Pro-Atherogenic Alterations in T-Lymphocyte Subpopulations Related to Acute Hyperglycaemia in Type 2 Diabetic Patients

Marzena Dworacka, MD, PhD; Hanna Winiarska, MD, PhD; Magdalena Borowska, MSc; Małgorzata Abramczyk, MD, PhD; Teresa Bobkiewicz-Kozłowska, PhD, DSc; Grzegorz Dworacki, MD, PhD*

Background T cells are among the earliest cells to infiltrate the arterial intima during the initial stages of atherosclerosis. Alterations in the peripheral blood lymphocyte distribution might be associated with intensive lymphocytes extravasation and stimulation of atherosclerotic plaque development. Epidemiological data reveal that short-term postprandial hyperglycaemia is a significant risk factor for coronary heart disease. Using a parameter that indicates recently-past acute hyperglycaemia, 1,5-anhydro-D-glucitol (1,5-AG), the aim of the present study was to elucidate which alterations in peripheral blood T-lymphocytes, if any, are associated with acute hyperglycaemia in patients with type 2 diabetes mellitus (DM) and, thus, might be involved in the progression of atherosclerosis.

Methods and Results Measurement of fasting glucose level, glycated hemoglobin A1c, 1,5-AG, lipid profile and lymphocyte receptors expression (CD3+, CD4+, CD8+, CD8+28+, CD8+28–) was performed in 97 patients with type 2 DM, 23 patients with coronary heart disease, and 15 healthy controls. The mean CD3+, CD4+, CD8+28+ and CD8+28– lymphocyte counts were significantly higher in the DM patients than in both control groups. Multiple regression analysis revealed that CD4+ and CD8+28– lymphocyte counts primarily were dependent on 1,5-anhydro-D-glucitol plasma levels.

Conclusions These results suggest that acute hyperglycaemia results in the progression of atherosclerosis in type 2 DM, at least in part through changes in CD4+ and CD8+28– lymphocyte subsets. (Circ J 2007; 71: 962–967)

Key Words: Acute hyperglycaemia; 1,5-Anhydro-D-glucitol; Atherosclerosis; Diabetes type 2; Lymphocytes

It is currently evident that T cells are among the earliest cells to infiltrate the arterial intima during the initial stages of atherosclerosis.1-2 and of the T-cell population, most are CD3+CD4+ T-cell receptor αβ+ cells, with the remaining being CD8+CD4+. Oxidized low-density lipoprotein (LDL) peptides, heat shock protein-60 and advanced glycation endproducts are antigens for T-cell populations in atherosclerotic lesions.3,4 A large proportion of T cells in atherosclerotic human plaques are activated, expressing adhesion and other surface molecules, secreting cytokines, and possibly proliferating. The activation of T cells, as well as macrophages, leads to an inflammatory state. Vascular endothelial cells and smooth muscle cells are important targets for inflammatory cytokines.1,4 Moreover, activated CD8+ lymphocytes, particularly CD8+28– cells, can cause some of the widespread apoptosis that is associated with atherosclerosis.5,6 These alterations in peripheral blood lymphocyte distribution, especially the CD4+ and CD8+ populations, might be associated with intensive lymphocyte extravasation and stimulation of atherosclerotic plaque development.

Type 2 diabetes mellitus (DM) is strongly associated with various changes in the lymphocyte distribution in peripheral blood; for example, T-cell lymphocytosis,7 T-cell lymphopenia8 and unchanged T-cell subpopulations.9 Some authors also suggest that, in diabetic patients, metabolic control influences lymphocyte distribution.10 Coronary artery disease (CAD) is known to be the major cause of the high morbidity and mortality among patients with type 2 DM. Current epidemiological data demonstrate that short-term postprandial hyperglycaemia is a greater risk factor for CAD development than are elevated fasting glycemia and glycated hemoglobin A1c (HbA1c).11,12 Consequently, it is evident that the progression of atherosclerosis in type 2 DM is markedly dependent upon acute hyperglycemic episodes. Unfortunately, the parameters routinely used as long-term markers of the overall glycemic state, such as HbA1c or fructosamine, are not designed to capture every acute, transient hyperglycemic spike.13,14 Even frequent self-monitoring of blood glucose cannot reveal the short-term fluctuations that may occur between measurements.15 A useful marker of glucose excursions and postprandial hyperglycaemia is the 1,5-anhydroglucitol (1,5-AG) plasma level.15,16 Even though 1,5-AG currently is not the standard marker for DM control, and except in Japan is not well known, it is the only parameter that detects short-term hyperglycemic spikes.14,17 1,5-AG, the concentration of which generally is stable in the plasma of non-diabetic persons, decreases rapidly immediately after a hyperglycemic episode, because 1,5-AG competes with glucose for trans-
port mechanisms within the renal tubules. Therefore, a decline in the 1,5-AG plasma level is closely related to hyperglycemia, even very brief episodes.

