**Relationship between Lipid Indices, Type IV Collagen Turnover and the Development of Microvascular Complications in Diabetic Patients with Arterial Hypertension**

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**Background and aims:** An important factor in the development of vascular wall lesions is the degradation of the major protein of connective tissue - type IV collagen. Type IV collagen peptides (CIVDP) derived from this degradation are present in the circulation and are a stimulus for production of anti-collagen type IV antibodies (ACIVAbs) IgM, IgG and IgA. The aim of this study was to find a possible association between ACIVAbs, lipid indices and the development of microvascular complications.

**Materials and methods:** Sera of 93 patients (mean age 61.4±11.3 yrs, diabetes duration 9.88±3.12 yrs; hypertension duration 9.28±4.98) with type 2 diabetes mellitus (T2DM) and arterial hypertension (AH) were investigated. ACIVAbs was determined using ELISA and then compared to serum ACIVAbs in 42 age- and sex-matched controls. Diabetics were divided into two groups according to presence (group 1, n=67) or absence (group 2, n=26) of microangiopathy. Lipid profile and lipid indices (log TG/HDL, LDL/HDL, TC/HDL and TG/HDL) were examined too.

**Results:** Patients with T2DM and AH showed statistically significant higher levels of serum ACIVAbs IgG than healthy controls [0.298 (0.237÷0.381) vs 0.210 (0.149÷0.262), KW=14.01, p<0.0001]. Group 1 had statistically significant higher levels of ACIVAbs IgG than patients without microangiopathy [0.323 (0.243÷0.391) vs 0.241 (0.207÷0.291), KW=7.66, p=0.006] and healthy controls [0.210 (0.149÷0.262), KW=17.52, p<0.0001]. ACIVAbs IgG correlated with duration of diabetes (r=0.49, p=0.01), retinopathy (r=-0.20, p=0.04) and BMI (r=-0.24, p=0.05), HbA1c (r=-0.21, p=0.04), SBP (r=0.16, p=0.05). ACIVAbs IgG correlated with log TG/HDL (r=0.21, p=0.01), LDL/HDL (r=0.19, p=0.02) TC/HDL (r=0.16, p=0.05) and with TG/HDL (r=0.15, p=0.05).

**Conclusion:** Our study shows relationship between elevation of ACIVAbs IgG, high lipid indices and development of microvascular complications in patients with type 2 diabetes mellitus and arterial hypertension.

**INTRODUCTION**

Total cholesterol (TC)/high-density lipoprotein cholesterol (HDL) and low-density lipoprotein cholesterol (LDL)/HDL ratios are used to predict ischemic heart disease risk. Atherogenic indices (AI) were estimated like log TC/HDL.¹ Non-HDL cholesterol (total cholesterol minus HDL-cholesterol) includes all known and potential atherogenic lipid particles that predict further cardiovascular disease.²⁴ Total cholesterol/HDL ratio has been reported to be associated with metabolic derangement predictive of cardiovascular risks and related to insulin resistance syndrome.⁵⁻⁸ Triglyceride/HDL ratio has been reported as a marker of insulin resistance and small LDL.⁹,¹⁰

Arterial hypertension is associated with decreased degradation of connective tissue proteins, while in type 2 diabetes the degradation of these proteins is elevated. Because it is very important to find characteristics of pathological activation of type IV collagen turnover we studied hypertensive diabetic patients with manifest vascular complications. Thickening of the basement membrane in capillaries and small vessels in diabetes is a well-known find-
ing that is important in the progression of diabetic microangiopathy. Type IV collagen (CIV) is uniquely present in basement membranes and represents their predominant structural element.11-13 Metabolic alteration of CIV occurs in micro- or macrovascular basement membrane of diabetic patients. Type IV collagen is the major component of basement membranes.14 Measurement of serum antibodies to fragments of CIV15,16 is now possible thus making it possible for changes to be detected. Narita et al.17 measured serum anti-type IV collagen antibody (IgG) in diabetic patients and found that the serum levels of this antibody were significantly higher in diabetics than in nondiabetics. However, there was no relationship between the levels of urinary albumin and the serum levels of anti-type IV collagen antibody.

