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مستوى السينديكان -١ و الإنترليوكين -٦ والبروتين سى التفاعلى فى مصل الدم لمرضى السكرى نوع (٢) المعالجون بالاستاتين.

Serum levels of syndecan-1, interleukin-6 and C-reactive protein in statin-treated patients with type 2 diabetes mellitus

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BACKGROUND

Diabetes mellitus is a complex metabolic disease affecting about 5% of people all over the world, characterized by hyperglycemia and associated with microvascular, macrovascular and neuropathic complications. [1] The increase in prevalence of type 2 diabetes is posing a massive health problem that results from the disease and from its association with obesity and cardiovascular (CV) risk factors, particularly dyslipidemia and hypertension. [2]

The hallmarks of type 2 diabetes are hyperglycemia, insulin resistance, and insulin deficiency. Inflammation has been implicated as an important etiological factor in the development of both insulin resistance and type 2 diabetes mellitus. In addition, it is increasingly recognized that insulin resistance contributes to the characteristic dyslipidemia associated with type 2 diabetes. [3] Dyslipidemia is manifested by raised levels of triglycerides (TG) carried in very-low-density lipoprotein (VLDL) particles, low levels of high-density lipoprotein cholesterol (HDL-C) and the more atherogenic low-density lipoprotein (LDL) particles.[4]

Previous studies have shown that VLDL is highly atherogenic since excessive uptake of these lipoproteins by macrophages causes massive cholesterol accumulation and foam cell formation. Apo E-VLDL clearance occurs primarily through heparan sulfate proteoglycans (HSPG)-mediated process. Specific HSPG, like those of the syndecans participate in the endocytic clearance of dietary lipids through binding to several protein particles like apoA, apoE and lipoprotein lipase. [5] Syndecans are type 1 transmembrane domain proteins that are thought to act as coreceptors, especially for G protein-coupled

receptors. These core proteins carry three to five heparan sulfate and chondroitin sulfate chains, which allow for interaction with a large variety of ligands. [6]

Syndecans have important roles during development, wound healing and tumor progression by controlling cell proliferation, differentiation, adhesion and migration. Mammals have four syndecan family members, syndecan-1 to 4. All cells express at least one member of the syndecan family, with the exception of erythrocytes. A plethora of ***in vitro*** data on the role of syndecans as coreceptors, signaling receptors and binding partners for chemokines, cytokines, growth factors, integrins and other adhesion molecules, supports their role as integral parts of inflammatory events. [6]

Syndecan-1 is a cell surface receptor that binds to structural extracellular matrix molecules via attached heparan sulfate chains. It is implicated in the regulation of heparin-binding growth factors and in regulating integrin signaling activity. Syndecan-1 is also involved in inflammation and lipoprotein physiology, and syndecan-1 shedding showed to be a critical mechanism that facilitates the resolution of neutrophilic inflammation by aiding the clearance of pro-inflammatory chemokines in type 2 diabetes.[7]

Interleukin-6 (IL-6), a major pro-inflammatory cytokine, is produced in a variety of tissues, including activated leukocytes, adipocytes, and endothelial cells, while C-reactive protein (CRP) is the principal downstream mediator of the acute phase response and is primarily derived via IL-6–dependent hepatic biosynthesis. [8] A recent study showed that IL-6 and CRP are two sensitive physiological markers of subclinical systemic inflammation associated with hyperglycemia, insulin resistance, and overt type 2 diabetes mellitus. [9]

Lipoprotein retention by extracellular proteoglycans (PGs) in the arterial intima is a key event in the initiation of atherosclerotic disease. Syndecan-1 provides a path for lipoprotein lipase-enriched LDL, and apoE-VLDL binding and internalization. [10] Syndecan-1 level was reported to be increased and negatively correlated with apolipoprotein-A1 (apoA1) in patients with type 2 diabetes. [11]

