Atherosclerotic plaque growth prediction in coronary arteries using a computational multi-level model; the effect of diabetes.

Dimitris S. Pleouras
Department of Biomedical Research, Institute of Molecular Biology and Biotechnology, FORTH,
Ioannina, Greece
pleouras@live.com

Antonis I. Sakellarios
Department of Biomedical Research, Institute of Molecular Biology and Biotechnology, FORTH,
Ioannina, Greece
ansakel13@gmail.com

Georgia Karanasiou
Department of Biomedical Research, Institute of Molecular Biology and Biotechnology, FORTH,
Ioannina, Greece
gkaranasiou@gmail.com

Savvas-Ioannis Kyriakidis
Department of Biomedical Research, Institute of Molecular Biology and Biotechnology, FORTH,
Ioannina, Greece
savvasik21@gmail.com

Panagiota I. Tsompou
Department of Biomedical Research, Institute of Molecular Biology and Biotechnology, FORTH,
Ioannina, Greece
panagiotatsompou@gmail.com

Vassiliki I. Kigka
Department of Biomedical Research, Institute of Molecular Biology and Biotechnology, FORTH,
Ioannina, Greece
kigkavaso@gmail.com

Dimitrios I. Fotiadis
Department of Biomedical Research, Institute of Molecular Biology and Biotechnology, Dept. of Materials Science and Engineering, Unit of Medical Technology and Intelligent Information Systems, University of Ioannina
Ioannina, Greece
fotiadis@cc.uoi.gr

***Abstract*— Atherosclerosis is the one of the major causes of mortality worldwide, urging the need for its treatment. This study is aiming to investigate the role of diabetes in the atherosclerotic plaque growth mechanisms through the utilization of a multi-level numerical model. To accomplish this, we developed a *proof-of-concept* mathematical model of the diabetes effect to plaque growth, that has been coupled to a *state-of-the-art* multi-level numerical model of plaque growth. Diabetes main effect is the increase of the average blood glucose concentration, which causes the decrease of the endothelial nitric oxide production rate by affecting several biologic pathways. Nitric oxide is a signaling molecule that regulates the endothelial flow rates, and any abnormal alteration leads to endothelial dysfunction, the major culprit of atherosclerosis. The derived model considers the modeling of blood flow in lumen and of species transport and reactions in the arterial wall. The considered factors include: (i) LDL, (ii) HDL, (iii) oxidized LDL, (iv) monocytes, (v) macrophages, (vi) cytokines, (vii) smooth muscle cells (contractile & synthetic), and (viii) collagen. The model is validated using 10 patients' reconstructed arterial data in two time-points. More specifically, baseline geometries are used as an input to our model, while follow-up geometries are used as benchmark for our model's output. The results presented a high coefficient of determination between the simulated with diabetes effect and the real follow-up geometries of 0.634.**

Keywords—atherosclerotic plaque prediction, stenosis prediction, diabetes, finite element modeling

I. INTRODUCTION

Coronary Artery Disease (CAD) remains one of the most common causes of morbidity and mortality, urging the need for its treatment [1]. This disease has been extensively investigated, revealing multiple culprits for its initiation and progression. The most common approaches take into account the accumulation of lipoproteins in the arterial wall, triggering several pathophysiological pathways to atherosclerosis [2]. Several studies that focused on the atherosclerosis progression, revealed the existence of inflammatory cells located in sites containing abnormal lipoprotein concentrations. More specifically, histological analyses identified the existence of clusters with foam cells (macrophages containing lipid droplets) in these areas, revealing type I lesions. In advanced lesions, an increased concentration of lipid-laden smooth muscle cells is observed, characterizing type II lesions, called fatty streaks. Exceeding this state, extracellular lipid particles are found in more advanced lesions, preventing the coherence of the smooth muscle cells in intima. This situation characterizes types III and IV, which differ in the size of the extracellular lipid droplets. These lesions can further advance, usually at the fourth decade of life, leading to type V lesions. These are characterized by the presence of thick layers of fibrous connective tissues in the lesions. Finally, type VI refers to lesions that further include fissure, hematoma or thrombus [3].

Despite the experimental research [4], several attempts have been made to study the progression of atherosclerosis by numerical methods. Initially, the modeling of the blood flow in the 3D reconstructed arterial segments, resulted in a correlation of the endothelial shear stresses (ESS) to the location of the atherosclerotic plaques [5]–[8]. Other computational models considered the plasma flow in the

arterial wall, along with several factors that mediate in the plaque formation, leading to an improvement of plaque formation prediction [2][9].

