JESIANA FERREIRA PEDROSA

CALCIFICAÇÕES NA AORTA TORÁCICA E NAS ARTÉRIAS CORONÁRIAS: ASSOCIAÇÕES COM OS FATORES DE RISCO CARDIOVASCULAR EM PARTICIPANTES DO ESTUDO LONGITUDINAL DE SAÚDE DO ADULTO (ELSA-BRASIL) EM MINAS GERAIS

Universidade Federal de Minas Gerais
Programa de Pós-Graduação em Saúde Pública
Belo Horizonte – MG
2020

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Volume final de Tese apresentada ao Programa de Pós-Graduação em Saúde Pública da Faculdade de Medicina da Universidade Federal de Minas Gerais, como requisito à obtenção do título de Doutor em Saúde Pública.

Orientadora: Professora Doutora Sandhi Maria Barreto
Coorientador: Professor Doutor Antonio Luiz Pinho Ribeiro

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JESIANA FERREIRA PEDROSA

Realizou-se, no dia 17 de fevereiro de 2020, às 14:00 horas, Sala 526, 5º andar, Faculdade de Medicina, da Universidade Federal de Minas Gerais, a defesa de tese, intitulada *CALCIFICAÇÕES NA AORTA TORÁCICA E NAS ARTÉRIAS CORONÁRIAS: ASSOCIAÇÕES COM FATORES DE RISCO CARDIOVASCULAR EM PARTICIPANTES DO ESTUDO LONGITUDINAL DE SAÚDE DO ADULTO (ELSA-BRASIL) EM MINAS GERAIS*, apresentada por JESIANA FERREIRA PEDROSA, número de registro 2016653595, graduada no curso de MEDICINA, como requisito parcial para a obtenção do grau de Doutor em SAÚDE PÚBLICA, à seguinte Comissão Examinadora: Prof(a). Sandhi Maria Barreto - Orientadora (UFMG), Prof(a). Antonio Luiz Pinho Ribeiro - Coorientador (UFMG), Prof(a). Andrea de Lima Bastos (UFMG), Prof(a). Márcio Sommer Bittencourt (USP), Prof(a). Murilo Foppa (UFRGS), Prof(a). Roberta Carvalho de Figueiredo (UFSJ).

A Comissão considerou a tese:

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Finalizados os trabalhos, lavrada a presente ata que, lida e aprovada, vai assinada pelos membros da Comissão.
Belo Horizonte, 17 de fevereiro de 2020.

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CALCIFICAÇÕES NA AORTA TORÁCICA E NAS ARTÉRIAS CORONÁRIAS: ASSOCIAÇÕES COM FATORES DE RISCO CARDIOVASCULAR EM PARTICIPANTES DO ESTUDO LONGITUDINAL DE SAÚDE DO ADULTO (ELSA-BRASIL) EM MINAS GERAIS

JESIANA FERREIRA PEDROSA

Tese submetida à Banca Examinadora designada pelo Colegiado do Programa de Pós-Graduação em SAÚDE PÚBLICA, como requisito para obtenção do grau de Doutor em SAÚDE PÚBLICA, área de concentração SAÚDE PÚBLICA.

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Realizou-se, no dia 20 de fevereiro de 2019, às 14:00 horas, Sala de videoconferência do Tele Saúde, ala oeste, 1º andar, Hospital das Clinicas, a apresentação do exame de qualificação da aluna **JESIANA FERREIRA PEDROSA**, número de registro 2016653595, intitulado *CALCIFICAÇÕES NA AORTA TORÁCICA E NAS ARTÉRIAS CORONÁRIAS: ASSOCIAÇÕES COM FATORES DE RISCO EM ADULTOS PARTICIPANTES DO ELSA-BRASIL*, perante a Comissão Examinadora composta pelos professores: Prof(a). Sandhi Maria Barreto - Orientador (UFMG), Prof(a). Antônio Luiz Pinho Ribeiro (UFMG), Prof(a). Jose Geraldo Mill (UFES), Prof(a). Rosa Weiss Telles (UFMG), Prof. Gabriel Assis Lopes do Carmo (UFMG). Terminada a apresentação, foi considerada:

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Belo Horizonte, 20 de fevereiro de 2019.

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DEDICATÓRIA

Aos meus amores, Ricardo, Daniel e Beatriz.

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“ Gratidão por nada ser em vão. Um passo de cada vez e a vida se torna evolução.”

Autor desconhecido

"*Somos do tamanho dos nossos sonhos e uma das maiores virtudes que possuímos é a capacidade de sonhar. Melhor ainda é a felicidade de realizá-los. Sonhe, busque, conquiste. Pois quem acredita, principalmente em si mesmo, sempre alcança.*"

Guimarães Júnior

PREFÁCIO

O interesse por estudar as calcificações na aorta torácica surgiu há 13 anos quando eu estava no primeiro ano da residência de radiologia aprendendo a analisar tomografias de tórax. As calcificações se destacavam tanto nas imagens que sempre foi a primeira coisa que eu enxergava. Elas estavam ali, disponíveis, gratuitas, facilmente detectáveis. Era possível definir a distribuição, localização, quantidade, densidade, volume, enfim, o que quiséssemos estudar sobre as calcificações na aorta era possível. Entretanto, todos os preceptores ensinavam a mesma frase para qualquer calcificação na aorta: "Presença de calcificações ateromatosas na parede da aorta. **Impressão diagnóstica: Ateromatose aórtica**". Era isso e pronto. Alguns diziam: "a presença de calcificações na aorta não tem significado, todo mundo tem com o envelhecimento." Eles não estavam totalmente errados, mas eu queria entender mais sobre a majestosa aorta que atravessa o tórax e o abdome e distribuí o sangue para o corpo todo.

Quando fui convidada para assumir as análises do escore de cálcio coronariano no ELSA-Brasil, agarrei a oportunidade com muita dedicação e responsabilidade. Tenho muito orgulho e alegria de dizer que participei de todas as etapas do "estudo tomográfico das calcificações vasculares do ELSA-Brasil em Minas Gerais". Elaboramos um Manual descrevendo os procedimentos, com os diálogos predefinidos para treinar os estagiários e prepará-los de forma muito cuidadosa para trabalharem diretamente com os participantes durante o agendamento dos exames, as entrevistas e as orientações pré, per e pós-exame. Descrevemos todo o protocolo de aquisição, processamento e armazenamento das imagens, documentamos a metodologia de análise das calcificações na aorta torácica, nas coronárias e nas carótidas, utilizando os softwares *Smart Score, Image J, Horos, Osirix e Carestream***.**

Foi durante este processo de planejamento do estudo que optamos por fazer um protocolo estendido do escore de cálcio para incluir o arco aórtico na aquisição tomográfica. O projeto foi maravilhoso, com uma equipe muito dedicada, responsável e que realmente trabalhava com prazer para atingir nossa meta de terminar as 2638 tomografias em um ano. De agosto de 2015 a agosto de 2016 conseguimos realizar todos os exames, analisar as imagens e entregar os resultados do valor final do escore de cálcio coronariano e de algum achado incidental que tenha aparecido nos exames para todos os participantes. Acompanhei de perto todos os processos e analisei todas as tomografias.

Contribuímos muito para a saúde dos nossos participantes, diagnosticamos tumores assintomáticos que puderam ser tratados, identificamos doença coronariana que pôde ser abordada antes de um evento agudo grave. Oferecemos oportunidades de treinamento para nossos alunos do Curso de Tecnologia em Radiologia e Medicina, e tivemos a felicidade de participar do crescimento deles como profissionais. Enfim, foram várias histórias gratificantes e que dão sentido a nossa vida de pesquisador, educador e profissional de saúde.

A análise das calcificações da aorta torácica foi realizada, num primeiro momento como uma única variável, incluindo a aorta ascendente, o arco aórtico e a porção descendente até a transição toracoabdominal. Foram vários os desafios na interpretação dos dados e comparação com os outros estudos de calcificações na aorta. Não havia padronização das análises, por isso sentimos a necessidade de escrever um artigo de revisão e que, por fim, despertou um interesse imenso de definir uma segmentação detalhada da aorta torácica, baseada nas descrições mais frequentes nas pesquisas, e de conhecer as calcificações por segmentos. Nossa questão era: “se há diferenças entre os territórios vasculares quanto a distribuição das calcificações vasculares, deve haver diferenças entre os segmentos da aorta, uma vez que cada segmento apresenta características hemodinâmicas, embriológicas e

estruturais bastante distintas.” Foi quando iniciamos a revisão das imagens para separar as calcificações por segmentos. Cumprimos com o nosso objetivo de estudar as calcificações na aorta torácica e ficamos muito felizes com todo o processo de evolução e amadurecimento da pesquisa durante cada etapa conquistada.

RESUMO

As calcificações na aorta torácica (TAC) e nas artérias coronárias (CAC) estão associadas com risco de doença cardiovascular (DCV) e morte. Entretanto, os fatores de risco associados às calcificações arteriais podem variar de acordo com o leito vascular. Verificamos se TAC estão associadas aos mesmos fatores de risco que CAC em adultos sem DCV estabelecida e, em seguida, averiguamos se existiam diferenças entre as associações dos fatores de risco para DCV com cada segmento da aorta torácica (porções ascendente, arco e descendente). Trata-se de estudo transversal, incluindo 2.433 participantes (entre 38 e 78 anos de idade) da coorte do ELSA-Brasil em Minas Gerais. Foram realizados exames de tomografia computadorizada multislice sincronizada com ECG para identificar cálcio na aorta torácica e nas coronárias (2015-2016). As associações tanto de CAC quanto de TAC, total e por segmentos, com os fatores de risco para DCV (tabagismo, índice de massa corporal [IMC], atividade física, uso excessivo de álcool, história familiar de DCV, LDL, HDL, HbA1c, níveis de pressão arterial, uso de medicamentos para hipertensão arterial, diabetes e hipolipemiantes) foram avaliadas através de regressão logística multivariada. A prevalência total de TAC e CAC foi de 69% e de 43%, respectivamente. A prevalência de CAC foi menor entre as mulheres (31%) do que entre os homens (56%). Após ajustes, negros apresentaram menor probabilidade de ter qualquer CAC comparado aos brancos. Nem sexo nem raça apresentaram associação significativa com TAC. O uso de medicamentos antidiabéticos permaneceu associado ao CAC, mas não ao TAC. Em relação ao estudo das associações entre os fatores de risco e cada segmento da aorta torácica, a prevalência das calcificações foi maior no arco (62%), seguido pelas porções descendente (31%) e ascendente (23%). Apesar da distribuição das calcificações ao longo da aorta ter sido heterogênea, não foram observadas diferenças

importantes entre as associações dos fatores de risco com cada segmento aórtico. Em nenhum segmento houve diferença estatisticamente significativa na prevalência das calcificações em homens e mulheres, ou entre a cor da pele/raça. O aumento da idade, os menores níveis de escolaridade, tabagismo, hipertensão arterial e IMC permaneceram associados a presença de cálcio em todos os segmentos estudados. Em conclusão, CAC e TAC apresentaram diferenças entre as associações com os fatores de risco, principalmente em relação ao sexo e a raça. Entretanto, a distribuição heterogênea das calcificações ao longo da aorta não determinou diferenças significativas entre as associações dos fatores de risco com cada segmento da aorta torácica.

Palavras-chave: Aorta Torácica - Vasos Coronários - Calcificação Vascular - Fatores de Risco

ABSTRACT

Thoracic aortic calcium (TAC) and coronary artery calcium (CAC) are associated with an increased risk of cardiovascular disease (CVD) and death. However, risk factors associated with arterial calcium may vary across vascular beds. We verified whether TAC is associated with the cardiovascular (CV) risk factors as is CAC in adults without established CVD, and compared the associations between the same risk factors to each segment of thoracic aorta (ascending, aortic arch, and descending portions). Cross-sectional analysis including 2,433 participants (aged 38 to 78 years) of ELSA-Brasil cohort in Minas Gerais. Nonenhanced ECG-gated multislice computed tomography were performed to detect calcium in the thoracic aorta and in the coronaries (2015 to 2016). Multivariate logistic regression evaluated the associations of both TAC, total and by segment, and CAC with CV risk factors (smoking, body mass index [BMI], physical activity, alcohol intake, family history of CVD, low-density lipoprotein- and high-density lipoprotein-cholesterol, HbA1c, blood pressure, antidiabetic, antihypertensive, and lipid lowering medications). Overall prevalence of TAC and CAC were 69% and 43%, respectively. CAC prevalence was lower among women (31%) than men (56%). After adjustments, black individuals were less likely to have any CAC as compared with whites. Neither sex, nor race/skin color were statistically associated with TAC. Use of antidiabetic medications remained associated with CAC, but not with TAC. Regarding to aortic segments, the higher prevalence of calcium was in the aortic arch (62%), followed by the descending (31%), and ascending portions (23%). Although the calcium distribution along the aorta is very heterogeneous, there were small differences between the associations of risk factors and each segment of thoracic aorta. There were no significant differences related to gender and race/skin color in any studied segment. Increasing age, lower

scholarities levels, smoking, arterial hypertension, and higher BMI remained associated with calcium in all segments. In conclusion, CAC and TAC had differences in the associations with risk factors, mainly related to gender and race/skin color. Moreover, the heterogeneous distribution of calcium along the aorta did not affected the associations between the cardiovascular risk factors and each segment, since the associations shared many similarities among the aortic segments.

Keywords: Thoracic Aorta - Coronary Vessels - Vascular Calcium - Risk Factors

LISTA DE ABREVIATURAS

AAC	Aortic Arch Calcium
ARC	Aortic Root Calcium
ARCH	Aortic arch
ATA	Ascending Thoracic Aorta
ATAC	Ascending Thoracic Aortic Calcium
AVC	Aortic Valve Calcium
BMI	Body Mass Index
CAC	Coronary Arteries Calcium
CAD	Coronary Artery Disease
CHD	Coronary Heart Disease
CT	Computed Tomography
CV	Cardiovascular
CVD	Cardiovascular Disease
DCV	Doença Cardiovascular
DTAC	Descending Thoracic Aortic Calcium
ECG	Electrocardiogram
EISNER	Early Identification of Subclinical Atherosclerosis by Noninvasive Imaging research
ELSA-Brasil	Estudo Longitudinal de Saúde do Adulto
FRFs	Framingham Risk Factors score
HbA1c	Hemoglobina A1c
HDL	High Density Lipoprotein
HU	Hounsfield Unity
IMC	Índice de Massa Corporal
LA	Liver Attenuation
LDL	Low Density Lipoprotein
MESA	Multi-Ethnic Study of Atherosclerosis
MetS	Metabolic Syndrome
MSCT	MultiSlice Computed Tomography
MVC	Mitral Valve Calcium
OR	Odds Ratio
PAT	Pericardial Adipose Tissue
SBP	Systolic Blood Pressure
SD	Standard Deviation
UH	Unidade de Hounsfield
SBP	Systoic blood pressure
TC	Tomografia Computadorizada

SUMÁRIO

1. APRESENTAÇÃO

O presente texto representa o volume final da Tese de Doutorado da aluna Jesiana Ferreira Pedrosa, intitulada: “Calcificações na aorta torácica e nas artérias coronárias: associações com os fatores de risco cardiovascular em participantes do Estudo Longitudinal de Saúde do Adulto (ELSA-Brasil) em Minas Gerais”. Esta Tese insere-se na linha de pesquisa *Epidemiologia das Doenças e Agravos não Transmissíveis e Ocupacionais* do Programa de Pós-Graduação em Saúde Pública da Faculdade de Medicina da Universidade Federal de Minas Gerais e integra o “Estudo Longitudinal de Saúde do Adulto” (ELSA-Brasil). A apresentação deste volume será no formato de Artigo Científico e consiste nas Considerações Iniciais, Objetivos, Métodos, Artigo de Resultados 1, Artigo de Revisão, Artigo de Resultados 2, Considerações Finais, Conclusões, Referências Bibliográficas, Apêndices e Anexos. O Artigo de Resultados 1 foi publicado na revista “The American Journal of Cardiology” em dezembro de 2019 e o Artigo de Revisão na “Current Atherosclerosis Reports” também no mês de dezembro de 2019. Os artigos publicados estão formatados conforme o restante do texto apresentado neste volume seguindo as recomendações da revista e foi anexada uma cópia das versões publicadas. O Artigo de Resultados 2 ainda não foi submetido.

2. CONSIDERAÇÕES INICIAIS

2.1 Epidemiologia da doença cardiovascular no Brasil e no mundo

A cardiopatia isquêmica e o acidente vascular cerebral são as maiores causas de morte no mundo. As duas doenças lideram como principais causas de morte há pelo menos 15 anos e foram responsáveis por cerca de 15,2 milhões de mortes no ano de 2016, o que correspondeu a 26,7% do total de mortes no mundo (WHO, 2018). No Brasil em 2016, ocorreram cerca de 1,3 milhões de mortes, sendo que as principais causas foram relacionadas às doenças do aparelho circulatório, responsáveis por 27,6% dos casos (SAÚDE, 2016). Os dados apresentados refletem a importância das doenças cardiovasculares (DCV) como principal causa de morte no Brasil e no mundo.

2.2 Fisiopatologia da Aterosclerose

A aterosclerose é uma doença inflamatória crônica que apresenta períodos cíclicos de atividade, variáveis em intensidade e duração entre os indivíduos (ROGNONI et al., 2015). Os mecanismos patogênicos da aterosclerose não são completamente definidos, sendo abordados através de hipóteses. As hipóteses clássicas continuam apresentando valor importante enquanto novas hipóteses vem sendo agregadas às anteriores, como as hipóteses da aterosclerose se tratar de um processo trombótico, inflamatório, dismetabólico e, mais recentemente, infeccioso, o que, dependendo das combinações possíveis destes diferentes processos, resulta em uma doença multifatorial (HAJJAR, 1991; MUNRO; COTRAN, 1988). Em outras palavras, um indivíduo pode apresentar placas ateroscleróticas em diferentes fases, com graus variáveis de inflamação, com graus de ativação diferentes das células inflamatórias, com diferentes composições da placa, com efeitos diferentes sobre os tecidos e órgãos envolvidos (ROGNONI et al., 2015).

A aterosclerose se inicia na infância e progride de estrias gordurosas a lesões elevadas em adolescentes e adultos jovens, evoluindo para ateroma maduro e lesões complexas mais tarde na vida adulta (ALLISON; CRIQUI; WRIGHT, 2004). No estudo MESA (*Multi-Ethnic Study of Atherosclerosis*), um terço dos indivíduos com menos de 50 anos não apresentaram calcificação em nenhum leito vascular, enquanto todos os participantes com mais de 70 anos tinham calcificação em pelo menos um território vascular. Patologicamente pode-se reconhecer as seguintes fases de evolução da aterosclerose (FILHO, 2016):

- Estrias lipídicas: primeira lesão visível da aterosclerose. Podem progredir e evoluir para ateromas ou estacionar. Microscopicamente, há acúmulo de células gordurosas, conhecidas como “espumosas” ou “xantomatosas”, que representam macrófagos ou células musculares lisas repletas de lipídeos na camada íntima da parede arterial. Vide Figura 1a.

- Placas ateroscleróticas (ateromas): representam a evolução das estrias lipídicas e são compostas por: lipídeos, células musculares lisas e macrófagos, e matriz de tecido conjuntivo que contem trombos em várias fases de organização (CAMPBELL et al., 1989). As lesões apresentam formas e tamanhos variados, às vezes confluentes, localizadas na íntima e que fazem saliência para a luz arterial. Normalmente, as placas são excêntricas, localizadas apenas em parte da circunferência do vaso. Ao microscópio, observa-se quantidade variada de células, matriz extracelular e lipídeos, que podem estar no espaço intra ou extracelular. Abaixo do endotélio, forma-se uma capa fibrosa, composta por fibras colágenas e células musculares lisas. A região central apresenta um núcleo necrótico formado por lipídeos, células espumosas, leucócitos e restos celulares. Vide Figura 1b. Nas margens da lesão, ocorre neoformação vascular. Neste estágio, podem ser identificados dois tipos de placas, dependendo dos elementos que predominam em seu interior:

1) placas “instáveis” – ricas em componentes lipídicos, restos celulares e leucócitos. A medida que a lesão cresce como placas moles, com maior conteúdo lipídico extracelular, a capsula fibrosa afina progressivamente, tornando a placa mais vulnerável a ruptura (BJORKERUD, 1996). Vide Figura 2a.

2) placas “estáveis” – compostas por tecido fibroso denso e pouco conteúdo lipídico. Portanto, é uma placa que não apresenta sangramento, ulceração ou trombose (ROGNONI et al., 2015). Vide Figura 2b.

- Placas complicadas: são placas que sofreram erosão ou ulceração do revestimento endotelial, com consequente formação de trombo. Se a placa provoca um grau significativo de estenose e não há circulação colateral suficiente, esta lesão resulta na síndrome coronariana aguda. Após a fase aguda, o trombo formado sobre a lesão ulcerada se organiza, podendo calcificar ou fibrosar, gerando uma lesão estenótica crônica (MORENO et al., [s.d.]).