Among the agents receiving more attention in the field of therapy of diabetes are the 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors, or statins. Statins are potent inhibitors of cholesterol biosynthesis. [12] In clinical trials, statins were found to be beneficial in the primary and secondary prevention of coronary heart disease. However, the overall benefits observed with statins appear to be greater than what might be expected from changes in lipid levels alone, suggesting "pleiotropic" effects of statins. [13]

Very recently, it has been shown that statins stimulated shedding of syndecan-1 from the surface of myeloma cells. [14] As inflammation plays an important role in the pathogenesis of type 2 diabetes and may predict it as mentioned previously, [9] syndecans could therefore serve as new targets for the prevention of pathologic inflammatory events. Accordingly, the beneficial effects of statins therapy by both inhibiting deposition of lipids and decreasing inflammation might be associated to changes in syndecan-1 level in patients with type 2 diabetes.

AIM OF THE WORK

The aim of this study is to assess the serum levels of syndecan-1, interleukin-6 and C-reactive protein in statin-treated patients with type 2 diabetes mellitus.

SUBJECTS AND METHODS

The present study will be conducted on 50 subjects recruited from the department of Internal Medicine in the Medical Research Institute categorized as follows:

Group 1: Including forty patients with type 2 diabetes mellitus subdivided into 2 subgroups:

Group A: Including twenty patients receiving a daily night dose of 40 mg simvastatin for 10 weeks.

Group B: Including twenty patients without statin treatment.

Group 2: Including ten healthy volunteers of matching age and sex to the patients, used as the control group.

Subjects with conditions other than diabetes that can affect serum levels of syndecan-1 and/or inflammatory markers as tumors or collagenic disorders are excluded from the study.

Patients and controls are asked to sign a written informed consent form indicating their acceptance to participate. The study will be conducted after institutional ethics requirements are met.

Methods

All enrolled subjects will undergo the following clinical and biochemical analyses**:**

A. Detailed personal history taking and thorough clinical examination with special stress on duration and type of treatment of diabetes, manifestations of diabetic complications and measurement of blood pressure.

B. Twelve leads standard electrocardiogram (ECG).

C. Laboratory investigations:

Blood samples are collected from all participants for the assessment of the following:

1- Fasting and postprandial serum levels of glucose. [15]

2- Fasting serum levels for the determination of total cholesterol, high density lipoprotein-cholesterol (HDL-C), low density lipoprotein-cholesterol (LDL-C), very low density lipoprotein (VLDL) and triglycerides (TG). [16]

3- Glycated hemoglobin (HbA1c). [17]

4- Serum aminotransferases (AST and ALT) and creatine phosphokinase (CPK). [18]

5- Serum Apolipoprotein A-1 and Apolipoprotein-E by turbidimetry. [16]

6- Determination of serum level of Syndecan-1 by ELISA technique. [19]

7- Determination of serum level of IL-6 by ELISA technique. [20]

8- Determination of serum high-sensitivity C-reactive protein (hs-CRP) levels by turbidimetry. [21]

Random urine samples are collected from all participants for the determination of urinary levels of albumin and creatinine [albumin excretion is expressed as the ratio of urinary albumin to urinary creatinine (mg/g)]. [22]

All diabetic patients will be informed about the main side effects of simvastatin and advised to:

1. Avoid any drug that may increase the risk of statin-induced myopathy. These drugs include gemfibrozil, niacin, verapamil, diltiazem, amiodarone, cyclosporine, azole and macrolides.

2. Report any muscle pain or weakness and to stop the medication immediately for severe muscle pain, brown urine or doubling of ALT and/or AST, and elevation of CPK.

ALT, AST and CPK assays are repeated every 4 weeks, while all laboratory investigations will be repeated for the patients group after the 10th week of simvastatin administration.

ANALYSIS OF RESULTS

The results of this study will be tabulated and statistically analyzed using ANOVA, paired-t and Chi-square tests.

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الملخص العربى

إختلال الدهون المصاحب لمرضى السكرى من النوع-٢ هو أحد عوامل الخطورة الرئيسية للإصابة بأمراض القلب و الاوعية الدموية و اللذين يعتبران من الأسباب الرئيسية للوفاة فى هؤلاء المرضى.