We aimed to elucidate which alterations in the peripheral blood T-lymphocytes, if any, are associated with acute hyperglycemic episodes in patients with type 2 DM, because this may indicate an involvement in the development and progression of atherosclerosis in such patients.

Table 1  Characteristics of the Study Subjects

<table>
<thead>
<tr>
<th></th>
<th>DM type 2</th>
<th>CAD (control-1)</th>
<th>Healthy individuals (control-2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>97</td>
<td>23</td>
<td>15</td>
</tr>
<tr>
<td>M/F</td>
<td>53/44</td>
<td>14/9</td>
<td>9/6</td>
</tr>
<tr>
<td>Age (years)</td>
<td>64.6±10.0*</td>
<td>62.3±7.9*</td>
<td>52.7±12.1</td>
</tr>
<tr>
<td>Diabetes duration (years)</td>
<td>7.2±4.3</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>31.4±2.2*</td>
<td>31.1±2.7*</td>
<td>29.3±3.2</td>
</tr>
<tr>
<td>Fasting glycemia (mmol/L)</td>
<td>9.2±2.8*</td>
<td>5.3±0.6</td>
<td>4.8±0.5</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>7.3±1.4**</td>
<td>5.1±0.7</td>
<td>–</td>
</tr>
<tr>
<td>1,5-Anhydro-D-glucitol (mg/L)</td>
<td>11.8±6.2*</td>
<td>–</td>
<td>23.9±3.1</td>
</tr>
<tr>
<td>TC (mmol/L)</td>
<td>5.9±1.4</td>
<td>6.1±1.9</td>
<td>–</td>
</tr>
<tr>
<td>HDL-cholesterol (mmol/L)</td>
<td>2.8±0.4</td>
<td>1.4±0.3</td>
<td>–</td>
</tr>
<tr>
<td>LDL-cholesterol (mmol/L)</td>
<td>3.3±0.7</td>
<td>3.3±0.9</td>
<td>–</td>
</tr>
<tr>
<td>TG (mmol/L)</td>
<td>2.4±1.0</td>
<td>2.2±0.8</td>
<td>–</td>
</tr>
</tbody>
</table>

*Statistically significant against every other group, **statistically significant against patients with CAD, #statistically significant against healthy individuals.

DM, diabetes mellitus; CAD, coronary artery disease; BMI, body mass index; HbA1c, glycated hemoglobin A1c; TC, total cholesterol; HDL, high-density lipoprotein; LDL, low-density lipoprotein; TG, triglycerides.

Glucose concentration was measured from a venous blood sample, by means of the glucose oxidase method, using a Cormay analyser (PZ Cormay).

Lipids were assayed using standard enzymatic methods (total cholesterol, high-density lipoprotein-cholesterol (HDL) and LDL-cholesterol by cholesterol esterase method; triglycerides by glycerophosphate oxidase method).

HbA1c (normal range: 4.1–6.0%) was assayed using high-performance liquid chromatography (Variant™ HbA1c, BIO-RAD), standardized according to the DCCT.21

The plasma concentration of 1,5-AG was measured using a modified-column enzymatic method. Briefly, 100 μL of a plasma sample was deproteinized with trichloroacetic acid, then passed through a 2-layer microcolumn packed with ion-exchange resins (cationite Dowex 50WX8; anionite Dowex 1x8, Sigma, St Louis, MO, USA) to remove glucose. 1,5-AG was recovered efficiently in the flow-through fraction. Hydrogen peroxide that had been formed in the enzymatic oxidation of 1,5-AG with pyranoate oxidase was detected by a standard method, using an enzymatic colour-developing system. The intra- and interassay coefficients of variation were 4.9% and 3.7%, respectively. The mean recovery was 96.6%. The reference range was between 14.4 and 30.2 mg/L.

