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STUDY OF CIRCULATING TUMOR NECROSIS FACTOR-ALPHA: RELEVANCE TO INSULIN-DEPENDENT AND NON INSULIN-DEPENDENT DIABETES MELLITUS

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ABSTRACT

Tumor necrosis factor - alpha (TNF- α) is a pleiotropic cytokine derived from activated macrophages and other cells, and proved to have tremendously diverse functions. Long term experimental diabetes has been found to be associated with enhanced serum TNF α activity.

We attempted to study the serum TNF- α levels in insulin-dependent diabetes mellitus (IDDM) and non-insulin-dependent diabetes mellitus (NIDDM) patients, to find out any possible correlation between TNF- α levels and the duration of diabetes, and abnormalities of serum lipid pattern.

This study was performed on non-smoker male subjects comprising

three groups. Group 1 included 33 IDDM patients, group 2 included 30 NIDDM patients and group 3 included 25 healthy control individuals. All patients and control subjects were age matched and selected from the attendants of the Outpatient Clinic of Internal Medicine Department, Mansoura University Hospital.

The results of the present study revealed a significant increase of total cholesterol, LDL cholesterol and triglycerides levels in diabetic patients compared to control group, and a significant increase of triglycerides levels in IDDM compared to NIDDM patients.

As regards serum TNF- α there is a significant increase in its level in dia-

betic patients compared to control subjects, and at the same time, there is a significant increase of TNF- α level in IDDM compared to NIDDM patients. Also, TNF- α shows a positive significant correlation with serum level of triglycerides and total cholesterol in both IDDM and NIDDM, while it shows a significant positive correlation with LDL cholesterol in IDDM patients only. TNF- α also, shows a significant positive correlation with C-peptide in NIDDM patients, while it doesn't show any significant correlation with C-peptide in both IDDM and healthy control subjects. As regards duration of diabetes, TNF- α shows a significant positive correlation with the duration of the disease in both IDDM and NIDDM.

From the data of the present study we can suggest that the release and action of TNF- α is altered in diabetes mellitus. It could be concluded that TNF- α has a pathogenic and pathogenic role in diabetic patients whether IDDM or NIDDM, and that serum TNF- α levels are increased and strongly positively correlated with the duration of diabetes, and serum lipid pattern abnormalities. This may allow for treatment of disorders involving resistance to insulin.

INTRODUCTION

Diabetes mellitus is among the most common metabolic disorders in the world and is considered a major cause of morbidity and mortality (Nathan, 1993). Diabetic patients show increased levels of circulating modified lipoproteins and enhanced oxidation of their plasma LDL (Babiy et al., 1992). Control of glycemia in non insulin dependent diabetes mellitus (NIDDM) rarely corrects completely the alteration in lipid metabolism, suggesting a participation of environmental and genetic factors (Sheu et al., 1993). Also, Pandey et al. (1999) postulated that NIDDM is a complex disease with a very high degree of heritability.

Insulin dependent diabetes mellitus (IDDM) is a T-cell mediated autoimmune disease localized to the pancreas that occurs spontaneously in genetically predisposed individuals (Castano and Eisenbarth, 1990). Because the etiology of IDDM is thought to be autoimmune, several clinical trials have utilized immunosuppression to treat newly diagnosed diabetic patients (Burke et al., 1994). At the same time, Yang et al. (1994) reported that TNF- α has a critical role in the early development of IDDM and that

administration of anti-TNF- α monoclonal antibodies resulted in complete prevention of IDDM. Also, Netea et al. (1997) suggested a proinflammatory imbalance in newly diagnosed IDDM patients and this may play an important role in beta cell loss.

It is difficult to determine whether abnormalities in the pattern of cytokines production are primary or secondary to the pathological process in IDDM (Cavallo et al., 1994). However, Lorini et al. (1995) suggested that aberrant tumor necrosis factor-alpha (TNF- α) synthesis may contribute to immune dysregulation thus favouring the development of autoimmune disease. Also, Mandrup-Poulsen, (1996) and Rabinovitch et al., (1996) reported that cytokines are critical elements involved in the process of initiating, promoting and effecting β -cell dysfunction and destruction in IDDM. Cytokines released by both T-lymphocytes and activated macrophages have been implicated as immunological effector molecules that both inhibit insulin secretion from pancreatic β -cells and induce beta cell destruction directly or indirectly through reactive oxygen intermediates (Mandrup-Poulsen et al., 1987; Corbett et al., 1993 and Nicoletti et al., 1998).

