Does microalbuminuria in diabetic patients affect the postoperative course after coronary artery bypass surgery?☆

Cem Yorgancioglu*, Hilmi Tokmakoglu, Kaya Suzer, Yaman Zorlutuna
Department of Cardiovascular Surgery, Bayindir Hospital Ankara, 06520 Söğütözü, Ankara, Turkey

Received 10 September 2001; received in revised form 21 December 2001; accepted 25 December 2001

Abstract

Objectives: Microalbuminuria is a predictor of microvascular disease and a marker for multiorgan damage in diabetic patients. It has been proposed that in diabetic patients who would undergo coronary artery bypass surgery (CABG), microalbuminuria is associated with poor postoperative outcome, higher incidence of early and late morbidity and mortality. Methods: Microalbuminuria was prospectively studied preoperatively in 24-h urinary collections for 257 consecutive diabetic patients in a 2-year period. One hundred and sixty-eight patients (65.4%) were defined as microalbuminuria negative (Group A), and 89 (34.6%) were microalbuminuria positive (Group B) with respect to the cut-off point 30 mg/24 h. Results: The two groups did not differ with respect to preoperative and operative data, except that preoperative blood glucose levels \( (P = 0.046) \), blood urea nitrogen \( (P = 0.001) \), and creatinine \( (P = 0.001) \) were higher and creatinine clearance was lower \( (P = 0.025) \) in Group B. Postoperative serum creatinine levels on different days were higher in microalbuminuria positive patients \( (P = 0.04) \). Also, positive inotropic agent usages at the time of leaving the operating room \( (21.3 \% \text{ vs. } 10.1 \%; \ P = 0.013) \) and on the 1st day in the intensive care unit (ICU) \( (29.2 \% \text{ vs. } 14.9 \%; \ P = 0.014) \), ICU stay day \( (2.3 \pm 2 \text{ vs. } 2.4 \pm 1.6; \ P = 0.02) \) and also atrial fibrillation rate \( (30.3 \% \text{ vs. } 17.9 \% \text{ in Group B}) \) were higher in Group B. Conclusions: Our findings suggest that postoperative period may be more problematic in diabetic patients with microalbuminuria, but microalbuminuria does not seem to have a major effect on the postoperative course in patients undergoing CABG. © 2002 Elsevier Science B.V. All rights reserved.

Keywords: Coronary artery bypass grafting; Diabetes mellitus; Microalbuminuria; Diabetic nephropathy; Diabetic cardiomyopathy; Low cardiac output

1. Introduction

Cross-sectional studies of both diabetic and non-diabetic patients have shown microalbuminuria to be associated with coronary heart disease and peripheral vascular disease \[1–3\]. In addition, it is also a sensitive index of generalized microvascular disease and a marker for multiorgan damage \[4–6\]. Albumin excretion rate between 30 and 300 mg/day or 20 and 200 μg/min is known as microalbuminuria, which is below the detection threshold of conventional methods for measuring urinary protein (e.g. dipstick). Above 300 mg/day is overt albuminuria. In prior studies, there has been consistent evidence that microalbuminuria was an independent factor of excess mortality regardless of the collection procedure used \[7\].

Epidemiological, autopsy, and non-invasive human studies have all provided substantial evidence for the existence of diabetic myocardial disease independent from coronary atherosclerosis \[8,9\].

It has been proposed that, in diabetic patients who would undergo coronary artery bypass surgery (CABG), microalbuminuria has to be associated with poor postoperative outcome, higher incidence of early and late morbidity and mortality. We therefore examined the relationship of microalbuminuria with preoperative and postoperative data of CABG patients.

2. Materials and methods

2.1. Patient selection

Following the institutional approval, in a prospective
study design, 257 consecutive diabetic patients who had undergone elective CABG from November 1996 to January 1999 were allocated in the study.

Preoperative fasting glucose levels were measured and the cut-off value was determined <200 mg/dl for operation.

Microalbuminuria was measured preoperatively in 24-h urinary collections for all. One hundred and sixty-eight patients (65.4%) were defined as microalbuminuria negative (Group A), and 89 (34.6%) as microalbuminuria positive (Group B) with respect to the cut-off point 30 mg/24 h.

2.2. Preoperative evaluation

Smoking, obesity, hypertension, duration of diabetes, family history of coronary artery disease (CAD), preoperative myocardial infarction (MI), preoperative percutaneous transluminal coronary angioplasty (PTCA), angina class, and prior usage of angiotensin converting enzyme (ACE) inhibitor were documented before operation. A risk assessment was performed with the Parsonnet risk scoring system. Besides standard hematological and biochemistry routines, creatinine clearance was studied preoperatively. Also, preoperative hemodynamic data were recorded.