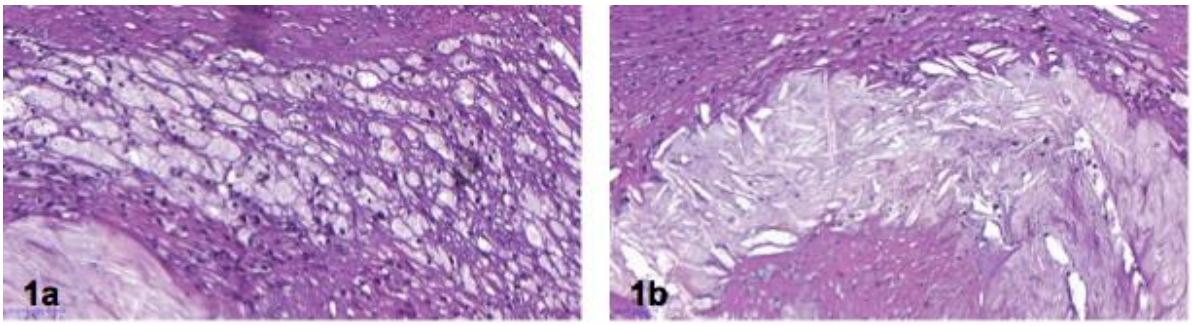


Figura 1a: estria lipídica - lâmina de parede arterial com aumento de 40x, destacando as células espumosas. **Figura 1b:** ateroma - lâmina de parede arterial com aumento de 30x, mostrando os cristais de colesterol em forma de fenda no interior da placa (*Imagens gentilmente cedidas pelos professores Geraldo Brasileiro Filho e Cristiana Buzelin Nunes do Departamento de Anatomia Patológica da Faculdade de Medicina da UFMG).*

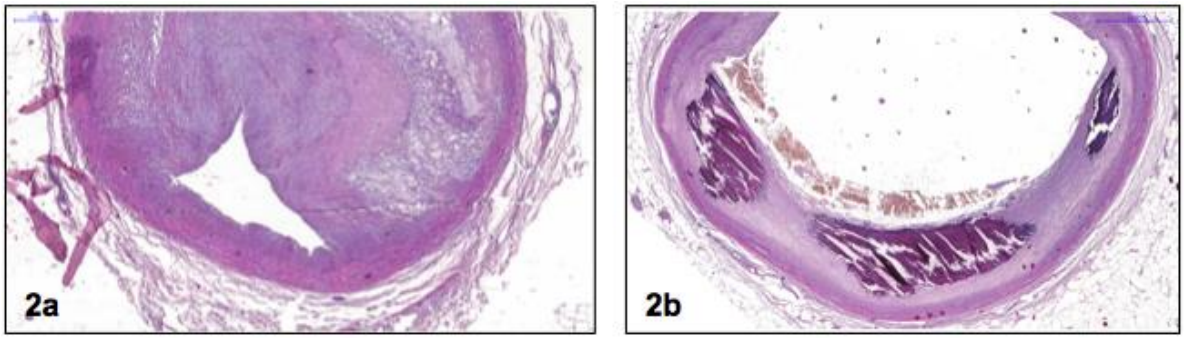


Figura 2a: placa instável - lâmina de corte transverso de artéria de médio calibre com aumento de 7x, apresentando enorme placa ateromatosa que reduz significativamente a luz do vaso. **Figura 2b:** placa estável - lâmina de corte transverso de artéria de médio calibre com aumento de 6x, mostrando placa predominantemente calcificada. A calcificação é corada pela hematoxilina e sofre fragmentação no preparo da lâmina. Podem-se observar três áreas de calcificação nesta lâmina (*Imagens gentilmente cedidas pelos professores Geraldo Brasileiro Filho e Cristiana Buzelin Nunes do Departamento de Anatomia Patológica da Faculdade de Medicina da UFMG).*

A aterosclerose afeta preferencialmente certas áreas do sistema arterial (ROGNONI et al., 2015). O processo inflamatório parece ser iniciado ou estimulado por dano endotelial, o qual pode ocorrer devido a presença de fluxo sanguíneo turbulento ou não laminar e que inibe a produção endotelial de óxido nítrico, potente anti-inflamatório e vasodilatador (ARBUSTINI et al., 1991). Os fatores de risco para aterosclerose (dislipidemia, hipertensão arterial, tabagismo, diabetes), estressores oxidativos, angiotensina II, infecção sistêmica e inflamação também inibem a produção de óxido nítrico e estimulam a produção de moléculas de adesão a leucócitos, citocinas pró-inflamatórias, proteínas quimiotáxicas e vasoconstritores (ROGNONI et al., 2015). O efeito conjunto destas substâncias provoca a migração de monócitos e células T para o espaço subendotelial, disparando e perpetuando a resposta inflamatória local.

A calcificação vascular ocorre por meio de processo ativo, complexo, organizado, e regulado, que é semelhante a formação de tecido ósseo (ZHU et al., 2012). Os macrófagos presentes na placa liberam citocinas pró-inflamatórias capazes de promover diferenciação

osteogênica (ZHU et al., 2012). A calcificação pode ser formada na camada íntima ou na média, porém as duas apresentam patogênese e consequências clínicas distintas (WANG et al., 2018). A calcificação na camada íntima (aterosclerótica) relaciona-se aos processos de desenvolvimento da placa no endotélio, com risco de ruptura e eventos tromboembólicos subsequentes. Por outro lado, a calcificação na camada média (arteriosclerótica) está relacionada a alterações em células musculares lisas e fibras elásticas, responsáveis por regular o fluxo sanguíneo e a pressão arterial (ZHU et al., 2012). Consequentemente, a calcificação da média causa rigidez arterial, redução da complacência e limitação da distensibilidade do vaso (MITCHELL, 2008). Enquanto as calcificações nas artérias coronárias ocorrem predominantemente na camada íntima, na aorta as calcificações ocorrem tanto na camada íntima quanto na média, portanto, na aorta a calcificação pode ser resultado de um processo aterosclerótico e não aterosclerótico (ABRAMOWITZ et al., 2015; DOHERTY et al., 2004). Porém, a distinção entre as calcificações da íntima e da média só é possível através da análise histológica, não sendo possível sua diferenciação por meio de tomografia computadorizada (WANG et al., 2018).

2.3 Tomografia computadorizada na avaliação da calcificação vascular

Em 1979, Cormack e Hounsfield, apesar de não se conhecerem e não terem formação ou interesse na área médica, receberam o prêmio Nobel em Física e Medicina pela criação da tomografia computadorizada axial, o maior avanço na radiologia médica desde a descoberta dos Raios-X em 1895 (GOODMAN, 2010). Os equipamentos de tomografia computadorizada (TC) passaram por várias fases de aprimoramento até os dias atuais. Em 1989, foram desenvolvidos os tomógrafos de quarta geração, capazes de adquirir imagens

de forma helicoidal, sem espaçamento entre os cortes tomográficos, o que representou um grande avanço na aquisição das imagens.

Por ser um método que utiliza radiação ionizante para a formação da imagem, a TC apresenta maior resolução espacial e maior capacidade de discriminar estruturas com densidade de cálcio se comparada com outros métodos de diagnóstico por imagem, como a ressonância magnética. Devido a maior sensibilidade para identificar a presença de cálcio, a TC é o método de imagem de escolha para avaliar as calcificações vasculares. As principais vantagens da TC estão relacionadas ao fato de ser um método não invasivo, rápido e sem necessidade de meio de contraste. A única desvantagem da TC está relacionada a dose de radiação utilizada, porém novos equipamentos têm sido desenvolvidos para realizar exames com doses muito baixas de radiação e já estão disponíveis em vários Centros de Diagnóstico por Imagem, inclusive no Brasil.

De acordo com as dimensões da calcificação vascular, ela pode ser classificada como microcalcificação e macrocalcificação, tendo como ponto de corte 50 micrômetros de diâmetro (KELLY-ARNOLD et al., 2013). A detecção de microcalcificação não é possível através dos equipamentos de TC atuais, que são capazes de identificar calcificações com no mínimo 200 micrômetros de diâmetro (RITMAN, 2007). As placas instáveis, com maior risco de ruptura são aquelas sem calcificação (com resposta inflamatória intensa) e com microcalcificações, as quais aumentam o estresse mecânico sobre a superfície fibrosa da placa (KELLY-ARNOLD et al., 2013). Entretanto, a TC detecta apenas as macrocalcificações que estão associadas a placas estáveis e com menor risco de ruptura (WANG et al., 2018).

Ainda que seja capaz de detectar apenas macrocalcificações, a avaliação tomográfica das calcificações em vários territórios vasculares despontou nos últimos anos como importante marcador de aterosclerose e do risco de eventos cardiovasculares (JACOBS et al., 2010). Sabe-se que um indivíduo pode apresentar placas ateroscleróticas em diferentes fases de gravidade, com espectro variável do processo inflamatório, em diferentes graus de ativação das células inflamatórias, compostas por substâncias diferentes e em concentrações distintas e com efeitos diferentes de acordo com o tecido ou órgão acometido (ROGNONI et al., 2015). Desta forma, a avaliação tomográfica das calcificações serve como marcador da extensão da aterosclerose e tem valor preditivo para eventos cardiovasculares e mortalidade (ALLISON et al., 2012; JOSHI et al., 2016).

A progressão da placa ocorre de forma assintomática, com risco de ruptura abrupta, e subsequente oclusão arterial trombótica (WANG et al., 2018). Portanto, a identificação da calcificação aterosclerótica através da TC pode contribuir na identificação mais precoce dos indivíduos com maior risco de DCV e no planejamento das medidas preventivas.

2.4 Calcificação nas artérias coronárias

Em 1990, Agatston descreveu um método de quantificação da calcificação nas artérias coronárias (CAC) através da TC (AGATSTON et al., 1990). O exame não necessita de meio de contraste e é sincronizado com o eletrocardiograma (ECG) para permitir que as imagens cardíacas não sofram artefatos relacionados aos batimentos cardíacos. O método de Agatston continua sendo amplamente utilizado e tem se expandido para a quantificação de calcificação em outros territórios vasculares (ONG et al., 2014; YEBOAH et al., 2014). Apesar dos escores que consideram o volume ou a massa de cálcio apresentarem melhor reprodutibilidade, os grandes bancos de dados populacionais que descrevem a distribuição

da CAC de acordo com a idade, etnia e sexo dos pacientes, são baseados no escore de Agatston e, portanto, esse é o mais utilizado na prática clínica (AZEVEDO; ROCHITTE; LIMA, 2012).

O cálculo da quantidade de CAC segundo o método de Agatston se baseia na densidade tomográfica (Unidade de Hounsfield – UH) que representa o tom de cinza de cada pixel da imagem tomográfica. Calcificação é definida como uma lesão hiperatenuante, com densidade acima de 130 unidades de Hounsfield (HU) e área ≥ 3 pixels adjacentes (pelo menos 1 mm^2) (AGATSTON et al., 1990). Cada lesão é calculada pelo produto da área de pixel (mm^2) por um fator de ponderação da densidade tomográfica das lesões que varia de 1 a 4 da seguinte forma: "1" se a densidade do pixel estiver entre 130 e 199 UH, "2" se entre 200 e 299 UH, "3" se entre 300 e 399 UH e "4" se ≥ 400 UH) (AGATSTON et al., 1990). O escore final é o resultado da soma das lesões calcificadas nos territórios das artérias coronária direita, tronco coronariano esquerdo, descendente anterior e circunflexa.

Lesão = área da calcificação (mm^2) x fator de ponderação da densidade (varia de 1 a 4)
ESCORE DE AGATSTON = Soma das lesões calcificadas

O escore de CAC é um método robusto, reprodutível e que demonstra, de forma não invasiva, a carga aterosclerótica nas artérias coronárias (BUDOFF et al., 2006). O escore de CAC se estabeleceu como o mais forte preditor de doença arterial coronariana (DAC) em pacientes assintomáticos, superando e demonstrando valor aditivo aos escores de risco tradicionais tal como o Escore de Risco de Framingham (DETRANO et al., 2008). Polonsky e colaboradores (2010) avaliaram 5878 participantes do estudo MESA (*Multi-Ethnic Study of Atherosclerosis*) e mostraram que, após um seguimento médio de 5,8 anos, a adição do escore de CAC a um modelo de predição de risco baseado nos fatores de risco tradicionais

resultou em melhora significativa da classificação de risco para a predição de DCV em diferentes grupos étnicos, em homens e mulheres (POLONSKY et al., 2010). Neste estudo, os indivíduos com risco cardiovascular intermediário foram os que obtiveram o maior benefício com o uso do escore de CAC para reclassificação de risco.

Resultados semelhantes aos do MESA foram obtidos nas coortes de Rotterdam, e Heinz Nixdorf (ELIAS-SMALE et al., 2010; ERBEL et al., 2010). Recentemente, Yeboah e colaboradores 2012 avaliaram o impacto adicional de diversos novos marcadores de risco no prognóstico determinado pelo escore de Framingham e após um seguimento mediano de 7,6 anos, o escore de CAC se associou de forma independente com DCV incidente e determinou o maior aumento da área sob a curva ROC (receiver operator characteristic curve) comparativamente à história familiar de doença coronariana, espessura médio-intimal carotídea, proteína-C-reativa e vasodilatação endotelial (YEBOAH et al., 2012). Ainda, em revisão sistemática que incluiu 13 estudos e mais de 29.000 pacientes, com seguimento médio de 50 meses, a incidência de eventos cardiovasculares em indivíduos com o escore de CAC = 0 foi igual a 0,47%, o que demonstra um excelente prognóstico na ausência de calcificações coronarianas em indivíduos assintomáticos (SARWAR et al., 2009).

2.5 Calcificação na aorta torácica

Os primeiros estudos que avaliaram a calcificação na aorta como preditor de mortalidade cardiovascular, avaliavam as calcificações através da radiografia simples, seja de tórax ou de abdome. Em 1986, Witteman *et al.* publicaram um artigo no Lancet sobre um estudo de coorte realizado na Holanda no qual avaliaram a presença de calcificação na aorta abdominal através de radiografias da coluna lombar dos participantes (WITTEMAN et al., 1986). No mesmo ano, Takeda *et al.* no Japão, publicaram um estudo utilizando tomografias

de abdome de pacientes com tumores malignos abdominais, primários ou metastáticos, e descreveram um método para quantificar as calcificações na aorta no nível das vértebras T11 e T12 nos cortes axiais da tomografia, cujos equipamentos ainda não eram capazes de realizar aquisições helicoidais (SHUMPEI TAKEDA; MATSUZAWA, 1986).

O valor preditivo do escore de calcificação na aorta torácica (TAC), o qual pode ser adicionalmente identificado nas mesmas imagens tomográficas do escore de CAC, não está bem estabelecido (BUDOFF et al., 2011). O estudo de Santos (2010) mostrou que a presença de TAC está associada a todas as causas de mortalidade e esta relação foi independente dos fatores de risco tradicionais para DCV e da presença de CAC (SANTOS et al., 2010). Já o estudo de Jacobs *et al*. (2010) evidenciou que a CAC é um preditor mais forte do que a TAC para todas as causas de mortalidade e para eventos cardiovasculares em uma população de tabagistas pesados, porém a TAC está mais associada a eventos não-cardíacos do que a CAC (JACOBS et al., 2010). O estudo de Budoff *et al*. (2011) indicou que a presença de TAC, independente da presença de CAC, é um preditor significativo de eventos coronarianos futuros apenas em mulheres (BUDOFF et al., 2011).

Em 2013, Kälsch e cols. demonstraram que a TAC apresentou maior prevalência que a CAC e compartilha com estes inúmeros fatores de risco cardiovascular. Porém, os autores sugerem mais estudos para investigar se a presença e a extensão da TAC alteram a relação já estabelecida entre os eventos coronarianos, o escore de CAC e os fatores de risco com a incidência e a mortalidade por DCV (KÄLSCH et al., 2013).

Craiem e cols., em 2014, questionaram a metodologia de aquisição das imagens para a quantificação da TAC, tradicionalmente realizada por meio das imagens tomográficas do escore de CAC, as quais não incluem o arco aórtico (CRAIEM et al., 2014). Neste estudo,

foi proposta a inclusão de todo o arco aórtico na avaliação da aorta torácica, estendendo um pouco os cortes do escore de CAC, para a investigação da prevalência e da distribuição espacial da calcificação ao longo de toda a aorta torácica. A conclusão do estudo foi que o arco aórtico e a porção proximal da aorta descendente, normalmente não avaliadas, concentram a maior quantidade de calcificação e que as mulheres de meia idade são mais propensas a apresentar calcificação nestes segmentos, tornando-as candidatas a reclassificação do risco cardiovascular (CRAIEM et al., 2014).

Recentemente, estudos do MESA têm mostrado que tanto a presença quanto a progressão de cálcio no arco aórtico estão associadas a fatores de risco cardiovascular, bem como à síndrome metabólica, ao diabetes e à doença coronariana (KATZ et al., 2016; TISON et al., 2015; YOUSSEF et al., 2015). Apesar de promissor, poucos estudos avaliaram o potencial preditivo do escore de cálcio no arco aórtico vis a vis em outros sítios.

2.6 Fatores de risco cardiovascular

As lesões da aterosclerose resultam da interação de fatores constitucionais (regulados geneticamente), de componentes ambientais e de agressões diversas (FILHO, 2016). Entretanto, a presença de apenas um destes fatores não é suficiente para produzir lesão aterosclerótica (ROGNONI et al., 2015). São considerados fatores de risco todas as condições que contribuem para a alteração da integridade e do funcionamento do endotélio, afetando a camada íntima vascular. Os fatores de risco tradicionais e amplamente estudados na literatura mundial são:

- Fatores genéticos: Muitos polimorfismos alélicos e variações de genes normais relacionadas com a aterogênese tem sido identificados na população em geral, assim como alterações genéticas envolvidas no metabolismo lipídico, nos fatores de coagulação e

fibrinogênio, responsáveis pelo aumento da trombogenicidade, na via renina-angiotensina, associada a hipertensão arterial e a doença coronariana (CHEN et al., 2007).

- Gênero: Sabe-se que estrógenos interferem no metabolismo lipídico e modulam a resposta inflamatória e que células musculares lisas da camada média de artérias possuem receptores de estrógeno e atuam como vasodilatadores (FILHO, 2016). Estudos mostram maior prevalência de CAC em homens, entretanto os achados para o TAC em relação às diferenças entre os sexos ainda são controversos (NASIR et al., 2007).

- Dislipidemia: Nas últimas décadas, o uso de estatinas, que inibem a síntese de colesterol no fígado e possuem ação anti-inflamatória, reduziu consideravelmente os danos da aterosclerose (FILHO, 2016). As lipoproteínas de baixa densidade (LDL) transportam o colesterol para as células do corpo, dessa forma o aumento do nível sérico dessas substâncias está diretamente associado ao aumento do risco de aterosclerose. De forma inversa, o aumento das lipoproteínas de alta densidade (HDL), que fazem o transporte do colesterol das células para o fígado, onde é excretado pela bile, reduz o risco de DCV.

- Hipertensão arterial: atua através de fatores genéticos, alteração em genes que produzem moléculas que estimulam a proliferação de células musculares lisas, e fatores hemodinâmicos (SCHWARTZ; REIDY, 1987). A elevação da pressão arterial aumenta o tônus muscular, estimula a proliferação de células musculares lisas e causa agressão mecânica ao endotélio, principal fator desencadeante da lesão ateromatosa (SCHULMAN; ZHOU; RAIJ, 2006).

- Tabagismo: está associado a agressão direta do endotélio por várias substâncias tóxicas presentes na fumaça do cigarro. Provoca aumento da viscosidade do sangue, da reatividade das plaquetas e da coagulação do sangue. Os radicais livres contidos na fumaça

aumentam a oxidação de LDL, lesivo para o endotélio e quimiotático para os leucócitos, amplificando o processo de agressão endotelial (FILHO, 2016).

- Diabetes: muitas vezes está associado a síndrome metabólica. A hiperglicemia forma produtos da glicosilação avançada (AGE), que se ligam a receptores (RAGE) em macrófagos, linfócitos T, endotélio e células musculares lisas, o que provoca liberação de citocinas pró-inflamatórias, fatores de crescimento e radicais livres, substâncias responsáveis pela oxidação de ácidos graxos, com consequente dano endotelial (FILHO, 2016).
- Obesidade: o excesso de tecido adiposo e o infiltrado de macrófagos nestes tecidos pode provocar a secreção desregulada de adipocitocinas, levando a redução dos níveis de adiponectina e aumento dos níveis de IL-6, com consequente aumento da resistência à insulina e inflamação crônica, fatores importantes na patogênese da aterosclerose (ONG et al., 2014). Além disso, a obesidade abdominal também está associada a outros fatores de risco como a dislipidemia, hemodinâmica cardíaca alterada, disfunção endotelial, estresse oxidativo sistêmico, os quais estão envolvidos na patogênese da aterosclerose coronariana calcificada (MARINOU et al., 2010).