Diabetes is a well-known risk factor of atherosclerosis [10], [11]. Specifically, diabetes is a metabolic disease that causes, among other, high blood sugar levels. This disease can result either from pancreas dysfunction and insufficient production of insulin, or from insulin resistance, a condition that characterizes failure of cell's response to insulin. In both conditions, insulin is the common factor. Insulin is responsible for the regulation of the glucose uptake from cells. Therefore, insulin insufficiency or insulin resistance leads to high glucose accumulation in the blood [12].

In this work, we developed a multi-scale numerical model of atherosclerosis growth that considers the diabetes effect. The developed model was applied to 10 patient-specific 3D reconstructed arteries using CTCA at baseline and the simulated area of the arterial wall was compared with the realistic arterial wall at the follow-up as depicted in CTCA imaging.

II. Materials & Methods

A. *Patient's data and 3D reconstruction*

Data from 10 patients' arterial data have been used. Each dataset includes CCTA imaging of the diseased coronary arterial segments in two different time points and blood examination data, which are used as input to the plaque growth model.

The CCTA imaging of each patient were used for the 3D reconstruction of the arterial segment. In brief, for the 3D arterial reconstruction the following steps have been performed: (i) image preprocessing, (ii) blooming effect removal, (iii) centerline extraction, (iv) weight function estimation, (v) lumen, arterial wall and plaque segmentation, and (vi) reconstruction of the 3D arterial models [13].

B. *Modeling diabetes pathway*

a) Diabetes & endothelial function: A prolonged high blood glucose concentration characterizes diabetes disease. Several experimental studies identified the correlation of glucose concentration to endothelial nitric oxide synthases (eNOS) [14]. Specifically, Liang *et al.* studied the effect of hyperglycemia to the eNOS activity in bovine aortic endothelial cells (BAECs) *in vitro*, using two incubating solutions of 5mM and 30 mM glucose [15]. Connell *et al*. confirmed the aforementioned correlation *in vitro* and refined the experiments by using human microvascular retinal endothelial cells both in static and in flow-mediated cultures [16]. The study of De Nigris *et al*. focused on the insulin signaling to eNOS activity under normal and hyperglycemic conditions [17]. Based on [15], [16] and [17], a regression analysis of the collected experimental data has been performed, showing a correlation of average blood glucose concentration ($\overline{c_{glucose}}$) with eNOS activity ($eNOS_{activity}$) (Fig. 1) with a coefficient of determination (R2) of 0.98:

$$xxxxx. \qquad (1)$$

However, blood glucose concentration is not constant but it presents variability during daytime of each individual. Therefore, diabetic patients are monitored using the average blood glucose concentration as a biological index. To accomplish this, measuring of the glycated hemoglobin (Hba1c) can result to the evaluation of the average blood glucose concentration of the last 3 months [18].

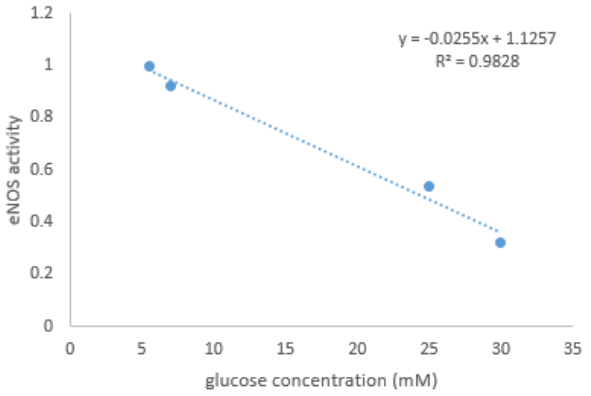

Fig. 1. Diagram of the dependency of eNOS activity to blood glucose concentration.

$$\overline{c_{glucose}}(mmol/l) = 1.77Hba1c - 3.83 \qquad (2)$$

In case of a patient with incomplete data of the glycated hemoglobin concentration, the average blood glucose concentration of 5.5mmol/l and 6.5 mmol/l is used, which represents the average value of a normal and a diabetic patient respectively.

b) eNOS & endothelial permeability: Several experimental studies and atherosclerotic models take into account the correlation of endothelial permeability to nitric oxide (NO) concentration [19], [20]. eNOS is located in the endothelial cells, the first layer of cells of the arterial wall, and produces NO which is a signaling molecule, mainly responsible for the vasorelaxation. However, in this process, nitric oxide causes an increased endothelial flux, maybe due to the relaxing of endothelial cell junctions during vasorelaxation [21]. Therefore, by modeling this pathway, blood glucose concentration can be integrated into the endothelial permeability.

