**MASTER I - IMAS**

**Academic year 2021-2022**

**Superviser :** Pr Philippe Obert

**Title : Effect of vitamin D3 supplementation on regional myocardial function by deformation imaging at rest and under stress dobutamine in type II diabetes.**

**Rational and aims.**

Numerous epidemiological studies have reported a prevalence of vitamin D deficiency in type 2 diabetes (Scragg et al. 2004, Isaia et al 2001, Kirii et al 2009, Svoren et al 2009, Mattila et al 2007, Hilger et al 2014, Rejnmark et al 2017 for review). A meta-analysis conducted on 76,000 subjects demonstrated that there was an inverse and significant association between circulating levels of vitamin D (eg 25-OH-D) and the risk of developing type 2 diabetes (Song et al 2013). Vitamin D may be involved in the development and progression of diabetes through its effects on β-pancreatic cells, insulin resistance and inflammation (Harris et al. 2012; Xuan et al. 2013).

Low levels of vitamin D are associated with an increased risk of cardiovascular disease, including coronary artery disease, heart failure, hypertension and hypertrophic heart disease (for review Majeed 2017, Rai & Agrawal, 2017). The recent randomized controlled trial VINDICATE reported that a one-year vitamin D supplementation improves heart function in patients with chronic heart failure (Witte et al 2016). A recent meta-analysis in patients with diabetes or glucose intolerance showed significant post-supplementation improvement in young blood sugar and insulin resistance (George et al, 2012). A significant reduction in metabolic syndrome, a risk factor for the development of diabetes, is also documented in connection with an improvement in vitamin D status in a cohort of 6,680 volunteers followed for 5 years (Pham et al 2015).

After synthesis in the skin, or intestinal absorption, vitamin D undergoes two successive hydroxylation, hepatic, then renal, and is transformed into its active metabolite: 1,25-OH-2 which acts in the tissues by the intermediate of a specific intranuclear receptor, VDR, for “Vitamin D Receptor”. 1,25 –OH-2 regulates the expression of nearly 500 genes; Apart from bone, cartilage and intestine, which are the preferred targets, many other tissues such as the myocardium, or immune cells are involved (Pike et al 2017). An effect of vitamin D on cardiovascular health is biologically plausible, as the enzyme 25OHD-1α-hydroxylase, which hydrolyzes 25-OH-D to 1,25-OH-2, the active form, as well as VDR have been identified at the level of cardiomyocytes and coronary arteries (Schantz and Manson 2014, Pike et al 2017). In vivo studies in animals deficient in vitamin D (Weischsar et al 1987, Gupta et al. 2012), or presented with VDR deletion (Glenn et al 2015, Chen et al 2011) revealed cardiac hypertrophy associated with increased cardiomyocyte size, as well as overall cardiac dysfunction. Assalin et al (2013) studied the effect of vitamin D deficiency on metabolism, morphology and cardiac function in rats. They found a significant association between vitamin D deficiency and heart inflammation, oxidative stress, changes in energy metabolism, cardiac hypertrophy, atrial and left ventricular (LV) remodeling associated with fibrosis and apoptosis, and left ventricular systolic dysfunction. In diabetic rats or mice, chronic vitamin D supplementation improves cardiac remodeling, via a reduction in tissue inflammation, fibrosis and apoptosis (Lee et al 2014, Wang et al 2014, Fan et al , 2015, Zengh et al 2017), and limits cardiac hypertrophy and interstitial fibrosis and improves cardiac function by mechanisms involving its VDR receptor and autophagy pathways (Wei et al 2017). Similar results on favorable cardiac remodeling are also described in diabetes after pharmacological activation of VDR (Fuji et al 2015). Very interestingly, in human diabetes, Chen et al (2014) recently reported an exacerbation of left ventricular longitudinal dysfunction assessed by strain imaging in vitamin D deficient patients compared to those with normal vitamin status. Also, in individuals deficient in vitamin D free from cardiovascular pathology, vitamin D status appears as an independent contributor of regional myocardial function and a 3-month supplementation improves myocardial function (Sunbul et al 2015).

Part of the cardioprotective effects of vitamin D may be through reduced inflammation and oxidative stress, which are exacerbated in diabetes. Several clinical studies have shown an inverse association between the levels of 25-OH-D and various markers of inflammation (TnF-α, IL-6, MCP1, etc.) at the systemic level, as well as at the level of visceral adipose tissue, including epicardial adipose tissue (Deluca and Cantorna 2001, Dozio et al, 2014, Norman and Powell, 2014, Dakshinamurti 2015). Significant effects of supplementation have also been established on the main markers of inflammation, and demonstrated a modulation of the NF-KB signaling pathway (Marcotorchino et al. 2012, Mutt et al 2012, Giulietti et al 2017 , Zangh et al 2012, Norman and Powell, 2014, Dakshinamurti 2015) as well as oxidative stress (Dong et al 2012, Polidoro et al 2013).

**To our knowledge, to date no study has documented in diabetes the effects of vitamin D supplementation in patients with nascent diabetic cardiomyopathy.**

The scientific objective of the project is therefore to assess in patients with type II diabetes the effects of a 3-month vitamin D3 supplementation on regional systolic and diastolic myocardial function assessed by echocardiography in deformation imaging mode (2D-strain) under two conditions: at rest and under stress conditions (eg dobutamine).

The main hypothesis of this work is that the intrinsic properties of myocardial contractility and relaxation, estimated from the collection of deformation imaging parameters, will be improved after treatment, regardless of glucido-lipid profile and insulin resistance.

**Laboratory.**

The Cardiovascular Pharm-Ecology Laboratory (EA4278) is affiliated with the University of Avignon. The themes of this laboratory are mainly focused on the study of cardiac and vascular dysfunctions and their prevention and rehabilitation through physical activity and nutrition.

Candidate profile

Master 1 research (Movement Sciences, biology, medicine, physiotherapy)

Knowledge of physiology and pathophysiology of the cardiovascular system.

The candidate will notably be in charge of post-processing analysis of morphology and myocardial function using deformation imaging techniques. He/she will also be trained under high resolution echocardiography to perform a cardiac analysis.