Atualmente tornou-se popular, divulgado em revistas leigas e páginas eletrônicas, os escores de risco para DCV e outras doenças (LOTUFO, 2008). O mais utilizado e já popularizado foi o escore originado no *Framingham Heart Study*. Porém, apesar de serem úteis em práticas de prevenção de DCV, nenhum deles foi validado para a população brasileira (LOTUFO, 2008).

2.7 Estudo Longitudinal de Saúde do Adulto – ELSA/Brasil

O presente projeto faz parte do Estudo Longitudinal de Saúde do Adulto (ELSA-Brasil) que é uma coorte, multicêntrica e multidisciplinar, cuja população é constituída por servidores efetivos de seis instituições públicas de ensino superior e pesquisa (UFBA, UFES, UFMG, UFRGS, USP e FIOCRUZ), com idade entre 35 a 74 anos na linha de base em 2009. A pesquisa tem como objetivo principal investigar a incidência e os fatores de risco para doenças crônicas, incluindo as cardiovasculares e metabólicas em adultos brasileiros (AQUINO et al., 2012; SCHMIDT et al., 2015).

Em 2015, o Centro de Investigação (CI) do ELSA-Brasil em Minas Gerais incorporou o exame tomográfico para identificação de calcificação em diferentes sítios arteriais, com a intenção de contribuir na predição e na progressão das DCV. O ELSA-Brasil é financiado pelo Ministério da Saúde (Departamento de Ciência e Tecnologia), pelo Ministério da Ciência, Tecnologia e Inovação (FINEP - Financiadora de Estudos e Projetos) e CNPq (Conselho Nacional de Desenvolvimento Científico e Tecnológico).

3. OBJETIVOS

3.1 Objetivo geral:

Fazer uma revisão da literatura sobre o estudo da calcificação na aorta torácica (TAC) e comparar as associações entre os fatores de risco cardiovascular e a presença de TAC, total e por segmentos, e nas artérias coronárias (CAC) dos participantes do Estudo Longitudinal de Saúde do Adulto (ELSA-Brasil) em Minas Gerais.

3.2 Objetivos específicos:

- Rever as metodologias utilizadas na avaliação de TAC em estudos recentes.

- Avaliar a prevalência de TAC, total e por segmentos, e de CAC em participantes do ELSA-Brasil em Minas Gerais.

- Comparar as características da população de acordo com a presença e a ausência de TAC, total e por segmentos, e de CAC.

- Verificar se a presença de TAC total está associada aos mesmos fatores de risco cardiovascular que a presença de CAC.

- Verificar se há diferenças entre os segmentos da aorta torácica em relação aos fatores de risco cardiovascular associados a cada um deles.

3.3 Hipóteses:

- As prevalências de TAC, total e por segmentos, e CAC aumentam com a idade e são maiores em homens do que em mulheres até a menopausa.

- A prevalência de TAC é maior do que a prevalência de CAC para todas as faixas etárias e em ambos os sexos.

- A prevalência de TAC no arco aórtico é maior do que nos demais segmentos da aorta torácica.

- TAC e CAC estão associadas aos mesmos fatores de risco cardiovascular.

4. MÉTODOS

4.1 Delineamento

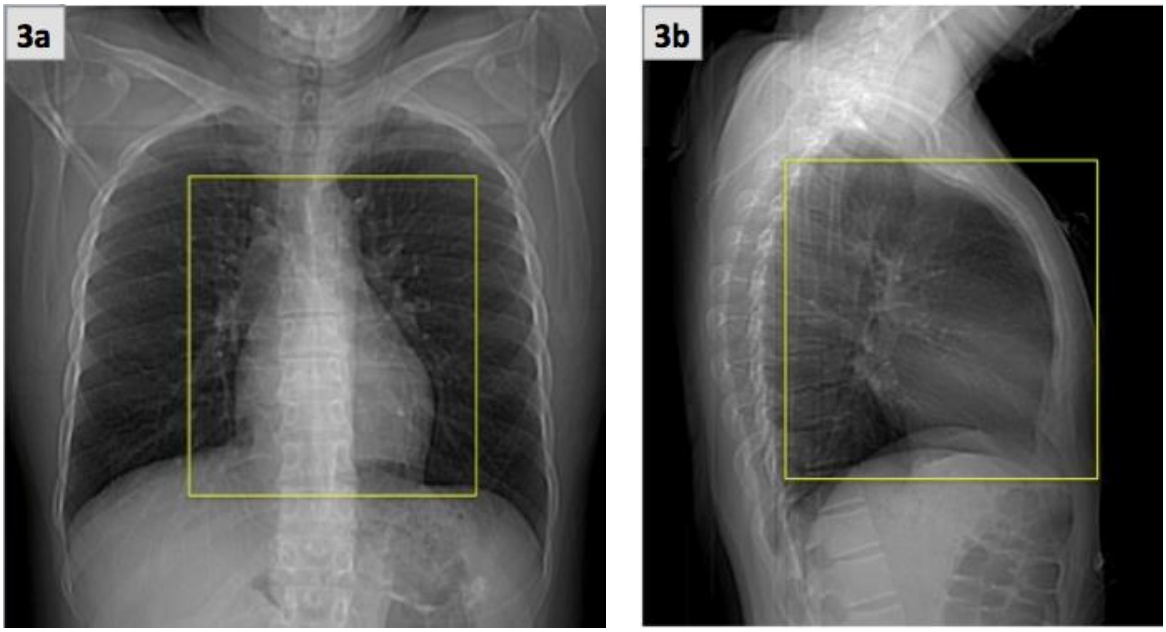
Trata-se de estudo transversal que utilizou dados epidemiológicos e clínicos dos 2.923 participantes incluídos na segunda onda de exames e entrevistas realizada no Centro de Investigação do ELSA-Brasil em Minas Gerais entre 2012-2014 e que realizaram os exames tomográficos para identificação de calcificação nas artérias coronárias (CAC) e na aorta torácica (TAC) no Centro de Tecnologia em Imagem Molecular da Faculdade de Medicina da UFMG entre 2015-2016.

4.2 População de estudo

Dos 2.923 participantes que concluíram a segunda onda de exames e entrevistas do ELSA-Brasil em Minas Gerais, 285 indivíduos não puderam realizar o exame tomográfico. Os critérios de exclusão previamente definidos foram gravidez; puerpério inferior a seis meses; radioterapia atual; exposição ocupacional à radiação ionizante; uso de marcapasso; presença de stent cardíaco, clip cirúrgico metálico intracraniano ou qualquer tipo de metal na região do coração, pescoço e crânio. No total, 2.638 participantes (90,2%) assinaram o termo de consentimento livre e esclarecido e realizaram a tomografia computadorizada (TC). Para o presente estudo, ainda foram excluídos os participantes cujo protocolo tomográfico não era suficiente para analisar a TAC e a CAC (142 exames) e aqueles com diagnóstico autorreferido de DCV [infarto agudo do miocárdio (n=15), insuficiência cardíaca congestiva (n=21), acidente vascular cerebral (n=24) e cirurgia cardíaca (n=13)]. Portanto, foram incluídos na análise 2.433 participantes (92,2% dos elegíveis).

4.3 Tomografia computadorizada

Todas as tomografias foram realizadas no Centro de Tecnologia em Imagem Molecular (CTMM) da Faculdade de Medicina da UFMG em equipamento de PET-CT *Discovery 690 (D-690)* da fabricante General Eletric (*GE*). O aparelho de tomografia que compõe o *D-690* é o *LightSpeed VCT* com 64 canais. Todos os participantes foram submetidos ao exame de TC sem o uso de meio de contraste, com sincronização do eletrocardiograma (ECG) e aquisição prospectiva a 70% do ciclo cardíaco. A varredura se estendeu de cerca de 1 cm acima do arco aórtico até a transição toracoabdominal, no ápice do coração, vide escanograma apresentado na figura 1. A quantidade de imagens axiais geradas em cada exame variou de 56 a 88. Os cortes foram de 2,5 mm de espessura, com 120 kVp e 100 mAs, utilizando algoritmo de reconstrução para partes moles (*Body Filter*). Para a realização do exame, foram colocados três eletrodos removíveis no tórax para a conexão do (ECG). O participante foi instruído a realizar uma apneia inspiratória de cerca de 8-12 segundos durante a aquisição das imagens, as quais eram transferidas para uma estação de trabalho dedicada (*ADW 4.5 da GE*) e para o servidor de imagens (*PACS*). A média calculada da dose de radiação efetiva foi de 1,75 mSv.



Figuras 3a e 3b: Escanograma. Imagens de referência nas incidências frontal e lateral para programação dos cortes tomográficos. A área de estudo se restringe ao interior dos retângulos amarelos destacados nas imagens.

4.4 Análise tomográfica da TAC e do CAC

Todas as tomografias foram realizadas no mesmo equipamento e analisadas por uma única radiologista, com 10 anos de experiência em imagem do tórax, e cega para as informações clínicas do participante. As calcificações de toda aorta torácica e das coronárias foram identificadas e selecionadas corte a corte em uma estação de trabalho dedicada (*ADW 4.5 da GE*) por meio de software específico (*SMART SCORE*) vide figura 2. Foi utilizado o método de Agatston para a quantificação das calcificações, descrito na seção 2.3 das Considerações Iniciais. As imagens foram analisadas com janela para partes moles, com largura entre 350 a 500 UH e centro entre 30 e 50UH.

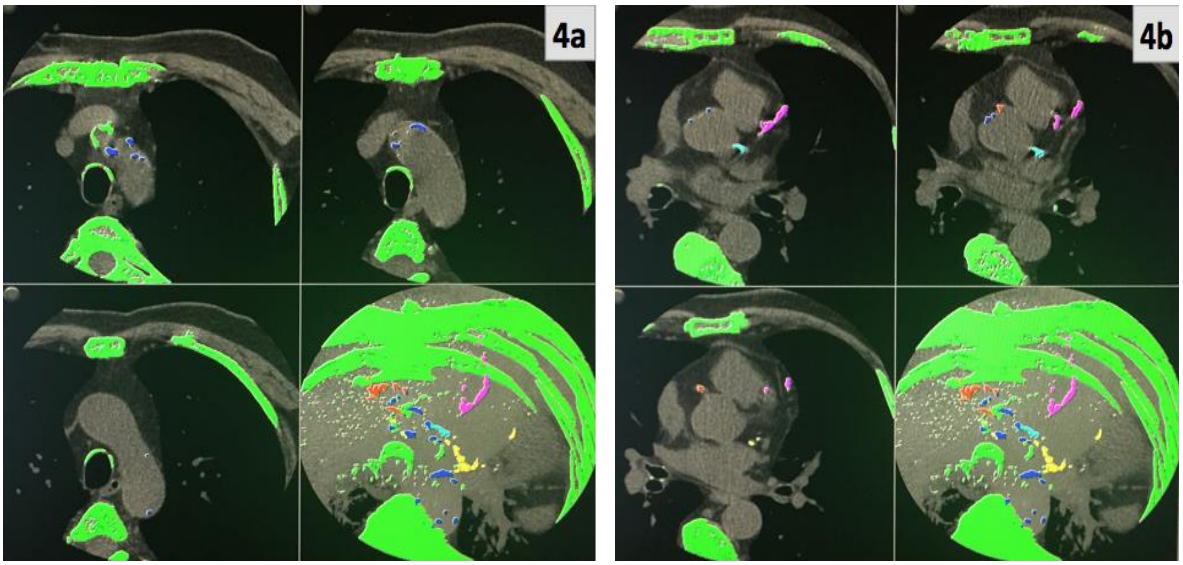


Figura 4a: Nível do arco aórtico - **Figura 4b:** Nível de origem das coronárias. Tela do programa SMART SCORE: as imagens axiais são apresentadas em sequência. A primeira é a superior esquerda, a segunda superior direita, a terceira inferior esquerda e a quarta é uma sobreposição de todos os cortes axiais. Note que todas as calcificações estão destacadas na cor verde. O observador delimita as calcificações de interesse e muda a cor de cada uma delas identificando para o software qual calcificação está em cada artéria. Azul: aorta torácica; vermelho: coronária direita; azul claro: tronco coronariano esquerdo; amarelo: circunflexa e rosa: descendente anterior.

Foi considerada calcificação na aorta torácica qualquer calcificação em sua parede, desde a junção sinutubular, tendo como referência a emergência da artéria coronária direita, acima do seio de Valsalva, incluindo a aorta ascendente, o arco aórtico e porção torácica da aorta descendente, até a transição toracoabdominal, no nível da última imagem axial do ápice cardíaco. A análise da calcificação nas artérias coronárias compreendeu qualquer calcificação na parede da artéria coronária direita, do troco coronariano esquerdo, da descendente anterior e da circunflexa, conforme método descrito por Agatston em 1990.

Após a publicação do primeiro artigo de resultados de TAC e CAC e avaliando estudos recentes que consideram os segmentos da aorta separadamente, foi realizada uma revisão de todas as imagens de tomografia para separar a quantidade de cálcio presente em

cada segmento da aorta torácica, utilizando o mesmo software (SMART SCORE) e considerando o valor de Agatston calculado. Esta reanálise foi realizada por uma tecnóloga qualificada, que se submeteu a treinamento específico para identificar a TAC e foi supervisionada durante todo o processo pela radiologista responsável pela primeira leitura das imagens. Das 2433 tomografias incluídas no estudo de TAC total, 2427 tomografias foram reanalisadas, uma vez que 6 exames não estavam disponíveis no período que a segunda leitura foi realizada. Durante a releitura foram identificadas 29 inconsistências: 4 devido a erros de digitação (2 passaram a ter TAC na segunda análise e 2 passaram a não ter TAC); 25 foram devido ao maior rigor na distinção dos detalhes anatômicos (possíveis *pitfalls*) durante a segunda leitura das imagens (20 passaram a não ter TAC e 5 passaram a ter TAC). Estas inconsistências representam os principais desafios da leitura de TAC, pois pequenas calcificações em tecidos adjacentes podem ser responsáveis por classificar como presença de TAC um indivíduo que não tem calcificação. A figura 5 mostra os principais exemplos de "*pitfalls*" encontrados durante o presente estudo: calcificações no remanescente do ducto arterioso (Figuras 5a e 5b), nos anéis traqueais (Figuras 5c e 5d) e osteófitos na porção anterior do corpo vertebral (Figuras 5e e 5f).

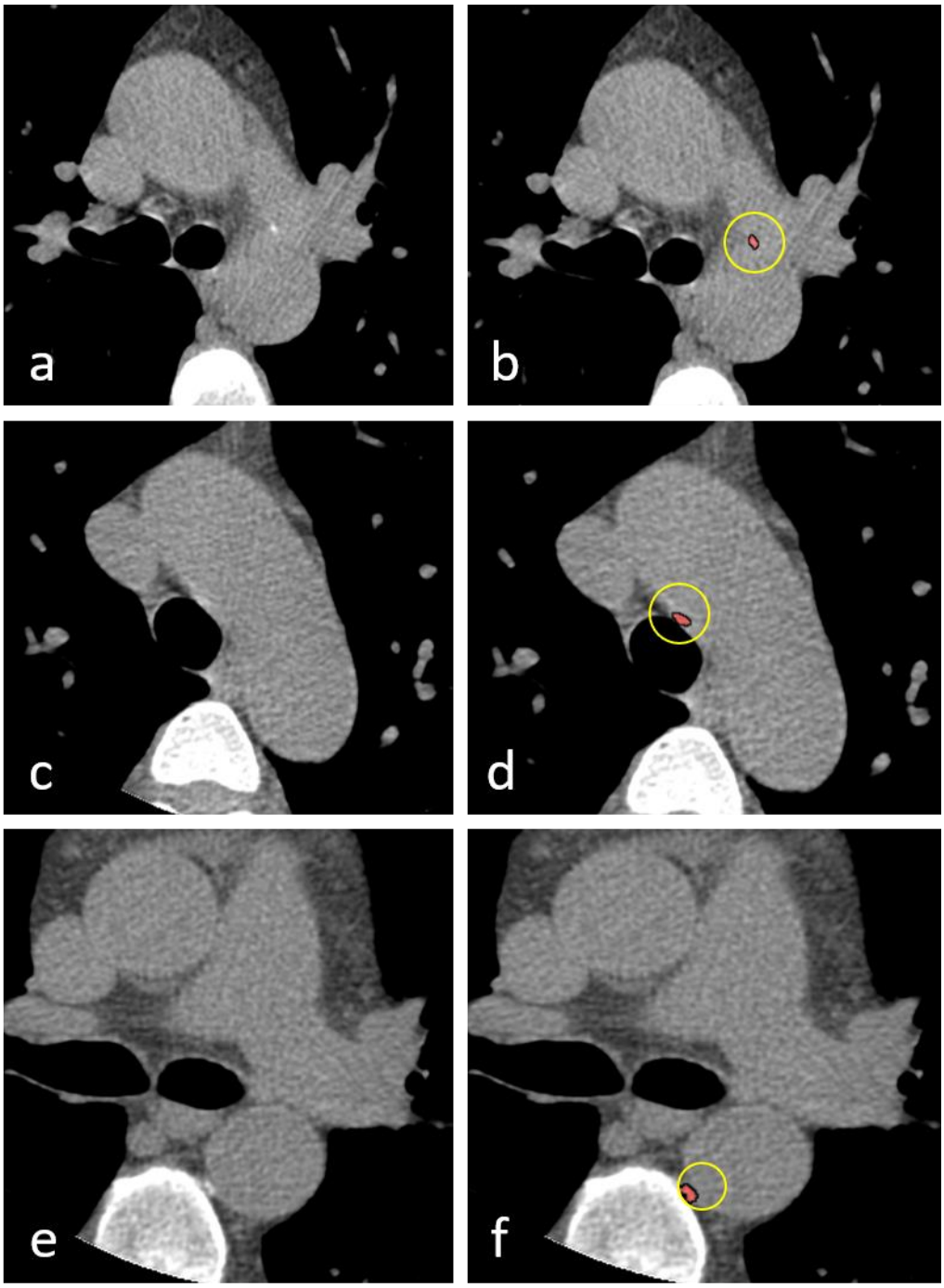


Figura 5: Possíveis "*pitfalls*" na análise do TAC - Figuras 5a e 5b mostram a calcificação no remanescente do ducto arterioso antes e após a marcação pelo observador. Note que o programa valida a calcificação, portanto, cabe ao observador considerá-la ou não. Figuras 5c e 5d mostram a calcificação no anel traqueal, cuja proximidade com a aorta tornam as duas estruturas indistinguíveis. Figuras 5e e 5f mostram o osteófito, sobre o ligamento longitudinal anterior, simulando perfeitamente a calcificação na parede da aorta.

4.5 Variáveis do estudo

4.5.1 Variáveis resposta

As análises tiveram como variáveis resposta a calcificação na aorta torácica (TAC) total, na aorta ascendente, no arco aórtico, na aorta descendente torácica e nas artérias coronárias (CAC). As variáveis foram analisadas de forma dicotômica, ou seja, de acordo com a presença ou ausência de calcificação em cada um dos leitos vasculares estudados.

4.5.2 Covariáveis

Todos os candidatos a realizar o exame tomográfico tinham que ter participado da segunda onda de exames e entrevistas realizados no Centro de Investigação do ELSA-Brasil em Minas Gerais. A história médica e as características sociodemográficos foram obtidos através de questionários. As orientações quanto ao preparo dos participantes para a segunda onda foram jejum de 10 a 14 horas, não consumir bebidas alcoólicas e cafeína e não se exercitar nas 12 horas anteriores aos exames. As amostras de sangue foram coletadas através de punção em veia do antebraço por pessoal treinado e armazenadas seguindo protocolo padronizado (AQUINO et al., 2012).

As **características sociodemográficas** incluídas foram idade, sexo, raça/cor, escolaridade e história familiar de doença cardiovascular (DCV). A raça/cor foi autorreferida e os participantes podiam escolher a categoria que se enquadravam segundo a Classificação do Censo Brasileiro: branco; pardo; preto; outras (amarela e indígena foram incluídos na mesma categoria devido ao pequeno número de participantes nestes grupos) (SCHMIDT et al., 2015). Em relação à escolaridade, a classificação constava de 4 categorias: ensino fundamental incompleto, fundamental completo, ensino médio completo e superior completo. História familiar positiva foi definida pelo relato de IAM, revascularização

miocárdica ou morte súbita em parentes de primeiro grau (se homens com idade ≤ 55 anos e se mulheres, ≤ 65 anos) (AQUINO et al., 2012).

