IDDM and vascular risk: A Meta-Analysis of current evidence based on Ultrasound measures of subclinical atherosclerosis

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Atheromatosis is a process initiating early in life, and progressing variably among individuals to produce end-point clinical events such as myocardial infarction and cerebrovascular attacks later in its course. Although pathological studies have proven the latter notion, imaging studies are often employed late in the course of the disease, to investigate an already established state of systemic atheromatosis marked by a defective vascular flow and the presence of plaques (1).

The recognition of factors contributing to the evolution of atheromatosis has led to a better understanding of the pathophysiology of the disease. Major predisposing factors include hypertension, hyperlipidemia, increased BMI, poor glycemic control, family history and genetics among others (2-4). Such factors have been collectively associated with the clinical end-points of the disease, such as myocardial infarction and stroke (5-7). However, the multifactorial nature of atheromatosis poses limitations on our ability to define clear associations of such factors - monitoring tools with the disease progression. The latter is the reason that measurements enabling us to estimate atheromatosis burden through the course of the disease and proceed to its management accordingly, would prove very significant in preventing cardiovascular diseases.

**CIMT and FMD MEASUREMENTS IN ATHEROSCLEROSIS**

Early detection of atheromatosis burden based on anatomical and physiological measurements is possible and radiological measures of subclinical atheromatosis such as Flow Mediated Dilation (FMD) and carotid Intima-Media Thickness (IMT) have been proved valuable independent tools in assessing the disease at an early stage of development. FMD and IMT have been extensively used for the assessment of atheromatic burden in adults and have been employed in large scale screening studies, however their utilization for the assessment and prevention of atheromatosis in children and adolescents is less evident in current literature (5-7).

FMD is a non-invasive measurement of the vasodilatory response of arteries, which is either endothelial-dependent or endothelial-independent, based on the method of vasodilation. The most common method of FMD assessment uses a blood pressure cuff to achieve occlusion of the vessel and measurements of its diameter are performed for up to five minutes after occlusion by Doppler Ultrasonography. A vasodilatory response based on nitric-oxide production causes an increase in the vessel diameter and serves as a tool for the assessment of impairment endothelial function based on the expected values for healthy people (6%-12%). The endothelial-independent response is measured by using Glycerin Trinitrate (GTN) to cause further vasodilation, in addition to the dilation of the previous technique and serves for the further assessment of vascular function and structure. FMD has been positively associated with early and late atheromatosis in studies involving both children and adults (8,9).
CIMT (Carotid intima-media thickness) is a method introduced by Pignoli et al. and is based on the linear distance perpendicular to the luminal axis, of the ultrasonic interfaces for the boundaries of the lumen-intimal and the median-adventitia surfaces of the carotid wall. The mean of various measurements and their maximal values provide a reference (mean CIMT and max IMT) for the thickness of the carotid wall in specific segments, [At the last 10-20 mm of the common carotid artery (CCA) towards the carotid bifurcation, 2) at the carotid bifurcation (or carotid bulb) and 10 mm proximal to that, 3) at the proximal 10 mm of the internal carotid artery (ICA)]. CIMT has been positively associated with the atheromatic burden of the vessel as well as with systemic atheromatosis and the risk of developing clinical CVD \(^{(5,6,10)}\).

**ATHEROMATOSIS ASSESSMENT IN IDDM**

High risk groups such as children with Insulin-Dependent Diabetes Mellitus (IDDM) could serve as good candidate groups for the implementation of FMD and cIMT as screening and monitoring tools for the progression of atheromatosis early in life as several studies suggest, however, the evidence on their use in children are not yet conclusive. As IDDM patients are concerned, such an approach could reveal valuable information on the progression of atherosclerosis, its correlation to known risk factors, and the effect of therapeutic measures taken in the course of the disease to prevent long-term complications \(^{(11,12)}\).

Based on the above, this study aims to not only to systematically review evidence but to provide data of high statistical significance on the association of IDDM and measurable accelerated atherosclerosis, through a meta-analysis of current evidence based on the use of FMD and cIMT in children and adults with IDDM. Through such associations this study aims to provide insights on the value of FMD and cIMT as screening and monitoring tools for groups of patients in high cardiovascular risk.
Methods and Materials

LITERATURE SEARCH - STUDY SELECTION

A web-based literature search on Pubmed, Web of Knowledge and Ovid Databases was performed using various combinations of relevant keywords. Keywords used included: FMD, IMT, endothelial function, cIMT, intima-media thickness, diabetes, children, IDDM, diabetes type 1.

Case-control studies on IDDM subjects were included only if they met the inclusion criteria. The latter were: a) Studies should be performed on human subjects, b) Measurement data on IMT and FMD should be provided including at least the mean, standard deviation and method of measurement, c) Studies should separate children from adults if performed in both groups, d) The study group should be coherent, including diabetes type 1 patients, or a clear subgroup division consisting only of diabetic patients should be included in the study. The studies selected were further subdivided in subgroups of studies, while in case of concerns in aspects of methodology and bias, analyses were reevaluated after subtracting low quality studies. An effort was also made to distinguish duplicated study populations and extract them from the final analyses.