To detect the lymphocyte subsets, samples of whole blood in EDTA were maintained at 4°C. Blood was processed within 6 h of collection. Flow cytometry (FCM-Scan, Becton-Dickinson) was used to quantify leukocyte populations. Cells were detected by mouse monoclonal antibodies conjugated with either fluorescein, phycoerythrin or peridinin-chlorophyll-protein (Becton-Dickinson). The following cell types were assessed with the corresponding antibodies: mature T lymphocytes (CD3+), T-helper lymphocytes (CD4+), and T-cytotoxic/suppressor lymphocytes (CD8+, CD8+28+, CD8+28-). Phenotypes were expressed as the percentage of total cells (relative values) analyzed by flow cytometry, or as an absolute cell count.

Table 2  Characteristics of the Study Subjects

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>M/F</th>
<th>Age (years)</th>
<th>Diabetes duration (years)</th>
<th>BMI (kg/m²)</th>
<th>Fasting glycemia (mmol/L)</th>
<th>HbA1c (%)</th>
<th>1,5-Anhydro-D-glucitol (mg/L)</th>
<th>TC (mmol/L)</th>
<th>HDL-cholesterol (mmol/L)</th>
<th>LDL-cholesterol (mmol/L)</th>
<th>TG (mmol/L)</th>
<th>Fasting glycemia (mmol/L)</th>
<th>glucose (%/mg/L)</th>
<th>BMI (kg/m²)</th>
<th>Age (years)</th>
<th>Diabetes duration (years)</th>
<th>Fasting glycemia (mmol/L)</th>
<th>HbA1c (%)</th>
<th>1,5-Anhydro-D-glucitol (mg/L)</th>
<th>TC (mmol/L)</th>
<th>HDL-cholesterol (mmol/L)</th>
<th>LDL-cholesterol (mmol/L)</th>
<th>TG (mmol/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>DM type 2</td>
<td>97</td>
<td>53/44</td>
<td>64.6±10.0*</td>
<td>7.2±4.3</td>
<td>31.4±2.2*</td>
<td>9.2±2.8*</td>
<td>7.3±1.4**</td>
<td>11.8±6.2*</td>
<td>5.9±1.4</td>
<td>2.8±0.4</td>
<td>3.3±0.7</td>
<td>2.4±1.0</td>
<td>9.2±3±10.0*</td>
<td>7.3±1.4**</td>
<td>11.8±6.2*</td>
<td>5.9±1.4</td>
<td>2.8±0.4</td>
<td>3.3±0.7</td>
<td>2.4±1.0</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CAD (control-1)</td>
<td>23</td>
<td>14/9</td>
<td>62.3±7.9*</td>
<td>–</td>
<td>31.1±2.7*</td>
<td>5.3±0.6</td>
<td>5.1±0.7</td>
<td>–</td>
<td>6.1±1.9</td>
<td>1.4±0.3</td>
<td>3.3±0.9</td>
<td>2.2±0.8</td>
<td>62.3±7.9*</td>
<td>5.3±0.6</td>
<td>31.1±2.7*</td>
<td>6.1±1.9</td>
<td>1.4±0.3</td>
<td>3.3±0.9</td>
<td>2.2±0.8</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Healthy individuals (control-2)</td>
<td>15</td>
<td>9/6</td>
<td>52.7±12.1</td>
<td>–</td>
<td>29.3±3.2</td>
<td>4.8±0.5</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>52.7±12.1</td>
<td>–</td>
<td>29.3±3.2</td>
<td>4.8±0.5</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
and CD3<sup>+</sup>, CD4<sup>+</sup> and CD8<sup>+</sup>28<sup>+</sup> lymphocyte counts in peripheral blood. All statistical analyses were performed using Statistica 6.0 (StatSoft, Inc). A p-value ≤0.05 was considered significant.

**Results**

The characteristics of all the subjects are shown in Table 1. Patients with DM or CAD were similar in terms of body mass and lipid profiles. Patients without overt carbo-