Os **dados comportamentais** considerados foram tabagismo, uso excessivo de álcool e atividade física. Os participantes que relataram ter fumado pelo menos 100 cigarros durante a vida foram classificados como tabagista atual ou ex-tabagista, caso não tenha fumado nos últimos 30 dias era considerado ex-tabagista (KIANOUSH et al., 2017). A categoria de referência era a dos que nunca fumaram, ou seja, aqueles que fumaram menos de 100 cigarros durante a vida. Foi considerado como uso excessivo de álcool, o consumo maior ou igual a 210g de etanol por semana para homens e maior ou igual a 140g por semana para mulheres, estimado a partir do tipo e da quantidade de bebida alcoólica consumida e frequência de consumo semanal (SCHMIDT et al., 2015). Atividade física foi avaliada segundo o Questionário Internacional de Atividade Física – IPAQ – e categorizada em leve, moderada e forte. A atividade "forte" era realizar 7 dias de qualquer combinação de caminhada ou qualquer atividade de intensidade moderada ou vigorosa, alcançando mais de 3.000 Equivalente Metabólico da Tarefa (MET) por minuto/semana . A atividade "moderada" foi definida pelos seguintes critérios 3 ou mais dias de atividade vigorosa de pelo menos 20 min/dia, ou 3 ou mais dias de atividade de intensidade moderada ou caminhada de pelo menos 30 min/dia, ou mais de 5 dias de qualquer combinação de caminhada ou atividades de intensidade moderada ou vigorosa, atingindo ≥ 600 MET-min/semana, ou mais de 3 dias de atividade vigorosa, atingindo ≥ 1.500 MET-min/semana (CRAIG et al., 2003). Os participantes que não preencheram nenhum dos critérios anteriores foram incluídos no grupo de intensidade "leve".

A **variável antropométrica** analisada foi o índice de massa corporal (IMC), calculado pelo peso dividido pela altura ao quadrado. O sujeito da pesquisa foi considerado eutrófico se o IMC foi < 25 kg/m^2, com sobrepeso se IMC ≥ 25 kg/m^2 e < 30 kg/m^2 e obeso se apresentou o IMC ≥ 30 kg/m^2 (SCHMIDT et al., 2015). O peso foi medido em quilogramas (Kg), usando balança Toledo® (precisão de 50g) e a altura foi medida em centímetros com estadiômetro (precisão de 0,1 cm).

Os **dados laboratoriais** utilizados foram as medidas de colesterol-HDL, colesterol-LDL e a hemoglobina glicada (HbA1c). A medida de colesterol-HDL foi realizada por meio de ensaio enzimático colorimétrico (ADVIA Chemistry), o colesterol-LDL foi calculado pela equação de Friedewald, porém se os níveis de triglicérides estivessem acima de 400 mg/dl era realizado o ensaio enzimático colorimétrico (ADVIA Chemistry) e os níveis de hemoglobina glicada foram avaliados utilizando a técnica de cromatografia líquida de alta pressão (Bio-Rad Laboratories, Hércules, Califórnia) (AQUINO et al., 2012).

Os **dados clínicos** dos participantes incluídos nas análises foram as medidas de pressão arterial sistólica (PAS), pressão arterial diastólica (PAD) e as informações sobre o uso de medicamentos anti-hipertensivos, hipolipemiantes e para diabetes. As medidas da pressão arterial sistólica e diastólica foram obtidas de forma padronizada com o participante em repouso, sentado há pelo menos cinco minutos e em ambiente adequado para evitar estresse. Foram realizadas três medidas no braço não dominante, 2 cm acima da fossa cubital, usando-se aparelho automático para medida oscilométrica (Omron 765CP; Omron, Kyoto, Japan) e a medida final foi a média da segunda e terceira medidas (BRANT et al., 2014). As variáveis sobre o uso de medicamentos foram obtidas durante das entrevistas, quando o participante era questionado quanto ao uso de medicamentos nas últimas 2 semanas, eles

eram instruídos a trazer as prescrições e os medicamentos que eles usavam para que os entrevistadores confirmassem estes dados e certificassem qual a categoria dos referidos medicamentos. Todas as classes de medicamentos eram consideradas em cada grupo e categorizadas de forma dicotômica, ou seja, usa medicamento (sim) ou não usa (não).

4.6 Aspectos Éticos

O Estudo Longitudinal de Saúde do Adulto (ELSA-Brasil) foi aprovado pelos Comitês de Ética e Pesquisa de todos os Centros de Investigação (CEPs). É um projeto que atende a todos os requisitos éticos necessários para ser realizado em seres humanos, tais como a participação voluntária, a privacidade dos participantes e a confidencialidade das informações. Em Minas Gerais, o ELSA-Brasil foi aprovado pelo Comitê de Ética em Pesquisa (COEP) da Universidade Federal de Minas Gerais (UFMG), em 28 de junho de 2006, sob o número de protocolo ETIC 186/06 e com o certificado de apresentação para apreciação ética (CAAE) de número 0186.1.203.000-06. Para a realização dos exames de tomografia computadorizada foi realizada uma emenda do Projeto ELSA-Brasil, cujo parecer do COEP da UFMG foi liberado na Plataforma Brasil no dia 27/07/2015, sob o número de parecer 1.154.359 e CAAE de número 47125015.4.1001.5149 . Todos os participantes do presente estudo foram informados sobre a emenda e assinaram o Termo de Consentimento Livre e Esclarecido (TCLE). A aprovação final da Emenda e o TCLE estão inseridos em **ANEXOS**.

4.7 Análises estatísticas:

A análise descritiva se baseou na média e desvio padrão para as variáveis contínuas e em números absolutos e proporções para as variáveis categóricas. As análises de associação univariadas foram realizadas utilizando o teste *t de Student* para comparar as médias das variáveis contínuas entre os grupos de participantes que apresentam e não apresentam a variável resposta e o teste *Qui-quadrado de Pearso*n para comparar as proporções das variáveis categóricas entre os dois grupos da variável resposta. As variáveis resposta foram avaliadas de forma dicotômica como presença de calcificação (Escore de Agatston > 0) ou ausência (= 0).

Os fatores associados à cada variável resposta foram estimados por meio de regressão logística. A análise foi realizada em 4 etapas para cada variável resposta, separadamente: modelo bruto (análise univariada); o modelo 1 incluiu ajustes por variáveis sociodemográficas (idade, sexo, raça/cor e escolaridade); o modelo 2 adicionou os dados comportamentais (uso excessivo de álcool, tabagismo e atividade física), IMC e história familiar de doença cardiovascular; e o modelo 3 acrescentou os dados clínicos e laboratoriais (HbA1c, colesterol-HDL, colesterol-LDL, PAS, PAD e uso de medicamentos anti-hipertensivos, hipolipemiantes e para diabetes). Todas as covariáveis associadas ao nível de $p < 0,20$ permaneceram nas análises, entretanto, no modelo final ficaram apenas as variáveis que se mantiveram associadas ao nível de significância de 0,05. Todos os resultados foram considerados significativos para uma probabilidade de significância inferior a 5% ($p < 0,05$), tendo, portanto, pelo menos 95% de confiança nas conclusões apresentadas. Todas as análises foram realizadas utilizando Stata/MP 14.0 for MAC (StataCorp LP, College Station, Texas, USA).

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6. ARTIGO DE RESULTADOS 1

(Publicado no "*American Journal of Cardiology*" – vide cópia da publicação no apêndice 1)

Relation of Thoracic Aortic and Coronary Artery Calcium to Cardiovascular Risk Factors (From the Brazilian Longitudinal Study of Adult Health [ELSA-Brasil])

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ABSTRACT

Thoracic aortic calcium (TAC) and coronary artery calcium (CAC) are associated with an increased risk of cardiovascular disease (CVD) and death. However, risk factors associated with arterial calcium may vary across vascular beds. We verified whether TAC is associated with the same risk factors as is CAC in adults without established CVD. Cross-sectional analysis including 2,433 participants (aged 38-78 years) of ELSA-Brasil cohort in Minas Gerais, Brazil. Non-enhanced ECG-gated multislice computed tomography were performed to detect calcium in the thoracic aorta and the coronaries (2015-2016). Multivariate logistic regression evaluated the associations of both TAC and CAC with CVD risk factors (smoking, body mass index, physical activity, alcohol intake, family history of CVD, LDL- and HDL-cholesterol, HbA1c, blood pressure, antidiabetic, antihypertensive, and lipid lowering medications). Overall prevalence of TAC and CAC were 69% and 43%, respectively. CAC prevalence was lower among women (31%) than men (56%) (Adjusted OR= 0.30; 0.24-0.38). After adjustments, black individuals were less likely to have any CAC as compared to whites (OR: 0.63; 0.47-0.86). Neither sex, nor race/skin color were statistically associated with TAC. Use of antidiabetic medications remained associated with CAC (OR: 1.80; 1.23-2.631.01), but not with TAC. All other risk factors, except education, alcohol, physical activity and HbA1c, persisted statistically associated with both TAC and CAC in the final analysis, with small differences in the magnitudes of the ORs. In conclusion, the only disagreements seen in the risk factors associated with CAC and TAC were sex, race/skin color and use of antidiabetic medications.

Keywords: vascular calcification, thoracic aorta, coronary artery, risk factors

Many studies have demonstrated that the presence of either coronary artery calcium (CAC) or thoracic aortic calcium (TAC), detected by computed tomography (CT), are markers of subclinical atherosclerosis and are associated with an increased risk of cardiovascular events.[1,2] Allison *et al.* (2012) followed up 4,544 individuals who underwent whole body CT to ascertain, and found after about 7.8 years, that the calcium in thoracic aorta, carotids and iliac arteries were associated with total mortality, whereas the presence of CAC was associated with cardiovascular disease (CVD) mortality.[3] Knowledge on the association of particular cardiovascular risk factors to the presence of calcium in thoracic aorta and/or coronary arteries may contribute to understand the different mechanisms of atherosclerosis. We performed a cross-sectional study to assess the prevalence of TAC and CAC and verify if TAC is associated with the same cardiovascular risk factors as is CAC in participants from Minas Gerais Investigation Center of ELSA-Brasil Study without overt CVD.

Methods

The study is embedded in the ELSA-Brasil Study, a multicenter cohort designed to investigate the determinants of CVD and diabetes.[4] The study started in 2008 and included 15,105 civil servants. Eligibility criteria included active and retired employees of 6 institutions, aged 35 to 74 year.[5] The present study was conducted in the Minas Gerais Investigation Center. Multislice Computed Tomography (MSCT) was performed in 2015-16 after the second visit (2012-14), which enrolled 2,923 participants. Exclusion criteria for MSCT scan was pregnancy, postpartum, breast-feeding (until 6 months post childbirth), exposure to radiation at work, any piece of metal in the chest (e.g., pacemaker and coronary stent), current radiotherapy, non-participation in second visit to Investigation Center and refusal to perform MSCT scan. A total of 2,638 participants were scanned. Of these, 63 reported a history of CVD at second visit and were excluded from this analysis. History of CVD was defined as medical history of myocardial infarction (n=15), congestive heart failure

(n=21), stroke (n=24) or cardiac surgery (n=13). Additionally, in 142 participants measurements of both CAC and TAC were not available due to use of different scan protocol, in which the aortic arch was not included. Thus, 2,433 participants were included in the present study.

Written informed consent was obtained from each participant included in the study. The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki and our protocol has been priorly approved by the Universidade Federal de Minas Gerais's ethics committee on research in humans.

Sociodemographic, behavioral and medical history factors were obtained by face-to-face questionnaires. Race/skin color were self-reported and participants could choose from a fixed set of categories based on Brazilian Census classification: white; brown or "pardo"; black and others (Indigenous and Asian were grouped in the same category because its smaller participants number).[5] Educational level was categorized into university degree, complete secondary school, complete elementary school and incomplete elementary school. Smoking was assessed by the following questions: "Are you or have you ever been a smoker, that is, have you smoked at least 100 cigarettes (five cigarette packs) throughout your life?" and "Do you currently smoke cigarettes?" (never smoker, former smoker, and current smoker).[6] Never smoker were the reference group. Physical activity was assessed by the short version of the International Physical Activity Questionnaire and participants were classified as Insufficient (< 600 metabolic equivalent-min/week), moderate (600 to 3000) and vigorous (≥ 3000).[7] Excessive use of alcohol was defined as ≥ 210 g of ethanol per week for men and ≥ 140 g for women.[5] Family history of premature CVD was defined as "positive" if the participant reported a case of acute myocardial infarction, myocardial revascularization or sudden death in first-degree relative (men aged ≤ 55 and women ≤ 65 years old).[4]

Body mass index (BMI) was calculated by dividing the participant's weight in kilograms by height in meters squared. Blood pressure was measured 3 times in the seated position after 5 minutes of rest, automatically (Omron 765CP; Omron, Kyoto, Japan) in the left arm, 2 cm above the cubital fossa, and the average of the second and third measurements was considered to obtain systolic and diastolic blood pressure as continuous variables in mmHg.[8] Blood samples were collected in after 12-hours overnight fast to measure hemoglobin A1c (HbA1c), HDL-cholesterol and LDL-cholesterol.[4] The use of antidiabetic, antihypertensive, and lipid lowering medications was self-reported. All participants were asked about the use of continuous medication in the prior two weeks and were instructed to bring prescriptions and/or drugs used to the study clinic.[9]

Imaging was performed with a 64-slice MSCT scanner *(Lightspeed*, General Electric). The scanogram encompassed all thoracic aorta, and the heart, from 1 cm above the top of the aortic arch to the heart apex as is shown in Figure 1. The scan consisted of 56 to 88 images. Before performing the scan, the participants exercised breath holding. Within a single breath hold consecutive non-overlapping 2.5 mm thick slices were acquired with 20 x 0.62 mm collimation, 120 kVp, 100 mAs and prospective electrocardiogram triggering at 70% of the cardiac cycle. The media of effective dose calculated was 1.75 mSv.

Calcium was identified and scored by only one experienced radiologist, using semiautomatic software (*Smart Score 4.0*). Correlation study was performed with a second experienced radiologist. A random sample of fifty participants was scored twice by the observer and once by the other radiologist, who has only participated in this correlation study. Intraclass correlation coefficients for all arteries scored were higher than 0.99 for intraobserver and interobserver analysis.

The software highlighted in green all calcium based on a threshold of 130 Hounsfield Unit (HU).[10] Then, the observer went over every axial image and clicked on the green lesions

to turn them another codified color as is shown in Figure 1. CAC presence consisted of any calcified lesions identified within left main, left anterior descending, left circumflex, and right coronary artery. The presence of TAC was defined as any calcium on the aortic arch, ascending, and descending aorta wall, from the sinutubular junction until the last image of heart apex. Calcium from Valsalva sinus and aortic valve was not included.

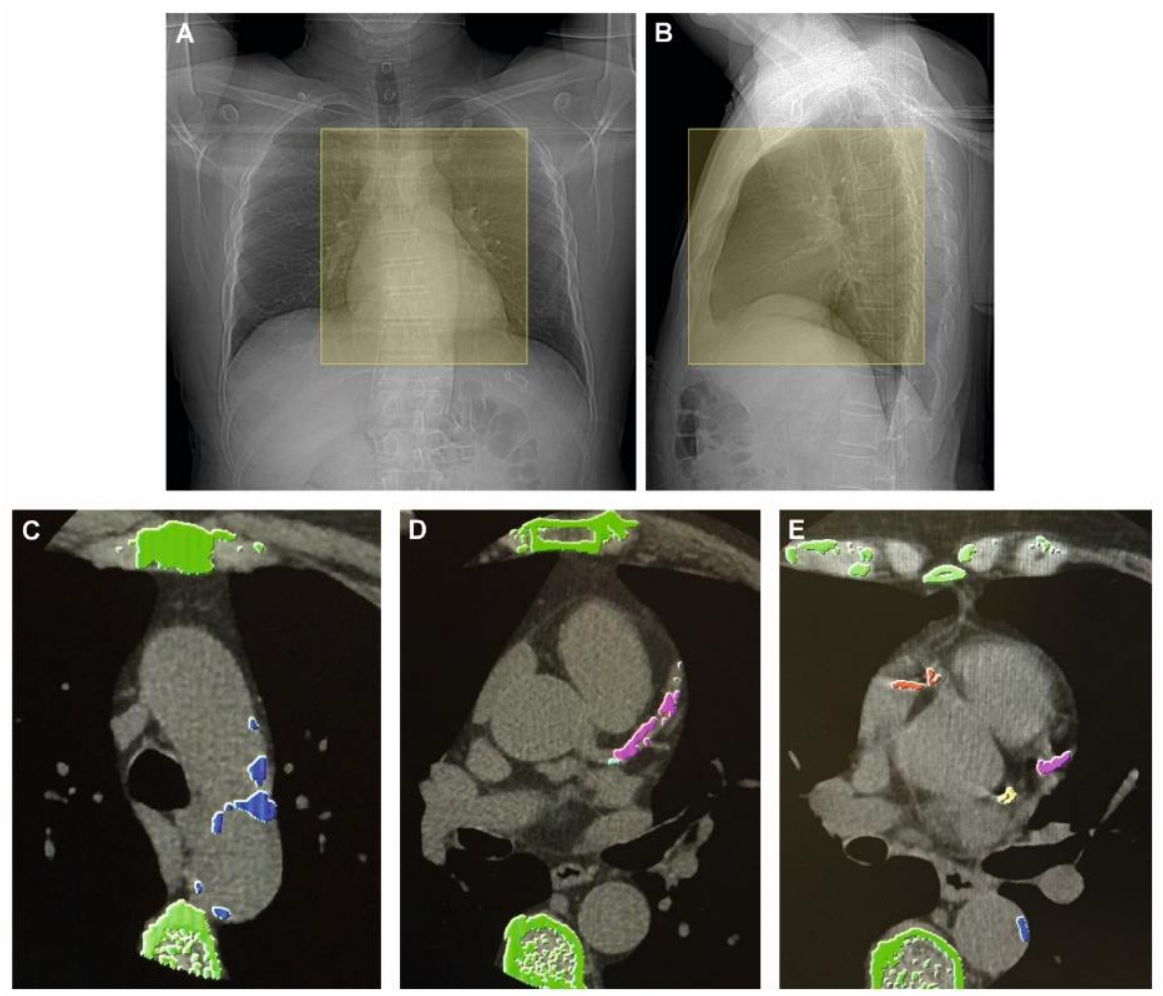


Figure 1A and 1B: Scanogram: frontal and lateral views. Yellow rectangles represent the tomographic acquisition area. Figure 1C, 1D and 1E: Screens obtained by "Smart Score" software showing any calcium area highlighted in green. Calcium in different vascular beds are shown according to codified colors: blue, aortic arch (1C and 1E); pink, anterior descending artery (1D and 1E); light blue, left main coronary artery (1D); red, right coronary artery and yellow, circumflex artery (1E).

Descriptive statistics was based on mean and standard deviation for continuous variables and frequency distribution for categorical variables. Continuous variables were compared with *Student t* test and categorical variable with *Pearson's chi-square* test. TAC and CAC were dichotomized as present (Agatston score > 0) or absent (=0). The independent association of sociodemographic, lifestyle, laboratory and clinical risk factors with TAC and CAC were assessed using multivariate logistic regression analyses. The analysis consisted of four stages for TAC and CAC separately: model zero (univariate analysis); Model 1 was adjusted for sociodemographic factors (age, gender, race/skin color, education); Model 2 added lifestyle factors (smoking, physical activity, alcohol intake), BMI, and family history of CVD; Model 3 included the remaining risk factors (LDL and HDL-cholesterol, HbA1c, blood pressure, antidiabetic, antihypertensive, and lipid lowering medications). All associated covariables with $p<0,20$ in the univariate analysis were considered in the multivariate models, but only the variables that remained statistically associated at the level of $p<0.05$ remained in the final analysis (Model 3) of TAC or CAC. The confidence interval corresponded to 95%. Statistical analyses were performed with Stata/MP 14.0 for MAC (StataCorp LP, College Station, Texas, USA).

Results

The overall prevalences of TAC and CAC were 69% and 43%, respectively. Figure 2 shows a Venn diagram with the intersection of all study participants according to the presence or absence of CAC and/or TAC. About 24% of participants were free from both TAC and CAC, while 37% had TAC and CAC, simultaneously. Almost all participants with CAC also had TAC (94%). Figures 3a and 3b shows the prevalences of TAC and CAC according to gender and age category. The prevalence of CAC was significantly lower in women than in men at all age groups, while the prevalence of TAC was quite similar between genders throughout age groups.

