Univerzita Karlova v Praze

1. lékařská fakulta

Doktorský studijní program

Studijní obor: Experimentální chirurgie

MUDr. Filip Thieme

Název závěrečné práce

Chirurgické modely studia proinflamačního vlivu tukové tkáně v rozvoji aterosklerózy

Title

Surgical models of the study of the pro-inflammatory effect of adipose tissue in the development of atherosclerosis

Typ závěrečné práce

Disertační

Školitel:

doc. MUDr. Jiří Froněk, Ph.D., FRSC

Konzultant

doc. MUDr. Libor Janoušek, Ph.D.

Klinika transplantační chirurgie, IKEM

Praha, 2021

Abstract

Background:

Atherosclerosis is a serious inflammatory systemic disease. Surgery mainly addresses its vascular complications. Conversely, surgery may also lead to the development and acceleration of atherosclerosis, e.g., in a living kidney donor. This would especially be the case in a donor who meets internationally recognized donation criteria but suffers from metabolic syndrome. The effort to refine assessments of living kidney donors in terms of eliminating the risk of developing atherosclerosis is a long-term project. Our aim is to determine risk factors for living kidney donors and to prevent long-term complications after donation. Collecting tissue from a living donor involves not oly subcutaneous tissue (SCAT) but also visceral (VAT) and perivascular tissue (PVAT), which could prove useful in the research of cardiovascular diseases. The project may increase the safety of living kidney donation and contribute to the knowledge of cardiovascular disease development.

Aims:

The primary goals are as follows: to find the mechanisms by which human adipose tissue could affect the development of cardiovascular disease; to compare macrophage subpopulations in different adipose tissues (SCAT, VAT and PVAT); and to demonstrate a relationship between metabolically activated macrophages (with high CD36 expression) and cardiovascular risk factors.

Methods:

We obtained adipose tissue (SCAT, VAT and PVAT) from different body compartments simulataneously, and flow cytometry was subsequently performed.

Results:

M1 macrophages express proinflamatory CD36 markers. The levels of proinflammatory macrophages was almost twice as high in visceral ($p < 0.0001$) and perivascular ($p < 0.0001$) adipose tissue as they were in subcutaneous tissue. Difference was more pronounced in the postmenopausal women subgroup. We observed that older women had a higher proportion of M1 macrophages than did younger women. Age, male sex and hypercholesterolaemia were positively associated with M1 macrophages in visceral adipose tissue, and their proportions were substantially decreased through statin therapy. Total macrophage numbers in subcutaneous adipose tissue ($p < 0.02$) increased as body mass index increased, with a similar

increase seen in the proportion in proinflammatory macrophages CD14+CD16+CD36high ($p < 0.01$).

Early renal graft function, measured as an average increase in the glomerular filtration rate (GFR) in the first seven days post-transplantation, had no correlation to donor BMI. We did not find an association between early renal graft function and the percentage of M1 macrophages in donor perirenal adipose tissue, adiponectin or plasma CRP. We confirmed a negative correlation between recipient BMI and an average increase of GFR in the first seven days posttransplantation ($p < 0.02$, $r = -0.325$, $N = 58$).

Conclusions:

We obtained detailed information regarding M1 and M2 macrophage phenotypes in human adipose tissue. The significance of the CD36 marker in the analysis of adipose tissue macrophages has been described. An effect of cardiovascular risk predictors on adipose tissue macrophage subpopulations was revealed. We documented a decreasing effect of the statins on proinflammatory macrophages. For postmenopausal women, a higher proportion of proinflammatory macrophages in the visceral adipose tissue may be related to their increased cardiovascular risk. We demonstrated that obesity-related proinflammatory changes in metabolically healthy subjects take place predominantly in subcutaneous adipose tissue. We were unable to confirm our hypothesis that there is a statistically significant negative correlation between donor BMI and an increase in GFR in the first seven days post-transplantation. Furthermore, we could not find a correlation between early renal graft function and the percentage of M1 macrophages in donor perirenal adipose tissue or plasma CRP.

This was the first phase in a long-term project that aims to find other parameters that could be used to assess the risk of atherosclerosis development in living kidney donors. Especially in obese living kidney donors, who should undergo a subcutaneous fat examination before the living kidney donation to determine the level of proinflammatory macrophages. The project may increase the safety of living kidney donation and contribute to the knowledge of cardiovascular disease development.

Key words: atherosclerosis, human adipose tissue, living-donor kidney transplant, metabolic syndrome