A relationship between lipid indices, immunological aspects of type IV collagen turnover in diabetics with arterial hypertension have not been studied until this moment. The aim of this study was to identify the possible association between lipid indices, ACIVAbs and development of microvascular complications in patients with type 2 diabetes and arterial hypertension. We present the results of the determination of anti-collagen type IV antibodies of different immunoglobulin classes (IgG, IgM and IgA) and lipid indices in patients with type 2 diabetes and arterial hypertension.

MATERIALS AND METHODS

The sera of 42 clinically healthy individuals (mean age 58.9±7.56 yrs) were used as controls. The selected controls were individuals with no family history of arterial hypertension, diabetes mellitus and atherosclerosis, who did not suffer from any inflammatory processes, collagenoses, and emphysema and had no history of hepatitis. Their routine clinical examinations, lipid profile and serum proteins showed no changes, and the ECGs were normal.

Apart from the clinically healthy individuals, 93 patients with type 2 diabetes and arterial hypertension were also examined. Their mean age was 61.4±11.3 years; the duration of diabetes was 9.88±3.12 years, and of arterial hypertension – 9.28±4.98 years. They were all from the region of the Medical University in Plevn. The diabetic patients were divided into two groups according to the presence or absence of microangiopathy (group 1 [n=67] and group 2 [n=26], respectively (Tables 1, 2). Ethical approval was obtained from the Ethics Committee, and the patients signed informed consent forms for their participation in the research.

PROCEDURES

I. ELISA

Serum antibodies (IgG, IgM and IgA) to CIV were measured by ELISA. In brief, each well of the microtiter plate was sensitized with 100 µl of 10 µg/ml of human CIV (SIGMA, USA) at room temperature for 3 h, followed by an overnight incubation at 4°C.

- The plate was washed with phosphate-buffered saline (PBS) containing 0.05% Tween 20 and 1% bovine serum albumin (BSA, SIGMA, USA).
- Then, 100 µl serum sample (diluted 1:10), was placed in each well of a microtiter plate, and incubated for 1 h at 37°C.
- After washing three times, 100 µl of immunoconjugates (anti-human immunoglobulin peroxidase conjugates (SIGMA, USA) to heavy chain of IgG, IgM and IgA) were added to each well for 1 h at 37°C. All immunoconjugates were diluted 1:10,000 with PBS containing 1% BSA and 0.05% Tween 20.
- The plate was incubated for 1 h at 37°C. o-Phenylenediamine (0.4 mg/ml) was added to citrate buffer, and 100 µl of this solution was added to each well and allowed to react for 30 min.
- The reaction was stopped by adding 50 µl 4 M H2SO4 to each well and the optical density was measured with a Microelisa Reader 210 (Organon Teknika, Belgium) at a wavelength of 492 nm.

II. Other tests

1. Ophthalmoscopy through dilated pupils was carried out in all diabetic patients by the same ophthalmologist.
2. Glycated haemoglobin was measured using HPLC method (normal range 4-5.6%) (Table 5).
3. Serum total cholesterol and triglyceride concentrations were measured using enzyme assay (Boehringer Mannheim, Mannheim, Germany).
4. Arterial blood pressure was measured using a standard mercury sphygmomanometer, to the nearest 2 mm Hg, in the dominant arm after at least 10 min rest in the supine position.
5. AER was determined by nephelometry using a commercial kit containing specific antibody (Behringwerke AG, Marburg, Germany).

STATISTICAL ANALYSIS

The research data were analysed using EXCEL (Microsoft Corporation, Redmond, WA) and STATGRAPHICS plus (Manugistics, Rockville, MD) for
RESULTS

Male patients with T2DM and AH showed statistically significant higher ratio of TG/HDL than female patients 3.3 (2.5±5.2) vs 2.0 (1.5±2.7) (KW=10.78; p<0.001).

