Efficacy of CD34\(^+\) Stem Cell Therapy in Nonischemic Dilated Cardiomyopathy Is Absent in Patients With Diabetes but Preserved in Patients With Insulin Resistance

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**Key Words.** Stem cells • Dilated cardiomyopathy • Insulin resistance • Diabetes

**ABSTRACT**

We evaluated the association of diabetes and insulin resistance with the response to cell therapy in patients with nonischemic dilated cardiomyopathy (DCM). A total of 45 outpatients with DCM received granulocyte colony-stimulating factor for 5 days. CD34\(^+\) cells were then collected by apheresis and injected transendocardially. Twelve patients had diabetes mellitus (DM group), 17 had insulin resistance (IR group), and 16 displayed normal glucose metabolism (no-IR group). After stimulation, we found higher numbers of CD34\(^+\) cells in the IR group (94 \pm 35 \times 10^6 cells per liter) than in the no-IR group (54 \pm 35 \times 10^6 cells per liter) or DM group (31 \pm 20 \times 10^6 cells per liter; \(p = .005\)). Similarly, apheresis yielded the highest numbers of CD34\(^+\) cells in the IR group (IR group, 216 \pm 110 \times 10^6 cells; no-IR group, 127 \pm 82 \times 10^6 cells; DM group, 77 \pm 83 \times 10^6 cells; \(p = .002\)). Six months after cell therapy, we found an increase in left ventricular ejection fraction in the IR group (+5.6\% \pm 6.9\%) and the no-IR group (+4.4\% \pm 7.2%) but not in the DM group (−0.9\% \pm 5.4\%; \(p = .035\)). The N-terminal pro-brain natriuretic peptide levels decreased in the IR and no-IR groups, but not in the DM group (−606 \pm 850 pg/ml; −698 \pm 1,105 pg/ml; and +238 \pm 963 pg/ml, respectively; \(p = .034\)). Transendocardial CD34\(^+\) cell therapy appears to be ineffective in DCM patients with diabetes. IR was associated with improved CD34\(^+\) stem cell mobilization and a preserved clinical response to cell therapy.

**SIGNIFICANCE**

The present study is the first clinical study directly evaluating the effects of altered glucose metabolism on the efficacy of CD34\(^+\) stem cell therapy in patients with nonischemic dilated cardiomyopathy. The results offer critical insights into the physiology of stem cell mobilization in heart failure and possibly an explanation for the often conflicting results obtained with stem cell therapy for heart failure. These results demonstrate that patients with dilated cardiomyopathy and diabetes do not benefit from autologous CD34\(^+\) cell therapy. This finding could serve as a useful tool when selecting heart failure patients for future clinical studies in the field of stem cell therapy.

**INTRODUCTION**

Stem cell therapy is evolving as a promising therapeutic option for heart failure; however, the clinical efficacy has been inconsistent [1, 2]. We have previously demonstrated that the transplantation of mobilized CD34\(^+\) cells leads to improved left ventricular ejection fraction (LVEF), greater exercise capacity, and better long-term outcome in patients with nonischemic dilated cardiomyopathy (DCM) [3, 4]. In these studies, we found that the individual patient response to therapy varied greatly and was closely related to the numbers of mobilized CD34\(^+\) cells retained in the myocardium early after transplantation. Therefore, the parameters affecting CD34\(^+\) mobilization and retention are likely significant for the overall clinical efficacy of stem cell therapy.

Abundant preclinical evidence has shown that diabetes negatively affects bone marrow structure and function, resulting in a reduced response to mobilizing stimuli and decreased numbers of circulating CD34\(^+\) cells [5]. Furthermore, a recent meta-analysis of clinical trials of mobilized CD34\(^+\) cell therapy for the treatment of cardiovascular disease has demonstrated that the presence of diabetes is strongly associated with poor mobilization of CD34\(^+\) cells [6]. This adverse...
association between glucose metabolism and cell therapy efficacy could be particularly salient in nonischemic DCM, where insulin resistance (IR) is highly prevalent, occurring in up to 59% of patients [7].