2.3. Operative technique and anesthesia

All patients underwent open-heart surgery. After premedication with midazolam (5 mg i.m.), a radial artery catheter, two peripheral intravenous catheters, a pulmonary artery catheter and a urinary catheter were inserted in the operating room. Hemodynamic parameters, including heart rate, mean arterial pressure, central venous pressure, pulmonary artery pressure, rectal temperature, arterial blood gases and urine output were monitored throughout the procedure.

Anesthesia was induced by fentanyl (5 mcg/kg) and etomidate (0.5 mg/kg), and continued with enflurane (1–1.5%), and muscle relaxation was established with pancuronium (0.1 mg/kg). The patients were intubated endotracheally and ventilated with 50–80% oxygen. Standard median sternotomy incision was used for the exposure of the heart. Cardiopulmonary bypass was instituted via the ascending aorta and single venous cannulation. Moderate hypothermia was induced at 32 °C. Following cross-clamping of the aorta, the heart was arrested by using 10–15 cc/kg cold blood cardioplegia and topical ice slush, continued with in every 20 min, and finally warm blood cardioplegia was administered before releasing the aortic cross-clamp. All patients were extubated in the Intensive Care Unit (ICU) after establishment of hemodynamic stability.

2.4. Operative and postoperative evaluation

Operative and early postoperative (in the ICU) blood glucose levels were controlled by insulin infusion in all patients; oral antidiabetic drugs in non-insulin-dependent diabetes mellitus (NIDDM) patients and long-standing insulin forms for insulin-dependent diabetes mellitus (IDDM) patients were given before transfer to the wards.

Serum creatinine and blood urea nitrogen (BUN) were studied on the 1st, 2nd, 3rd and 5th postoperative days in addition to other routines. Incisional infection was checked and recorded for each patient.

Patients who were considered to be in low cardiac output (LCO) state, and received positive inotropic agents (dopamine or adrenaline or both) were assessed by persistent systemic pressure below 90 mmHg, mixed venous oxygen saturation <60%, urinary output lower than 20 cc/h, and the state of peripheral circulation in the presence of adequate preload and optimal afterload.

2.5. Follow-up and statistical analysis

Almost all of the patients discharged from the hospital were followed at our institution for routine postoperative controls on the 1st, 4th and 10th months following surgery, afterwards follow-up periods were every 6 months. Before the end of the study, all patients whose medical records were older than 6 months were called from their contact phone by one of the authors (C.Y.) to check for late mortality and other cardiovascular events. One hundred and eighty-four (71.6%) patients were contacted.

Data evaluation was carried out using a computer statistical package (SPSS 9.05 for Windows, SPSS, Inc., Chicago, IL) and are expressed as means ± SD or as frequencies or percentages. The relationships between independent preoperative and operative variables and postoperative outcome measures were investigated by Mann–Whitney U-test, analysis of variance (ANOVA) with Bonferroni correction, Kaplan–Meier and log-rank tests. A P value of <0.05 was considered significant.

3. Results

3.1. Patient characteristics and details of initial renal and hemodynamic status

There were 168 patients in Group A and 89 patients in Group B. The mean patient age was 59.7 ± 7.9 and 58.8 ± 7.7 years, and the female ratio was 38.7 and 27%, respectively. Duration of diabetes was 8.4 ± 7.2 years in Group A and 10.3 ± 8.5 years in Group B. Table 1 compares the demographics and the initial status of the microalbuminuria negative and positive group populations. These results indicate that the groups were essentially similar, except for the IDDM patients’ ratio, preoperative blood glucose levels and renal functions. The remaining factors of age, gender, duration of diabetes, smoking, hypertension, family history of CAD, obesity, mean preoperative angina as assessed by Canadian Cardiovascular Society Classification, previous MI, previous PTCA, use of previous ACE inhibitors, left ventricular hypertrophy (LVH), left main coronary artery (LMCA) stenosis, triple vessel disease, ejec-
tion fraction (EF), end-diastolic pressure (EDP), preoperative low density lipoprotein (LDL), high density lipoprotein (HDL) and Parsonnet risk scores showed no statistical differences between the two groups.

3.2. Operative outcomes of the patients

Table 2 summarizes the perioperative outcomes and compares two groups. Cardiopulmonary bypass time, cross-clamp time, mean number of anastomosis, use of the internal mammary artery (IMA), number of patients who needed aneurysmectomy, perioperative MI and perioperative urine output did not differ between groups. The percentage of patients who needed positive inotropic agents at the time of leaving the operating room was significantly higher in the microalbuminuria positive group ($P = 0.013$). However, intra-aortic balloon pump (IABP) usage at the same period did not differ between groups.