Male patients with T2DM and AH showed statistically significant higher ratio of TC/HDL than female patients 7.2 (5.3±9.0) vs 5.2 (3.9±6.2) (KW=8.07; p=0.004).

Male patients with T2DM and AH showed statistically significant higher ratio of LDL/HDL than female patients 4.1 (3.1±5.8) vs 2.9 (2.0±4.5) (KW=5.85; p=0.01).

Log TG/HDL values in men were higher than these in women but these differences did not reach statistical significance (Table 3) (Fig. 2).

Patients with T2DM and AH were found to have statistically significant higher levels of serum ACIV-Abs IgG than healthy controls 0.298 (0.237±0.381) vs 0.210 (0.149±0.262) (KW=14.01; p=0.0001). Group 1 had statistically significant higher levels of ACIVAbs IgG than patients without microangiopathy 0.323 (0.243±0.391) vs. 0.241 (0.207–0.291) (KW=7.66; p=0.006) and healthy controls 0.210 (0.149±0.262) (KW=17.52; p<0.0001) (Table 4) (Fig. 1). ACIVAbs IgG showed correlation with

Table 1. Clinical data of patients with T2DM and AH

| Clinical data | Group 1 | Group 2 | Controls |
|---------------|---------|---------|----------|
| Age (yrs)     | 62.5±12.58 | 60.4±8.4 | 58.9±7.56 |
| Gender (male/female) | 26/41 | 11/15 | N/A |
| Mean diabetes duration (yrs) | 9.30±5.36 | 9.16±7.59 | N/A |
| Mean hypertension duration (yrs) | 9.50±7.63 | 8.68±7.26 | N/A |
| HbA1c         | *7.63±2.03 | 7.27±1.63 | N/A |
| SBP (mmHg)    | 142.83±18.05 | 140.58±20.51 | 114.29±15.74 |
| DBP (mmHg)    | 82.23±11.52 | 81.35±11.96 | 72.5±10.4 |
| BMI           | 29.62±4.99 | 28.42±3.96 | 22.61±2.27 |
| TCL (mmol/l)  | *5.26±1.40 | 5.18±0.93 | 3.99±0.65 |
| HDL (mmol/l)  | *0.88±0.30 | 0.93±0.30 | 0.96±0.20 |
| LDL (mmol/l)  | 3.18±1.19 | 3.16±1.09 | 2.43±0.64 |
| TGL (mmol/l)  | 2.91±1.68 | 2.53±1.49 | 1.31±0.61 |
| Insulin dose (U/kg/24h) | 2.57±0.52 | 2.03±0.93 | N/A |
| MAU (µg/min)  | *78.94±52.87 | 8.53±4.69 | N/A |

*All data are presented as mean ±SD

**Table 3.** (Fig. 2)
### Table 2. Smokers in groups (%)

|         | Group 1 |               | Group 2 |               | Controls |               |
|---------|---------|---------------|---------|---------------|----------|---------------|
|         | Men     | Smokers       | Men     | Smokers       | Men      | Smokers       |
|         | 39%     | 55%           | 42%     | 58%           | 45%      | 27%           |
| Women   | Non-smokers |           | Women   | Non-smokers   | Women    | Non-smokers   |
|         | 61%     | 45%           | 58%     | 42%           | 55%      | 73%           |

### Table 3. Lipid indices in male and female patients with T2DM and AH

| Lipid indices   | Men with T2DM and AH | Women with T2DM and AH | p    |
|-----------------|-----------------------|-------------------------|------|
| TG/HDL          | 3.3 (2.5–5.2)         | 2.0 (1.5–2.7)           | p<0.001 |
| TC/HDL          | 7.2 (5.3–9.0)         | 5.2 (3.9–6.2)           | p=0.004 |
| LDL/HDL         | 4.1 (3.1–5.8)         | 2.9 (2.0–4.5)           | p=0.01 |
| AIP (log TG/HDL)| 0.14 (0.12–0.16)      | 0.13 (0.11–0.14)        | NS   |