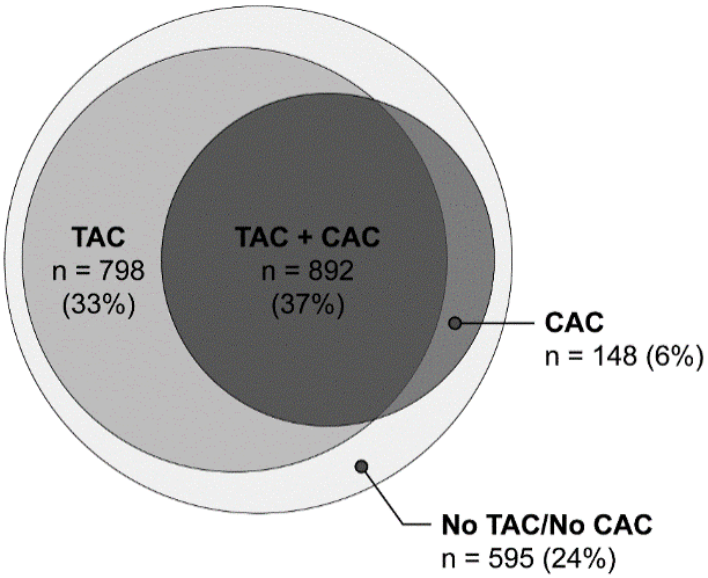
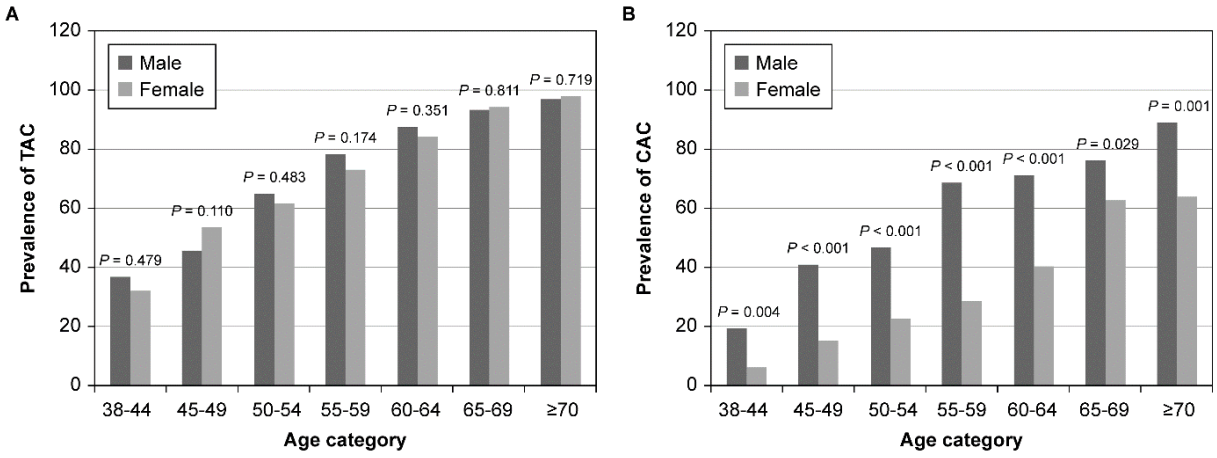


Figure 2: Venn diagram showing the intersection of individuals according to presence or absence of coronary artery calcium (CAC) and thoracic aortic calcium (TAC). Percentages refer to the overall population (N=2,433). ELSA-Brasil, 2015-2016.



Figures 3A and 3B: Prevalences of thoracic aortic calcium (TAC) and coronary artery calcium (CAC) according to gender and age, respectively. ELSA-Brasil, 2015-2016.

Table 1 shows the distribution of the study population characteristics in total and according to presence or absence of TAC and CAC. Overall, the mean age was 55.6 ± 8.7 years; 54% women; nearly half were whites (49%); about 67% had university degree. Thirty eight percent were either current or former smoker; and 33% had a family history of CVD.

Among all the factors included in Table 1, only gender, race/skin color, physical activity, excessive use of alcohol, and HDL-cholesterol were not statistically associated with the presence of TAC at the level of $p<0.05$. Whereas only physical activity and LDL-cholesterol had nonsignificant association with CAC in the univariate analysis. The results of the multivariate analysis for cardiovascular risk factors associated with the presence of TAC and CAC are shown in tables 2 and 3, respectively. Increasing age, current smoking, family history of CVD, higher BMI, LDL-cholesterol and systolic blood pressure, lower HDL-cholesterol, use of lipid and blood pressure lowering medications, all remained associated with greater OR for TAC and CAC, with small differences in the magnitude of the associations. The chance of having CAC was lower among women than men, but there was no statistical differences between genders regarding TAC. Race/skin color differences were also observed only for CAC, with blacks being less likely to have any CAC compared to whites. Similarly, the use of antidiabetic drugs remained associated only with CAC in the final Model.

Table 1 – Characteristics of all population and according to presence or absence of thoracic aortic calcium (TAC) and coronary artery calcium (CAC). ELSA-Brasil, 2015-2016.

VARIABLES	Population N=2433 (100%)	TAC = 0 N=743 (30.5%)	TAC > 0 N=1690 (69.5%)	*p* values	CAC = 0 N=1393 (57.3%)	CAC > 0 N=1040 (42.7%)	*p* values
Age (years)	55.6 ± 8.7	50.2 ± 6.8	58.0 ± 8.4	**< 0.001**	52.9 ± 8.0	59.2 ± 8.3	**< 0.001**
Women	1314 (54.0%)	400 (53.8%)	914 (54.1%)	0.910	903 (64.8%)	411 (39.5%)	**< 0.001**
Race/ Skin color				0.378			**< 0.001**
White	1169 (48.6%)	337 (46.2%)	832 (49.7%)		625 (45.4%)	544 (53.1%)	
Brown	850 (35.4%)	276 (37.8%)	574 (34.3%)		501 (36.4%)	349 (34.0%)	
Black	319 (13.3%)	97 (13.3%)	222 (13.3%)		208 (15.1%)	111 (10.8%)	
Others (Asian, Indigenous)	65 (2.7%)	20 (2.7%)	45 (2.7%)		44 (3.2%)	21 (2.1%)	
Educational level				**< 0.001**			**< 0.001**
University degree	1627 (66.9%)	540 (72.8%)	1087 (64.4%)		958 (68.8%)	669 (64.4%)	
Complete secondary school	616 (25.3%)	174 (23.4%)	442 (26.2%)		354 (25.5%)	262 (25.2%)	
Complete elementary school	102 (4.2%)	17 (2.3%)	85 (5.0%)		42 (3.0%)	60 (5.8%)	
Incomplete elementary school	86 (3.5%)	11 (1.5%)	75 (4.4%)		38 (2.7%)	48 (4.6%)	
Smoker				**< 0.001**			**< 0.001**
Never	1494 (61.5%)	539 (72.6%)	955 (56.5%)		961 (69.1%)	533 (51.3%)	
Past	705 (29.0%)	161 (21.7%)	544 (32.2%)		318 (22.8%)	387 (37.3%)	
Current	232 (9.5%)	42 (5.7%)	190 (11.3%)		113 (8.1%)	119 (11.4%)	
Physical activity				0.078			0.064
Insufficient	1732 (71.2%)	543 (73.2%)	1189 (70.4%)		1016 (73.0%)	716 (68.9%)	
Moderate	498 (20.5%)	132 (17.8%)	366 (21.7%)		263 (18.9%)	235 (22.6%)	
Vigorous	201 (8.3%)	67 (9.0%)	134 (7.9%)		113 (8.1%)	88 (8.5%)	
Excessive use of alcohol	254 (10.4%)	69 (9.3%)	185 (10.9%)	0.220	109 (7.8%)	145 (14.0%)	**< 0.001**
Family history of CVD	807 (33.2%)	202 (27.2%)	605 (35.8%)	**< 0.001**	409 (29.4%)	398 (38.3%)	**< 0.001**
Body mass index (kg/m^2)	27.0 ± 4.7	26.1 ± 4.4	27.4 ± 4.8	**< 0.001**	26.6 ± 4.6	27.5 ± 4.8	**< 0.001**
LDL-cholesterol (mg/dL)	115.0 ± 30.3	112.2 ± 28.7	116.3 ± 30.9	**0.002**	115.0 ± 29.3	115.1 ± 31.6	0.926
HDL-cholesterol (mg/dL)	53.6 ± 13.4	54.3 ± 13.7	53.3 ± 13.3	0.113	55.2 ± 13.3	51.4 ± 13.4	**< 0.001**
Hemoglobin A1c (%)	5.5 ± 0.9	5.3 ± 0.7	5.5 ± 1.0	**< 0.001**	5.3 ± 0.7	5.6 ± 1.1	**< 0.001**
Systolic blood pressure (mmHg)	120.5 ± 15.5	116.2 ± 13.4	122.4 ± 15.9	**< 0.001**	117.6 ± 14.6	124.4 ± 15.8	**< 0.001**
Diastolic blood pressure (mmHg)	77.6 ± 9.7	76.4 ± 9.1	78.1 ± 9.9	**< 0.001**	76.7 ± 9.5	78.8 ± 9.8	**< 0.001**
Use of lipid lowering medications	525 (21.7%)	87 (11.8%)	438 (26.1%)	**< 0.001**	194 (14.0%)	331 (32.0%)	**< 0.001**
Use of antidiabetic medications	191 (7.9%)	26 (3.5%)	165 (9.8%)	**< 0.001**	56 (4.0%)	135 (13.0%)	**< 0.001**
Use of blood pressure lowering medications	861 (35.4%)	145 (19.5%)	716 (42.4%)	**< 0.001**	374 (26.9%)	487 (46.9%)	**< 0.001**

Data were presented as mean ± standard deviation, or n (%). CVD: cardiovascular disease; HDL: high density lipoprotein; LDL: low density lipoprotein.

Table 2 – Variables associated with thoracic aortic calcium (TAC) in the univariate and multivariate analysis. ELSA-Brasil, 2015-2016. (N=2,419)

VARIABLES	MODEL 0 (Univariate)	MODEL 1	MODEL 2	MODEL 3 (Final)
Age (years)	**1.14 (1.12-1.15)***	**1.14 (1.12-1.15)***	**1.14 (1.12-1.15)***	**1.12 (1.11-1.14)***
Women	1.01 (0.85-1.20)	0.93 (0.77-1.13)	0.92 (0.75-1.12)	1.10 (0.88-1.39)
Smoker				
Never	1.00		1.00	1.00
Past	**1.91 (1.55-2.34)***		**1.19 (0.94-1.49)**	**1.21 (0.95-1.53)**
Current	**2.55 (1.80-3.62)***		**2.19 (1.51-3.18)***	**2.16 (1.48-3.14)***
Body mass index (kg/m^2)	**1.06 (1.04-1.08)***		**1.07 (1.05-1.09)***	**1.04 (1.02-1.07)***
Family history of CVD	**1.49 (1.24-1.81)***		**1.29 (1.04-1.59)****	**1.25 (1.01-1.55)****
LDL-cholesterol (mg/dL)	**1.00 (1.00-1.01)****			**1.01 (1.00-1.01)***
HDL-cholesterol (mg/dL)	0.99 (0.99-1.00)			**0.99 (0.98-0.99)****
Systolic blood pressure (mmHg)	**1.03 (1.02-1.04)***			**1.01 (1.00-1.02)****
Use of blood pressure lowering medications	**3.03 (2.47-3.72)***			**1.67 (1.31-2.12)***
Use of lipid lowering medications	**2.64 (2.06-3.39)***			**1.37 (1.03-1.82)****

Data were presented as odds ratio (95% confidence interval). CVD: cardiovascular disease; HDL: high-density lipoprotein; LDL: low-density lipoprotein. *$p \leq 0.001$; **$p \leq 0.05$.

Table 3 – Variables associated with coronary artery calcium (CAC) in the univariate and multivariate analysis. ELSA-Brasil, 2015-2016 (N=2,388)

VARIABLES	MODEL 0 (Univariate)	MODEL 1	MODEL 2	MODEL 3 (Final)
Age (years)	**1.10 (1.08-1.11)***	**1.11 (1.09-1.12)***	**1.10 (1.09-1.12)***	**1.09 (1.07-1.10)***
Women	**0.35 (0.30-0.42)***	**0.28 (0.23-0.34)***	**0.27 (0.23-0.33)***	**0.30 (0.24-0.38)***
Race/ Skin color				
White	1.00	1.00	1.00	1.00
Brown	**0.80 (0.67-0.96)****	0.97 (0.79-1.18)	0.94 (0.77-1.15)	0.87 (0.70-1.07)
Black	**0.61 (0.47-0.79)***	**0.77 (0.58-1.03)****	**0.70 (0.53-0.94)****	**0.63 (0.47-0.86)****
Others (Asian, Indigenous)	**0.55 (0.32-0.93)****	0.69 (0.39-1.24)	0.75 (0.42-1.34)	0.69 (0.38-1.26)
Smoker				
Never	1.00		1.00	1.00
Past	**2.19 (1.83-2.63)***		**1.39 (1.13-1.71)****	**1.41 (1.14-1.75)****
Current	**1.90 (1.44-2.51)***		**1.74 (1.28-2.37)***	**1.67 (1.22-2.30)***
Body mass index (kg/m^2)	**1.04 (1.02-1.06)***		**1.06 (1.04-1.08)***	**1.03 (1.01-1.05)****
Family history of CVD	**1.49 (1.26-1.77)***		**1.43 (1.18-1.74)***	**1.35 (1.10-1.64)****
HDL-cholesterol (mg/dL)	**0.98 (0.97-0.98)***			**0.99 (0.98-0.99)****
LDL-cholesterol (mg/dL)	1.00 (1.00-1.00)			**1.01 (1.00-1.01)***
Systolic blood pressure (mmHg)	**1.03 (1.02-1.04)***			**1.01 (1.00-1.02)****
Use of antidiabetic medications	**3.57 (2.58-4.93)***			**1.80 (1.23-2.63)****
Use of blood pressure lowering medications	**2.40 (2.03-2.85)***			**1.47 (1.19-1.82)***
Use of lipid lowering medications	**2.89 (2.37-3.53)***			**2.01 (1.58-2.56)***

Data were presented as odds ratio (95% confidence interval). CVD: cardiovascular disease; HDL: high-density lipoprotein; LDL: low-density lipoprotein. *$p \leq 0.001$; **$p \leq 0.05$.

Discussion

The present study showed a much higher prevalence of TAC compared to CAC. After full adjustments, the chances of CAC were higher in men and lower among black individuals as compared to white ones. However, there were no differences in TAC chances regarding gender and race/skin color. All other cardiovascular risk factors but the use of antidiabetic medication, were statistically associated with both TAC and CAC with subtle differences in the OR.

Considering the few studies that compared the overall prevalences of TAC and CAC and that have also included the aortic arch in TAC analysis, our results contrast with those of Craiem *et al.* as they found similar prevalences of TAC (64%) and CAC (62%) in a sample of 970 adults (77% men), aged 57± 9 years.[11] On the other hand, our results agree with Jacobs et al. findings concerning the greater prevalence of TAC (97%) than CAC (75%), even though their prevalences were much higher than ours, possibly because they studied a high-risk population of heavy smokers, 83% men.[12]

Even though extensive evidences exist that men are more likely to have CAC,[12–15] the absence of gender differences in the chances of having TAC remains controversial. Some studies found greater prevalence of TAC in men and others in women. Nasir et al. studied 8549 individuals (69% men, mean age: 52 ± 9 years) and demonstrated slightly higher prevalence of TAC among women,[16] while the Heinz Nixdorf Study analyzed 4025 participants (47% men, mean age: 59 ± 9 years) and showed higher TAC prevalence among men.[13] However, the CT scan protocols of these latter studies did not include the aortic arch and, hence their prevalences cannot be directly compared with ours as this may impact gender differences in the prevalence of TAC. Reports including the aortic arch are scarce, but some show that women concentrate more calcium in this segment than men,[11,17,18] even though the inclusion of the aortic arch in the analysis will increase the prevalence of TAC in both

genders. Craiem et al. investigated a population of asymptomatic subjects at increased cardiovascular risk, and showed that TAC prevalence doubled from 31% to 64% after using the scan method covering the aortic arch.[11]

Our study found an absence of race/skin color difference in the prevalence of TAC, whereas CAC was 40% lower in black individuals as compared to white ones, and this difference was not explained by cardiovascular risk factors. Our results on CAC are in accordance with the MESA study, as they also found lower chance of CAC (OR: 0.78; 95% CI 0.74-0.82) among blacks as compared to whites.[19] However, they disagree with MESA concerning the prevalence of TAC, as they reported lower prevalence of TAC in African Americans (27%) than in whites (42%).[20] Such differences might be related to the inclusion of the aortic arch in our study, as there appear to be race differences concerning the distribution of calcium along the aorta. In the MESA cohort, blacks had higher prevalence of calcium in the ascending portion of the aorta than whites, while they showed lower calcium in the descending aorta segment.[21] Unfortunately, studies comparing TAC prevalence among different race/skin color are scarce, indicating an important gap to be pursued in future research, and do not know whether race differences also exist regarding the aortic arch that could account for the absence of race/skin color difference in TAC prevalence that we found. Finally, race/skin color findings in the Brazilian population must be interpreted considering two important facts: (1) self-referred race/skin color does not equate biological ancestry information;[22] (2) different from other multiethnic populations, the Brazilian population has not only intrapopulation ethnic diversity, but also intraindividual ancestry variety.[23]

The finding of no statistical association between variables related to diabetes and TAC in the present study may reflect a true weaker association of diabetes and calcification in the aortic territory, when compared to coronary arteries. Indeed, in the MESA Study insulin resistance, evaluated by the homeostasis model assessment index (HOMA-IR), was

associated with the presence of CAC, but not TAC among individuals without diabetes, even though significant associations were seen between insulin resistance and TAC among individuals in the 3rd tertile of subcutaneous and visceral fat areas.[24] On the other hand, a recent study showed that higher HbA1c and the presence of diabetes were associated with thoracic aorta calcium after adjustment for several risk factors.[25] However, we cannot discard that our finding of no association reflect differences in diabetes contribution to the pathophysiologic pathways of atherosclerosis in distinct arterial territories.

The race/skin color and gender differences in TAC and CAC prevalences found here may also express different underlying pathophysiologic processes relevant to different diseases. There are two mechanisms of vascular calcium: intimal (atherosclerotic) and medial (artheriosclerotic).[26] Whereas CAC is mostly intimal, medial calcium is common in the aorta and uncommonly reported in the coronary arteries.[27] Abramowitz *et al.* posit that TAC can be the result of both atherosclerotic and nonatherosclerotic processes, with the former occurring in the tunica intima of the vessel wall and the latter occurring in the tunica media.[28] Thomas *et al*. suggested that medial calcium may reflect biological aging.[29]

The present study has limitations. It is cross-sectional analysis and the temporality of the associations cannot be stablished. The prevalences found cannot be extrapolated to the Brazilian population, given that ELSA-Brasil is a cohort of civil servants in urban areas, and in this study they come from just one Brazilian state.[4] To counterbalance these limitations, the strengths of our study include: a large multiethnic well-characterized sample; measurements of calcium from aortic arch, ascending, and descending thoracic aorta segments for which there is very limited literature; the comparison with CAC, and simultaneous adjustments for most risk factors for CVD.

In conclusion, we found differences between TAC and CAC prevalences among genders and race/skin color that might be related to the mechanisms of calcium formation

across different vascular beds. Further studies using similar protocols, including aortic arch and the analysis of each segment of the aorta separately, might shed some light in the potential contribution of TAC in the classification of cardiovascular risk and whether it varies by gender, race/skin color or diabetes status.

Conflict of interest

The authors have no conflicts of interest to disclose. The funding sources had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit for publication.

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7. ARTIGO DE REVISÃO

(Publicado em "*Current Atherosclerosis Reports*" - vide cópia da publicação no apêndice 2)

Foi criado um vídeo para ilustrar os segmentos da aorta torácica nos cortes axiais da tomografia, que foi publicado como material suplementar eletrônico.

Anatomical References to evaluate Thoracic Aortic Calcium by Computed Tomography

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Anatomical References to evaluate Thoracic Aortic Calcium by Computed Tomography

Abstract

Purpose of Review Thoracic aortic calcium (TAC) has received some interest in recent studies as an important subclinical marker of atherosclerosis. Besides that, using computed tomography (CT) scans performed with cardiac or chest protocols, ECG-gated or non-gated, TAC can be easily evaluated with no addition in radiation dose. This review discusses the particularities of the aortic wall calcium formation, as well as the differences between the aortic segments and summarizes the current status of TAC evaluation, mainly concerning the anatomical references used in the studies.

Recent Findings The studies have evaluated TAC considering different anatomical references. It was identified two different study groups. In the first one, researchers have analyzed the aorta as the sum of calcium in the ascending aorta (ATAC), aortic arch (AAC) and descending thoracic aorta (DTAC). The second group has used cardiac CT scans to assess TAC, therefore they did not include AAC, however the aortic root calcium (ARC) was added in the analysis. So, caution is advisable when interpreting and comparing studies that used different TAC anatomical references.