Long-term experimental diabetes has been found to be associated with enhanced serum TNF- α activity (Tanaka et al., 1992). Also, elevated serum TNF- α levels have recently been documented in NIDDM (Hussain et al., 1996).

The objective of this work is to study the serum TNF- α levels in IDDM and NIDDM patients, and to find out any possible correlation between TNF- α levels and the duration of diabetes, and abnormalities of serum lipid pattern.

SUBJECTS AND METHODS

This study was performed on non-smoker male subjects comprising three groups:

Group 1 : Included 33 IDDM patients, their ages range from 24 to 48 years (mean = 36.12).

Group 2 : Included 30 NIDDM patients, their ages range from 33 to 53 years (mean = 43.5).

Group 3 : Healthy control group included 25 apparently healthy individuals, their ages range from 27 to 47 years (mean = 38.5).

All subjects in this study were se-

lected from attendants of the Outpatient Clinic of the Internal Medicine Department, Mansoura University Hospital.

All individuals in this study were subjected to complete history taking, and thorough clinical examination. Any subject with hypertension, cardiac disease, hepatic affection, acute or chronic infection or malignancy was excluded from this study. Also, all diabetic patients were receiving only anti-diabetic regimen: Insulin therapy for IDDM patients and Sulphonylurea plus/or minus Metformin for NIDDM.

Laboratory investigations

All subjects were instructed to come fasting for 12 hours on the day of the study. A blood sample was collected from each individual. Serum was separated, and glucose and lipids were determined on the day of collection and the rest of serum was divided into aliquots and stored at -20°C until analysed for C-peptide, and $\text{TNF-}\alpha$. Also, a second blood sample was collected from each individual after 2 hours from intake of 75 g glucose load orally for determination of post prandial blood glucose level (World Health Organization, 1985).

- Fasting and post prandial blood

glucose levels were determined by glucose oxidase method (Trinder, 1969) using kits of Bio-Merieux Laboratory - France.

- Serum levels of total cholesterol (Allain et al., 1974) HDL cholesterol (Warnick et al., 1982) and triglycerides (Wahlefeld, 1974) were estimated by Kits of Bio-Merieux Laboratory - France.

- Serum LDL cholesterol was calculated according to Friedewald et al. (1972).

- Determination of serum C-peptide by radioimmunoassay procedure according to Kuzuya et al. (1976) using Kits supplied by Immunotech - France.

- Determination of serum $\text{TNF-}\alpha$ by an enzyme immunoassay procedure (Kallmann et al., 1997) using Kits supplied by Medgenix Diagnostics S.A, Fleurus, Belgium.

STATISTICAL ANALYSIS

The data of this study were recorded and calculated on an IBM Compatible PC using SPSS/PC+ Statistical Package version 5 (SPSS Inc Chicago IL). Comparisons between groups were calculated using the Mann-Whitney- μ test (Daly et al., 1992). Also, Spearman's correlation coefficient (r) was used to study the

correlation between circulating TNF- α and the other variables. A value of $P < 0.05$ was considered significant.

RESULTS

Table (1) reveals that there is a significant increase of total cholesterol, LDL cholesterol and triglycerides levels in diabetic patients compared to control group ($P = <0.001$) and significant increase of triglycerides level in IDDM patients compared to NIDDM ($P = 0.006$) while there is a non significant difference between IDDM and NIDDM as regards total cholesterol, HDL cholesterol and LDL cholesterol.

As regards C-peptide levels table (1) reveals a significant decrease in IDDM patients compared to NIDDM and control subjects while there is a significant increase of serum C-peptide level in NIDDM compared to control subjects ($P = <0.001$).