Sakellarios *et al*. presented a plaque growth model which correlates endothelial permeability with endothelial nitric oxide concentration (c_{NO}) and endothelial shear stress (ESS) [20]. Endothelial permeability (P) is described by the following equation:

$$xxxx \qquad (3)$$

while nitric oxide concentration is calculated by the equations:

$$xxxx \qquad (4)$$

$$xxxx \qquad (5)$$

$$xxxx \qquad (6)$$

Blood glucose concentration affects eNOS activity decreasing nitric oxide concentration. Therefore, this effect is integrated by including the eNOS activity to the equation of maximum nitric oxide concentration ($c_{NO,max}$):

$$xxx. \qquad (7)$$

C. *Plaque growth model*

To evaluate this model, a state-of-the-art plaque growth model was implemented [3][22]. The validation process is

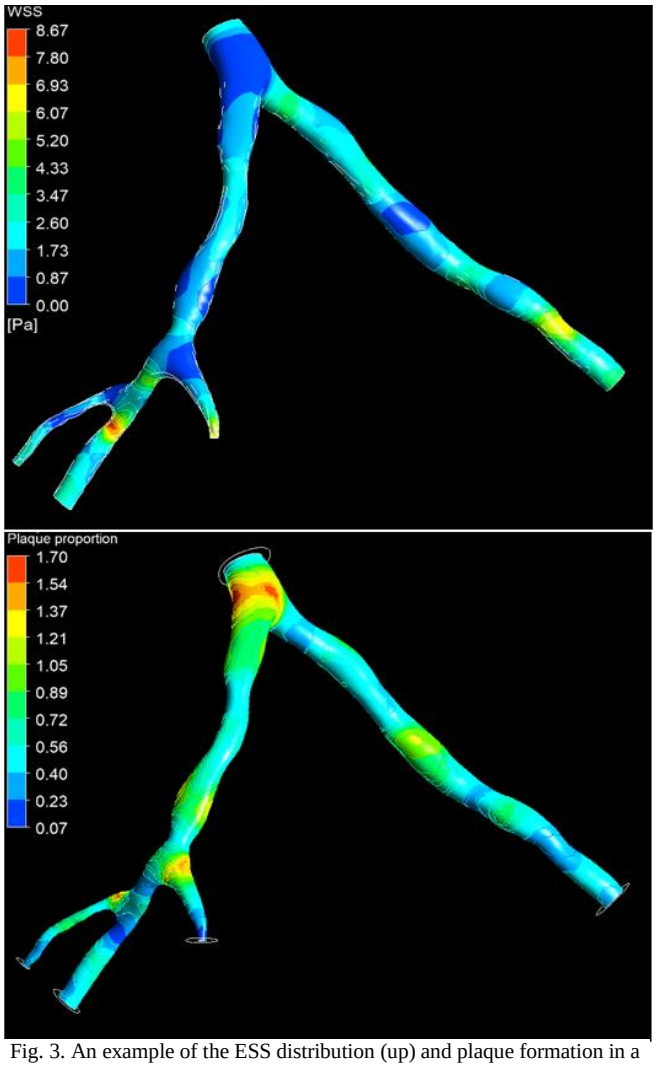

Fig. 3. An example of the ESS distribution (up) and plaque formation in a coronary arterial tree.

based on comparing the simulated patients' geometries to their follow-up geometries.

The plaque growth model predicts the initiation and progression of plaque formation, by modeling the transport and the reactions of several species and factors. The atherosclerotic process initiates when ESS-dependent endothelial fluxes, that regulate the plasma and lipoprotein (HDL & LDL) flow through the endothelium, become abnormal. Specifically, the eNOS produces nitric oxide (NO), which is a regulator of endothelial fluxes. NO production rate is inversely proportional to the magnitude of the applied ESS. Therefore, high LDL and low ESS values are the key factors for the initiation of atherosclerosis. After the accumulation of LDL within the arterial wall, free radicals oxidize LDL, attracting monocytes that differentiate into macrophages, uptaking the oxidized LDL and forming foam cells. However, the infiltrated HDL prevents this process, reducing the free radical concentration by oxidizing itself. The infiltrated macrophage cells, secrete inflammatory chemoattractants, of which cytokines cause the contractile smooth muscle cells (SMCs) differentiation into synthetic SMCs, which is a basic component of fibrous fatty plaques [22].