من البصمات المميزة لمرضى السكرى النوع-٢ هو إرتفاع مستوى السكر فى الدم و مقاومة الأنسولين و نقصه. كما يلعب الإلتهاب المصاحب لمرضى السكرى دوراً فعالاً فى استمرار المقاومة للإنسولين و التى بدورها تؤدى إلى إختلال الدهون المصاحب و المميز لمرضى السكرى من النوع-٢.

يعتبر سينديكان-١ -أحد البروتيوجلايكينات- من المستقبلات الكبدية الرئيسية لبقايا البروتينات الدهنية والليبوبروتينات الغنية بالدهون الثلاثية التى لها دوراً فعالاً فى هدم هذه الجزيئات بالكبد. علاوة على هذا، فإن للسينديكان-١ المرتبط بالغشاء الخلوى دوراً وسيطا فى عملية إبتلاع الليبوبروتينات الغنية بصميم البروتين الشحمى-باء (apo-B) و المقترنة بإنزيم ليبيز البروتين الشحمى. كما أن تحرر جزئ السينديكان-١ من سطح أغشيه الخلايا الحاملة له يساهم فى تقليل الإلتهاب المصاحب لمرضى السكرى من خلال التخلص من الكيموكينات المصاحبة للإلتهاب.

الاستاتينات هى من أوائل العقاقير المستخدمة في علاج ارتفاع الكولسترول. بصرف النظر عن دورها الأساسى فى خفض الدهون ألا أن لها خصائص أخرى كمضادات للإلتهابات و مكافحة تصلب الشرايين .

استهدف البحث دراسة تقييم التغير فى مستويات كل من السينديكان-١، والدهون، و الإنترليوكين-٦ و بروتين سي التفاعلي في مصل مرضى السكرى من النوع-٢ و كذلك دراسة التأثير المحتمل (بعيدا عن تقليل الكولستيرول) لاستخدام أحد الاستاتينات (السيمفاستاتين) على مستوى سينديكان-١ مستهدفا تقليل الإلتهاب المصاحب لداء السكرى.

وقد أجريت هذه الدراسة على عدد ٤٠ مريضا يعانون من داء السكري نوع-٢ مقسمين الى مجموعتين:

الأولى: وشملت عدد ٢٠ مريضا بداء السكرى نوع-٢ يتلقون العلاج التقليدى لمرض السكرى.

الثانيه: و شملت عدد ٢٠ مريضا بداء السكرى نوع-٢ يتلقون العلاج التقليدى لمرض السكرى بالإضافه الى جرعه من السيمفاستاتين (٤٠ ملجرام/يوم) عن طريق الفم بمعدل قرص واحد يوميا لمدة عشرة أسابيع.

كما اشتملت الدراسه أيضا على عشرة أصحاء كمجموعة ضابطة.

و قد تم فحص جميع الاشخاص فحصا اكلينيكيا و تعيين بعض المعايير البيوكيميائية فى مصل الدم فى بداية الدراسة و بعد عشرة أسابيع من العلاج لكلتا المجموعتين من المرضى شاملة: قياس مستوى الجلوكوز (صائم و بعد الإفطار بساعتين)، و السكر التراكمى، و الكولسترول الكلى، و البروتين الشحمى مرتفع الكثافه، و البروتين الشحمى منخفض الكثافه، و الدهون الثلاثية، صميم البروتين الشحمى (أ،هـ). بالإضافه الى قياس معدل الزلال البولى الى نسبه الكرياتنين فى البول. كما تم قياس مستويات إثنين من المؤشرات الحيوية للإلتهاب وهما بروتين سى التفاعلى والإنترليوكين-٦، علاوة على ذلك، تم قياس مستوى السينديكان-١ بطريقة الاليزا.

و قد أسفرت النتائج عن:

١) وجود زيادة ذات دلالة إحصائية في مستوى كل من: الجلوكوز (صائم و بعد الإفطار) و السكر التراكمى فى مصل دم مجموعتى المرضى مقارنه بالمجموعة الضابطة.

