International Journal of Chemical and Biochemical Sciences
(ISSN 2226-9614)

Journal Home page: www.iscientific.org/Journal.html

Subclinical Atherosclerosis in Children with Diabetic Nephropathy

Hadeel Mohamed Abdalrahman[1], Amal S. El-Shal[2, 3], Marwa Elsaid Abdalhamid[4], Amany Elsayed Mohamed[1]*

[1]*Pediatrics Department, Faculty of medicine, Zagazig University, Egypt*

[2] *Medical Biochemistry Department, Faculty of Medicine, Zagazig University, Cairo, Egypt.*

[3] *Medical Biochemistry and Molecular Biology Department, Armed Forces college of Medicine (AFCM), Cairo, Egypt.*

[4] *Radiology Department, Faculty of medicine, Zagazig University, Egypt*

Abstract

Numerous comorbidities, such as retinopathy, neuropathy, nephropathy, and cardiovascular disease, are linked to the onset of diabetes. Diabetic nephropathy (DN) is a prevalent complication in children with type 1 diabetes, leading to significant morbidity. Recent evidence indicates that children with DN are at increased risk for atherosclerosis, a condition characterized by the buildup of plaques in arterial walls. Compared to non-diabetics, the risk of macro vascular consequences, such as myocardial infarction and stroke, is increased two- to three-fold. The rapid development of atherosclerosis confers the greater risk. This is mediated by increased inflammation of the plaque due to activation and proliferation of macrophages in the plaque, as well as insulin resistance and hyperglycemia-induced monocyte recruitment. Moreover, pathogenic processes that play a critical role in promoting the development of atherosclerosis include endothelial dysfunction and disturbance of the glycocalyx. Albuminuria and a reduction in renal function are also caused by endothelial dysfunction and disruption of the glycocalyx, which creates a pathogenic notion that connects atherogenesis and diabetic nephropathy. Individuals with diabetic nephropathy exhibit a significantly elevated risk of cardiovascular events in contrast to those without the condition. In order to reduce the risk of future occurrences, it is therefore critical to acknowledge the cardiovascular hazard that diabetics with albuminuria and/or decline in renal function are facing and to optimize their treatment to minimize the risk of future events.

Keywords: Atherosclerosis, Diabetes, Nephropathy.

Mini review article **Corresponding Author*, e-mail: amanyalagooz99@gmail.com

1. Introduction

Subclinical atherosclerosis refers to early changes in the arterial wall that precede clinically evident cardiovascular disease. In the early stages of atherosclerotic disease, known as subclinical atherosclerosis, atheromatous plaques are seen in one or more arterial locations, but the patient has not yet displayed any clinical signs or events connected to atherosclerosis in those regions. Because it can offer an early warning of the body's total atherosclerotic burden, this early stage of the disease is important. By early detection and prevention of subclinical atherosclerosis, the risk of future cardiovascular events, including heart attacks, strokes, and other consequences, can be decreased [1].

2. Risk Factors

2.1. Several risk factors contribute to the development of subclinical atherosclerosis in children with DN

- Poor Glycemic Control: HbA1c levels are closely linked to both renal and cardiovascular outcomes [2].
- Hypertension: High blood pressure is a significant predictor of cardiovascular risk.
- Dyslipidemia: Abnormal lipid profiles, particularly elevated triglycerides and low HDL cholesterol, exacerbate cardiovascular risk.

2.2. Pathogenesis of subclinical atherosclerosis

A sequence of phases can be used to describe the incompletely understood process of atheroma production. The main cause of atherosclerosis is the build-up of lipids, specifically lipoproteins carrying apolipoprotein B, inside the walls of the arteries. This accumulation causes an inflammatory reaction, which accelerates the development

of atherosclerosis [2]. The most common atherogenic lipoproteins in the bloodstream, circulating low-density lipoprotein (LDL) particles, can penetrate the monolayer of endothelial cells (EC) and enter the sub-endothelial region in a process known as transcytosis. Once there, the LDL particles experience oxidation and become trapped [3]. Monocytes are drawn to the region by the activated endothelial cells' increased expression of adhesion molecules in response to atherogenic stimuli. After migrating into the intima, these monocytes develop into macrophages, which then consume the oxidized LDL and become foam cells [3].

Foam cells consume modified lipoproteins until they die as a result of their accumulation. This process causes the intima's natural structure to be disrupted, which in turn causes cells, lipids, and debris to accumulate. These components combine to create a soft, unstable core in the middle of the plaque. Smooth muscle cells (SMC) move simultaneously from the blood vessel's outer (adventitia) to inner (intima) layers. These cells cover the plaque's center with a thick fibrous covering made of collagen and elastin [2]. At this point, the plaque rupture may allow platelets to stick to the damaged area and form a blood clot, or thrombosis, which might eventually completely block the blood vessel [3]. The atherosclerotic plaque is described as consisting of a collagen-rich fibrous crown encircling a lipid-rich core that is made up of foam cells, debris, and lipids. Atheroma plaque development comprises multiple critical phases [4]:

- The process is started by lipid infiltration into the sub-endothelial area.
- Dysfunction and activation of endothelial cells (EC) result in increased expression of adhesion molecules on their surface. This makes it easier for inflammatory cells to adhere to and penetrate the intima.
- Recruited monocytes undergo differentiation into macrophages, which then consume altered lipids to produce foam cells.
- Smooth muscle cells (SMC) produce matrix proteins, move, and multiply simultaneously. As a result, the expanding plaque core is surrounded by a fibrous cap that forms.

