Role of Ischemia-Modified Albumin in Type 2 Diabetes Mellitus


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Abstract

Ischemia-modified albumin (IMA) is regarded as a biomarker of oxidative stress related to ischemia-reperfusion in different clinical conditions associated with oxidative stress, such as chronic kidney disease, hypercholesterolemia, systemic sclerosis and also, as showed on a preliminary report, in type 2 diabetes.

Subjects and Methods: This study included 75 subjects. The study groups were classified into 5 groups: Group 1 (Control): Included 15 normal healthy subjects (10 males & 5 females). Group 2 (Renal): Included 15 patients under renal dialysis (10 males & 5 females). Group 3 (DM): Included 15 diabetic patients with diabetes mellitus type 2 (9 males & 6 females). Group 4 (DM & Renal): Included 15 patients with combined diabetes mellitus type 2 & renal dialysis (8 males & 7 females). Group 5 (HCV): Included 15 patients with chronic hepatitis C infection (8 males & 7 females).

Aim: Evaluation of ischemia-modified albumin (IMA) in patients with type 2 diabetes mellitus, chronic renal failure with haemodialysis and hepatitis C patients.

Results: Mean of IMA highly significantly elevated in group 2 (renal haemodialysis patients) (at \( p < 0.001 \)), followed by group 5 (Hepatitis C patients) (at \( p < 0.001 \)), followed by group 3 (type 2 diabetes patients) (at \( p < 0.001 \)) and group 4 (type 2 diabetes patients with renal haemodialysis) (at \( p < 0.001 \)) compared to control group.

Conclusion: IMA is increased in chronic diseases than control subjects. Our study revealed that IMA is a good however non-specific indicator for chronic conditions (diabetes mellitus type 2, chronic renal failure with haemodialysis and hepatitis C infection).

Key Words: Type 2 diabetes mellitus – Hepatitis C infection – Chronic renal failure with haemodialysis – IMA.

Introduction

HUMANS are constantly exposed to free radicals created by electromagnetic radiation from the manmade environment such as pollutants and cigarette smoke. Natural resources such as radon, cosmic radiation, as well as cellular metabolisms (respiratory burst, enzyme reactions) also add free radicals to the environment [1].

Reactive oxygen species (ROS) is a general term that refers to not only oxygen-centered radicals but also includes non radical but reactive derivatives of oxygen (e.g., hydrogen peroxide) [2].

Reactive oxygen species can influence cell function and damage proteins, lipids, and nucleic acids [3].

Antioxidants are classified as exogenous (natural or synthetic) or endogenous compounds, both responsible for removal of free radicals, scavenging ROS or their precursors, inhibiting formation of ROS and binding metal ions needed for catalysis of ROS generation [1].

Albumin is the major plasma protein that is primarily synthesized in the liver [4].

In addition to acting as an osmotically active agent, albumin has been shown to exert various functions including fatty acid-binding, metal-chelating, drug-binding and antioxidant capacity. Under oxidative stress, the structure and function of serum albumin are altered [5].

This abnormal molecule of human serum albumin is known as Ischemia-Modified Albumin (IMA) [6].

Ischemia-modified albumin (IMA) is the variant form of human serum albumin, in which the N-terminal end is altered after exposure to oxidative stress or ischemia [7].

In many diseases that are accompanied by ischemia, including peripheral vascular disease, end-stage renal disease, advanced liver cirrhosis, acute infection, malignancies, systemic sclerosis, intrau-

These results suggest that IMA formation may occur not only under acute but also chronic oxidative stress conditions and also at extra cardiac sites [8].

The aim of the study is to evaluate Ischemia-modified albumin in diabetes mellitus type 2, chronic renal failure with haemodialysis and hepatitis C patients, and to investigate whether it can be used as an indicator or diagnostic tool.

