CYP27A1 GENETIC POLYMORPHISM IN CHOLESTEROL METABOLISM ON RELATIONSHIP BETWEEN OBESITY, CARDIOVASCULAR RISK AND PREMATURE AGING: RESULTS FROM A HUMAN CROSS-SECTIONAL STUDY ON OBESE POPULATION ENROLLED IN THE SPHERE PROJECT

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The dramatic escalation of obesity prevalence, leading to earlier onset of aging-related cardiovascular disease (CVD), represents an emerging worldwide public health threat (WHO, 2015). This preventable disorder, often associated with cholesterol dismetabolism (Eriksson et al., 2016), is challenging to prevent and to treat (Locke et al., 2015). The sterol 27-hydroxylase (CYP27A1), a largely distributed mitochondrial P450 cytochrome enzyme, by converting extrahepatic cholesterol to 27-hydroxycholesterol (27HC), primarily speeds its elimination, by the so-called “reverse transport”, an emerging antiatherogenic mechanism (Bjorkhem, Diczfalusy, 2002). Lack in CYP27A1 activity (Umetami et al., 2011), due to mutations in the CYP27A1, found in patients with cerebrotendinous xanthomatosis disease (CTX), determines cholesterol accumulation in the vascular endothelium and severe premature development of atherosclerosis (Björkhem, 2013). Similarly low hydroxylation CYP27A1 activity related to 3 CYP27A1 polymorphisms (SNPs) [rs4674345 A, rs1554622 A, rs4674338 G] (Diekstra et al., 2012) by diminishing 27HC levels and favoring cholesterol accumulation, might rise individual atherogenic risk.

In view of advances in a tailored health care in this study we test the hypothesis that obese subjects carrying of an high number (>3) of CYP27A1 decreasing activity alleles [rs4674345 A, rs1554622 A, rs4674338 G] are more likely to present an altered cholesterol metabolism, higher levels of CVD risk factors as well as a consequent premature aging (shorter leucocyte telomere length (LTL)) than those with a normal metabolism.

We genetically characterized, by the 3 CYP27A1 functional SNPs, n=1457 obese subjects [overweight (n=959 BMI<35 Kg/m2) and sever obese (n=498 BMI>=35 Kg/m2)] enrolled in the SPHERE project, collected epidemiological and clinical data, as well as personal information through lifestyle and diet questionnaires. Simple univariate and multivariable linear regression models were carried out to evaluate the relationship between low and normal CYP27A1 activity subjects, presenting ≥3 (LV:3-6) and <3 low-hydroxylation (LV:0-2) SPNs, and CVD risk factors, that included classic modifiable risk factors (systolic blood pressure (SBP), heart rate) lipid profiles (Total Cholesterol (TC), High Density Lipoprotein-C (HDL-C), triglyceride (TG), glucose homeostasis (HOMA index and glycated hemoglobin); behavioral risk factors (BMI, smoking) and additional behavioral risk factors (lack of exercise, excess alcohol) and novel risk factors such as biological aging (LTL detected by RT-PCR), inflammation markers (such as C-reactive protein (CRP), Interferon-Gamma, Macrophage Inflammatory Protein-1-alpha, Monocyte Chemoattractant Protein-1 (MCP_1), Interleukine-10, Tumor Necrosis Factor alpha Cytokines), coagulation markers (fibrinogen). A 10 Cardiovascular Risk Scores for estimating the probability of CVD was also calculated (http://cvrisk.mvm.ed.ac.uk/calculator/excelcalc.htm).

Unadjusted and adjusted regression models, showed that most (12/17, 71%) of the classic risk factors (SBP, heart rate, waist to hip), lipid profiles (HDL-C and TG) and novel risk factors such as inflammation markers (CRP, white blood cells (WBC) and MCP_1), coagulation markers (fibrinogen) and glucose homeostasis (HOMA index and glycated hemoglobin) and even biological aging (shorter LTL), were significant altered in subjects with low-(hydroxylation)activity CYP27A1 both in overweight ($p<0.01$) and even more in severe obese ($p<0.001$). In particular for HDL-C, TG, glycated hemoglobin, inflammation and coagulation markers, fibrinogen and WBC, the whole 10 Cardiovascular Risk Scores, and even for shorter LTL, the differences were distinctly towered.

The study's findings support the hypothesis that the CYP27A1 genetic characterization identifies persons at higher risk to develop CVD on which better converge preventive measure, representing a new possible target in personalized medicine.