**Table 2 Distribution of Peripheral Blood Lymphocyte Subpopulations**

<table>
<thead>
<tr>
<th></th>
<th>DM type 2</th>
<th>CAD (control-1)</th>
<th>Healthy individuals (control-2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>97</td>
<td>23</td>
<td>15</td>
</tr>
<tr>
<td>M/F</td>
<td>53/44</td>
<td>14/9</td>
<td>9/6</td>
</tr>
<tr>
<td>CD3 (%)</td>
<td>87.5±8.9*</td>
<td>59.7±10.7</td>
<td>55.0±9.6</td>
</tr>
<tr>
<td>CD3 (cells/µl)</td>
<td>1,351.0±140.6*</td>
<td>921.0±168.3</td>
<td>859.7±145.5</td>
</tr>
<tr>
<td>CD4 (%)</td>
<td>58.6±9.2*</td>
<td>31.6±7.7</td>
<td>31.4±6.3</td>
</tr>
<tr>
<td>CD4 (cells/µl)</td>
<td>905.6±143.6*</td>
<td>488.1±120.5</td>
<td>488.6±94.5</td>
</tr>
<tr>
<td>CD8 (%)</td>
<td>28.6±11.5</td>
<td>32.6±12.2</td>
<td>24.8±8.4</td>
</tr>
<tr>
<td>CD8 (cells/µl)</td>
<td>442.0±177.4</td>
<td>502.4±189.5</td>
<td>394.0±130.3</td>
</tr>
<tr>
<td>CD4/CD8</td>
<td>2.5±1.5*</td>
<td>1.4±0.6</td>
<td>1.4±0.7</td>
</tr>
<tr>
<td>CD8&lt;sup&gt;+&lt;/sup&gt;+28&lt;sup&gt;+&lt;/sup&gt; (%)</td>
<td>10.3±5.0*</td>
<td>6.6±3.3</td>
<td>5.7±2.7</td>
</tr>
<tr>
<td>CD8&lt;sup&gt;+&lt;/sup&gt;+28&lt;sup&gt;+&lt;/sup&gt; (cells/µl)</td>
<td>158.7±77.5*</td>
<td>101.3±51.2</td>
<td>88.0±42.7</td>
</tr>
<tr>
<td>CD8&lt;sup&gt;+&lt;/sup&gt;28&lt;sup&gt;+&lt;/sup&gt; (%)</td>
<td>19.8±12.3*</td>
<td>27.0±12.2*</td>
<td>17.1±7.8</td>
</tr>
<tr>
<td>CD8&lt;sup&gt;+&lt;/sup&gt;28&lt;sup&gt;+&lt;/sup&gt; (cells/µl)</td>
<td>305.4±190.3*</td>
<td>416.3±188.0*</td>
<td>265.0±120.1</td>
</tr>
</tbody>
</table>

*Statistically significant against every other group. Abbreviations see in Table 1.

**Fig 1.** Correlation between 1,5-AG plasma levels and CD4<sup>+</sup> and CD8<sup>+</sup>28<sup>+</sup> lymphocyte counts; R=(−0.29) for p≤0.05. 1,5-AG, 1,5-anhydro-D-glucitol.

**Fig 2.** Correlation between 1,5-AG plasma levels and CD8<sup>+</sup>28<sup>+</sup> lymphocyte counts; R=(−0.56) for p≤0.05. 1,5-AG, 1,5-anhydro-D-glucitol.
hydrate metabolism deterioration (ie, healthy subjects and patients with CAD) had lower levels of fasting glycemia and HbA1c than diabetic individuals. Plasma 1,5-AG concentrations were significantly lower in diabetic patients than in either control group. Table 2 shows the distribution of peripheral blood lymphocyte subpopulations in the 3 subject groups. The mean CD3+, CD4+, and CD8+ lymphocyte counts, expressed either as relative or absolute values, and the CD4/CD8 ratio were significantly higher in diabetic patients than in either control group. The absolute and relative counts of CD8+ lymphocytes were significantly higher in patients with either CAD or DM than in healthy controls. There were no significant intergroup differences in CD8+ lymphocyte counts.

Significant negative correlations were found between 1,5-AG and CD3+, CD4+, and CD8+ lymphocyte counts in diabetic patients (CD3+ relative and absolute count, R=−0.30; CD4+ relative count, R=−0.29; CD4+ absolute count, R=−0.30; CD8+ relative count, R=−0.56; and CD8+ absolute count, R=−0.57, respectively) (Figs 1, 2). Expression of CD8+ receptors also correlated with fasting glycemia (absolute and relative count, R=0.30), and HbA1c (absolute and relative count, R=0.22) and HDL-C levels (relative count, R=−0.22). No correlation was identified between CD8+ lymphocyte counts and 1,5-AG levels.

Multiple regression analysis showed that the CD4+ lymphocyte count is dependent on 1,5-AG (standardized coefficient SBC=(−0.37), R2=0.22) and on HDL-C levels (standardized coefficient SBC=−0.36, R2=0.35) (Fig 3), whereas the CD8+ lymphocyte count was primarily determined by the 1,5-AG level (standardized coefficient SBC=−0.52, R2=0.35) (Fig 4). The multiple regression model with CD3+ lymphocyte count as the dependent variable was rejected because of a very low R2 value (0.1).