To date, reports on the effects of diabetes on the clinical response to stem cell therapy have been limited to patients with ischemic cardiomyopathy, in whom transendocardial transplantation of bone marrow mononuclear cells resulted in virtually no clinical benefit if diabetes was present [8]. Thus, the aim of the present study was to evaluate the effects of diabetes and IR on CD34+ cell mobilization and clinical response to CD34+ cell therapy in patients with nonischemic DCM.

**MATERIALS AND METHODS**

**Patient Population**

The present study used an open-label study design and was conducted at the Advanced Heart Failure and Transplantation Center in Ljubljana, Slovenia, between January 1, 2013 and January 1, 2014. The patient inclusion criteria were as follows: age 18–65 years, diagnosis of DCM according to the European Society of Cardiology position statement [9], optimal medical management for at least 6 months, left ventricular ejection fraction (LVEF) <40%, and New York Heart Association functional class III on stable medical therapy for at least 3 months before referral. Patients with acute multorgan failure or a history of hematologic neoplasms were excluded. All the patients provided informed consent before participation in the study, and the National Medical Ethics Committee approved the study protocol. The trial was registered according to the Slovenian Drug Law and with ClinicalTrials.gov (NCT02445534).

**Study Design**

At baseline, we analyzed the metabolic status of all the patients and classified them into three groups according to their metabolic status: the diabetes mellitus (DM) group, patients who had been previously diagnosed with diabetes and were treated with oral antihyperglycemic agents and/or insulin; the IR group, patients with no history of diabetes who had a homeostasis model assessment (HOMA) index >2; and the no-IR group, patients with a HOMA index ≤2.

In the first phase, patients received granulocyte colony-stimulating factor (G-CSF) therapy (5 mg/kg for 5 days). The plasma concentration of the CD34+ cells was then assessed, and the cells were collected via apheresis. In the second phase, we performed electroanatomical mapping of the left ventricle and transendocardial injections of the CD34+ cell solution. The patients were followed up for 6 months after the procedure.

Peripheral blood bone marrow cells were mobilized by daily subcutaneous injections of G-CSF (5 μg/kg b.i.d.). On the fifth day, a full blood count and peripheral blood CD34+ cell count were performed. Peripheral blood stem cells were then collected using the Amicus cell separator (Baxter Healthcare, Chicago, IL, http://www.baxter.com), and immunomagnetic-positive selection of CD34+ cells was performed using a magnetic cell separator, Isolex 300i (Nexell Therapeutics Inc., Irvine, CA, http://www.nexell.net). After immunomagnetic selection, all recovered CD34+ cells were assessed for viability using methylene blue stain and stored in a cell suspension with a total volume of 6 ml. All recovered cells were then used for transendocardial delivery.

Transendocardial Cell Delivery

Electroanatomical mapping was performed using the Biosense NOGA system (Biosense-Webster, Diamond Bar, CA, http://www.biosensewebster.com), as described previously [11]. The mapping catheter was advanced into the left ventricle, and points were acquired when the catheter tip was stable on the endocardium. This occurred after the documentation of local activation were measured in heparinized plasma using a two-site chemiluminescent immunometric assay (Diagnostic Products Corp., Los Angeles, CA, http://www.usa.healthcare.siemens.com). Insulin resistance was estimated using the HOMA index, defined as a fasting insulin level multiplied by the fasting glucose and divided by 22.5. Insulin resistance was defined as a HOMA index >2 [10].