As regards serum TNF- α there is a significant increase in its level in diabetic patients compared to control subjects, and at the same time there is a significant increase in TNF- α level in IDDM patients compared to NIDDM ($P = <0.001$).

It is clear from table (2) that

TNF- α level is positively correlated with fasting and post prandial blood glucose levels in IDDM and NIDDM ($P = <0.001$) while not significant with sugar levels in healthy control.

As regards serum lipid levels TNF- α shows a positive significant correlation with total cholesterol in IDDM ($r = 0.650$, $P = <0.001$) and NIDDM ($r = 0.376$, $P = 0.041$), while it shows a significant positive correlation with LDL cholesterol in IDDM only ($r = 0.542$, $P = 0.001$). Also, TNF- α shows a significant positive correlation with triglycerides levels in IDDM ($r = 0.409$, $P = 0.018$) and NIDDM ($r = 0.447$, $P = 0.013$), while there is a non significant correlation with the other lipid parameters in all groups.

Also, TNF- α level shows a significant positive correlation with C-peptide in NIDDM patients ($r = 0.644$, $P = <0.001$) while it doesn't show any significant correlation with C-peptide in both IDDM patients and control subjects.

As regards duration of diabetes, TNF- α shows positive correlation with the duration of the disease in both IDDM ($r = 0.694$, $P = <0.001$) and NIDDM ($r = 0.806$, $P = <0.001$).

Table (1) : Comparison of the serum levels of different biochemical parameters in the studied groups.

Variables	Group (1) IDDM n = 33	Group (2) NIDDM n = 30	Group (3) Control n = 25	P Value		
				1 vs 2	1 vs. 3	2 vs. 3
Fasting Bl. Glucose (mg/dL)	256.70 ±46.32	157.27 ±21.74	82.52 ±6.95	<0.001	<0.001	<0.001
Post prandial Bl. Glucose (mg/dL)	295.67 ±48.33	219.97 ±30.68	107.36 ±9.14	<0.001	<0.001	<0.001
Total Cholesterol (mg/dL)	221.00 ±18.08	218.87 ±18.7	188.64 ±16.10	N.S.	<0.001	<0.001
HDL cholesterol (mg/dL)	40.88 ±3.19	41.67 ±3.66	45.72 ±5.18	N.S.	<0.001	0.003
LDL cholesterol (mg/dL)	142.58 ±19.70	143.90 ±19.39	124.72 ±10.88	N.S.	<0.001	<0.001
Triglycerides (mg/dL)	188.18 ±33.04	165.33 ±21.87	107.00 ±11.24	0.006	<0.001	<0.001
C-peptide (ng/ml)	0.61 ±0.18	4.04 ±0.86	2.27 ±0.36	<0.001	<0.001	<0.001
TNF- α (pg/ml)	25.45 ±4.77	17.57 ±4.28	9.08 ±2.29	<0.001	<0.001	<0.001

- Data are expressed as mean \pm standard deviation (S.D.) of mean.

- N.S. = Non significant.

Table (2) : Correlation study between serum TNF- α level and all different variables in the studied groups.

Variables	Group (1) IDDM n = 33	Group (2) NIDDM n = 30	Group (3) Control n = 25
Fasting Bl. glucose r = P value	0.689 <0.001	0.714 <0.001	-0.174 N.S.
Post prandial Bl. glucose r = P value	0.689 <0.001	0.566 <0.001	-0.205 N.S.
Total cholesterol r = P value	0.650 <0.001	0.376 <0.001	-0.085 N.S.
HDL cholesterol r = P value	0.199 N.S.	0.077 N.S.	-0.181 N.S.
LDL cholesterol r = P value	0.542 0.001	0.266 N.S.	0.040 N.S.
Triglycerides r = P value	0.409 0.018	0.447 0.013	-0.216 N.S.
C-peptide r = P value	0.075 N.S.	0.644 <0.001	0.262 N.S.
Disease duration (year) r = P value	0.694 <0.001	0.806 <0.001	- -

r = Correlation coefficient

N.S. = Non significant

DISCUSSION

TNF- α is a pleiotropic cytokine derived from activated macrophages and other cells, and proved to have tremendously diverse functions (Vilcek and Lee, 1991).