**Subjects and Methods**

This study included 75 subjects from both sexes (45 males and 30 females). Their ages ranged from 21 to 65 years selected from Hurghada Military Hospital and Ghamra Military Hospital from October 2012 to March 2014. All subjects gave an informed written consent for participation and the study was approved by the ethics committee of the General Organization for Teaching Hospitals and Institutes.

The study groups were classified into five groups: Group (1) included 15 healthy control subjects they were 10 males and 5 females. Group (2) included 15 renal haemodialysis patients they were 10 males and 5 females. Group (3) included 15 patients of type 2 diabetes they were 9 males and 6 females. Group (4) included 15 patients of type 2 diabetes with renal haemodialysis they were 8 males and 7 females. Group (5) included 15 Hepatitis C patients they were 8 males and 7 females.

**Blood sampling and assays:**

Blood samples were collected from all patients and control subjects after an overnight fasting by venous puncture technique into Vacutainer tubes. Serum was used to measure the levels of fasting glucose, GOT, GPT, albumin, total cholesterol, triglycerides, HDL cholesterol, urea, creatinine and IMA. Serum IMA was measured with ELISA kit for human (WKEA MED SUPPLIES CORP, USA). Low density lipoprotein cholesterol (LDL-C) was calculated by equation; [VLDL = 0.2 x triglyceride, LDL-c = Total cholesterol – ( VLDL-c + HDL-c)] [9].

**Statistical analysis:**

Data are expressed as mean ± standard deviation. The differences between studied groups were compared by using ANOVA and least significant difference (LSD) test. The relationship between IMA and other parameters was analyzed by Pearson’s correlation test. Significance was assumed when the *p*-value was *<0.050 **<0.001.

**Results**

IMA in group 1 (healthy control) ranged from 61.2-112.1 U/L with a mean ±SD of 85.5±12.8 U/L, IMA in group 2 (renal haemodialysis patients) ranged from 350.2-564.1 U/L with a mean±SD of 433.2±67.1 U/L, IMA in group 3 (type 2 diabetes patients) ranged from 211.7-340.2 U/L with a mean±SD of 287.0±40.9 U/L, IMA in group 4 (type 2 diabetes patients with renal haemodialysis) ranged from 219.7-394.9 U/L with a mean±SD of 287.0±47.6 U/L, while IMA in group 5 (hepatitis C patients) ranged from 256.5-421.4 U/L with a mean±SD of 334.8±49.9 U/L (Table 1).

| Table (1): Biochemical characteristics of study patients and control subjects. |
|-----------------------------------------------|-----------------|---------------|-----------------|-----------------|-----------------|
|                                | G1   | G2   | G3   | G4   | G5   |
| Age (year)                     | 48.5±6.6 | 50.5±10.2 | 51.9±9.1 | 47.3±10.4 | 48.6±9.3 |
| Sex (male/female)              | 10/5 | 10/5 | 9/6  | 8/7  | 8/7 |
| GOT (U/L)                      | 19.5±3.6 | 18.6±4.9  | 25.8±8.4 | 20.5±4.4 | 87.3±29.5** |
| GPT (U/L)                      | 20.3±5.8 | 19.1±6.0  | 26.0±6.9 | 23.4±4.7 | 86.1±37.5** |
| Albumin (mg/dl)                | 4.5±0.4 | 4.1±0.3*  | 4.5±0.4 | 3.9±0.8** | 3.7±0.4** |
| FBS (mg/dl)                    | 83.5±6.2 | 76.3±11.8 | 170.1±35.2** | 110.3±16.2** | 85.7±7.4 |
| Urea (mg/dl)                   | 26.7±7.2 | 91.8±25.9** | 26.7±3.4 | 72.2±12.8** | 29.6±9.3 |
| Creatinine (mg/dl)             | 0.88±0.12 | 8.09±3.73** | 0.88±0.17 | 4.7±1.30** | 0.78±0.26 |
| Cholesterol (mg/dl)            | 156.8±46.3 | 145.9±16.0 | 182.6±40.6 | 158.9±39.2 | 166.1±39.6 |
| Triglycerides (mg/dl)          | 107.5±31.4 | 92.1±25.2 | 139.2±32.6* | 113.2±33.3 | 148.7±41.7** |
| HDL-C (mg/dl)                  | 46.3±7.0 | 45.3±6.9  | 43.5±6.1 | 40.9±6.3* | 45.2±5.9 |
| LDL-C (mg/dl)                  | 87.1±43.3 | 82.7±17.2 | 115.1±36.8* | 97.3±41.0 | 108.9±45.7 |
| IMA (U/L)                      | 85.5±12.8 | 433.2±67.1** | 279.2±37.8** | 287.0±47.6** | 334.8±49.9** |