**Figure 1.** Flowchart of the study design. After assessing the metabolic status, all patients received stimulation with granulocyte colony-stimulating factor (5 μg/kg b.i.d. for 5 days; phase 1). On the fifth day, we measured the peripheral blood CD34+ cell count, performed apheresis, and again measured the CD34+ cell numbers after apheresis. In phase 2, we performed electroanatomical mapping of the left ventricle and transendocardial injections of the CD34+ cell solution. The patients were followed up for 6 months after the procedure.
time stability, location stability, loop stability, and cycle length stability. The catheter was removed from the left ventricle when all endocardial regions were represented on the reconstructed map. For each patient, color-coded unipolar voltage and linear shortening maps and their corresponding “bull’s eye” maps, consisting of at least 150 sampling points, were generated. In accordance with previous studies of nonischemic DCM [12, 13], hibernating segments were defined as areas with average unipolar voltage \( \geq 8.27 \text{ mV} \) and average linear shortening of \( \leq 6\% \). Scarred myocardium was defined as areas with a unipolar voltage \( < 8.27 \text{ mV} \) and normal myocardium was defined as areas with a unipolar voltage of \( \geq \) 8.27 mV and linear shortening of \( \geq 6\% \).

The target area for cell delivery was defined as the myocardial segments with unipolar voltage potentials of \( \geq 9 \text{ mV} \) and linear shortening \(< 6\% \). Transendocardial delivery of cell suspension was performed using the MyoStar (Biosense-Webster) injection catheter. After acquiring a stable mapping point with the tip of the catheter perpendicular to the endocardial surface, the needle was advanced into the myocardium, and transendocardial injections were performed. Each patient received 20 injections (0.3 ml each).

### Echocardiography, 6-Minute Walk Test, and NT-proBNP Measurement

The echocardiogram data were recorded and analyzed at 6 months by an independent echosonographer who was unaware of the timing of the recordings. Analysis of the left ventricular dimensions and global function was performed in accordance with the American Society of Echocardiography guidelines [14]. All NT-proBNP assays were performed by a central independent laboratory, who was unaware of the clinical data, using a commercially available kit (Roche Diagnostics, Mannheim, Germany, http://www.rochediagnostics.com). In all patients, the 6-minute walk test was performed by a blinded observer according to the standard protocol [15].

### Follow-Up and Endpoints

The primary endpoint was the change in LVEF 6 months after cell therapy. The secondary endpoints included changes in exercise capacity and NT-proBNP levels 6 months after cell therapy and changes in the concentration of CD34+ cells in the peripheral blood after G-CSF stimulation and apheresis.

### Statistical Analysis

Continuous variables are expressed as the mean ± SD, and categorical variables are expressed as the numbers and percentages. Continuous variables were explored for normal distribution with the Shapiro-Wilk test. Differences within the groups were analyzed using a \( t \) test for continuous variables with correction for unequal variance when appropriate, and with the chi-square or Fisher exact test when appropriate. Differences between DM group, IR group, and no-IR group were analyzed with one-way analysis of variance (ANOVA), and intergroup differences for any given cell dose were analyzed using two-way ANOVA. A \( p \) value \(< .05 \) was considered significant.

### RESULTS

#### Patient Characteristics

Of the 45 patients enrolled, 12 (27%) were diabetic (DM group), 17 (38%) had evidence of insulin resistance (IR group), and 16
Effects of insulin resistance and diabetes on CD34+ stem cell mobilization in patients with nonischemic dilated cardiomyopathy. (A): Concentration of CD34+ stem cells after 5 days of stimulation with granulocyte colony-stimulating factor in patients with nonischemic dilated cardiomyopathy with diabetes (right), nondiabetic patients with IR (middle), and nondiabetic patients without IR (left). We found a significantly increased CD34+ mobilization capacity in nondiabetic patients with IR. Abbreviation: IR, insulin resistance.

**DISCUSSION**

We examined the effect of diabetes and IR on CD34+ cell mobilization and clinical efficacy of CD34+ cell therapy in 45 patients with nonischemic DCM undergoing autologous percutaneous transcatheter stem cell transplantation. We found that CD34+ therapy was ineffective in diabetic patients. In addition, although the clinical parameters improved equally and significantly in the patients with and without IR, a higher dose of injected cells was required for the patients with IR, indicating the reduced efficacy of stem cell therapy. The net clinical effect, however, was the same in both groups owing to a significantly increased mobilization of CD34+ cells in patients with IR.