To determine whether chronic hyperglycemia causes increased levels of serum cytokines (TNF- α , IL-1- α and IL-1- β), Mooradian et al. (1991) reported that except for a modest increase in the prevalence of detectable serum TNF- α levels in diabetic patients, the other cytokines did not appear to be altered in diabetes. On the other hand, Morohoshi et al. (1996) reported that hyperglycemia may have a stimulatory effect on IL-6 and TNF- α production by human peripheral blood monocytes in poorly controlled diabetic patients at the level of mRNA transcription and turnover.

Tanaka and his coworkers (1992) suggested that factor(s) associated with long term diabetic state (whether IDDM or NIDDM) may prime macrophages to produce TNF- α . At the same time, Foss and his colleagues (1992) postulated that TNF- α levels progressively increased from well-to poorly controlled diabetics which suggests a relationship between the

levels of the cytokine and protein glycosylation.

The macrophage-derived TNF- α release is caused by the accumulation of cholesterol esters in the macrophages due to immunogenic action of modified lipoproteins (oxidized and glycated lipoproteins) which are present in the diabetic state (Lopes-Virella and Virella, 1996).

Netea et al. (1997) and Rabinovitch (1998) reported that TNF- α , IL-1- β and IFN- γ may be directly cytotoxic to pancreatic beta cells by inducing nitric oxide (NO) and free radicals, so they are important for pancreatic islets β -cell lysis in IDDM. So, the increase of TNF- α levels leads to NO generation and NO-mediated injury, thus leading to progress of the IDDM disease and occurrence of complications (Hotamisligil et al., 1997).

The results of the present study revealed that serum TNF- α concentrations were significantly higher in IDDM group compared to healthy control. This is in agreement with the previous results of Hussain et al. (1996). This indicates that TNF- α is implicated in the pathogenesis of IDDM, and coincides with the hypoth-

esis of Limb et al. (1999). Also, Obayashi et al. (1999) reported that TNF- α gene is located in the HLA region and has been implicated in the pathogenesis of type I diabetes mellitus (IDDM).

Also, recent studies have shown that IDDM is associated with an increase in protein-tyrosine phosphatase activity which leads to over expression of major histocompatibility (MHC) class I molecules. In addition cytokines may sensitize beta cells to T-cell mediated cytotoxicity by upregulating MHC class I expression on the beta cell, and concomitant destruction of pancreatic beta cells (Rabinovitch, 1998 and Holden et al., 1999).

On the contrary, Ohno et al. (1993) reported that the TNF- α production by in vitro cultured monocytes did not differ between IDDM patients and normal subjects. On the other hand, they recorded that the TNF- α production was significantly higher in NIDDM patients than in IDDM and normal subjects.

Increased lipoprotein oxidation in diabetes (or in states of chronic hyperglycemia) may be responsible for the increase in expression of circulat-

ing adhesion molecules and the production of TNF- α which is a key mediator of insulin resistance in NIDDM subjects (Ohno et al., 1993 and Husain et al., 1996).

Although the results of our study revealed that TNF- α levels in NIDDM are significantly lower than IDDM, significant higher levels of TNF- α in NIDDM compared to control group were demonstrated. This is previously documented by Atlan Gepner et al. (1996) who reported that the production of TNF- α by the macrophages of the diabetic patients in presence of insulin were dramatically increased in comparison with control subjects. Also, Pfeiffer et al. (1997), Desfaits et al. (1998) and Nilsson et al. (1998) demonstrated a slight but significant increase in serum TNF- α levels in NIDDM patients as compared with control subjects.

The selective enhancement of monocyte TNF- α production in NIDDM patients may theoretically contribute to the pathogenesis of atherosclerosis associated with NIDDM (Desfaits et al., 1998).