2.3. Development of atherosclerosis in Diabetic Nephropathy

- Atherosclerosis involves multiple processes: Endothelial Injury: Hyperglycemia and hypertension damage endothelial cells, leading to impaired nitric oxide production and reduced vasodilation.
- Lipid Accumulation: Dyslipidemia, often seen in DN, facilitates lipid infiltration into arterial walls, promoting plaque formation. Inflammatory Response: Activated immune cells and inflammatory cytokines exacerbate atherosclerotic change.

2.4. Role of Triglycerides in diabetic nephropathy and cardio vascular disease

Elevated plasma triglyceride (TG) levels are common in DN patients, and this may contribute to the disease's advancement. The development of DN may be facilitated by anomalies in the synthesis and clearance of TG and TG-associated lipoprotein particles. Major promoters of DN have been shown to be TG-rich lipoprotein (TRL) particles, especially those carrying apolipoproteins E, C, and B. [7]. ApoCIII is regarded as a risk factor for DN and regulates serum TG levels significantly. Lipoprotein lipase (LPL), an enzyme that breaks down TG in VLDL and helps remove it from the bloodstream, is inhibited by ApoCIII. Furthermore, through interfering with VLDL and LDL's interaction with hepatic lipoprotein receptors, ApoCIII obstructs their plasma clearance. This inhibition may result in increased amounts of TG and LDL, which would accelerate the development of DN [8].

Triglyceride-rich lipoprotein (TRL) remnants have a longer half-life in the bloodstream due to ApoC-III's inhibition of their clearance, which may have an atherogenic effect [9]. Usually, transcytosis is how lipoproteins enter and exit the artery wall. Large chylomicrons and the VLDL are too big for this procedure, but their smaller fragments can still pierce the artery intima. Due to their high cholesterol content, TRL remnants directly cause cholesterol buildup in the intima and trigger inflammatory processes [10]. Lipoproteins containing the apolipoprotein B are known to accumulate subendothelially, and the ApoC-III is involved in this process. While the apoC-III does not directly attach to proteoglycans in the arterial wall, it has the ability to change the lipid composition of the lipoproteins, which can change the shape of the Apo lipoprotein B. This alteration may facilitate the lipoprotein binding to arterial wall proteoglycans [11].

2.5. Evidence of Subclinical Atherosclerosis in Children with Diabetic Nephropathy

Recent studies have demonstrated increased CIMT: Children wits [12].h DN show significantly higher CIMT compared to healthy peers, indicating early atherosclerotic changes. Impaired Endothelial Function: Decreased FMD has been observed in children with DN, correlating with disease duration and glycemic control.

Inflammatory Markers: Elevated levels of inflammatory markers, such as C-reactive protein (CRP) and the interleukin-6 (IL-6), have been associated with both DN and the atherosclerosis [12].

2.6. Assessment of subclinical atherosclerosis

1. Imaging techniques

•Carotid Intima-Media Thickness (CIMT): An increase in CIMT is a strong predictor of cardiovascular events.

•mode Ultrasound: Used to visualize plaques and assess arterial stiffness.

•Brachial Artery Reactivity: Endothelial function can be evaluated through flow-mediated dilation (FMD), which is often impaired in this population**.**

•Magnetic Resonance Imaging (MRI) and Computed Tomography (CT): Advanced imaging for assessing plaque burden and arterial stiffness.

2. Biomarkers

Measurement of inflammatory markers (e.g., C-reactive protein) and lipid profiles to evaluate cardiovascular risk.

3. Functional Assessments

Exercise testing and heart rate variability studies can provide insight into autonomic function and cardiovascular health.

4. Lifestyle Assessment

Evaluate diet, physical activity, and obesity status. These factors significantly impact cardiovascular risk.

5. Screening Guidelines

Current guidelines recommend regular screening for cardiovascular risk factors in diabetic children, especially those with poor metabolic control or additional risk factors.

6. Longitudinal Studies

Follow-up studies to assess progression or regression of atherosclerotic changes are essential for understanding long-term risks [13]. Research has indicated that the carotid arteries usually experience early manifestation of the atherosclerosis process. For this reason, assessing the carotid arteries is crucial when determining cardiovascular risk. Noninvasive assessments of atherosclerotic alterations, such as carotid intima media thickness (CIMT) measurement, carotid plaque presence and extent, and arterial stiffness, can be performed using carotid B-mode ultrasonography. The presence of thicker CIMT or carotid plaque is suggestive of the morphological alterations brought about by the advancement of atherosclerosis in the carotid artery. The functional characteristics of atherosclerotic alterations in the carotid artery are reflected in local common carotid artery (CCA) stiffness parameters, such as elastic modulus, distensibility coefficient, strain, and strain rate. These functional alterations appear before structural alterations, such as the carotid plaque and intimal thickening of the artery wall [12].
Management Strategies: Addressing atherosclerosis in children with DN involves a multifaceted approach:
Optimizing Glycemic Control: Tight glycemic management is essential for slowing both nephropathy and atherosclerosis progression.
Blood Pressure Control: Use of antihypertensive agents, particularly ACE inhibitors, has renal protective effects and reduces cardiovascular risk.
Lipid Management: Statins and lifestyle modifications aimed at normalizing lipid levels can help mitigate cardiovascular risk.
Lifestyle Interventions: Encouraging a heart-healthy diet, regular physical activity, and smoking cessation can substantially reduce risk [14].