3.3. Early outcomes

Postoperative repeated measurements such as BUN and serum creatinine were tested with ANOVA. There were significant differences within repeated measurements of BUN ($P = 0.003$) and creatinine ($P = 0.011$). Although creatinine levels were found to be significant between groups ($P = 0.04$), BUN levels were insignificant between groups ($P = 0.603$; Table 3). The ratio of inotropic agent receiving patients on the first day after surgery ($P = 0.014$) and ICU stay length ($P = 0.019$) was significantly high in Group B. Also, postoperative atrial fibrillation was found to be higher in the microalbuminuria positive group ($P = 0.019$; Table 2). The remaining factors of postoperative bleeding, revision due to excess bleeding, total hospital stay length and hospital wound infection showed no statistical difference between the two groups. There was no correlation between ACE inhibitor usage and postoperative need for inotropic agent in both groups, also no significance was detected between ACE inhibitor usage and postoperative inotropic agent receiving patients in both groups.

3.4. Late outcomes

Two hundred and fifty-three patients discharged from the hospital were followed-up for a mean length of 30.6 ± 16.2 months (range, 0.98–51.4 months; 30.9 ± 16.2 months in Group A and 30.1 ± 16.5 months in Group B). Over 24 months, 69.4% of patients were followed-up; eight additional patients died in Group B within 30 days after operation. Two additional patients died in Group B within 30 days after operation, giving an operative mortality rate of 0.6 vs. 3.4% ($P = 0.019$; Table 2). The remaining factors of postoperative bleeding, revision due to excess bleeding, total hospital stay length and hospital wound infection showed no statistical difference between the two groups. There was no correlation between ACE inhibitor usage and postoperative need for inotropic agent in both groups.
rate was 3% in Group A and 7.9% in Group B, whereas the 24-month cardiac mortality was 2.4 and 5.6%, respectively (Table 2). Late survival was demonstrated by Kaplan–Meier analysis (Fig. 1). In the microalbuminuria negative group, 97.6% survival is expected in 53.11±0.64 months (95% confidence interval: 51.86–54.36 months), and in the microalbuminuria positive group 94.4% survival is expected in 50.46±1.29 months (95% confidence interval: 47.93–52.99 months). In statistics for equality of survival distributions for microalbuminuria, log-rank = 0.16. Also, the reoperation rate was not significant.

4. Discussion

The high risk of developing CAD in diabetes has been long recognized, but the superimposed risk of microalbuminuria has been studied in the last decade. An outstanding paper showing the direct relation of proteinuria and cardiovascular mortality in insulin-dependent diabetic patients was published from Steno Memorial Hospital [3]. In a controlled study of IDDM patients followed from the onset of microalbuminuria, CAD developed eight times more frequently than in diabetic patients of similar age, gender and duration of diabetes [10]. Nearly by the same period, some prospective studies have demonstrated that in NIDDM patients, microalbuminuria is also an independent predictor of increased cardiovascular mortality [1,11].

As microalbuminuria is a marker for microvascular disease and renal damage as well as multiorgan damage [4,5,12], it is not surprising that IDDM patients’ ratio, preoperative blood glucose levels, and renal function tests

