

Dapagliflozin counteracts the pro-apoptotic effects of the secretome of visceral adipose cells from obese subjects in human cardiac progenitor cells via the SGLT2 co-transporter

Giuseppe Palma, Cristina Caccioppoli, Rossella D'Oria, Valentina Annamaria Genchi, Isabella Calderoni, Antonio Braun, Giuseppe Santarpino, Aldo Domenico Milano, Angelo Cignarelli, Annalisa Natalicchio, Luigi Laviola, Angela Pezzolla, Francesco Giorgino, Sebastio Perrini

Dipartimento di Medicina di Precisione e Rigenerativa e Area Jonica - (DiMePRE-J), Università di Bari, Italy

<https://doi.org/10.56095/eaj.v2i1.40>

Giuseppe Palma: giuseppopalma1990@yahoo.it

Aim: Dapagliflozin (DAPA), an SGLT2 inhibitor, has been shown to counteract heart failure outcomes in subjects with obesity and diabetes. We investigated the protective mechanisms of DAPA in human cardiac progenitor cells (hCPC) exposed to the conditioned medium (CM) from abdominal visceral (AV) and epicardial (E) adipose stem cells (ASC) and from AV mature adipocytes from obese subjects.

Methods: ASC and mature adipocytes were isolated from AV adipose tissue biopsies of 27 obese (Ob) and 19 non-Ob subjects (n-Ob), and from E adipose tissue biopsies of 9 Ob and 10 non-Ob subjects, respectively. hCPC were isolated from right auricle biopsies of 10 healthy non-Ob donors.

Results: Exposure of hCPC to the CM of adipose cells from Ob, but not from non-Ob subjects, induced apoptosis, c-Jun phosphorylation, and impairment of actin filaments, while these effects were not observed when hCPC were pretreated with DAPA. The CM of adipose cells from Ob compared to n-Ob subjects displayed a different pattern of cytokines. The levels of pro-inflammatory cytokines RANTES and MIP1 β were increased in the CM from AV-ASC with higher BMI ($p < 0.05$), while the levels of the cardioprotective factor GCSF in the CM of E-ASC were inversely correlated with BMI ($p < 0.05$). SGLT2 was found to be expressed as both mRNA and protein in hCPC, and silencing of SGLT2 with a specific siRNA abrogated the capacity of DAPA to counteract the pro-apoptotic effects of the CM.

Conclusions: In human obesity, the CM of both AV- and E-ASC and mature adipocytes is characterized by pro-inflammatory cytokines that induce stress kinase activation and apoptosis in hCPC. DAPA prevents the hCPC damage induced by the CM through an SGLT2-dependent mechanism.

Extreme cardiovascular risk in cardiological rehabilitation: prevalence and impact on patient's functional improvement

Alfonso Riccio¹, Eleonora Senini¹, Saverio Fabbri¹, Claudio Ciampi¹, Matteo Regazzetti¹, Massimiliano Monticelli¹, Roberto Pirola², Cristina Giannattasio^{1,2}

¹*School of Medicine and Surgery, Milano-Bicocca University, Milan, Italy*

²*Cardiology 4, ASST GOM Niguarda, Milan, Italy*

<https://doi.org/10.56095/eaj.v2i1.41>

Alfonso Riccio: alfonsoutility@gmail.com

Background and Aims: Among patients at very high cardiovascular risk, some are more likely to experience recurrent cardiovascular events. In May 2022, an article was published in the European Heart Journal proposing different definitions of patients at extreme cardiovascular risk. However, the process of defining such patient is still ongoing and more data on its prevalence are needed. Our aims consisted in assessing the prevalence of patients at extreme cardiovascular risk in cardiological rehabilitation and in evaluating the clinical features of such patients. Furthermore, we wanted to establish how the extreme cardiovascular risk condition correlates with the functional improvement obtained during cardiac rehabilitation.

Methods: The study included 938 patients suffering from atherosclerosis who attended the cardiological rehabilitation of Niguarda Hospital in Milan. Patients classified as at extreme cardiovascular risk were compared with the remaining patients and a multivariate linear regression was performed with absolute functional improvement as the dependent variable.

Results: Among 938 patients, 26.9% belong to the category of extreme cardiovascular risk. Patients at extreme cardiovascular risk showed a higher average age (67.8 ± 10.4 vs 64.1 ± 11.1 years; $p \leq 0.001$), a higher prevalence of significant comorbidities (peripheral arterial disease, cerebrovascular disease, dyslipidemia, diabetes, chronic kidney disease, hypertension) and a lower functional improvement during cardiac rehabilitation (102.9 ± 68.6 vs 138.1 ± 86.5 m; $p \leq 0.001$). At multivariate analysis extreme cardiovascular risk remains a significant determinant of the absolute functional improvement at Six-Minute Walking Test obtained during cardiac rehabilitation with $b = -0.137$ and $p = 0.035$, together with female sex ($b = -0.136$; $p = 0.035$).

Conclusions: Extreme cardiovascular risk is a widespread condition among patients with chronic coronary syndrome and adversely affects the patient's functional improvement during cardiac rehabilitation. The identification of patients at extreme cardiovascular risk is a goal to be pursued in order to intensify secondary prevention strategies.