Our overall positive results are in line with the findings of our previous trials [3, 4], which consistently demonstrated improvement in left ventricular function, exercise capacity, and NT-proBNP levels after CD34+ cell transplantation for patients with nonischemic DCM. Our findings in diabetic patients, although observed for the first time in patients with nonischemic cardiomyopathy, should be considered confirmatory and not unexpected based on data previously reported in ischemic cardiomyopathy, in which diabetes was identified as an important risk factor for a decreased response to cell therapy [8]. Although the underlying mechanisms for our findings remain to be fully elucidated, they are clearly in part related to decreased stem cell mobilization and possibly to changes in stem cell function and/or altered myocardial...
properties in patients with longstanding diabetes [7]. From the preclinical evidence, it appears that the stem cell mobilization capacity is primarily dependent on the function of the hematopoietic bone marrow niche, which consists of osteoblastic and vascular elements [16]. G-CSF stimulation normally depletes osteoblasts and reduces CXCL12 expression, thereby inducing transmigration

Figure 3. The effect of metabolic status on changes in left ventricular function, NT-proBNP levels, and exercise capacity in patients with nonischemic dilated cardiomyopathy (DCM) undergoing transendocardial CD34+ cell therapy. The changes in left ventricular ejection fraction (A), NT-proBNP (B), and 6-MWK distance (C) after transendocardial CD34+ cell therapy in nonischemic DCM patients with diabetes, nondiabetic patients with IR, and nondiabetic patients without IR. We found a significant increase in LVEF and a significant decrease in NT-proBNP in nondiabetic patients with or without insulin resistance. In contrast, we found no significant effects of CD34+ cell therapy on LVEF and NT-proBNP in patients with diabetes. Exercise capacity, as measured by the 6-MWK distance, showed a trend for improvement in the IR group and no-IR group, but not in the DM group. Abbreviations: 6-MWK, 6-minute walk; DM, diabetes mellitus; IR, insulin resistance; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro-brain natriuretic peptide.
of hematopoietic stem cells into vascular sinuses and peripheral circulation. In diabetes, however, G-CSF is not associated with reduced bone marrow CXCL12 expression; thus, transmigration of hematopoietic stem cells is reduced. This phenomenon is known as “diabetic mobilopathy” [17] and has been validated in several clinical trials demonstrating decreased CD34+ cell mobilization capacity in patients with diabetes [5, 18–20]. Importantly, in our study cohort, the patients with diabetes also had more advanced heart failure as evidenced by more areas of myocardial scar on electroanatomical mapping, decreased exercise capacity, higher values of NT-proBNP, and (albeit statistically insignificant) lower LVEF. This raises the question of whether the lack of cell therapy efficacy we observed truly resulted from diabetes or simply from more advanced heart failure. A close association of diabetes and disease progression in chronic heart failure has been well established [21]. Diabetes was associated with increased apoptosis of cardiac myocytes and significant myocardial contractile dysfunction [22], possibly rendering the myocardium no longer amenable to reparative interventions.

In contrast to our findings in diabetic patients, we observed an excellent clinical response to cell therapy in DCM patients without diabetes. Within that cohort, no differences were found in LVEF, exercise capacity, or NT-proBNP levels between the patients with and without IR. Despite this comparable heart failure state, we found CD34+ cell therapy to be less effective in patients with IR, as evidenced by a blunted dose-dependent response to cell therapy (Fig. 4). Nevertheless, the overall response was comparable owing to a surprising finding of increased mobilization of CD34+ cells.