The elevated TNF- α initially increases, and then inhibits, the activity

of a number of key enzymes including: protein-tyrosine kinase and protein-tyrosine phosphatase. Of primary importance is the inhibiting effect of TNF- α on protein-tyrosine kinase, since this induces insulin resistance in NIDDM (Holden et al., 1999)

Elevated levels of the stress hormones, glucorticoids and epinephrine, are observed in animals infused with TNF- α and rendered insulin-resistant, both of these hormones can cause insulin resistance (Douglas et al., 1991). TNF- α induced-insulin resistance could be attributed to inhibition of the insulin-stimulated glucose uptake due to transcriptional suppression of the transporter GLUT4 gene and due to impaired autophosphorylation of the insulin receptor (Hotamisligil et al., 1994). In addition to its chronic inhibitory effects on the basal and insulin-mediated glucose uptake, acute TNF- α treatment rapidly blocks insulin-stimulated glycogen synthesis (Begum and Ragolia, 1996).

Ciaraldi et al. (1998) studied the effects of TNF- α on glucose uptake and glycogen synthase activity in human skeletal muscle cell cultures from non diabetic and NIDDM subjects.

They reported that both acute and prolonged treatment with TNF- α up-regulate glucose uptake activity by elevation of glucose transporter-1 protein in human muscle cells, but reduce glycogen synthase activity. Also, they postulated that the increased skeletal muscle glucose uptake in conditions of TNF- α excess may serve as a compensatory mechanism in the insulin resistance in NIDDM.

Recently, Winkler et al. (1998) and Zinman et al. (1999) reported that individuals with normal glucose tolerance had lower TNF- α concentrations than those with impaired glucose tolerance or type 2 diabetes mellitus (NIDDM). Also, they concluded that circulating TNF- α concentrations are positively correlated with insulin resistance, and the possible role of TNF- α in the pathophysiology of insulin resistance.

The results of the present study, revealed a highly significant correlation between serum TNF- α and C-peptide levels in cases of NIDDM, at the same time, there was a non significant correlation between TNF- α , and C-peptide levels in cases of IDDM or healthy control. This is in agreement with the previous

results of Winkler et al. (1998).

As regards lipid metabolism, TNF- α causes an increase in serum triglycerides and rarely low-density lipoproteins (LDL) in human and rats. The observation that TNF- α can modulate triglyceride metabolism provides support for considering TNF- α locus as a susceptibility genetic region in hypertriglyceridemia of NIDDM (Vendrell et al., 1995). With respect to adipocytes, TNF- α causes a suppression of most lipogenic enzymes including lipoprotein lipase and stimulation of lipolysis (Hauner et al., 1995). The finding of association between high plasma levels of TNF- α and several metabolic abnormalities characteristic for the insulin resistance syndrome suggests that TNF- α may be involved in the pathogenesis of NIDDM (Nilsson et al., 1998).

The results of the present work revealed a significant positive correlation between TNF- α levels and fasting and postprandial blood sugar levels in both IDDM and NIDDM. As regards serum lipid pattern the results of the present study revealed a significant positive correlation with total cholesterol in both IDDM and NIDDM patients, while it shows a significant positive

correlation with LDL cholesterol in IDDM only. Also, TNF- α shows a low but statistically significant positive correlation with triglycerides levels in both IDDM and NIDDM patients. These results are partially in agreement with that of Nilsson et al. (1998) who reported that TNF- α levels were significantly related to fasting blood glucose levels, serum triglyceride levels and body mass index, while it is inversely related to the high density lipoprotein cholesterol levels.

On the contrary, Pfeiffer et al. (1997) reported that TNF- α correlated with serum triglycerides levels in healthy controls but not in NIDDM. While, recently, Zinman et al. (1999) reported a moderate, but statistically significant, correlation between TNF- α and fasting insulin, and triglyceride levels in NIDDM patients.

As regards disease duration, the results of the present study revealed a significant positive correlation between serum TNF- α levels and the disease duration in both IDDM and NIDDM. This is previously documented by Hussain et al. (1996) who reported that patients with long standing IDDM and NIDDM have significantly higher TNF- α levels.