Summary The broad methodological variability, in addition to the variations in the population characteristics of the studies on TAC, may be in part contributing to the differences between results of different studies. Currently TAC does not have a role in clinical decisions, so it is necessary to create a standard protocol for the aortic calcium research as well as exists for the coronary artery calcium evaluation.

Keywords Computed tomography – Thoracic aorta – Vascular calcification – Cardiovascular disease – Aortic Atherosclerosis – Aortic Arteriosclerosis

Introduction

Atherosclerosis is a systemic, progressive and chronic condition that can affect the entire vascular tree [1]. Calcium in the artery wall is considered a direct marker of atherosclerotic disease [1] and can be easily evaluated through computed tomography (CT) [2]. There are remarkable mass of robust data supporting the prime role of coronary artery calcium (CAC) in cardiovascular risk assessment of the intermediate-risk population, as well as specific subgroups, as patients with diabetes and family history of premature coronary heart disease (CHD) [3]. Several studies have shown that thoracic aortic calcium (TAC) is also a marker of subclinical atherosclerosis [4]. Distinct associations of TAC arouse interest in its particularities compared with CAC analysis. TAC also impacts the CV system, as aortic wall calcium worsen arterial stiffening [5], which is associated with several implications for end-organ damage [6]. CAC and TAC prevalence also seem to differ between men and women and race/skin color [7–11], though results are inconsistent. Moreover, unlike CAC, TAC has not been evaluated through standard CT protocol, mainly with regard to TAC anatomical extension [12–14] and the use of ECG synchrony during exam. [15]

Because differences in TAC definition and acquisition might impair the evaluation of study's results on the predictive value of TAC both at individual and population levels, our aim was to review recent studies about TAC, discussing the particularities of the aortic wall calcium formation and the differences between the aortic segments. And, finally, emphasize the anatomical references and the extension of the aorta included in the TAC studies.

Mechanisms related to the calcium formation in the thoracic aorta wall

The distribution of calcium along the aorta is usually very heterogeneous. It is possible to identify coarse calcium in one segment, while there is no calcium in another segment from the same individual, as shown in fig. 1. In the first case (images 1a and 1b) there was calcium in

large amount in the arch and descending thoracic segments, while there was no calcium in the ascending aorta. In the second case (images 1c and 1d) the calcium concentration was much higher in the aortic arch compared with ascending and descending thoracic portions.

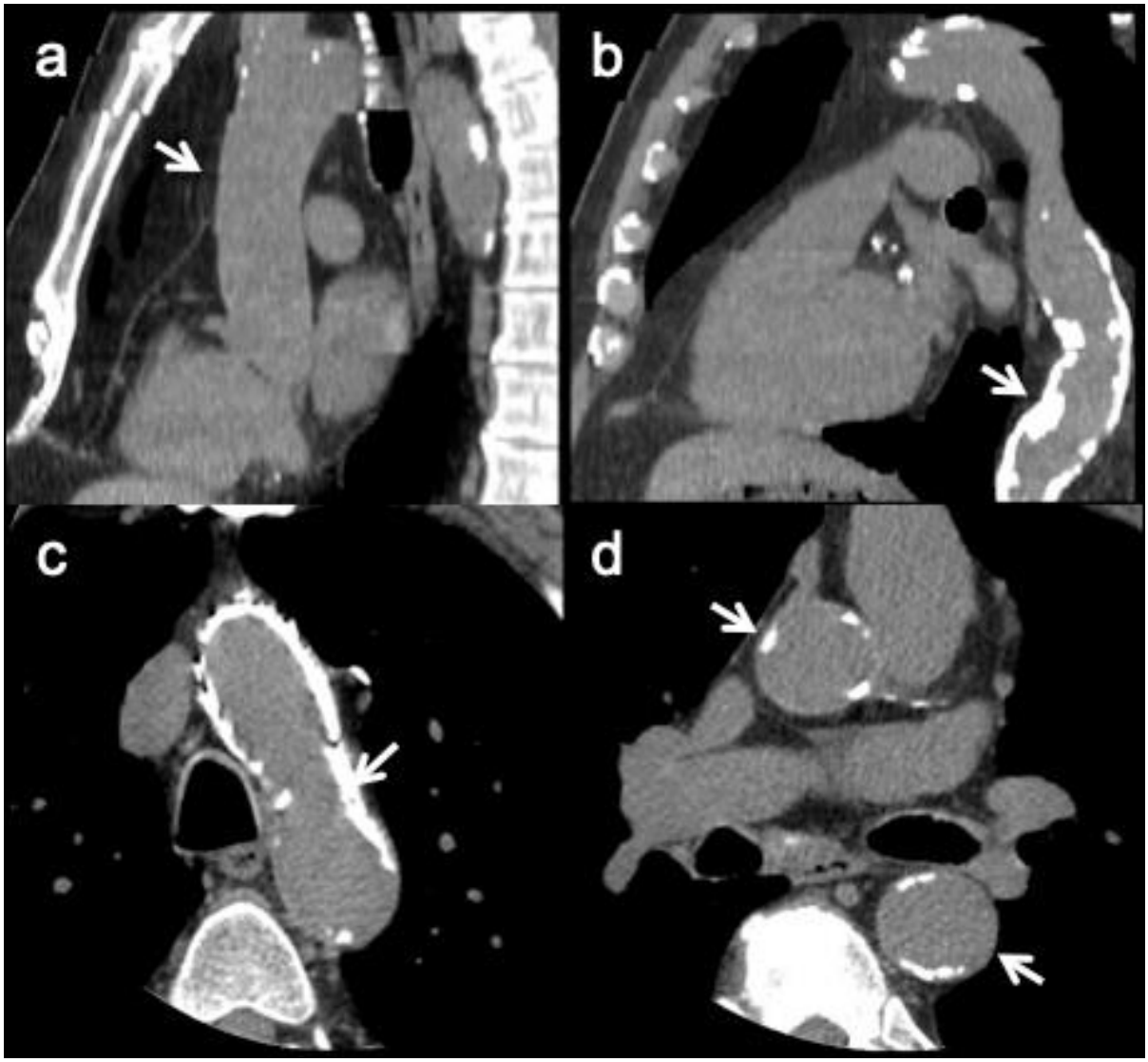

Fig. 1: Heterogeneous distribution of calcium along the aorta. a, b CT reconstructions in the parasagittal plane. In this case, ascending aorta had no calcium (arrow in image1a), whereas in the arch and descending portions (arrow in b) there were circumferential plaques covering almost all aortic wall. C, d CT reconstructions in the axial plane. The most calcium concentration was in the aortic arch (arrow in c), while in ascending (superior arrow in d) and descending (inferior arrow in d) segments calcium were coarse, but sparse.

The variation in the distribution of calcium across aorta segments may be in part associated with different embryonic origin of the vascular smooth muscle cells colonizing the aorta, which in the aortic arch derives from cardiac neural crest cells, whereas the calcium found in the descending aorta derives from the mesoderm [16]. The Leroux-Berger et al. study found correlation between the embryonic origin of vascular smooth muscle cells and the timing of the appearance of calcium [16]. Thus each aortic segment differs in their embryonic origin and is subject to different hemodynamic stress, which also appears to affect susceptibility to calcium [16], as the rate of calcium seems to differ among individuals [17]. Therefore, the calcium found in each aortic segment may be associated differently to cardiovascular risk factors [18] and probably has distinct predictive value for cardiovascular (CV) and non-CV morbidity and mortality, as suggested in some studies [12,13,19–21].

Another important particularity refers to the molecular mechanism of plaque calcium in the aortic wall, which is mainly composed by two mechanisms:

1) Intimal calcium: atherosclerosis, inflammatory response of tunica intima;
2) Medial calcium: occurs independently of intimal calcium in the tunica media.

The intimal layer consists of endothelial cells that eventually form atheromatous plaques which can rupture and cause thromboembolic events, whereas the medial layer consists of smooth muscle cells and elastic fibers that are associated with blood flow and arterial pressure regulation [2]. Medial calcium is thought to cause arterial stiffening, reduce compliance, and limit distensibility [2]. Actually the way to distinguish intimal and medial calcium is through *ex vivo* histological analysis [22]. Then CT scans cannot define if the calcium is in the intimal or medial layer of aortic wall [2].

However, the patterns of calcium distribution observed in CT scans may suggest the predominance of intimal or medial calcium. Intimal calcium usually has a patchy distribution within atherosclerotic lesions and is most commonly amorphous without distinct architecture

[23]. On the other hand vascular medial calcium is generally concentric, appears more circumferential, and has a diffuse distribution [23]. The fig. 2 shows schematically the patterns of calcium distribution in the tunica intima and media.

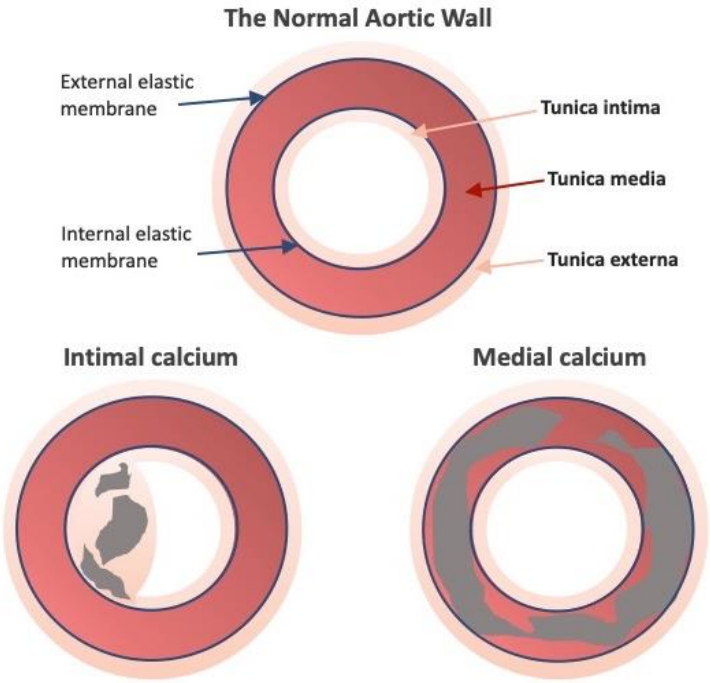

Fig. 2: Patterns of calcium distribution in the aortic wall. Intimal calcium has a patchy distribution in the atherosclerotic lesion and medial calcium is generally diffuse and circumferential.

Frequently, medial calcium is associated with uremia, radiotherapy or vascular inflammation which induces a phenotypic change of vascular smooth muscle cells into osteoblasts, a process of metabolite-induced (toxic) vascular changes in the absence of lipid deposits [24]. However aging, Chronic Kidney disease, *Diabetes Mellitus* and Mediastinal Radiation are also associated with accelerated intimal atherosclerosis. [24]. Therefore, the overlap of these two processes in the aortic wall might explain some differences in findings on cardiovascular risk factors associated with calcium in different vascular beds, and mainly between distinct aorta territories.

Differences in the anatomical references used at TAC evaluation

The differences in TAC evaluation can impact both the identification of calcium as well as its quantification either in volume or using the Agatston score. So, caution is advisable when interpreting and comparing studies that used different TAC extensions. Table 1 shows selected studies published in the last five years evaluating calcium in the thoracic aorta. They were grouped based on the aortic segments included in the analysis. The first group evaluated calcium in three segments: ascending thoracic aorta (ATA), aortic arch and descending thoracic aorta (DTA). The aortic root calcium was not included in this group. The second group represents the largest one, and evaluated TAC in the ATA, DTA and in the aortic root, but not in the aortic arch. The third, fourth and fifth groups included each a single study that used distinct anatomical references, respectively: the extended versions of ATA plus DTA, aortic arch, and aortic root. These studies shown in Table 1 also differ with respect on how they measured or analyzed the presence of calcium: yes/no [11], and/or Agatston [4,12,13,25–32] and/or volume [5,33–36], and/or density [19–21], and/or semi-qualitative evaluation [14]

Table 1 Recent thoracic aorta calcium studies organized according to each group of thoracic aorta anatomical references used in the CT evaluation.

Anatomical references	Study reference (design)	Population	TAC analysis	Objective	Conclusion
Total TAC: from the apex of the heart until the top of the aortic arch. **Total TAC = ATAC + AAC + DTAC** ATAC: from the origin of left coronary artery to the lower edge of the pulmonary bifurcation Aortic arch: above ATAC and DTAC DTAC: From the lower edge of pulmonary artery bifurcation to cardiac apex Obs.: aortic root was not included.	Craiem et al. 2014 (cross sectional)	n=970; 77% men; mean age 57 ± 9 years	Agatston	To investigate the prevalence and spatial distribution of TAC all along the thoracic aorta.	Aortic arch and proximal descending thoracic aorta concentrated most of the calcium. Middle-aged women were more prone to have calcium in those segments. TAC prevalence doubled from 31% to 64% comparing TAC evaluation without and with aortic arch, respectively.
	Craiem et al. 2016 (cross sectional)	n=1000; 78% men; mean age 57 ± 9 years		To assess TAC and CAC relations with non-CV events history in a cohort of subjects at risk for CVD and compare the findings between total TAC, partial TAC, and only aortic arch calcium	History of non-CV events was significant for total TAC, partial TAC, aortic arch, but not for CAC. But when entering total TAC and CAC together in the logistic regression as well as risk factors, of all covariates, OR was significant only for total TAC.
	Pedrosa et al. 2019 **ELSA-Brasil** (cross sectional)	n=2433; 54% women; mean age 56 ± 9 years	Calcium presence or absence	To assess the prevalence of TAC and CAC and verify if TAC is associated with the same cardiovascular risk factors as is CAC	Prevalence of TAC was much higher than CAC. Chances of CAC were higher in men and lower among blacks. There were no differences in TAC chances regarding gender and race/skin color.
	Rodríguez-Granillo et al. 2019 (Longitudinal)	n=1250; women 55%; mean age 56.5 ± 10.1 years; Follow up 3.7 years; Patients underwent clinically indicated chest CT scans for nonmalignant conditions.	Segment-involvement score	To explore the interplay and prognostic value of vascular calcifications and adipose tissue depots.	Age, pericardial fat volume upper tertile, and extensive CAC were independent predictors of all-cause death. Aortic calcium was not identified as predictor of death.
	Cho et al. 2015 (Longitudinal)	n=164; 100% men; mean age 73 years; Patients with hypertension	Volume	To investigate the relationship between TAC, arterial stiffening, left ventricular hypertrophy, and diastolic dysfunction	Heavy TAC and resultant arterial stiffening might underline left ventricular hypertrophy and diastolic dysfunction in elderly male patients with hypertension.
	Cho et al. 2016 (Longitudinal)	n=702; 58% women; mean age 69 ± 4 years Elderly individuals without obstructive CAD (Luminal stenosis < 50%)		To investigate the relationship of TAC and exercise SBP with all-cause death, (Heart failure, obstructive CAD, and stroke)	TAC was related to SBP response during exercise and was an independent predictor for outcomes, especially stroke, regardless SBP

Table 1 Recent thoracic aorta calcium studies organized according to each group of thoracic aorta anatomical references used in the CT evaluation.

Anatomical references	Study reference (design)	Population	TAC analysis	Objective	Conclusion
TAC = ATAC + DTAC ATAC: from the aortic annulus to the lower edge of the pulmonary artery bifurcation Obs.: Aortic root was included. DTAC: from the lower edge of pulmonary artery bifurcation to apex of the heart. Obs.: Aortic arch was not included.	Ong et al. 2014 **MESA** (cross sectional)	n=1632; Participants without diabetes with valid data on homeostasis model assessment index.	Agatston	To investigate the association of insulin resistance with AAC, CAC and TAC, and whether it differs according to different levels of subcutaneous fat area and visceral fat area.	There was a modest association of insulin resistance with the presence but not extent of calcified atherosclerosis, especially CAC. For TAC, the association tended to be stronger in participants with abdominal obesity.
	Yeboah et al. 2014 **MESA** (Longitudinal)	N= 5745; Follow up 9 years; Diabetics were excluded		To assess the improvement in discrimination afforded by the addition TAC, AVC, MVC, pericardial adipose tissue volume (PAT) and liver attenuation (LA) to FRFs plus CAC for incident CHD and CVD	CAC, TAC, AVC, MVC were independent predictors of incident CHD and CVD. When added to the FRFs, CAC has superior discriminative ability compared with TAC, AVC, MVC, PAT or LA. Compared with FRFs plus CAC, the addition of TAC, AVC, MVC, PAT or LA to the FRFs and CAC resulted in significant worsening of discrimination.
	Youssef et al. 2015 **MESA** (Longitudinal)	n=5886; 52% women; mean age 62 years; Follow up 2.4 ± 0.8 years	Agatston	To evaluate TAC progression.	Traditional CV risk factors were related to both TAC incidence and progression. Blacks had the lowest incidence and median changes across ethnic groups. The strongest risk factors for TAC incidence and progression were smoking, age, and hypertension.
	Kim et al. 2017 **MESA** (Longitudinal)	n=3415; 63% women; median age 55 years; Follow up 11 years; CAC=0 at baseline		To study the association between TAC and incident CHD, CVD events and all-cause mortality.	TAC did not improve 10-year estimation of prognosis beyond traditional risk factors.
	Katz et al. 2016 **MESA** (cross sectional)	n=6778; 53% women; mean age 62 years (range 45-84 years); Follow up 5 years	Agatston and volume	To examine the relation of the MetS, and each of its components, to the prevalence of TAC	MetS and diabetes are both independently associated with increased prevalence and severity of TAC after adjustment for age, gender and ethnicity.
	Thomas et al. 2017 **MESA** (Longitudinal)	n=6811; Follow up 10 years	Density and volume	To teste the hypothesis that ATAC volume and density predict incident CVD events independently of CAC.	One-SD higher ATAC density was associated with a lower risk of CHD and CVD after full adjustment, while ATAC volume was not associated with outcomes after full adjustments
	Thomas et al. 2018 **MESA** (Longitudinal)	n=5887; Follow up 2.4 years .		To evaluate changes in ATAC volume and density scores and incident atherosclerotic CVD.	After adjusting for CVD risk factors and baseline levels of ATAC volume and density, there were a significant association between an increase in ATAC volume over time and incident CHD, CVD, and ischemic stroke, while an increase in ATAC density over time was associated with a lower incidence of CHD and CVD, but not stroke.
	Thomas et al. 2018 **MESA** (Longitudinal)	n=6765; mean age 62 years Follow up 12 years		To evaluate the association of DTAC with non-CV morbidity and mortality.	DTAC is associated with non-CV morbidity and mortality.

Table 1 Recent thoracic aorta calcium studies organized according to each group of thoracic aorta anatomical references used in the CT evaluation.

Anatomical references	Study reference (design)	Population	TAC analysis	Objective	Conclusion
TAC = ATAC + DTAC ATAC: from the aortic annulus to the lower edge of the pulmonary artery bifurcation Obs.: Aortic root was included. DTAC: from the lower edge of pulmonary artery bifurcation to apex of the heart. Obs.: Aortic arch was not included.	Kälsch et al. 2017 **Heinz Nixdorf Recall Study** (Longitudinal)	n=3270; 53% women; 45-74 years of age; Follow up 5 ± 0.3 years	Agatston	To investigate associations of CV risk factors with incident TAC, of baseline TAC with incident CAC, and for baseline CAC with incident TAC.	TAC and CAC share similar major determinants for incidence and progression of calcification. High extent of TAC, especially ATAC, revealed considerably elevated risk of incidence and accelerated progression of CAC.
	Mahabadi et al. 2016 **Heinz Nixdorf Recall Study** (Longitudinal)	n=3630; 54% women; mean age 59 ± 8 years; Follow up of 10 ± 3 years		To determine whether noncoronary measures from cardiac CT may enhance the prognostic value of this diagnostic imaging tool.	Combined assessment of left ventricular and atrial axial area index, epicardial adipose tissue volume and TAC from cardiac CT improves the prediction of incident hard CV events above CAC and established CV risk factors.
	Hoffmann et al. 2016 **Framingham Heart Study** (Longitudinal)	n=3486; 51% women; mean age 50 ± 10 years; Follow up 8 years		To determine whether TAC, CAC, MVC and AVC predict incident major CHD, CVD, and all-cause mortality independent of FRFs.	After adjustment for age and sex, FRFs, and CAC, TAC was not statistically significant for prediction of CHD events and major CVD. However, TAC remained significantly associated with all-cause mortality even after these adjustments.
	Brodov et al. 2015 **EISNER** (Longitudinal)	n=1648; 54% men; mean age 52 ± 9; Follow up 5 years; CAC=0 at baseline		To evaluate the predictive value of TAC for CAC conversion.	TAC ≥ 100 Agatston is an independent predictor of CAC
TAC = ATAC + DTAC ATAC: above the origin of the right coronary artery to the end of scan range or up to the origin of the brachiocephalic artery. Obs.: aortic root was not included. DTAC: distal from the origin of the left subclavian artery up to the diaphragm. Obs.: aortic arch was not included.	Dudink et al. 2018 (Longitudinal)	n=327; 66% men; mean age 56 years; Follow up 67 ± 12 months; Low-risk population	Agatston	To determine the feasibility of assessing ATAC and DTAC on standard CAC scans and their associations of with coronary events	In patients without CAC, the event rate was higher in the patients with DTAC than in those without, which is comparable with patients with CAC without DAC. The event rate in patients with both CAC and DTAC was the highest. DTAC appears to improve the identification of those patients that will experience coronary events. ATAC showed no significant association with the occurrence of coronary events.