Owing to the previously referenced “diabetic mobilopathy,” we expected stem cell mobilization to also be reduced in patients with IR. However, our data indicated that stem cell mobilization is increased in the presence of IR in those with DCM. How can we explain this finding? Is it possible that the effects of prediabetes (i.e., IR) are the opposite of those of fully developed diabetes requiring pharmacotherapy? In this context, a series of elegantly conducted animal experiments on bone marrow functionality in short-term versus long-term diabetes are worth mentioning. A significant increase in bone marrow hematopoietic cells was observed in mice with short-term diabetes in contrast to the reduced numbers of bone marrow hematopoietic cells in mice with long-term diabetes [23]. This observation was in accordance with our clinical findings, demonstrating a significantly greater “stem cell reserve” in patients with IR but not in diabetic patients. Thus, one might speculate that in DCM patients, increased CD34+ mobilization in the presence of IR represents a response-to-injury mechanism that becomes activated at the early stages of the disease but eventually declines in later disease stages. However, the cross-sectional nature of our study did not allow more than speculation in this regard.

To date, data on CD34+ cell mobilization in patients with nonischemic DCM have been scarce and inconsistent. Compared with healthy subjects and patients with ischemic heart disease, patients with DCM have been reported to have higher numbers of circulating CD34+ cells in the absence of G-CSF stimulation but not after G-CSF therapy [24–26]. The results of the present study suggest that these discrepancies might be at least partly related to the heterogeneity of metabolic status of patients with nonischemic DCM.

What are the practical implications of our findings for stem cell therapy? Our data from patients with diabetes add to the growing body of studies suggesting that stem cell therapy might not be advisable in the presence of long-standing diabetes and that such patients should possibly be excluded from clinical trials. We also previously reported that diabetes and/or IR in the presence of heart failure might be partially or fully reversed by restoration of normal cardiac output after longstanding mechanical circulatory support [27]. Therefore, it is tempting to speculate that the optimization of patients’ hemodynamic and metabolic status before cell delivery might improve the efficacy of CD34+ cell therapy in DCM patients. Clearly, further study on the dynamic nature of insulin resistance, stem cell reserve, and their interactions in heart failure is needed.

In previous preclinical and clinical studies, CD34+ cell therapy has been primarily associated with myocardial neovascularization [28, 29], which could be of benefit when targeting the hibernating myocardial areas. However, because the capacity of CD34+ cells to form new myocardial tissue is limited, larger scar areas in diabetic patients might significantly affect the efficacy of this therapy.

Study Limitations

The results of our study are subject to several limitations. For instance, our patient population included patients with DCM. However, no biopsies were performed to exclude secondary cardiomyopathies, although we obtained careful clinical history and coronary angiograms for all patients. Our sample size was small, but the groups of patients with and without IR were well matched at baseline, and definitive future studies could possibly be powered using our preliminary results. We found no effect of metabolic status on cell viability as assessed by methylene blue staining; however, we did not measure cell proliferation and migration parameters. Finally, we recognize that patients with DCM are a heterogeneous patient population, and the dynamic changes in stem cell mobilization and ventricular function could be multifactorial.
Conclusion

In nonischemic DCM, insulin resistance is associated with improved CD34+ stem cell mobilization and preserved, but less-efficient, clinical response to cell therapy. In contrast, overt diabetes is associated with impaired CD34+ cell mobilization and inferior clinical response. Further studies are warranted to better define the underlying mechanisms and investigate whether optimization of the metabolic status could further improve the therapeutic effects of CD34+ cell therapy in this patient population.

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AUTHOR CONTRIBUTIONS

B.V.: conception and design, provision of study material or patients, collection and/or assembly of data, data analysis and interpretation, manuscript writing; M.S.: conception and design, provision of study material or patients, collection and/or assembly of data, data analysis and interpretation; M.J., G.P., A.J., N.K., G.Z., M.C.: conception and design, provision of study material or patients, collection and/or assembly of data, data analysis and interpretation; P.C., F.H., J.C.W., U.P.J.: data analysis and interpretation, manuscript writing, final approval of manuscript.

DISCLOSURE OF POTENTIAL CONFLICTS OF INTEREST

The authors indicated no potential conflicts of interest.

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