Table 2
Operative and postoperative outcomes

<table>
<thead>
<tr>
<th></th>
<th>Group A</th>
<th>Group B</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>CPB time (min)</td>
<td>61.8 ± 19.3</td>
<td>60.3 ± 19.1</td>
<td>NS</td>
</tr>
<tr>
<td>CCT (min)</td>
<td>31.8 ± 10.8</td>
<td>31.4 ± 12.7</td>
<td>NS</td>
</tr>
<tr>
<td>Mean anastomosis</td>
<td>3.21 ± 1.21</td>
<td>3.10 ± 1.17</td>
<td>NS</td>
</tr>
<tr>
<td>Use of IMA</td>
<td>167 (98.8)</td>
<td>89 (100)</td>
<td>NS</td>
</tr>
<tr>
<td>LV aneurysmectomy</td>
<td>7 (4.2)</td>
<td>8 (9.0)</td>
<td>NS</td>
</tr>
<tr>
<td>Patients with inotropes when leaving OR</td>
<td>17 (10.1)</td>
<td>19 (21.3)</td>
<td>0.013</td>
</tr>
<tr>
<td>IABP usage when leaving OR</td>
<td>1 (0.6)</td>
<td>1 (1.1)</td>
<td>NS</td>
</tr>
<tr>
<td>Perioperative MI</td>
<td>3 (1.7)</td>
<td>2 (2.2)</td>
<td>NS</td>
</tr>
<tr>
<td>Perioperative urine output (ml)</td>
<td>478.4 ± 267.9</td>
<td>440.5 ± 203.1</td>
<td>NS</td>
</tr>
<tr>
<td>Inotropic agent receiving patients on the 1st day</td>
<td>25 (14.9)</td>
<td>26 (29.2)</td>
<td>0.014</td>
</tr>
<tr>
<td>Revision for excess bleeding</td>
<td>4 (2.4)</td>
<td>4 (4.5)</td>
<td>NS</td>
</tr>
<tr>
<td>Bleeding (ml)</td>
<td>946</td>
<td>1074</td>
<td>NS</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>30 (17.9)</td>
<td>27 (30.7)</td>
<td>0.019</td>
</tr>
<tr>
<td>ICU stay length(days)</td>
<td>2.38 ± 2.04</td>
<td>2.45 ± 1.15</td>
<td>0.02</td>
</tr>
<tr>
<td>Total hospital stay (days)</td>
<td>7.58 ± 2.98</td>
<td>7.20 ± 1.38</td>
<td>NS</td>
</tr>
<tr>
<td>Hospital wound infection</td>
<td>1 (0.6)</td>
<td>0 (0)</td>
<td>NS</td>
</tr>
<tr>
<td>Mean follow-up</td>
<td>30.68 ± 16.22</td>
<td>30.15 ± 16.54</td>
<td>NS</td>
</tr>
<tr>
<td>30-day mortality</td>
<td>1 (0.6)</td>
<td>3 (3.4)</td>
<td>NS</td>
</tr>
<tr>
<td>24-month cardiac mortality</td>
<td>4 (2.4)</td>
<td>5 (5.6)</td>
<td>NS</td>
</tr>
<tr>
<td>24-month total mortality</td>
<td>5 (3.0)</td>
<td>7 (7.9)</td>
<td>NS</td>
</tr>
<tr>
<td>Reoperation</td>
<td>0 (0)</td>
<td>1 (1.1)</td>
<td>NS</td>
</tr>
</tbody>
</table>

a CPB, cardiopulmonary bypass; CCT, cross-clamp time; IMA, internal mammary artery; LV, left ventricle; OR, operating room; IABP, intra-aortic balloon pulsation.

b Figures in parentheses represent percentage values.

c Mann–Whitney U-test.

Table 3
Postoperative repeated measurements

<table>
<thead>
<tr>
<th></th>
<th>Group A</th>
<th>Group B</th>
<th>P within valuesa</th>
<th>P between groupsa</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st day BUN (mg/dl)</td>
<td>16.1 ± 4.9</td>
<td>18.9 ± 7.0</td>
<td>0.003</td>
<td>NS</td>
</tr>
<tr>
<td>2nd day BUN (mg/dl)</td>
<td>22.9 ± 8.1</td>
<td>25.7 ± 8.4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3rd day BUN (mg/dl)</td>
<td>30.1 ± 11.5</td>
<td>35.1 ± 5.4</td>
<td>0.003</td>
<td>NS</td>
</tr>
<tr>
<td>5th day BUN (mg/dl)</td>
<td>20.7 ± 7.6</td>
<td>25.6 ± 11.1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1st day creatinine (mg/dl)</td>
<td>1.06 ± 0.21</td>
<td>1.44 ± 1.09</td>
<td>0.003</td>
<td>NS</td>
</tr>
<tr>
<td>2nd day creatinine (mg/dl)</td>
<td>1.18 ± 0.26</td>
<td>1.49 ± 0.43</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3rd day creatinine (mg/dl)</td>
<td>1.26 ± 0.41</td>
<td>1.15 ± 0.28</td>
<td>0.04</td>
<td></td>
</tr>
<tr>
<td>5th day creatinine (mg/dl)</td>
<td>1.19 ± 0.27</td>
<td>1.53 ± 0.47</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

a ANOVA test with Bonferroni correction.
(BUN, creatinine, creatinine clearance) were significantly worse, and the duration of diabetes was insignificant but slightly higher in the microalbuminuria positive group (Group B) by the time of preoperative evaluation.

Diabetic nephropathy develops in approximately 35% of patients with IDDM and between 15 and 60% of patients with NIDDM. The frequency of nephropathy changes depending on the ethnic origin, lowest in the European patients, whereas the highest cumulative incidence is among Pima Indians and Japanese people [5,13,14]. Although glomerular filtration rate (GFR) is well preserved or slightly diminished before overt renal insufficiency in both IDDM and NIDDM patients, in the presence of microalbuminuria, some microscopic and ultrastructural changes can be found out [4,15]. Many studies showed that ACE inhibitors and angiotensin II antagonists stabilized microalbuminuria and provided renal protection [16]. We could not find any significance between prior ACE inhibitor usage and postoperative renal function, as well as need for inotropic agents in both groups.