**Discussion**

Many other investigators have identified alterations in different lymphocyte subsets in type 2 DM7–10 and we also detected significant lymphocyte subset redistribution in the present diabetic patients vs healthy controls and non-diabetic patients with CAD; increases were noted particularly in CD3+, CD4+, CD8+ lymphocytes.
It is well documented that glucose abnormalities are related to poor prognosis in patients with CAD. Recent epidemiological, clinical and experimental data have suggested that controlling blood glucose in the non-fasting state, especially in the postprandial period, can reduce the risk of the macro-angiopathic complications of DM. Monitoring of the HbA1c levels assists in reducing the risk of microvascular complications but unfortunately, low HbA1c levels are not sufficient to decrease the risk of macrovascular complications, especially the risk of coronary heart disease. Plasma 1,5-AG levels reflect short-term (mainly postprandial) changes in serum glucose and can be used to retrospectively detect recent acute hyperglycemic episodes.

The present study determined that CD3+, CD4+ and CD8+ lymphocyte counts are associated with 1,5-AG levels in the plasma of diabetic patients, and this relationship suggests that acute hyperglycemic spikes might stimulate changes in lymphocyte subsets. Moreover, taking into consideration chronic hyperglycemia, fasting glycemia, the lipid profile and acute hyperglycemia, multivariate regression analysis revealed that acute hyperglycemia is the most significant metabolic deterioration that determines increases in the CD4+ and CD8+ lymphocyte counts. Increased lymphocytes counts usually are associated with lymphocyte activation and proliferation. Oxidative stress seems to be the element linking acute hyperglycemia with increased counts of CD4+ and CD8+ lymphocytes. George et al revealed a significant increase in activated T-lymphocytes induced by oxidative stress. However, it has been well established that hyperglycemia stimulates oxidative stress by various mechanisms. Additionally, in vitro studies have confirmed the role of hyperglycemia in activating human T-lymphocytes. Why, then, did the present study show that acute hyperglycemia induces alterations in immunophenotype, but chronic hyperglycemia does not? There are 2 possible explanations. First, HbA1c levels among the diabetic patients examined here averaged 7.3±1.4%, which is only slightly above the gold standard (HbA1c ≤7.0%) for glycemic control, established by DCCT as being appropriate for reducing the risk of vascular complications. Therefore, in this patient population, the influence of chronic hyperglycemia on oxidative stress was possibly quite limited. Second, numerous previously published data have demonstrated that acute glucose fluctuations exhibit a more specific triggering effect on oxidative stress than chronic sustained hyperglycemia.

The present study is the first to report an association between acute, short-term hyperglycemic episodes and increased CD8+ lymphocyte counts. Interestingly, the level of another lymphocyte subpopulation, CD8+ lymphocytes, was not related to any glycemic parameters. CD8+ lymphocytes primarily exert cytotoxic effects, whereas CD8+ lymphocyte activity mainly results in cytokine secretion. Thus, it is possible that CD8+ lymphocytes alone cause some of the widespread apoptosis that is associated with the progression of atherosclerosis. Smooth-muscle cells in the fibrous cap tend to undergo apoptosis, and this is the main mechanism behind ‘vulnerable’ atherosclerotic plaque formation. Interestingly, CD8+ cells have been detected adjacent to ruptured plaque. Accordingly, the CD8+ cytotoxic subpopulation conceivably could kill smooth-muscle cells in the fibrous cap. An increased number of CD4+ T cells in the peripheral blood may enhance their migration into the arterial vessel wall, resulting in initiation and promotion of atherosclerosis. Nilsson suggested that, in the absence of CD4+ T cells, MHC class II restricted activation of T cells is impaired to such an extent that endogenous pro-atherogenic immune responses are significantly reduced.

In conclusion, it could be stated that the progression of atherosclerosis in type 2 DM is related, at least in part, to an acute hyperglycemia-induced increase in CD4+ and CD8+ lymphocyte counts in the peripheral blood.