NS: non-significant

### Table 4. Serum levels of ACIVAbs IgG in patients with T2DM and AH

| Groups               | ACIVAbs IgG (ng/ml) | Comparison with other groups |
|----------------------|---------------------|-----------------------------|
|                      | M+(Q1 to Q3) | Group 1 | Group 2 | All diabetics |
| All diabetics        | 0.298 (0.237–0.381)| NS | p<0.01 | - |
| Group 1              | 0.323 (0.243–0.391)| - | p=0.006 | NS |
| Group 2              | 0.241 (0.207–0.291)| p=0.006 | - | NS |
| Controls             | 0.210 (0.149–0.262)| p<0.0001 | NS | p<0.0001 |

### Table 5. Reference range of normal lipid indices values and normal HbA1c range

| Lipid indices   | Men | Women |
|-----------------|-----|-------|
| TG/HDL          | >4.0 | >4.0  |
| TC/HDL          | >4.5 | >4.0  |
| LDL/HDL         | >3.6 | >3.2  |
| AIP (log TG/HDL)| >0.11 | >0.11 |
| HbA1c range     | 4%–5.6% | 4%–5.6% |

CVR: cardiovascular risk
duration of diabetes \( (r=0.49); \ (p=0.01) \), retinopathy \( (r=-0.20); \ (p=0.04) \) and BMI \( (r=-0.24); \ (p=0.05) \), SBP \( (r=0.16); \ (p=0.05) \). ACIVAbs IgG correlated with log TG/HDL \( (r=0.21); \ (p=0.01) \), LDL/HDL \( (r=0.19); \ (p=0.02) \) TC/HDL \( (r=0.16); \ (p=0.05) \) and with TG/HDL \( (r=0.15); \ (p=0.05) \). Serum ACIV IgM and IgA levels in patients with T2DM and AH were lower than these in controls, but the differences were not statistically significant.

**DISCUSSION**

Extracellular matrix proteins: type IV collagen (CIV) and elastin are uniquely present in basement membranes and represent their predominant structural element. Metabolic alteration of CIV occurs mainly in the microvascular basement membrane of diabetic patients. Arterial hypertension and diabetes mellitus are connected with an elevated degradation of elastic tissue, loss of elasticity, increasing
rigidity of arterial wall, and abnormal increase in the collagen/elastin ratio. As a result, soluble type IV collagen derived peptides (CIVDP) are released in the circulated blood acting there as pathological stimulus for an increased production of anti-collagen type IV (ACIVAbs) antibodies.

Collagens are known to be immunogenic in animals, and antibodies to various collagens are present in human serum in several diseases, particularly those of autoimmune origin. The detection of serum CIV in animals or humans with arterial hypertension shows that CIV macromolecule is not fully degraded by collagenases in vivo. These CIV fragments may become an increased stimulus for immunocompetent cells for pathological production of anti-CIV antibodies. Changes in the levels and pattern of antibodies to CIV may occur with time.

The atherogenic index of plasma (AIP) (log TG/HDL) is calculated in an attempt to predict cardiovascular risk. AIP is based on the ratio of the values of triglycerides to high-density lipoprotein (HDL) levels. When placed into the scope of AIP, triglycerides and HDL refers to the relationship of atherogenic lipids to protective lipids. The AIP has demonstrated cardiovascular risk in clinical trials. Values less than 0.11 are classified as low cardiovascular risk, between 0.11 to 0.21 there is an intermediate cardiovascular risk, and if greater than 0.21 there is increased risk. The total cholesterol TC/HDL ratio is more indicative of cardiovascular disease than TC (total cholesterol). The amount of HDL and LDL in the blood are added together, this number for all practical purposes, indicates the amount of total cholesterol. For men an acceptable ratio of TC/HDL is 4.5 or below, and women is 4.0 or below.

HDL levels have an inverse relationship with coronary heart disease. The ability of HDL to predict the development of coronary atherosclerosis has been estimated to be four times greater than LDL and eight times greater than TC. The triglyceride/HDL ratio: 2 or less is considered ideal, 4 - high, 6 - much too high. The ratio of triglycerides to HDL was the strongest predictor of a heart attack, even more accurate than the LDL/HDL ratio.