4. Conclusions

Children with diabetic nephropathy face an elevated risk of developing atherosclerosis, highlighting the need for early detection and intervention. Comprehensive management focusing on glycemic control, blood pressure, and lipid levels is crucial in preventing cardiovascular complications. Further research is necessary to understand the underlying mechanisms and to develop targeted therapies for this vulnerable population.

References

[1] K. Kawai, A.V. Finn, R. Virmani. (2023). Subclinical Atherosclerosis: Part 1: What Is it? Can it Be Defined at the Histological Level? Arteriosclerosis, Thrombosis, and Vascular Biology. 44(1): 12-23.

[2] S. Jebari-Benslaiman, U. Galicia-García, A. Larrea-Sebal, J.R. Olaetxea, I. Alloza, K. Vandenbroeck, A. Benito-Vicente, C. Martín. (2022). Pathophysiology of atherosclerosis. International journal of molecular sciences. 23(6): 3346.

[3] S. Mundi, M. Massaro, E. Scoditti, M.A. Carluccio, V.W. Van Hinsbergh, M.L. Iruela-Arispe, R. De Caterina. (2018). Endothelial permeability, LDL deposition, and cardiovascular risk factors—A review. Cardiovascular research. 114(1): 35-52.

[4] S.H. Han, S.J. Nicholls, I. Sakuma, D. Zhao, K.K. Koh. (2016). Hypertriglyceridemia and cardiovascular diseases: revisited. Korean circulation journal. 46(2): 135-144.

[5] J. Heeren, L. Scheja. (2021). Metabolic-associated fatty liver disease and lipoprotein metabolism. Molecular metabolism. 50: 101238.

[6] E. Wieczorek, A. Cwiklinska, A. Kuchta, B. Kortas-Stempak, Gliwi nska, A.; Jankowski, M. Decreased Efficiency of Very-Low-Density Lipoprotein Lipolysis Is Linked to Both Hypertriglyceridemia and Hypercholesterolemia, but It Can Be Counteracted by High-Density Lipoprotein. Nutrients 2021, 13, 1224. In s Note: MDPI stays neutral with regard to jurisdictional claims in published …: 2021.

[7] C.M. Barbagallo, A.B. Cefalù, A. Giammanco, D. Noto, R. Caldarella, M. Ciaccio, M.R. Averna, E. Nardi. (2021). Lipoprotein abnormalities in chronic kidney disease and renal transplantation. Life. 11(4): 315.

[8] P.L. Gordts, R. Nock, N.-H. Son, B. Ramms, I. Lew, J.C. Gonzales, B.E. Thacker, D. Basu, R.G. Lee, A.E. Mullick. (2016). ApoC-III inhibits clearance of triglyceride-rich lipoproteins through LDL family receptors. The Journal of clinical investigation. 126(8): 2855-2866.

[9] J. Borén, C.J. Packard, M.-R. Taskinen. (2020). The roles of ApoC-III on the metabolism of triglyceride-rich lipoproteins in humans. Frontiers in endocrinology. 11: 474.

[10] D. Goldberg, S. Khatib. (2022). Atherogenesis, transcytosis, and the transmural cholesterol flux: A critical review. Oxidative Medicine and Cellular Longevity. 2022(1): 2253478.

[11] I. Dib, A. Khalil, R. Chouaib, Y. El-Makhour, H. Noureddine. (2021). Apolipoprotein C-III and cardiovascular diseases: when genetics meet molecular pathologies. Molecular Biology Reports. 48: 875-886.

[12] M.N. Cerit, H.N. Şendur, B. Bolayır, E.T. Cerit, E. Cindil, M.Y. Aktürk, F.B. Törüner, S.Ö. Oktar. (2021). Evaluation of common carotid artery in type 1 diabetes mellitus patients through speckle tracking carotid strain ultrasonography. Diagnostic and Interventional Radiology. 27(2): 195.

[13] M. Mahdavi-Roshan, A. Salari, M. Doostdar-Sanaye. (2015). Brachial endothelial function and carotid intima-media thickness in patients with coronary artery disease. Archives of Advances in Biosciences. 6(4): 15-19.

[14] N.S. Elbarbary, E.A.R. Ismail, S.A. Mohamed. (2023). Omega-3 fatty acids supplementation improves early-stage diabetic nephropathy and subclinical atherosclerosis in pediatric patients with type 1 diabetes: A randomized controlled trial. Clinical Nutrition. 42(12): 2372-2380.