References

11. Turek-Kurkutschiev TS, Kohler T. Postchallenge plasma glucose and glycemic spikes are more strongly associated with atherosclerosis than fasting glucose or HbA1c level. Diabetes Care 2000; 23: 1830 – 1834.
17. Yamanouchi T, Tachibana Y, Akanuma H, Minoda S, Shinohara T, N, et al. Post-load glucose measurements in oral glucose tests correlate well with 1,5-anhydroglucitol, an indicator of overall glycaemic control, established by DCCT as being appropriate for reducing the risk of vascular complications. Therefore, in this patient population, the influence of chronic hyperglycemia on oxidative stress was possibly quite limited. Second, numerous previously published data have demonstrated that acute glucose fluctuations exhibit a more specific triggering effect on oxidative stress than chronic sustained hyperglycemia. It is well documented that glucose abnormalities are related to poor prognosis in patients with CAD. Recent epidemiological, clinical and experimental data have suggested that controlling blood glucose in the non-fasting state, especially in the postprandial period, can reduce the risk of the macro-angiopathic complications of DM. Monitoring of the HbA1c levels assists in reducing the risk of microvascular complications but unfortunately, low HbA1c levels are not sufficient to decrease the risk of macrovascular complications, especially the risk of coronary heart disease. Plasma 1,5-AG levels reflect short-term (mainly postprandial) changes in serum glucose and can be used to retrospectively detect recent acute hyperglycemic episodes.

The present study determined that CD3+, CD4+ and CD8+ lymphocyte counts are associated with 1,5-AG levels in the plasma of diabetic patients, and this relationship suggests that acute hyperglycemic spikes might stimulate changes in lymphocyte subsets. Moreover, taking into consideration chronic hyperglycemia, fasting glycemia, the lipid profile and acute hyperglycemia, multivariate regression analysis revealed that acute hyperglycemia is the most significant metabolic deterioration that determines increases in the CD4+ and CD8+ lymphocyte counts. Increased lymphocytes counts usually are associated with lymphocyte activation and proliferation. Oxidative stress seems to be the element linking acute hyperglycemia with increased counts of CD4+ and CD8+ lymphocytes. George et al revealed a significant increase in activated T-lymphocytes induced by oxidative stress. However, it has been well established that hyperglycemia stimulates oxidative stress by various mechanisms. Additionally, in vitro studies have confirmed the role of hyperglycemia in activating human T-lymphocytes. Why, then, did the present study show that acute hyperglycemia induces alterations in immunophenotype, but chronic hyperglycemia does not? There are 2 possible explanations. First, HbA1c levels among the diabetic patients examined here averaged 7.3±1.4%, which is only slightly above the gold standard (HbA1c ≤7.0%) for glycemic control, established by DCCT as being appropriate for reducing the risk of vascular complications. Therefore, in this patient population, the influence of chronic hyperglycemia on oxidative stress was possibly quite limited. Second, numerous previously published data have demonstrated that acute glucose fluctuations exhibit a more specific triggering effect on oxidative stress than chronic sustained hyperglycemia.

The present study is the first to report an association between acute, short-term hyperglycemic episodes and increased CD8+ lymphocyte counts. Interestingly, the level of another lymphocyte subpopulation, CD8+ lymphocytes, was not related to any glycemic parameters. CD8+ lymphocytes primarily exert cytotoxic effects, whereas CD8+ lymphocyte activity mainly results in cytokine secretion. Thus, it is possible that CD8+ lymphocytes alone cause some of the widespread apoptosis that is associated with the progression of atherosclerosis. Smooth-muscle cells in the fibrous cap tend to undergo apoptosis, and this is the main mechanism behind ‘vulnerable’ atherosclerotic plaque formation. Interestingly, CD8+ cells have been detected adjacent to ruptured plaque. Accordingly, the CD8+ cytotoxic subpopulation conceivably could kill smooth-muscle cells in the fibrous cap. An increased number of CD4+ T cells in the peripheral blood may enhance their migration into the arterial vessel wall, resulting in initiation and promotion of atherosclerosis. Nilsson suggested that, in the absence of CD4+ T cells, MHC class II restricted activation of T cells is impaired to such an extent that endogenous pro-atherogenic immune responses are significantly reduced.

In conclusion, it could be stated that the progression of atherosclerosis in type 2 DM is related, at least in part, to an acute hyperglycemia-induced increase in CD4+ and CD8+ lymphocyte counts in the peripheral blood.


23. Macugowska M. The role of various biochemical parameters in differentiation between stress-induced hyperglycaemia and impaired glucose tolerance. MSc thesis, 2002, Poznan University of Medical Sciences, Poland.


34. Cerillo A. New insights on oxidative stress and diabetic complications may lead to a “causal” antioxidant therapy. Diabetes Care 2003; 5: 1589–1596.