*p*-values in relation to control group were presented as *<0.050 **<0.001.
Statistical analysis using one-way ANOVA revealed that mean of IMA highly significantly elevated in group 2 (renal haemodialysis patients) (at $p<0.001$), followed by group 5 (hepatitis C patients) (at $p<0.001$), followed by group 3 (type 2 diabetes patients) (at $p<0.001$) and group 4 (type 2 diabetes patients with renal haemodialysis) (at $p<0.001$) compared to control group.

Highly significantly elevated mean level of GOT (at $p<0.001$) and GPT (at $p<0.001$) in group 5 (hepatitis C patients) compared to other groups.

Highly significantly decreased mean level of albumin in group 5 (hepatitis C patients) (at $p<0.001$) and group 4 (type 2 diabetes patients with renal haemodialysis) (at $p<0.001$) compared to other groups.

Highly significantly elevated mean level of FBS in group 3 (type 2 diabetes patients) (at $p<0.001$), and group 4 (type 2 diabetes patients with renal haemodialysis) (at $p<0.001$) compared to other groups.

Highly significantly elevated mean levels of Urea and Creatinine in group 2 (renal haemodialysis patients) (at $p<0.001$) and group 4 (type 2 diabetes patients with renal haemodialysis) (at $p<0.001$) compared to other groups.

Significant elevated mean levels of Cholesterol, Triglycerides (at $p<0.050$) and LDL (at $p<0.050$) in group 3 (type 2 diabetes patients) compared to other groups. Also, highly significantly elevated mean level of Triglycerides in group 5 (hepatitis C patients) (at $p<0.001$) compared to other groups.

Significant decreased mean level of HDL-C in group 4 (type 2 diabetes patients with renal haemodialysis) (at $p<0.050$) compared to other groups.

There were not significant correlation between IMA and other studied parameters except the significant positive correlation between IMA and Creatinine (at $p=0.020$) & GOT (at $p=0.028$) in group 3 (type 2 diabetes patients).

Discussion

Diabetes is characterized by high glucose concentrations that lead, via several mechanisms to an increased production of reactive oxygen species [10].

The generation of ROS can transiently modify the N-terminal region of albumin and produce an increase in the concentration of ischemia-modified albumin (IMA), a new marker for ischemia [11]. Oxidative stress is involved in the pathogenesis of different chronic diseases.

The patients with type 2 diabetes had significantly higher levels of fasting glucose and the resultant hyperglycemia promotes an increase of IMA in type 2 diabetes, probably due to mechanisms of hypoxia and oxidative stress provoked mainly by hyperglycemia in diabetes [12].

In hepatitis C patients, HCV mainly infects liver resulting in acute and chronic infections that can lead to fibrosis, cirrhosis and hepatocellular carcinoma [13]. So the alteration in liver functions caused by virus C infection leading to increasing levels of both GOT and GPT, where both of them present in greater concentration in liver compared to other tissues, and decreased level of albumin where liver is the site of albumin synthesis.

Disturbance in antioxidant function of circulating albumin is seen in hepatitis C patients due to Hypoabluminemia. Under oxidative stress, the structure and function of serum albumin are altered and IMA concentration is increased.