The included studies were retrieved from databases and their data on mean and SD of cIMT and FMD measurements, on group characteristics (Male:Female ratio, Age, Diabetes Duration, LDL measurements, Blood pressure) were recorded. In certain studies the necessary data could be formulated from the provided data using statistical formulas.

DATA ANALYSIS

The data recorded on cIMT were converted from "mm" to 10µm units \(10^{-5}\) meters) to obtain a standard measurement unit and aid the graphic representation of revealed associations. CIMT measurements using the mean value of measurements in various segments of the carotid wall were recorded separately to measurements of the maximum int, and the same principle was used for measurements in different segments of the carotid (ICA, CCA, Bifurcation). Data on FMD were recorded as percentage values of the maximal brachial artery dilation following occlusion.

Meta-analyses of the available data were performed using Cochrane Revman 5.1 (Review Manager Version 5.1, Chochrane Collaboration, http://www.cc-ims.net/
Revman). A random-effects model of the available data was used, and the weighted mean differences were calculated according to the DerSimonian and Laird method (13). The results of the analysis were illustrated using forest plots produced by Revman 5.1. To assess heterogeneity between studies, we used the I^2 estimation produced by the Revman software, which indicates the percentage of variability that is present in the effect estimates that cannot be attributed to chance. For the same purpose, the P value of the chi-squared (x^2) test was used to validate the significance of heterogeneity or inconsistency described by the I^2 test. The publication bias by small studies was examined using the funnel plots produced by the Revman software (14).

Meta-regression analysis was performed using the SPSS v.7 statistical software.
Results

STUDY SELECTION RESULTS

Initially 566 studies were detected and 68 studies with 6927 total subjects were included. Further selection yielded 48 studies in the final analysis due to issues concerning data extraction and duplicated studies. The studies analyzed after the final selection included 4521 subjects. A flowchart of the study selection procedure is provided in Fig. 1 on page 8. A full table of the included studies and their population characteristics can be provided upon request but is not excibited due to the limitations of a poster presentation.

DATA ANALYSIS

Children with IDDM had increased mean cIMT (MD=30.1 µm [20.7, 41.3 95% CIs]; Overall effect (P<0.00001);Heterogeneity : I²=81%) after all relevant studies were included.

Correction for duplicated studies and studies of low quality yielded similar results : [MD=30.2 µm [19.2, 41.2 95% CIs]; Heterogeneity: Chi²= 114.4 df = 18 (P < 0.00001); I² = 84%, Test for overall effect: Z = 5.39 (P < 0.00001)] (Forest plot: Fig. 2 on page 8, Funnel plot: Fig. 3 on page 9).

Subgroup analyses were conducted using studies that provided detailed data on their methodology and were homogenous concerning the method of cIMT measurements. Subgroup analysis for studies that measured the mean of multiple measurements of the segment of ICA-IMT extending 1 cm above the carotid bifurcation yielded highly homogenous results: [MD=20.2 µm [11.3, 29.1 95% CIs]; Heterogeneity: Chi²=2.95, df = 6, (P = 0.82); I² = 0%, Test for overall effect: Z = 4.43 (P < 0.00001)] (Forest plot: Fig. 4 on page 10, Funnel plot: Fig. 5 on page 11).

Subgroup analysis for studies that measured the maximal cIMT or the mean of maximal cIMT measurements in various segments of the carotid was highly heterogenous: [MD=87.7 µm [33.8, 14.16 95% CIs]; Heterogeneity: Chi² = 92.65, df = 4, (P < 0.00001) I² = 96%, Test for overall effect: Z = 3.19 (P < 0.001)] .

Children FMD meta - analysis yielded positive association of IDDM with a lower FMD in children (MD=-3.15%[-3.84,-2.47 95% CIs]; Heterogeneity: Chi²=25.28, df = 10, (P =
CIMT measurements in adults showed similar associations [MD=100.31 (76, 132.2 95% CIs); Heterogeneity: \( \chi^2 = 160.75, df = 14, (P<0.00001); I^2=91\% \), Test for overall effect: \( Z = 7.27 (P < 0.00001) \)]. Subgroup analysis for maximum IMT measurements was also highly significant but included heterogeneity among studies: [MD=109.5 (93.3, 125.8 95% CIs); Heterogeneity: \( \chi^2=161.66, df = 3, P<0.00001 \); \( I^2=89\% \), Test for overall effect: \( Z = 13.21 (P < 0.00001) \) (Forest plot: Fig. 7 on page 12, Funnel plot: Fig. 8 on page 12).

Subgroup analysis was performed including only the studies measuring a segment of ICA-IMT extending 1 cm above the carotid bifurcation and yielded positive associations with less heterogeneity. [MD= 142.2 µm (115.1, 169.3 95% CIs); Heterogeneity: \( \chi^2 = 25.77, df= 6, (P = 0.0002) \); \( I^2 = 77\% \); Test for overall effect: \( Z = 10.29 (P < 0.00001) \)] (Fig. 9 on page 13).