٢) نقص ذو دلالة إحصائية فى مستويات الكولسترول الكلى، والبروتين الشحمى منخفض الكثافه، و الدهون الثلاثية و صميم البروتين الشحمى-هـ (apo-E) و كذلك إرتفاع ذو دلالة إحصائية فى مستويات البروتين الشحمى مرتفع الكثافة، و صميم البروتين الشحمى-أ في مصل دم مرضى السكري المعالجون بالاستاتين مع العلاج التقليدى للسكرى مقارنة بالمستويات المناظرة قبل بدء العلاج بالاستايتن. في المقابل، لم تكن هناك تغييرات كبيرة في هذه المعايير بعد عشرة أسابيع في مرضى السكري المعالجون بالعلاج التقليدي مقارنه مع المستويات المناظره قبل عشرة اسابيع من بدء الدراسة.

٣) وجود نقص ذو دلالة احصائية فى مستويات كل من بروتين سى التفاعلى و الإنترليوكين-٦ في مصل دم مرضى السكري المعالجون بالاستاتين مع العلاج التقليدى للسكرى مقارنة بالمستويات المناظرة قبل بدء العلاج بالاستايتن. في المقابل، لم تكن هناك تغييرات ملحوظة في هذه المعايير بعد عشرة اسابيع في مرضى السكري المعالجون بالعلاج التقليدي مقارنة مع المستويات المناظرة قبل عشرة أسابيع من بدء الدراسة.

٤) وجود زيادة ذات دلالة احصائية فى مستوى السينديكان-١ فى مصل دم مرضى السكري المعالجون بالاستاتين مع العلاج التقليدى للسكرى مقارنة بالمستويات المناظرة قبل بدء العلاج بالاستاتين. في المقابل، لم يكن هناك تغيير ملحوظ في هذا المعيار بعد عشرة أسابيع في مرضى السكري المعالجون بالعلاج التقليدي مقارنه مع المستوي المناظر قبل عشرة أسابيع.

الإستنتاج:

من خلال هذه الدراسة يمكن إستنتاج أن زيادة تحرر جزئ السينديكان-١ من سطح الغشاء الخلوى بواسطة الاستاتين يمكن أن يكون هدفا جديدا للوقاية من تصلب الشرايين و الإلتهابات المصاحبه لمرضى السكرى من النوع-٢.

على الرغم أن هذه الدراسة بإمكانها القاء الضوء على أهمية السينديكان-١ فى منع حدوث تصلب الشرايين وتقليل الإلتهاب المصاحب لمرضى السكرى من النوع-٢ إلا أن طبيعة و أهمية الدور الذى يلعبه السينديكان-١ بحاجة إلى مزيد من الأبحاث المستفيضة.

التوصية:

من خلال هذه الدراسة يوصى بإجراء أبحاث أخرى إضافيه لدعم إستنتاجات هذا البحث باستخدام الاستاتينات لفترة أطول من الوقت على عدد أكبر من مرضى السكري النوع-٢.

مستوى السينديكان -١ و الإنترليوكين -٦ والبروتين سى التفاعلى فى مصل الدم لمرضى السكرى نوع (٢) المعالجون بالاستاتين.

رسالة

مقدمة إلى معهد البحوث الطبية– جامعة الإسكندرية
ايفاءا جزئيا لشروط الحصول على درجة

الدكتوراه

فى

الكيمياء الحيوية

مقدمة من

محمد عبد اللطيف محمود

ماجستير في المناعه الطبية
معهد البحوث الطبية
جامعة الاسكندرية
٢٠٠٨

معهد البحوث الطبية
جامعة الإسكندرية
٢٠١٤

مستوى السينديكان -١ و الإنترليوكين -٦ والبروتين سى التفاعلى فى مصل الدم لمرضى السكرى نوع (٢) المعالجون بالاستاتين.

مقدمة من
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٢٠٠٨

للحصول على درجة
الدكتوراه
فى
الكيمياء الحيوية

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السادة المشرفون	التوقيع
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