After the inflammation modeling, the resulted concentration values of each species are used for the calculation of the plaque volume distribution. The plaque volume distribution is used for the calculation of the volumetric strain matrix, which is supplied as an input to a stress-strain model, enabling arterial wall thickening.

III. Results

Plaque growth simulations were performed to the baseline geometries, with and without diabetes effect, and resulted to the wall-thickened geometries (Fig. 3). The deformed geometries were compared to the real follow-up geometries, by applying the well-accepted measure of comparison between the simulated and the real follow-up geometries [22], which is the comparison of the area values of common cross-sections.

In this work, the cross-sections that were extracted had an intermediate spacing 0.5mm. To avoid any registration error of the previous procedure, the comparison was performed utilizing the mean areas of every six cross-sections as a benchmark.

Fig. 2. Correlation of follow-up and simulated with diabetes effect cross-section areas.

To extract a quantitative correlation of the results, we performed a regression analysis between the real follow-up and the simulated geometries. The correlation between the simulated without diabetes effect and the follow-up cross-section areas, has a coefficient of determination R^2=xxx1. If the diabetes effect is included, the regression model has a coefficient of determination R^2=xxx (Fig. 2).

Another measure of comparison, is the Bland-Altman plot which is used to analyze the agreement between two different assays. The Bland-Altman plot presents a distribution mainly within the standard deviation ranges (±xxxx), resulting in a good agreement of the simulated with diabetes effect and the follow-up cross-section areas (Fig. 4).

IV. Discussion & Conclusions

In this study, it was assumed that diabetes effect to plaque growth was exclusively the increase of the blood glucose concentration. However, multiple other diabetes effects have been proven experimentally to affect plaque growth enabling several other pathways to atherosclerosis, such as the effects of the abnormal production of insulin or the insulin resistance. Also, it was assumed that blood glucose concentration has a single impact to the eNOS activity. Although an effect of diabetes may be a novel addition to the atherosclerotic plaque growth models, these limitations must be addressed in the future to result in models with better prediction capabilities.

The results demonstrate that the computational model of the diabetes effect to plaque growth, improves the atherosclerotic plaque growth model's prediction of both the regions that are prone to atherosclerotic plaque progression and of the plaque growth rates. To our knowledge this is the first study that introduces an effect of diabetes disease to atherosclerotic plaque growth modeling, resulting in a beyond the state-of-the-art model.

Acknowledgment

This work is supported by the InSilc project that has received funding from the European Union's Horizon 2020 research and innovation program under grant agreement No 777119. This work reflects only the author's view. The Commission is not responsible for any use that may be made of the information it contains.

REFERENCES

[1] Benjamin Emelia J. *et al.*, "Heart Disease and Stroke Statistics—2019 Update: A Report From the American Heart Association," *Circulation*, vol. 139, no. 10, pp. e56–e528, Mar. 2019.

[2] H. C. Stary, "Natural History and Histological Classification of Atherosclerotic Lesions," *Arterioscler. Thromb. Vasc. Biol.*, May 2000.

[3] H. C. Stary *et al.*, "A Definition of Advanced Types of Atherosclerotic Lesions and a Histological Classification of Atherosclerosis," *Circulation*, Sep. 1995.

[4] P. N. Hopkins, "Molecular Biology of Atherosclerosis," *Physiol Rev*, vol. 93, p. 226, 2013.

Fig. 4. Bland-Altman plot of follow-up and simulated with diabetes effect, cross-section areas.

[5] P. H. Stone *et al.*, "Regions of low endothelial shear stress are the sites where coronary plaque progresses and vascular remodelling occurs in humans: an in vivo serial study," *Eur. Heart J.*, vol. 28, no. 6, pp. 705–710, Mar. 2007.

[6] A. I. Sakellarios *et al.*, "SMARTool: A tool for clinical decision support for the management of patients with coronary artery disease based on modeling of atherosclerotic plaque process," in *2017 39th Annual International Conference of the IEEE Engineering in Medicine and Biology Society (EMBC)*, Seogwipo, 2017, pp. 96–99.