Table 1 Recent thoracic aorta calcium studies organized according to each group of thoracic aorta anatomical references used in the CT evaluation.

Anatomical references	Study reference (design)	Population	TAC analysis	Objective	Conclusion
TAC = ARCH Aortic arch: from the slice on which the ascending and descending aorta merge into the inner curvature of the arch to the first centimeter of the common carotid arteries, vertebral arteries, and subclavian arteries beyond the origin of the vertebral arteries.	Bos et al. 2015 **Rotterdam Study** (Longitudinal)	n=2408; 52% women; mean age 69 ± 7; Follow up 15775 person-years	Volume	To investigate associations of CAC, aortic arch, extracranial and intracranial internal carotid arteries with mortality adjusting for age, sex, and CV risk factors	Independent of calcification elsewhere, aortic arch calcium was related to a higher risk of CV mortality and non-CV mortality.
TAC = ARC ARC: the region of ATAC between the aortic annulus and the sinutubular junction.	Tesche et al. 2017 (Longitudinal)	n=189; 53% women; mean age 60 ± 11 years; Patients with intermediate pre-test probability of CAD	Volume and Agatston	To evaluate the correlation between ARC and CAC and their ability to predict obstructive CAD.	ARC is a strong and independent predictor of CAC and obstructive CAD.

Legend: ARC: aortic root calcium; ARCH; aortic arch; ATAC: ascending thoracic aorta calcium; AVC: aortic valve calcium; CAC: coronary artery calcium; CAD: coronary artery disease; CHD: coronary heart disease; CV: cardiovascular; CVD; cardiovascular disease; DTAC: descending thoracic aorta calcium; EISNER: Early Identification of Subclinical Atherosclerosis by Noninvasive Imaging research; FRFs: Framingham risk factors score; LA: liver attenuation; MVC: mitral valve calcium; MESA: Multi-ethnic Study of Atherosclerosis; MetS: metabolic syndrome; OR: *Odds ratio*; PAT: pericardial adipose tissue; SBP: systolic blood pressure; SD: Standard Deviation; TAC: thoracic aortic calcium.

Does the aortic arch add relevant information to TAC?

As shown by Craiem et al., the inclusion of aortic arch in combination with ATA and DTA doubled the TAC prevalence, mainly in middle-aged women [26]. Besides the impact on the overall and sex-specific prevalence of TAC, the inclusion of the aortic arch in TAC evaluation might also relate to TAC predictive value on morbidity and mortality. Bos et al., for instance, analyzed only the aortic arch and found that the volume of calcium in this segment was related to increased CV and non-CV mortality, after adjustment for many CV risk factors including CAC, intracranial and extracranial internal carotids calcium [33]. A recent study of Cho et al. used the same TAC extension described by Craiem et al. and followed 702 patients without obstructive coronary artery disease (CAD) during 64 months and also found TAC as an independent predictor for outcomes, especially stroke [34]. Thus, taking account these latter results, it appears that calcium in the aortic arch might contribute to TAC prediction, but we cannot rule out that it may be also a marker of calcium in other thoracic aorta segments.

What do we know about the presence of calcium in ATA and DTA?

The largest study group presented in Table 1 are the ones that assessed TAC using the same scan performed for CAC assessment. Thus, only the presence of calcium in the ascending thoracic aorta (ATAC) and descending thoracic aorta (DTAC) were evaluated. Eight studies are from Multi-ethnic Study of Atherosclerosis (MESA) and they measured calcium using Agatston, volume and/or density [19–21,28–31,35]. The others are from Heinz Nixdorf Recall Study [12,32], Framingham Heart Study [25] and EISNER [4], and all of them used Agatston to measure TAC. All these studies included the aortic root in the TAC and excluded

the aortic arch. As demonstrated by Tesche et al., calcium in the aortic root is a stronger and independent predictor of CAC and of obstructive CAD [36], suggesting that a similar process lead to calcium in these vascular beds. Thus, like the CAC [37], it is possible that calcium in aortic root reflects more localized than generalized atherosclerosis, differently from other thoracic aorta segments.

When taken together, results on ATAC plus DTAC associations and predictive value are controversial [25,28–32,35]. However, when Thomas et al. and Kälsch et al. studied the ATAC and DTAC separately, they found that while greater ATAC volume predicted the incidence and progression of CHD and CVD [12,21], DTAC was associated with the occurrence of non-CV morbidity and mortality [20]. These authors also showed that greater ATAC density, contrary to greater volume, was associated with lower risk of CAD [19,21], and explained such differences between aorta segments in terms of embryology, wall constitution and pathophysiologic mechanisms of calcium formation. It is thus, possible, that such differences in DTAC and ATAC also account for the controversial results reported by the other studies included in this group, as they are based on ATAC plus DTAC [25,28,29,31]. In light of these recent findings, further research using the same anatomical references for each thoracic aorta segment should be stimulated.

Anatomical references for TAC segmentation

Based on the current anatomical references used in some TAC studies, and understanding the possible value of studying each aortic segment separately, including the aortic arch, we created the video 1 to show each portion of the aorta slice-by-slice in axial CT images. Since aorta has an oblique path, some details are of importance. The following anatomical references were used for TAC segmentation:

1) ATAC: from the sinutubular junction to the lower edge of pulmonary artery bifurcation (Some caution with the first slices, because of the initial curvature of ascending aorta above aortic root, where there are some slices that both appear in the same axial slice).
2) Aortic arch calcium: from ascending to descending thoracic aorta at the same anatomical reference, which is the level of the lower edge of pulmonary artery bifurcation.
3) DTAC: from the lower edge of pulmonary artery bifurcation to the apex of the heart.

What is the best way to measure TAC?

In addition to anatomical definitions, other methodological TAC parameters deserve to be considered. Agatston method has been widely used, however the quantification of TAC can vary considerably between different CT systems once the acquisition of CAC scans, usually used to measure TAC, was not created for this application [38]. Mori et al. in 2015 described and validated a new volume-rendering approach to quantify TAC that demonstrated an excellent agreement of the pixel-based TAC score with volumetric TAC score and observed that volume-based score was less influenced by slice thickness as compared to pixel-based score [39]. Agatston score depends nonlinearly on the measured Hounsfield Unit density of each pixel in the calcium, which changes with different x-ray energies, while the calcium volume is only slightly affected by scanning at different energies [40]. Since TAC is in the early development phase, perhaps now is the time to think about more accurate measures of quantifying the TAC [38].

Is TAC radiation exposure justified?

The last, but a very important consideration to be made refers to the radiation dose involved in TAC extended exams (all segments). Although the increase in the radiation dose of

extended CAC, necessary to include the aortic arch, is lower than that delivered for a bilateral mammogram [26], its value remains uncertain. So far, there appear to be no doubt regarding the value of evaluating DTAC and ATAC on CAC scans, as CAC clinical indication is already established. Lung cancer screening trials [41] seem to offer some opportunity to evaluate the predictive value of all segments, especially the aortic arch.

Limitations

The current review of the literature is limited mostly due to the high variability across the studies included in the analysis. As previously detailed, there is no current standards to define which aortic segments to include or the most appropriate tool to quantify the presence and extent of TAC. Moreover, the outcomes included in each analysis are not similar. Collectively, those issues limit the comparison between studies and the potential to fully interpret those results in other populations or scenarios.

Future directions

Future studies should focus on the standardization of image acquisition, areas of the thoracic aorta to be included and most appropriate tools to quantify TAC. Moreover, detailed investigation on the different role of each thoracic aorta segment for the prediction of different outcomes, including separate analysis for coronary artery disease events, cerebrovascular events and incidence of acute aortic syndromes.

Additionally, more studies on the implications of such findings for clinical management are needed. Currently, TAC is understood to be atherosclerosis. However, the clinical management of asymptomatic individuals with atherosclerosis is currently based on the individual´s clinical risk profile with the potential use of other diagnostic tools, such as

CAC scores in selected individuals. Yet, not clear role for TAC in selecting the most appropriate management strategy for those individuals exist.

Conclusions

TAC has been considered as subclinical marker of atherosclerosis; however, the lack of standard protocol regarding the anatomical segments included and measurement analytical unit have contributed to controversial results and studies comparability. The accumulated evidences indicate that each aorta segment should be evaluated separately, as they differ in terms of structural characteristics, embryologic origin and pathophysiologic mechanisms of calcium formation along the aorta and predictive value.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

Abbreviations: ATA: ascending thoracic aorta; ATAC: ascending thoracic aorta calcium; CAC: coronary artery calcium; CAD: coronary artery disease; CHD: coronary heart disease; CV: cardiovascular; CVD; cardiovascular disease; CT: computed tomography; DTA: descending thoracic aorta; DTAC: descending thoracic aorta calcium; MESA: Multi-ethnic Study of Atherosclerosis; TAC: thoracic aortic calcium.

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8. ARTIGO DE RESULTADOS 2

Relation of Calcium in each segment of Thoracic Aortic to Cardiovascular Risk Factors (from The Brazilian Longitudinal Study of Adult Health [ELSA-Brasil])

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Relation of Calcium in each segment of Thoracic Aortic to Cardiovascular Risk Factors (from The Brazilian Longitudinal Study of Adult Health [ELSA-Brasil])

Abstract

Thoracic aortic calcium (TAC) has received an increased interest in recent researches as subclinical marker of atherosclerotic disease. However, the distribution of calcium along the aortic segments is heterogeneous. The purpose of the present study is to evaluate the prevalence of calcium in each segment of thoracic aorta, separately, and to compare the associations of cardiovascular (CV) risk factors with each of them. Cross-sectional analysis, including 2,427 participants (mean age 55.6 ± 8.7; 54,1% women) of the ELSA-Brasil cohort in Minas Gerais, Brazil. Nonenhanced ECG-gated multislice computed tomography were performed in 2015-2016. Multivariate logistic regression was used to determine the CV risk factors associated with each segment. Overall prevalence of ascending thoracic aortic calcium (ATAC), aortic arch calcium (AAC), and descending thoracic aortic calcium (DTAC) was 23.1%, 62.1%, and 31.2%, respectively. About 90.4% of the individuals with TAC had AAC and only 19,5% had calcium in all segments. In the multivariate, increasing age, lower levels of schooling, current smoking, higher body mass index, and use of blood pressure lowering medications remained associated with all segments. There were no gender differences and the use of antidiabetic medications were not associated with any segment. Although the prevalence of calcium was very different among the segments of the aorta, the associations with CV risk factors were similar.

Keywords: ascending aorta, aortic arch, descending aorta, risk factors, computed tomography, vascular calcification

Introduction

Thoracic aortic calcium (TAC) is a common imaging finding that reflects systemic atherosclerosis.(1) TAC has showed to impact to cardiovascular (CV) system as aortic wall calcium worse arterial stiffening,(2) which is associated with several end-organ damage.(3) Several studies have shown distinct associations of TAC compared to CAC analysis.(4–7) However, unlike CAC, TAC has not been performed through standard CT protocol, mainly with regard to anatomical extension evaluated and the use of ECG synchrony during exam.(8) Thus, studies that evaluated each aortic segment, separately, are very scarce, and even the majority of TAC studies do not include the aortic arch in the analysis.(9–13) The calcium distribution along the aorta is typically very heterogeneous.(8) Each aortic segment has different embryonic origin and is subject to assorted hemodynamic stress, which also appears to affect susceptibility to calcium(14), once the rate of calcium differs among individuals.(15) Since the calcium found in each aortic segment may be associated differently to CV risk factors(16), and probably has distinct prediction value for CV and non-CV morbidity and mortality(10,17–20), our aim is to evaluate the prevalence of ascending thoracic aortic calcium (ATAC), aortic arch calcium (AAC), and descending thoracic aortic calcium (DTAC) and to compare the associations of CV risk factors with each aortic segment.

Methods

The ELSA-Brasil Study is a multicenter cohort designed to investigate the determinants of CV disease and diabetes.(21) This prospective study was initiated in 2008 and included 15,105 civil servants, aged 35 to 74 years, active and retired employees of 6 Brazilian Institutions.(22) The present study was conducted in the Minas Gerais Investigation Center in 2015-2016, after the second examination of ELSA-Brasil cohort, which enrolled 2,923 participants. Pregnancy, postpartum, breast-feeding (until 6 months post

childbirth), exposure to radiation at work, any piece of metal in the chest (e.g., pacemaker and coronary stent), current radiotherapy, nonparticipation in second visit to Investigation Center and refusal to perform the exam were defined as exclusion criteria. Multislice computed tomography (MSCT) was performed in 2,638 participants. Individuals that reported medical history of myocardial infarction (n = 15), congestive heart failure (n = 21), stroke (n = 24) and/or cardiac surgery (n = 13) were excluded from the analysis. Additionally, 142 participants were submitted to a different scan protocol, in which the aortic arch was not included. Thus, 2,427 participants were included in the present study.

All participants had assigned a written informed consent. The study protocol has been priorly approved by the Universidade Federal de Minas Gerais's Ethics Committee on research in human and our protocol conforms to the Ethical Guidelines of the 1975 Declaration of Helsinki.

Medical history, anthropometric measurements, and laboratorial data for the present study were taken from the second examination of the ELSA-Brasil study (2012-2014). Information about age, gender, race/skin color, and medical history were obtained by face-to-face questionnaires. Race/skin color were self-reported and categorized according to Brazilian Census into white; brown or "pardo"; black; and others (Indigenous and Asian were included in the same group because its smaller participants number).(22) Educational level was classified as university degree; complete secondary school; complete elementary school; and incomplete elementary school. Smoking was defined as never smoker; former smoker; and current smoker. The reference to differentiate the group "never smoker" from the "smoker groups" (former and current) was at least 100 cigarettes (5 packs) throughout its life. After that, if the participant has not smoked in the last 30 days, he was considered "former smoker", otherwise, he would be a "current smoker".(23) Physical activity was classified as insufficient, moderate, and

vigorous based on the assessment of the short version of the International Physical Activity Questionnaire.(24) Excessive use of alcohol was defined as ≥ 210 g of ethanol per week for men and ≥ 140 g for women.(22) A case of acute myocardial infarction, myocardial revascularization or sudden death in first-degree relative (men aged ≤ 55 and women ≤ 65 years old) was considered as family history of premature cardiovascular disease (CVD).(21)

Body mass index (BMI) was calculated from the equation weight (Kg)/height (m^2). Resting blood pressure was measured three times in the seated position, in the left arm, 2 cm above the cubital fossa, using an Omron model 765CP automated oscillometric sphygmomanometer (Omron, Kyoto, Japan) and the average of the second and third readings was recorded to obtain systolic and diastolic blood pressure as continuous variables in mmHg.(25) Blood samples were collected in after 12-hours overnight fast to measure hemoglobin A1c (HbA1c), high-density lipoprotein (HDL)-cholesterol and low-density lipoprotein (LDL)-cholesterol.(21) The participants were asked about the use of continuous medication in the previous 2 weeks and were instructed to bring prescriptions and/or drugs used to assess the use of antidiabetic, anti-hypertensive, and lipid lowering medications.(26)

All participants underwent the same 64-slice MSCT scanner (*Lightspeed,* General Electric). The scanogram encompassed from 1 cm above the top of the aortic arch to the heart apex. The method has been reported previously.(4) The CT scan parameters were 2.5 mm thick slices with 20 x 0.62 mm collimation, 120 kVp, 100 mAs and prospective ECG triggering at 70% of the cardiac cycle. The reconstruction algorithm used body filter. The media of effective dose calculated was 1.75 mSv.

The images were firstly analyzed by one radiologist with 10 years of thoracic imaging experience that identified the presence of calcium in the thoracic aorta (TAC).

Correlation studies were performed using a random sample of 50 CT scans, which were scored twice by the observer and once by other general radiologist with 10 years of experience, resulting in intraclass correlation coefficients higher than 0.99 for intra and interobserver analysis. Finally, for the present study, all the images were reviewed by the observer together with a qualified technologist to separate TAC by segments.

Calcium was identified using semiautomatic software (*Smart Score 4.0*), that highlighted in green all calcium based on a threshold of 130 Hounsfield Unit (HU) and calculated the Agatston score.(27) The observer went over every axial image and delineated the calcium localized in the arterial beds to be validated. The anatomical references to evaluate the thoracic aorta by segments were based on a detailed description presented by a recent review article.(8) In summary, the ascending thoracic aortic calcium (ATAC) was considered from the sinutubular junction until the lower edge of pulmonary artery bifurcation, therefore calcium from Valsalva sinus and aortic valve was not included. The descending thoracic aortic calcium (DTAC) was defined from the level of the lower edge of pulmonary artery bifurcation to the heart apex. Consequently, the aortic arch calcium (AAC) was found above ATAC and DTAC using the same anatomical level as reference (the lower edge of pulmonary artery bifurcation).

Descriptive statistics were presented as mean and standard deviation for continuous variables and frequency distribution for categorical variables. Continuous variables were compared with Student *t* test and categorical variable with Pearson's chi-square test. ATAC, AAC and DTAC were dichotomized as present (Agatston > 0) or absent (=0). The independent association of sociodemographic, lifestyle, laboratorial, and clinical risk factors with ATAC, AAC and DTAC were assessed using multivariate logistic regression analysis. The analysis consisted of 4 stages for ATAC, AAC and DTAC, separately: Model zero (univariate analysis); Model 1 was adjusted for

sociodemographic factors (age, gender, race/skin color, and education); Model 2 added lifestyle factors (smoking, physical activity, and excessive use of alcohol), BMI, and family history of premature CVD; Model 3 included the remaining risk factors (LDL- and HDL-cholesterol, HbA1c, blood pressure, and the use of antidiabetic, antihypertensive, and lipid lowering medications). All associated covariables with $p < 0.20$ in the univariate analysis were considered in the multivariate models, but only the variables that remained statistically associated at the level of $p < 0.05$ remained in the final analysis (Model 3). The confidence interval corresponded to 95%. Statistical analysis was performed with Stata/MP 14.0 for MAC (StataCorp LP, College Station, Texas).

Results

The study population (2427 individuals) was assessed to demonstrate the distribution and prevalence of TAC by segments. Overall, 1669 (68.8%) participants demonstrated TAC. A total of 1508 (62.1%) individuals had AAC, which corresponds to 90.4% of the population with TAC. The prevalence of DTAC was 31.2% and ATAC prevalence was 23.1%. About 13.4% of TAC population had calcium in all segments and 28.4% had only AAC. Figure 1 shows a Venn diagram with the intersections of the study participants according to the distribution of TAC by segments. Figure 2 demonstrates no significant differences in the calcium prevalence between sexes in all aortic segments.

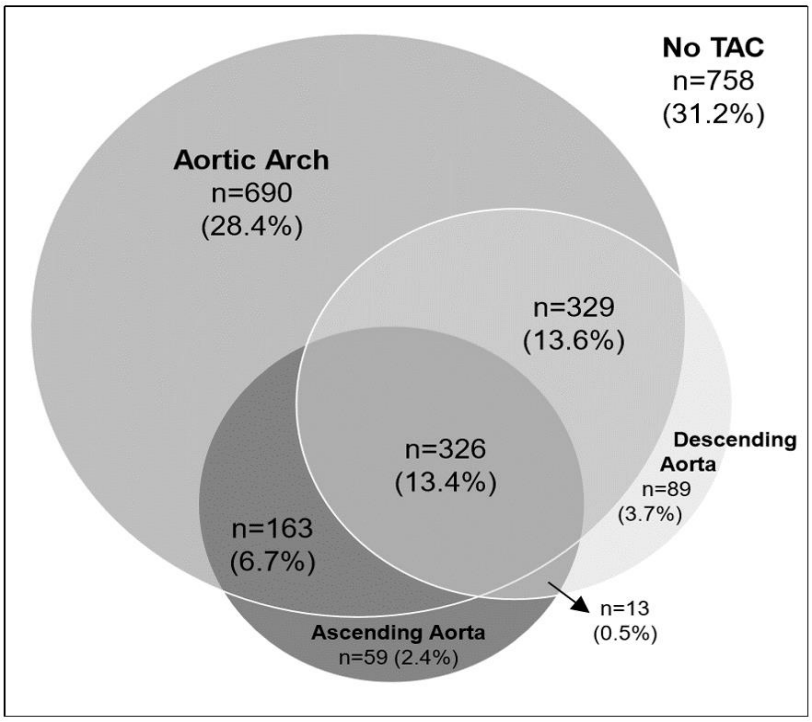

Figure 1. Venn diagram showing the distribution of calcium and the intersections of individuals according to aortic segments. Percentages refer to the total population (n=2427).