FMD meta-analysis in adults revealed a lower FMD in adults with IDDM than controls: [MD=3.79 (-4.47, -3.10 95% CIs); Heterogeneity: \( \chi^2=106.34 (P < 0.00001) \) \( I^2 = 88\% \); Test for overall effect: \( Z = 10.81 (P < 0.00001) \)].

Meta-regression analyses revealed positive association of higher CIMT and lower FMD with the mean age of the patients group, the recorded duration of diabetes and LDL levels of the study group. However, such associations were unclear in the case of the "low heterogeneity" subgroup analyses.
Fig. 1: Study selection

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Fig. 2: Meta-analysis of studies measuring CIMT difference between children with IDDM and controls - Forest Plot. The statistical weight of each individual study is represented by the size of the corresponding square, while the 95% CIs are represented by the horizontal lines for each study and the width of the diamond for the pooled effect. The deviation of the pooled effect from the mean, reveals an increase (if it deviates to the right) or decrease (if it deviates to the left) of CIMT in IDDM patients in relation to controls. As the funnel plot reveals, CIMT is increased in IDDM patients compared to controls. The same representation is used in all subsequent forest plots.

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Fig. 3: Meta-analysis of studies measuring CIMT difference between children with IDDM and controls - Funnel Plot

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**Fig. 4:** Subgroup Meta-analysis of studies measuring CIMT 1cm above the carotid bifurcation (CHILDREN) - Forest Plot

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**Fig. 5:** Subgroup Meta-analysis of studies measuring CIMT 1cm above the carotid bifurcation - Funnel Plot

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**Fig. 6:** Meta-analysis of studies measuring FMD difference between children with IDDM and controls - Forest Plot

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**Fig. 7:** Meta-analysis of studies measuring CIMT difference between Adults with IDDM and controls - Forest Plot

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**Fig. 8**: Meta-analysis of studies measuring CIMT difference between Adults with IDDM and controls - Funnel Plot

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**Fig. 9**: Subgroup Meta-analysis of studies measuring CIMT 1cm above the carotid bifurcation (ADULTS) - Forest Plot

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Conclusion

DISCUSSION ON STATISTICAL FINDINGS

The evidence presented provide an insight to the association of IDDM status with lower FMD and higher CIMT in children and adults. These associations were higher in adult patients than in children, as expected due to the effects of age on FMD and CIMT but also as expected due to a prolonged effect of diabetes in vascular health (16-18).

The clarity of the associations presented however, is affected by the presence of heterogeneity in most of the analyses, most probably pertaining to issues such as inconsistency among the studied groups and among methodological approaches to measurements as well as publication bias.

Heterogeneity, as measured by the Chi$^2$ and I$^2$ tests is evident in most analyses, however it should be taken under consideration that when a large number of studies is included in a meta-analysis, these tests often have too much power in detecting heterogeneity (15). Based on the above, it can be said that subgroup analyses such as "CIMT in children with IDDM measured 1cm above the carotid bifurcation" yield exceptionally low heterogeneity, while "CIMT in adults with IDDM measured 1cm above the bifurcation" and "FMD in children with IDDM" analyses showed low or borderline heterogeneity when the degrees of freedom of the Chi$^2$ test and the I$^2$ test were taken under consideration. Thus such associations could be considered as more definitive than those revealed by the rest of the analyses. The lowest heterogeneity subgroup analysis reveals the significance of a consistent methodology of measurements among the combined studies.

The presence of publication bias is also evident in some of the analyses but not all, as it is revealed by the corresponding assymetrical funnel plots that in comparison to the one in fig.5 appear skewed due to a higher effect reported by smaller studies.

The random-effect model employed is considered as valid for the reduction of the effects of heterogeneity to the final outcomes, by including expected heterogeneity in the statistical analysis. However, results of subgroup analyses with high heterogeneity should be set under consideration for further investigation before considered as valid, despite their statistical significance.

SIGNIFICANCE OF FMD AND CIMT AS TOOLS FOR ATEROMATOSIS ASSESSMENT AND IDDM MANAGEMENT
The results of this analysis imply that current research reveals an association of FMD and CIMT with the presence of IDDM in children and adults. Based on the further association of these surrogate markers of subclinical atheromatosis with end-point clinical events such as stroke and myocardial infarction, it can be said that FMD and CIMT could prove as valuable tools in assessing IDDM patients through the course of their disease. Technical issues that limit the value of these tools due to low reproducibility can be overcome through the use of modern techniques to assess endothelial function and CIMT (18-22).

Large scale prospective studies following patients from childhood through adulthood have revealed cardiovascular risk factors with high credibility and some of these have been set as standards for the management of high-risk groups such as IDDM patients (18, 23). Such studies can further include radiological tools for the assessment of their subjects providing a valuable set of reference data on the progression of atheromatosis as measured non-invasively in specific groups of patients. The use of assessment methods such as FMD and CIMT could aid the clinicians in the management of IDDM patients and similar high risk groups throughout the course of the disease, limiting the emergence of cardiovascular diseases in these groups of patients.
References


children and adolescents with type 1 diabetes are influenced by physical activity", The Journal of Pediatrics, vol. 157, no. 4, pp. 533-539.