[7] A. Sakellarios *et al.*, "The effect of coronary bifurcation and haemodynamics in prediction of atherosclerotic plaque development: a serial computed tomographic coronary angiographic study," *EuroIntervention J. Eur. Collab. Work. Group Interv. Cardiol. Eur. Soc. Cardiol.*, vol. 13, no. 9, pp. e1084–e1091, Oct. 2017.

[8] A. Sakellarios *et al.*, "Prediction of atherosclerotic disease progression using LDL transport modelling: a serial computed tomographic coronary angiographic study," *Eur. Heart J. – Cardiovasc. Imaging*, vol. 18, no. 1, pp. 11–18, Jan. 2017.

[9] M. R. Kaazempur-Mofrad and C. R. Ethier, "Mass Transport in an Anatomically Realistic Human Right Coronary Artery," *Ann. Biomed. Eng.*, vol. 29, no. 2, pp. 121–127, Feb. 2001.

[10] Y. Naka *et al.*, "RAGE axis: Animal models and novel insights into the vascular complications of diabetes," *Arterioscler. Thromb. Vasc. Biol.*, vol. 24, no. 8, pp. 1342–1349, Aug. 2004.

[11] A. Soro-Paavonen *et al.*, "Receptor for advanced glycation end products (RAGE) deficiency attenuates the development of atherosclerosis in diabetes," *Diabetes*, vol. 57, no. 9, pp. 2461–2469, Sep. 2008.

[12] A. T. Kharroubi and H. M. Darwish, "Diabetes mellitus: The epidemic of the century," *World J. Diabetes*, vol. 6, no. 6, pp. 850–867, Jun. 2015.

[13] V. I. Kigka *et al.*, "3D reconstruction of coronary arteries and atherosclerotic plaques based on computed tomography angiography images," *Biomed. Signal Process. Control*, vol. 40, pp. 286–294, Feb. 2018.

[14] T. Thum *et al.*, "Endothelial Nitric Oxide Synthase Uncoupling Impairs Endothelial Progenitor Cell Mobilization and Function in Diabetes," *Diabetes*, vol. 56, no. 3, pp. 666–674, Mar. 2007.

[15] X. L. Du, D. Edelstein, S. Dimmeler, Q. Ju, C. Sui, and M. Brownlee, "Hyperglycemia inhibits endothelial nitric oxide synthase activity by posttranslational modification at the Akt site," *J. Clin. Invest.*, vol. 108, no. 9, pp. 1341–1348, Nov. 2001.

[16] P. Connell, T. Walshe, G. Ferguson, W. Gao, C. O'Brien, and P. A. Cahill, "Elevated Glucose Attenuates Agonist- and Flow-Stimulated Endothelial Nitric Oxide Synthase Activity in Microvascular Retinal Endothelial Cells," *Endothelium*, vol. 14, no. 1, pp. 17–24, Jan. 2007.

[17] V. De Nigris, G. Pujadas, L. La Sala, R. Testa, S. Genovese, and A. Ceriello, "Short-term high glucose exposure impairs insulin signaling in endothelial cells," *Cardiovasc. Diabetol.*, vol. 14, no. 1, p. 114, Dec. 2015.

[18] "eAG/A1C Conversion Calculator | American Diabetes Association." [Online]. Available: https://professional.diabetes.org/diapro/glucose_calc. [Accessed: 18-Jul-2019].

[19] S. Y. Yuan, "New insights into eNOS signaling in microvascular permeability," *Am. J. Physiol.-Heart Circ. Physiol.*, vol. 291, no. 3, pp. H1029–H1031, Sep. 2006.

[20] A. I. Sakellarios *et al.*, "Modelling LDL accumulation in the case of endothelial dysfunction," vol. 5, no. 2, p. 11, 2011.

[21] D. Tousoulis, A.-M. Kampoli, C. Tentolouris Nikolaos Papageorgiou, and C. Stefanadis, "The Role of Nitric Oxide on Endothelial Function," *Curr. Vasc. Pharmacol.*, vol. 10, no. 1, pp. 4–18, Jan. 2012.

[22] A. I. Sakellarios *et al.*, "Prediction of Atherosclerotic Plaque Development in an In Vivo Coronary Arterial Segment Based on a Multilevel Modeling Approach," *IEEE Trans. Biomed. Eng.*, vol. 64, no. 8, pp. 1721–1730, Aug. 2017.