In our study, although the microalbuminuria positive group seems a little sicker statistically when compared with the microalbuminuria negative group, the Parsonnet risk scores of groups were similar, and the mean preoperative BUN and creatinine levels of the microalbuminuria positive group were within the normal range when assessed uniquely. Also, as seen in our study group (Table 1), the longer duration of diabetes and microalbuminuria as an index for microvascular disease is closely associated with and provokes the extent of renal disease [2,4,5]. In the early postoperative period, BUN and creatinine on different postoperative days have significant differences within measurements. Postoperative creatinine levels were found to be significant between groups, but there was no significance between groups in postoperative BUN levels. Improvement of glycemic control by standard antidiabetic treatment can reduce increased urinary albumin excretion rate, but high values cannot be lowered in a considerable number of patients. As a limitation of this study, we did not detect hemoglobin A1C levels, which may give a perspective about a long-term distribution of blood glucose.

As we have experienced a higher incidence of sternal infection and dehiscence with bilateral IMAs, especially in diabetics, we usually hardly prefer bilateral use of IMAs. Our perioperative wound infection is very low and this probably depends on the meticulous precautions and close follow-up of the institutional infection control committee. No important late infections were noted.

Microalbuminuria represents the renal manifestation of a generalized vascular endothelial dysfunction, which may underline the link with cardiovascular disease [14,17]. Endothelial dysfunction and lipoprotein disorders in the presence of microalbuminuria both can promote the formation of atherosclerotic plaques and the occurrence of acute events [18]. Endothelial dysfunction precedes both the macrovascular and microvascular complications of diabetes [14].

Small vessel coronary disease is one of the major factors implicated in the pathogenesis of diabetic cardiomyopathy, and diastolic abnormalities have been noted to occur early in the course of diabetes in the absence of or with only mild microvascular involvement [9]. Also, some studies have demonstrated a lower EF in response to dynamic exercise in the presence of normal resting EF [19,20], suggesting that contractile reserve decreased in many asymptomatic patients with diabetes [21].

There was no difference in perioperative MI incidence between groups. The higher usage of inotropes and significant difference in ICU stay length in the microalbuminuria positive group (Group B) could be due the close relationship between microalbuminuria and associated microvascular involvement, and also with a possibly combined subclinical cardiomyopathy with reduced myocardial reserve, that may become clinically important in the presence of myocardial ischemia during cardioplectic arrest. The higher incidence of atrial fibrillation in microalbuminuric patients also may be relevant to the LCO state (higher need for inotropic agents) and poorer metabolic condition due to diminished renal functions. Total hospital stay length was similar between groups.

The 30-day mortality was found to be 0.6% in Group A and 3.4% in Group B, which, although higher, was statistically unimportant ($P = 0.088$). The 24-month cardiac mortality rates were 2.4% in Group A and 5.6% in Group B. The freedom from death plot showed the estimated survival probability by the Kaplan–Meier method with log-transformed 95% point wise confidence intervals. Log-rank analysis demonstrates no significance between groups in late survival.

In conclusion, this study implies two outcomes. Since the renal status of the microalbuminuria positive patients...
usually had a higher risk preoperatively, this becomes worse in the early postoperative period. Early postoperative hemodynamic variables of the same group of patients may slightly deteriorate and ICU stay length may be affected. However, microalbuminuria does not seem to have a major effect on the postoperative course in CABG patients.

References


Appendix A. Conference discussion

Mr C. Satur (Stoke-On-Trent, UK): Microalbuminuria is clearly an indication of a disease process which is further down the line for diabetics, and clearly these patients have greater involvement and so they may have neurological involvement, et cetera, and have elements of vasoplasgia at this stage in their disease process.

Do you think that the greater requirement for inotropes, noradrenaline, et cetera, is an indication that they are further down the disease process of diabetes, or do you think that because they have got microalbuminuria, the diabetologists are also treating them with ACE inhibitors and you are seeing the complication of the use of ACE inhibitors rather than the complication of the diabetic disease?

Dr Yorgancioglu: I don’t know, but perhaps both.

Mr Satur: Perhaps both. Did you differentiate between the use of anti-hypertensive agents and the use of ACE inhibitors?

Dr Yorgancioglu: We checked for ACE inhibitors usage prior to the operation, and both groups did not differ statistically. Also ACE inhibitors using patients and non-using patients did not differ in the results and the mortality and the high usage of inotropes.