The kidney performs essential physiological jobs ranging from metabolic waste excretion to homeostatic functions like osmoregulation [14].

Chronic kidney disease is typified by the progressive loss of kidney function over time due to fibrosis and the erosion of healthy tissue. Kidney disease leads to organ failure, known as end-stage renal disease (ESRD), which requires renal replacement therapy with dialysis or transplantation [14].

We found also, decreased levels of albumin in diabetic patients under maintenance haemodialysis this may be due to the increased excretion of albumin in urine in patients with haemodialysis resulting in decreased level of albumin in blood especially when subject being combined with diabetes mellitus type 2 where hyperglycemia causing production of oxidative stress which causing oxidation of albumin molecules altering its function.

Uremia result in an imbalance between free radical production and antioxidant defenses [15].

The resultant oxidative stress in haemodialysis patients and those with combined diabetes mellitus and haemodialysis leads to modification in N-terminal region of albumin and produce an increase in the concentration of ischemia-modified albumin (IMA).
We found highly significant elevated mean levels of Cholesterol, Triglycerides and LDL-C, and highly significant decreased mean levels of HDL-C in diabetic patients under haemodialysis compared to other groups. This is may be due to abnormal lipid metabolism caused by hyperglycemia in diabetes mellitus type 2.

Triglycerides also, highly significantly elevated in hepatitis C patients due to disturbance in lipid metabolism caused by hepatic viral infection.

As, The liver plays a vital role in lipid metabolism and is the principal site of lipoprotein formation and clearance. Thus, in severe liver disease, lipid metabolism is profoundly disturbed [16].

**Conclusion:** IMA is increased in chronic diseases than control subjects. Our study revealed that IMA is a good however non-specific indicator for chronic conditions (diabetes mellitus type 2, chronic renal failure with haemodialysis and hepatitis C infection).

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الملخص العربي

البروتين المتحور بفعل نقص تزويج الدم للأنسجة والأعضاء يعتبر علامة بيلوجية للاجهاد التاكسدي المرتبط باستعادة ضخ الدم للأنسجة أو الأعضاء. في الحالات الأكينيكية المختلفة المرتبطة بالإجهاد التاكسدي مثل مرض الكلي المزمن، ارتفاع الكولستيرول في الدم، التصلب الجاهري وأيضاً، كما تبين في تقرير أولاً، في السكرى من النوع 2.

طريقة العمل: شملت هذه الدراسة 75 شخص. تم تصنيف مجموعات الدراسة إلى 5 مجموعات.


الهدف: الهدف الرئيسي من هذه الدراسة هو تقييم البروتين المتحور بفعل نقص تزويج الدم للأنسجة والأعضاء في المرضى الذين يعانون من داء السكري من النوع 2 ومرضى الفشل الكلوي المعالج بالفسيل الكلوي ومرضى الالتهاب الكبدى الوبائي سى.

النتائج: مستوى البروتين المتحور بفعل نقص تزويج الدم للأنسجة والأعضاء مرتفع بشكل ملحوظ في المجموعة 2 (مرضى غسيل الكلوي).

تبين المجموعة 5 (مرضى التهاب الكبدى الوبائي S، تتبين المجموعة 2 (مرضى السكري النوع 2 والمجموعة 4 (مرضى السكري النوع 2 مع الفشل الكلوي) مقارنة بمجموعات الأشخاص السيئة.

الاستنتاج: البروتين المتحور بفعل نقص تزويج الدم للأنسجة والأعضاء يزيد في الأمراض المزمنة مقارنة بالأشخاص السليم. كما تكشف دراستنا على أن البروتين المتحور بفعل نقص تزويج الدم للأنسجة والأعضاء يعتبر مؤشر جيد ولكن غير محدد للحالات المزمنة (مرض السكرى من النوع 2 الفشل الكلوي المزمن المعالج بالفسيل الكلوي والالتهاب الكبدى الوبائي سى).