UNIVERSITÀ DEGLI STUDI DI PADOVA

PROJECT

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1) Project title

PCSK9 inhibitors and erectile function: exploring the vascular link between lipid-lowering therapy and sexual health

2)Abstract (max 500 words)

Erectile dysfunction (ED) is defined as the inability to achieve or maintain a sufficient penile erection for satisfactory sexual activity and is recognized as an early sign of cardio-vascular disease. Growing evidence supports a strong pathophysiological link between ED and atherosclerotic cardiovascular disease (ASCVD) through the sharing of pathophysiological mechanisms: endothelial dysfunction, reduced nitric oxide bioavailability and increased arterial stiffness. In this frame, hypercholesterolemia plays a central role contributing to vascular impairment and ED.

Proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors are an innovative class of lipid-lowering agents that significantly reduce low-density lipoprotein cholesterol (LDL-C) levels, typically by 50–60%, and lower cardiovascular risk. Their primary mechanism involves inhibition of PCSK9-mediated degradation of hepatic LDL receptors, thereby enhancing LDL clearance. Beyond their lipid-lowering efficacy, emerging data suggest that PCSK9 inhibitors may exert pleiotropic vascular effects, including modulation of endothelial function and arterial stiffness, both of them are critical determinants of erectile function. Moreove reducing inflammation and enhancing blood flow may indirectly benefit sexual performance.

Available preliminary evidence support an association between PCSK9 inhibition and sexual function. A prospective observational study in male patients with familial hypercholesterolemia showed that six months of PCSK9 inhibitor therapy significantly reduced LDL-C levels (- 48.7%), improved arterial stiffness measured by pulse wave velocity (PWV) and significant increased sexual function evaluated by the Male Sexual Health Questionnaire (MSHQ) scores. Improvements in sexual function suggests an interplay between lipid lowering, vascular compliance and erectile performance. However, no statistically significant changes were observed using the International Index of Erectile Function (IIEF-5) scores, highlighting inconsistencies across assessment tools and the need for standardized endpoints.

Additional mechanistic insights suggest that PCSK9 inhibition may improve endothelial function independently from lipid lowering. For example, randomized data with evolocumab have shown improvements in vascular reactivity parameters such as vasoactive range, supporting a direct vascular effect. These findings are particularly relevant given that endothelial dysfunction is a key primer in both atherosclerosis and ED.

Despite these encouraging observations, current evidence is limited by small sample sizes, observational designs and short follow-up. Furthermore, the absence of direct assessments of penile vascular function and molecular biomarkers limits the findings. Notably, ED is a multifactorial condition influenced not only by vascular factors but also by hormonal, neurological and psychological components, which may confound clinical outcomes.

This PhD project proposal aims to comprehensively investigate the role of PCSK9 inhibitors in erectile function through a prospective observational study. The primary aim is to evaluate the erectile function before and after the therapy with PCSK9 inhibitors. To achieve this aim, the project will consider patients eligible for PCSK9 inhibitor therapy. A baseline assessment will be performed using questionaires such as IIEF5 and MSHQ, along with baseline hormone levels of total testosterone, SHBG, LH, FSH, and estradiol. These assessments will be repeated one month and six months after starting PCSK9 inhibitor therapy. The expected results obtained thorught this project may contribute to a more integrated understanding of ED as a vascular disorder and support the development of targeted pharmacological interventions.