From the previous data, we can conclude that the release and action of TNF- α has been reported to be increased in diabetes mellitus and strongly positively correlated with the duration of diabetes, and associated abnormalities of serum lipid pattern. So, it can be suggested that TNF- α has a pathogenic and pathognomonic role in diabetes mellitus. This may allow for treatment of disorders involving resistance to insulin.

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دراسة مستوى معامـل التنخر الورمى - ألفا وعلاقته بمرض البول السكرى المعتمد وغير المعتمد على الأنسولين

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أثبتت الاختبارات طويلة الأجل أن مرض البول السكرى مرتبط بزيادة فى نشاط معامـل التنخر الورمى - ألفا. استهدف هذا البحث دراسة مستوى معامـل التنخر الورمى - ألفا فى مرضى البول السكرى المعتمد وغير المعتمد على الأنسولين ومحاولة إيجاد علاقة بين مستوى معامـل التنخر الورمى - ألفا وفترة دوام المرض ودرجة السيطرة على المرض بالإضافة إلى الخلل فى مستوى دهون الدم .

أجريت هذه الدراسة على عدد من الرجال غير المدخنين تم تقسيمهم إلى ثلاثة مجموعات : المجموعة الأولى تتكون من ٣٣ مريضاً بمرض البول السكرى المعتمد على الأنسولين. والمجموعة الثانية تتكون من ٣٠ مريضاً بمرض البول السكرى الغير معتمد على الأنسولين. كما تتكون المجموعة الثالثة من ٢٥ من الأصحاء المتطوعين كمجموعة ضابطة. وتم إختيار المشاركين فى البحث من مجموعة عمرية متقاربة من المترددين على العيادة الخارجية لقسم الأمراض الباطنة - مستشفى المنصورة الجامعى.

أثبتت نتائج هذا البحث وجود زيادة معنوية فى مستوى الكولسترول الكلى، والكولسترول منخفض الكثافة ودهون الدم الثلاثية فى مرضى البول السكرى مقارنة بالمجموعة الضابطة، كما كانت زيادة دهون الدم الثلاثية فى مرضى البول السكرى المعتمد على الأنسولين ذات دلالة معنوية مقارنة بمرضى البول السكرى الغير معتمد على الأنسولين .

وبالنسبة لمستوى معامـل التنخر الورمى - ألفا فقد وجدت زيادة معنوية فى مرضى البول السكرى مقارنة بالأصحاء كما كانت هذه الزيادة ذات دلالة معنوية فى مرضى البول السكرى المعتمد على الأنسولين مقارنة بمرضى البول السكرى الغير معتمد على الأنسولين.

بالنسبة لمعامـل الارتباط الاحصائى فقد كان هناك ارتباط ذو دلالة إحصائية إيجابية بين مستوى

معامل التنخر الورمى - ألفا ومستوى الكولسترول الكلى والدهون الثلاثية فى كل من مرضى البول السكرى المعتمد وغير المعتمد على الأنسولين، بينما كان الارتباط إيجابياً مع الكولسترول منخفض الكثافة فى مرضى البول السكرى المعتمد على الأنسولين فقط. أيضاً وجد ارتباط ذو دلالة إيجابية بين مستوى معامل التنخر الورمى - ألفا ومستوى البيب تيد سى فى مرضى البول السكرى الغير معتمد على الأنسولين .

كما وجد ارتباط ذو دلالة إحصائية إيجابية بين مستوى معامل التنخر الورمى - ألفا وفترة دوام المرض فى مرضى البول السكرى المعتمد وغير المعتمد على الأنسولين.

توحى النتائج السابقة بتغير فى إنتاج وفعالية معامل التنخر الورمى - ألفا فى مرضى البول السكرى. كما يمكن أن نستخلص أن معامل التنخر الورمى - ألفا يلعب دوراً مسبباً ومميزاً لمرض البول السكرى سواء المعتمد أو غير المعتمد على الأنسولين، وأن زيادة مستوى معامل التنخر الورمى - ألفا ترتبط ارتباطاً إيجابياً مع فترة دوام المرض والخلل فى مستوى دهون الدم. وهذا ربما يساعد فى علاج مرضى البول السكرى والمقاومة للأنسولين .