In diabetic patients morbidity and mortality are mainly related to the presence of late complications, namely macro- and microangiopathy. Diabetes mellitus (both type 1 and type 2) is a major risk factor for cardiovascular disease. In the Framingham Study, the risk of cardiovascular disease was doubled by the presence of diabetes.

In a recent study, patients with microvascular complications showed statistically significant higher levels of ACIVAbs IgG than patients without microangiopathy and healthy controls. ACIVAbs IgG showed correlation with duration of diabetes, BMI, systolic blood pressure, total cholesterol and triglycerides. Serum levels of ACIVAbs IgM and IgA in patients with T2DM and AH were lower than those in controls, but this differences were not statistically significant. A possible explanation of this result is the fact that IgM is the first immunoglobulin synthesized during the early phase of a pathologically activated immune response. The immune system then switches on to production of IgG. The elevation of ACIVAbs of IgG types is therefore the first indicator of the pathological turnover of elastin and the development of vascular complications in diabetics. In our study, it was not possible to detect the ‘active’ phase of vascular disease, because of patients’ diabetes duration of 9.88±3.12 years. During this ‘active’ phase the levels of IgM and IgA were probably elevated, while during the chronic phase levels of both types of ACIVAbs were decreased and only the level of IgG ACIVAbs was increased.

In our study we found correlation of anti-CIV IgG with retinopathy. These findings are supported by the results of Balashova et al. among patients with preclinical, nonproliferative, preproliferative, and proliferative diabetic retinopathy. The authors found that diabetic retinopathy is characterized by a notable increase in antibody-dependent immune response, associated with appearance of antibodies to collagen of the II and IV types in the lachrymal fluid and serum, with the ‘local’ reactions predominating. The level of reactions of cellular autoimmune response (tumor necrosis factor-alpha) and cell-to-cell reactions in the lachrymal fluid and serum was low. According to the authors increased level of circulating immune complexes in the serum and almost complete absence of free antibodies to collagen in the blood may be indicative of formation of pathogenic immune complexes precipitating on vascular walls and in other tissues.

We found that the values of ACIVAbs IgG in patients with vascular complications were significantly higher than those in patients without vascular damage and healthy controls. This means that group 1 diabetics show pathologically high immune response to type IV collagen. Although the data from group 2 reveals levels of ACIVAbs IgG higher than those of the controls, these levels still remain lower than the measured in patients with vascular complications.
from group 1. It is extremely important to monitor if the group of patients with high levels of ACIV-Abs IgG will develop vascular lesions before the patients without such elevated levels of ACIVAbs IgG. We suggest that an association exist between the activity of collagen turnover, high lipid indices and vascular complications.

There was a correlation established between ACIVAbs IgG and log TG/HDL (r=0.21); (p=0.01), LDL/HDL (r=0.19); (p=0.02) TC/HDL (r=0.16); (p=0.05) and with TG/HDL (r=0.15); (p=0.05). A possible explanation of this result is the evidence that the ECM fibers may be involved in the process of lipid precipitation in arteries. Our results support these findings.

Our data indicate that traditional serum lipid measures such as total cholesterol, LDL, triglycerides and HDL levels are less prognostic for development of vascular injuries than high lipid indices, especially TC/HDL and TG/HDL ratio for identification of subjects who are more susceptible for microvascular complications. Moreover, ACIVAbs IgG (which are biological markers for impaired connective tissue function showed correlation with high lipid indices AIP (log TG/HDL) TC/HDL, LDL/HDL, TG/HDL), but did not show a correlation with serum triglycerides and total cholesterol levels. That is why we suppose that lipid indices are more strongly associated with development of ECM dysfunction in patients with T2DM and AH and development of vascular lesions than widespread use of routine lipid markers.

