at the 0.01 level

Table4. Multiple linear regression analysis of C-peptide as the dependent variable with some variable as independent.

Independent variable	C-peptide
	Beta
BMI	-0.121*
Duration	-0.652**
Family history	-0.299**
HOMA-IR	-0.108*
HOMA-S	-0.499**
HOMA-B	0.523**
R^2	0.721

*P<0.05 was considered significant, and **P<0.01 is a highly significant.

Table5: correlation of duration with variables according to family history of DM.

Variables	Duration	
	FH+	FH-
C-peptide	-0.126*	-0.013
FSG	0.288**	0.127*
HbA1c	0.262**	0.130*
Age	0.121*	0.034
BMI	-0.013	-0.011
HOMA-B	-0.229**	-0.021

* Correlation is significant at the 0.05 level
**Correlation is significant at the 0.01 level

Discussion:

The present study showed that mean fasting serum c-peptide level was significantly higher in diabetic patients as compared with healthy control, which is in consistent with La-or Chailurkit et al[19]. This fact might be explained by high insulin resistance level and a consequent compensatory increase in beta cell mass and hypertrophy of existing beta cells to meet the increased demand and to avoid more severe hyperglycemia [20]. However, there were significant reduce in insulin secretion (B%) , insulin sensitivity (S%) and sign with significant increase in the insulin resistance (IR) in diabetic group than in healthy control group, which could be a defect of either islet cell function or ß-cell mass. Insulin secrtory capacity is dependent on both function and mass of cells. ß-cell secretion is hetrogeneouse; and increasing glucose concentrations result in recruitment of ß-cells into the secretory pool, indicating a large reserve of secretory capacity that can be recruited in insulin resistance conditions [21].Moreover, the present study reported that there was significant positive correlation between C-peptide level and both B% and IR, and negative correlation with S% in diabetic groups. Asakawa et al (2001) [22] have suggested that diabetic patients with poor glycemic control for a long period show suppressed insulin secretion due to glucotoxicity, therefore HOMA B% is lower in ongoing diabetic patients. The phenomenon is probably related to hexosamine accumulation in muscle and fat tissue that, in turn inhibits glucose transport across the cell membrane [23]. It is stated that as glucose and other substrates increase, they would feed forward in a vicious cycle that begets more insulin resistance and poorer beta-cell function [22], determination of the contribution of a reduction of ß-cell secretion is complicated by parallel changes in insulin resistance that accompany onset of type 2 DM , the reduced insulin secretion results from cellular dysfunction of an appropriate number of ß-cells[21]. A family history of type 2 diabetes has been known to be a risk factor for the development of diabetes[24]. The current study demonstrated that patients with family history of DM had a progressive decline of fasting serum C-peptide level. As well as, the current study showed that patients with FH had longer duration; and the concentration of C-peptide was associated negatively with diabetic duration in the patients with family history. Pancreatic β-cells can respond normally to insulin resistance by increasing insulin secretion. Failure of the β-cell to compensate for insulin resistance results in the development of type 2 diabetes. The imperfection in such insulin secretion may be related with altered β-cell function and/or decreased β-cell mass; In addition, type 2 diabetes mellitus may be a progressive disorder, which is characterized by a gradual reduction in β-cell function over time after the development of the disease[25]. These defects may be related to progressive increase in blood glucose levels[26]. However, the current study showed increases in the fasting serum glucose and HbA1c

in group with family history of DM. Thus, the current study showed that over time β-cell dysfunction was progressive in relation to HbA1c and fasting plasma glucose levels. These results are consistent with previous reports [26,27]. Kahn et al. [27] reported that there were progressive decline of glycemic control over the years despite treatment in type 2 diabetic patients. In this study, we found that patients with family history were at younger ages, so the younger age of onset was expected to lead to longer duration and more complications compared to those in patients without family history. Furthermore, the familial T2DM group showed a heavier body weight, and higher blood TG level, LDL-cholesterol. Nevertheless, BMI, WC, systolic and diastolic blood pressures, total cholesterol were not different between the two groups. Some studies have reported no correlation between obesity related factors and family history of T2DM [28,29], but others [30-32] have shown a close relation between obesity and family history. The present study also establish that body weight and serum triglyceride level, which are known to be related to obesity and metabolic syndrome, were significantly higher in the group with family history of DM. This finding, along with those of other studies, suggests that more complications related with metabolic syndrome were expected in T2DM patients with a family history of diabetes.

In the current study, patients with a family history of DM show signs of significantly higher LDL-cholesterol, and TG levels than those without FH. The dyslipidemia in diabetes mellitus is characterized by augmented triglycerides and reduced HDL-cholesterol levels[33]. Our results suggest that the patients with a family history of diabetes may be more associated with atherogenic lipid profiles, which are not typical in type 2 diabetic patients. In this study there was a significant positive correlation between fasting C-peptide levels and BMI. Chan et al (2004) [34] have showed that fasting C-peptide levels were correlated positively with BMI, obesity (BMI) seems more closely related to insulin resistance, it is well known that weight loss improves insulin sensitivity and glycemic control in the spontaneous condition of hyperglycemia, BMI has an effect on both hepatic and peripheral insulin resistance of type 2 diabetes, Yoshinori etal[35] found Strong correlations between visceral adiposity/total body FM and peripheral/ hepatic insulin resistance, respectively, were observed, independent of gender. Moreover, there was a significant positive correlation between C-peptide and triglyceride, as well as, negative correlation with HDL-C, this is due to that only total triglyceride and fasting C-peptide, two variables linked physiologically to insulin resistance and associated with coronary heart disease [36], C-peptide and BMI have been the associated factors with dyslipidemia [37]. Increased level of free fatty acids can result in insulin resistance in muscle and liver tissue. Furthermore, resulting lipotoxicity can impair pancreatic ß-cell function in patients with type 2 DM and the increase catabolism rate of HDL particles leading to decrease in HDL-C levels [38]. To establish the association between fasting serum C-peptide level and a family history of diabetes, multivariate analysis including diabetes duration and BMI as independent factors were executed, as these factors had been reported as major determinants influencing pancreatic β-cell function [39]. Multivariate analysis revealed a strong negative association between family history of type2 DM and fasting serum C-peptide levels, even after adjustments for age, sex, HbA1c, fasting serum glucose, SBP, and DBP; indicating these were not factors that significantly affected the relationship. Thus, the difference in lowering of serum C-peptide in type 2 diabetic patients, according to family history of DM, suggests that one or more environmental and genetic factors shared by a family may continue to make β-cell function more vulnerable among type 2 diabetic patients.

In conclusion, the current results showed that family history of type 2 diabetic patients is thought to have a deep impact on C- peptide, lipid profile, insulin resistance, HOMA-IR, insulin sensitivity HOMA-S, and lead to higher prevalence of diabetic complications compared to patients without family history. Therefore, different strategies of treatment and follow-up should be concerned depending on the existence of a family history. Patients with a family history of diabetes should undergo early screening for complication and to get more measures to prevent any complications of the disease.

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