It is known that elevated levels of serum triglycerides which contain multiple types of potential atherogenic lipoproteins enrich the picture of diabetic dyslipidemia. It is the most common deviation in poorly controlled diabetes. In patients with microvascular complications attachment of triglycerides to the arterial wall can lead to the conversion of type IV collagen to an immunogenic form. In the present study, the triglycerides were elevated over the normal range in patients with vascular complications which supports the idea about this feature.

Identification of biomarkers would allow more aggressiveness in the achievement of tight glycemic control and search for initial lesions in those patients who are predisposed to complications than in those who are not. The understanding of the relation between high lipid indices, the altered pattern of expression of various types of antibodies against components of ECM and the deregulated vascular remodeling at the level of the target tissue would allow design of therapeutic approach targeted to the individual tissue and to the relevant biochemical, functional and structural alterations. Our study shows, that determination of biological markers of collagen type IV turnover and lipid indices can be useful in monitoring development of vascular injury.

CONCLUSIONS

The results suggest an association between the level of anti-collagen type IV IgG antibodies, high lipid indices and the development of vascular wall lesions. Elevation of ACIVAbs IgG may indicate increased collagen turnover and development of microvascular complications. However, further study is necessary for clarification of these possibilities.

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Взаимосвязь между липидными показателями, биохимическим циклом коллагена IV типа и развитием микрососудистых осложнений у больных сахарным диабетом с артериальной гипертонией

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Введение и цели: Важным фактором в развитии поражений сосудистой стенки является деградация основного белка соединительной ткани - коллагена IV типа. Пептиды коллагена IV типа (CIVDP), полученные в результате этой деградации, присутствуют в кровообращении и являются стимулом для производства антител антиколлагена IV типа (ACIVAbs) IgM, IgG и IgA. Целью данного исследования было найти возможную связь между ACIVAbs, липидными показателями и развитием микрососудистых осложнений.

Материалы и методы: Обследовано 93 пациента (средний возраст 61,4 ± 11,3 года, продолжительность диабета 9,88 ± 3,12 г, продолжительность гипертонии 9,28 ± 4,98) с сахарным диабетом 2 типа (СДТ2) и артериальной гипертонией (АГ). ACIVAb определяли с помощью ELISA и затем сравнивали с сывороточным ACIVAb 42 человек из контрольной группы, сопоставимых по возрасту и полу. Пациенты с диабетом были разделены на две группы в зависимости от наличия (группа 1, n = 67) или отсутствия (группа 2, n = 26) микроангиопатии. Липидный профиль и липидные показатели (log TG / HDL, LDL / HDL, TC / HDL и TG / HDL) также были исследованы.

Результаты: Пациенты с СДТ2 и АГ имели статистически значимые более высокие уровни IgG ACIVAb в сыворотке по сравнению с участниками из контрольной группы [0,298 (0,237 ÷ 0,381) против 0,210 (0,149 ÷ 0,262), KW = 14,01, р <0,0001]. Группа 1 имела статистически значимые более высокие уровни IgG ACIVAbs по сравнению с пациентами без микроангиопатии [0,323 (0,243 ÷ 0,391) против 0,241 (0,207 ÷ 0,291), KW = 7,66, р = 0,006] и участниками из контрольной группы [0,210 (0,149 ÷ 0,262), KW = 17,52, р &lt; 0,0001]. ACIVAbs IgG показали корреляцию с продолжительностью диабета (r = 0,49, p = 0,01), ретинопатией (r = -0,20, p = 0,04) и ИМТ (r = -0,24, p = 0,05), HbA1c (r = -0,21, p = 0,04), СБП (r = 0,16, p = 0,05). ACIVAbs IgG коррелируют с log TG / HDL (r = 0,21, p = 0,01), LDL / HDL (r = 0,19, p = 0,02) TC / HDL (r = 0,16, p = 0,15, p = 0,05).

Заключение: Наше исследование пока показало взаимосвязь между повышением IgG ACIVAbs, высокими липидными показателями и развитием микрососудистых осложнений у пациентов с сахарным диабетом 2 типа и артериальной гипертонией.