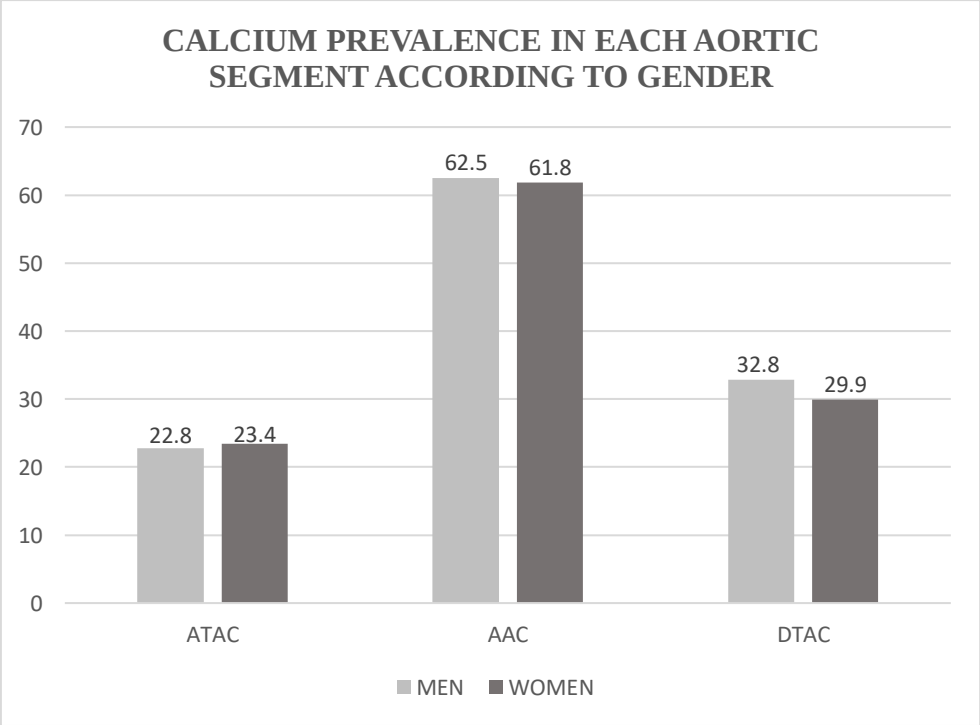

Figure 2. Clustered column graph demonstrating similar prevalences of calcium between sexes in all aortic segments. AAC: aortic arch calcium; ATAC: ascending thoracic aortic calcium; DTAC: descending thoracic aortic calcium.

Table 1 shows the characteristics of the study population in total and according to the presence or absence of ATAC, AAC and DTAC. Overall, the mean age was 55.6 ± 8.7 years; 54% women; nearly half were whites (49%); about 38% were either former or current smoker. Of the variables included in table 1, there were statistically no difference in TAC prevalence between the sexes and the levels of LDL- and HDL-cholesterol in any segment at the level of $p < 0.05$. Race/skin color showed a borderline significance for ATAC ($p = 0.05$) and the excessive use of alcohol, similarly, demonstrated statistically significant differences in ATAC prevalence, but not in AAC and DTAC prevalences. Physical activity and family history of premature CVD were not different only with DTAC.

The results of the multivariate analysis for CV risk factors with the presence of ATAC, AAC and DTAC are shown in table 2. The univariate and the models 1, 2 and 3 of multivariate analysis are included in the section *Supplemental Material*. Increasing age, lower levels of schooling, current smoking, higher BMI, and use of blood pressure lowering medications, all remained associated with greater odds ratio (OR) for ATAC, AAC and DTAC, with small differences in the magnitude of the associations. There were no statistical differences between genders regarding ATAC, AAC and DTAC in the final models. The association with past smoker was observed for ATAC and AAC. LDL-cholesterol and HDL-cholesterol were associated with ATAC and AAC, while the use of lipid lowering medications were related to ATAC and DTAC. Systolic blood pressure (SBP) kept on related to ATAC and DTAC, however the use of blood pressure lowering medication remained associated with all segments. Family history of premature CVD continued associated with only AAC, whereas HbA1c persisted associated with ATAC and DTAC in the final model of multivariate analysis. No aortic segment studied remained associated with the use of antidiabetic medications.

Table 1 – Characteristics of all population and according to presence or absence of calcium in each thoracic aortic segment (ELSA-Brasil, 2015-2016).

VARIABLES	Population N=2427 (100%)	ATAC = 0 N=1866 (76.9%)	ATAC > 0 N= 561 (23.1%)	*p* values	AAC = 0 N= 919 (37.9%)	AAC > 0 N=1508 (62.1%)	*p* values	DTAC = 0 N=1670 (68.8%)	DTAC > 0 N=757 (31.2%)	*p* values
Age (years)	55.6 ± 8.7	53.9 ± 8.2	61.1 ± 7.9	**< 0.001**	50.9 ± 7.2	58.5 ± 8.2	**< 0.001**	53.2 ± 7.7	60.8 ± 8.5	**< 0.001**
Women	1313 (54.1%)	1006 (53.9%)	307 (54.7%)	0.735	501 (54.5%)	812 (53.8%)	0.748	921 (55.1%)	392 (51.8%)	0.123
Race/ Skin color				**0.050**			0.156			0.163
White	1169 (48.7%)	869 (47.1%)	298 (53.8%)		418 (46.1%)	749 (50.2%)		779 (47.2%)	388 (51.9%)	
Brown	846 (35.3%)	667 (36.2%)	179 (32.3%)		336 (37.1%)	510 (34.2%)		601 (36.4%)	245 (32.8%)	
Black	319 (13.3%)	256 (13.9%)	63 (11.4%)		122 (13.5%)	197 (13.2%)		222 (13.5%)	97 (13.0%)	
Others (Asian, Indigenous)	65 (2.7%)	51 (2.8%)	14 (2.5%)		30 (3.3%)	35 (2.4%)		48 (2.9%)	17 (2.3%)	
Educational level				**< 0.001**			**< 0.001**			**< 0.001**
University degree	1626 (67.0%)	1271 (68.2%)	354 (63.2%)		667 (72.7%)	958 (63.6%)		1151 (69.0%)	474 (62.7%)	
Complete secondary school	613 (25.3%)	473 (25.4%)	139 (24.8%)		216 (23.5%)	396 (26.3%)		419 (25.1%)	193 (25.5%)	
Complete elementary school	102 (4.2%)	70 (3.7%)	32 (5.7%)		18 (2.0%)	84 (5.6%)		60 (3.6%)	42 (5.6%)	
Incomplete elementary school	86 (3.5%)	51 (2.7%)	35 (6.3%)		17 (1.8%)	69 (4.6%)		39 (2.3%)	47 (6.2%)	
Smoker				**< 0.001**			**< 0.001**			**< 0.001**
Never	1491 (61.5%)	1235 (66.2%)	256 (45.6%)		660 (72.0%)	831 (55.1%)		1082 (64.9%)	409 (54.0%)	
Past	705 (29.0%)	473 (25.4%)	230 (41.0%)		201 (21.9%)	502 (33.3%)		450 (27.0%)	253 (33.4%)	
Current	231 (9.5%)	156 (8.4%)	75 (13.4%)		56 (6.1%)	175 (11.6%)		136 (8.1%)	95 (12.6%)	
Physical activity				**0.007**			**0.006**			0.918
Insufficient	1729 (71.2%)	1352 (72.5%)	376 (67.0%)		671 (73.2%)	1057 (70.1%)		1190 (71.3%)	538 (71.1%)	
Moderate	497 (20.5%)	355 (19.1%)	141 (25.2%)		159 (17.3%)	337 (22.4%)		338 (20.3%)	158 (20.9%)	
Vigorous	201 (8.3%)	157 (8.4%)	44 (7.8%)		87 (9.5%)	114 (7.6%)		140 (8.4%)	61 (8.1%)	
Excessive use of alcohol	254 (10.5%)	177 (9.5%)	77 (13.7%)	**0.004**	87 (9.5%)	167 (11.1%)	0.216	162 (9.7%)	92 (12.1%)	0.069
Family history of CVD	804 (33.1%)	585 (31.3%)	219 (39.0%)	**0.001**	250 (27.2%)	554 (36.7%)	**< 0.001**	526 (31.5%)	278 (36.7%)	0.011
Body mass index (kg/m^2)	27.0 ± 4.7	26.6 ± 4.5	28.1 ± 5.3	**< 0.001**	26.2 ± 4.4	27.4 ± 4.9	**< 0.001**	26.6 ± 4.6	27.7 ± 5.0	**< 0.001**
LDL-cholesterol (mg/dL)	115.0 ± 30.3	114.9 ± 29.3	115.3 ± 33.6	0.777	113.8 ± 28.6	115.7 ± 31.3	0.134	115.2 ± 29.6	114.6 ± 31.8	0.635
HDL-cholesterol (mg/dL)	53.6 ± 13.5	53.9 ± 13.6	52.7 ± 12.8	0.066	54.0 ± 13.6	53.4 ± 13.4	0.223	53.9 ± 13.5	53.0 ± 13.3	0.122
Hemoglobin A1c (%)	5.5 ± 0.9	5.4 ± 0.8	5.7 ± 1.2	**< 0.001**	5.3 ± 0.7	5.6 ± 1.0	**< 0.001**	5.4 ± 0.8	5.7 ± 1.1	**< 0.001**
Systolic blood pressure (mmHg)	120.5 ± 15.5	118.9 ± 14.6	125.7 ± 17.0	**< 0.001**	116.9 ± 14.1	122.7 ± 15.9	**< 0.001**	117.9 ± 13.9	126.2 ± 17.2	**< 0.001**
Diastolic blood pressure (mmHg)	77.6 ± 9.7	77.2 ± 9.4	78.9 ± 10.4	**< 0.001**	76.7 ± 9.4	78.2 ± 9.8	**< 0.001**	76.9 ± 9.1	79.2 ± 10.7	**< 0.001**
Use of lipid lowering medications	524 (21.7%)	304 (16.4%)	219 (39.2%)	**< 0.001**	126 (13.8%)	397 (26.5%)	**< 0.001**	277 (16.7%)	246 (32.7%)	**< 0.001**
Use of antidiabetic medications	190 (7.6%)	97 (5.2%)	92 (16.4%)	**< 0.001**	41 (4.5%)	148 (9.8%)	**< 0.001**	76 (4.6%)	113 (14.9%)	**< 0.001**
Use of blood pressure lowering medications	859 (35.4%)	552 (29.6%)	306 (54.5%)	**< 0.001**	199 (21.7%)	659 (43.7%)	**< 0.001**	449 (26.9%)	409 (54.0%)	**< 0.001**

Data were presented as mean ± standard deviation, or n (%). AAC = artic arch calcium; ATAC = ascending thoracic aortic calcium; CVD = cardiovascular disease; DTAC = descending thoracic aortic calcium; HDL = high density lipoprotein; LDL = low density lipoprotein.

Table 2

Variables associated with ascending thoracic aortic calcium (ATAC), aortic arch calcium (AAC), and descending thoracic aortic calcium (DTAC) in the multivariate analysis. ELSA-Brasil, 2015-2016.

VARIABLES	ATAC	AAC	DTAC
Age (years)	**1.09 (1.07-1.11)*** **	**1.12 (1.11-1.14)*** **	**1.10 (1.09-1.12)*** **
Women	1.19 (0.93-1.52)	0.99 (0.80-1.22)	0.85 (0.69-1.04)
Educational level			
University degree	1.00	1.00	1.00
Complete secondary	0.96 (0.75-1.24)	1.17 (0.94-1.46)	0.97 (0.77-1.22)
Complete elementary	0.88 (0.54-1.44)	**1.78 (1.02-3.11)***	0.88 (0.56-1.40)
Incomplete elementary	**1.66 (1.00-2.75)***	1.62 (0.90-2.92)	**1.57 (0.96-2.59)**$^{+}$
Smoker			
Never	1.00	1.00	1.00
Past	**1.85 (1.46-2.34)*** **	**1.29 (1.03-1.60)***	0.95 (0.76-1.19)
Current	**2.47 (1.75-3.48)*** **	**2.02 (1.43-2.87)*** **	**1.78 (1.29-2.47)*** **
Body mass index (kg/m^2)	**1.05 (1.03-1.08)*** **	**1.05 (1.02-1.07)*** **	**1.04 (1.02-1.06)****
Hemoglobin A1c (%)	**1.14 (1.02-1.27)***	**1.39 (1.13-1.70)***	**1.17 (1.05-1.30)***
HDL-cholesterol (mg/dl)	**0.99 (0.98-0.99)***	**0.99 (0.98-1.00)***	-
LDL-cholesterol (mg/dl)	**1.01 (1.00-1.01)*** **	**1.00 (1.00-1.01)***	-
Systolic blood pressure (mmHg)	**1.01 (1.00-1.02)****	-	**1.02 (1.01-1.03)*** **
Use of blood pressure lowering medications	**1.48 (1.18-1.86)****	**1.66 (1.34-2.06)*** **	**1.80 (1.46-2.22)*** **
Use of lipid lowering medications	**2.35 (1.83-3.01)*** **	-	**1.36 (1.08-1.71)***

Data were presented as odds ratio (95% confidence interval). HDL: High density lipoprotein; LDL: low density lipoprotein. * $p \leq 0.05$; ** $p \leq 0.01$; *** $p \leq 0.001$; + $p=0.075$.

Discussion

Calcium distribution differs among TAC segments. In the present study we found the highest calcium concentration in the aortic arch (62%) and the lowest in the ascending aorta (23%). Few studies have compared the prevalences of TAC by segments. Craiem et al. have studied the segments of thoracic aorta, separately, and found results very similar with ours. While they showed 64% of total TAC prevalence and 31% of prevalence only for AAC, our results were 62.1% and 28.4%, respectively.(28) Thus, AAC has concentrated almost 50% of the calcium in the thoracic aorta. The differences in the prevalence of each aortic segment may be explained by the sheer forces on the wall, once ascending aorta usually has the largest diameter, high blood velocity and no branch vessels.(29) Though high velocity can cause shear stress, most raised lesions occur at sites where shear stresses are low but rapidly fluctuating, such as branch vessels or abrupt changes in vessel diameter, events that mostly occur in the aortic arch followed by descending aortic segment.(30)

Age, lower levels of schooling, current smoking, higher BMI, and use of blood pressure lowering medications remained associated with all the thoracic aortic segments in the final multivariate analysis. There are a robust evidence that smoking, hypertension and body mass index are important risk factors for aortic calcification independently of the segment and even studying abdominal aorta.(5,29,31–33) Regarding to HDL-cholesterol, LDL cholesterol and the use of lipid lowering medications, they were all associated with ATAC, while the cholesterol levels were associated with AAC and the use of lipid lowering medications was associated with DTAC. These associations may be related to the proximity of ATAC with CAC, once both were associated with HDL-cholesterol, LDL cholesterol and the use of lipid lowering medications, as shown in Pedrosa et. al. 2019.(4)

The variable HbA1c remained associated with ATAC and DTAC in the final model, but the use of antidiabetic medications was not associated with any aortic segment. Probably due to the high prevalence of AAC, that may has decreased the possibility of finding the association. On the other hand, our results may be reflecting a lesser influence of diabetes on aortic calcium. Ong et al. 2014, studying a population of 1632 participants that did not have diabetes, showed that HOMA-IR was associated with the presence of CAC, while TAC did not differ by HOMA-IR levels.(9) Differently of CAC, calcium formation in the aortic wall occur by two mechanisms: intimal (atherosclerotic) and medial (artheriosclerotic) processes.(34) Thus, whereas CAC is mostly intimal, medial calcium is common in the aorta.(35) This distinct pathophysiologic process of calcium formation in the vascular beds is probably related to the different associations between the CV risk factors and the presence of calcium in the coronaries and in the aorta, as previously described by Pedrosa et al. 2019.(4)

The higher levels of SBP were associated either with ATAC and DTAC, but not with AAC, probably again due to the high prevalence of AAC. In addition, the use of blood pressure lowering medications remained associated with AAC in the final model, suggesting that AAC is still related to high blood pressure. Our results also showed that current smoking was associated with all segments, however, considering the former smoking, the highest magnitude of association was with ATAC ($p < 0.001$), followed by AAC ($p=0.025$), while there was no association with DTAC. The possibility to explain these findings may be due to the way that nicotine influences cardiac function by increasing systolic and diastolic pressure, heart rate, force of myocardial contraction, myocardial oxygen consumption, and myocardial excitability through the release of endogenous epinephrine.(36) Consequently, it is possible

that ascending aortic wall is more directly influenced by smoking than others. It was also found by Takasu et al. in MESA cohort.(29)

There were no sexes differences in the univariate and multivariate analysis for any aortic segment. Comparing to CAC, that are significantly more frequent in men(4), the absence of differences between genders in all aortic segments reinforced the distinct pathologic processes involved in the calcium formation in different vascular beds. However, we would not expect that among the aortic segments this finding would be so similar. Reviewing the results of other researches, we found diverse associations. Takasu et al. investigated 6,814 participants (49% men, mean age: 63 ± 10 years) and demonstrated higher prevalence of DTAC in women, while for ATAC it was found only in persons younger than 55 years.(29) In contrast, the Heinz Nixdorf Study evaluated 4,025 individuals considering TAC as ATAC plus DTAC (47% men; mean age: 59 ± 9 years) and showed higher TAC prevalence in men.(5) And even considering the few studies including aortic arch, they have shown that women concentrate more calcium in this segment than men.(28,37,38) Thus, this is still a controversial topic.

The limitations of our study are related to the cross-sectional analysis, that cannot stablish the temporality of the associations. Since ELSA-Brasil is a cohort of civil servants in urban areas and our population came from one Brazilian state, the prevalence found cannot be extrapolated to the Brazilian population. On the other hand, the advantages of our study are a large multiethnic well-characterized sample; measurements of calcium in the segments of the thoracic aorta, separately, for which there is very limited literature; the adjustments for most risk factors for CVD.

In conclusion, we found small differences in the associations between CV risk factors and each aortic segment. Our findings awaken to the question about the importance of including the AAC in TAC analysis. So, since the prevalence of calcium in the aortic arch is high and the associations with CV risk factors are very similar among the thoracic aortic segments, the extended protocol seems to be not justified. However, future longitudinal studies evaluating the predictive value of calcium in each aortic segment would be of great importance to clarify the worth of calcium in each aortic segment as subclinical marker of CV morbidity and mortality.

Disclosures

The authors have no conflicts of interest to disclosure. The funding sources had no role in the design and conduct the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit for publication.

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Supplemental Material

Table 1

Variables associated with ascending thoracic aortic calcium in the univariate and multivariate analysis. ELSA-Brasil, 2015-2016. (N=2,407)

VARIABLES	MODEL 0 (Univariate)	MODEL 1	MODEL 2	MODEL 3 (Final)
Age (years)	**1.11 (1.09-1.12)*** **	**1.11 (1.09-1.12)*** **	**1.11 (1.09-1.12)*** **	**1.09 (1.07-1.11)*** **
Women	1.03 (0.85-1.25)	0.99 (0.81-1.22)	1.06 (0.85-1.30)	1.19 (0.93-1.52)
Educational level				
University degree	1.00	1.00	1.00	1.00
Complete secondary	1.06 (0.84-1.32)	1.11 (0.88-1.41)	1.02 (0.80-1.30)	0.96 (0.75-1.24)
Complete elementary	**1.64 (1.06-2.53)***	1.20 (0.76-1.90)	1.00 (0.63-1.60)	0.88 (0.54-1.44)
Incomplete elementary	**2.46 (1.58-3.85)*** **	**1.83 (1.14-2.94)***	**1.74 (1.07-2.81)***	**1.66 (1.00-2.75)***
Smoker				
Never	1.00		1.00	1.00
Past	**2.35 (1.91-2.89)*** **		**1.81 (1.44-2.27)*** **	**1.85 (1.46-2.34)*** **
Current	**2.32 (1.71-3.15)*** **		**2.43 (1.74-3.39)*** **	**2.47 (1.75-3.48)*** **
Body mass index (kg/m^2)	**1.06 (1.04-1.08)*** **		**1.08 (1.05-1.10)*** **	**1.05 (1.03-1.08)*** **
Hemoglobin A1c (%)	**1.45 (1.32-1.60)*** **			**1.14 (1.02-1.27)***
HDL-cholesterol (mg/dl)	**0.99 (0.99-1,00)**			**0.99 (0.98-0.99)***
LDL-cholesterol (mg/dl)	**1.00 (0.99-1.00)**			**1.01 (1.00-1.01)*** **
Systolic blood pressure (mmHg)	**1.03 (1.02-1.03)*** **			**1.01 (1.00-1.02)****
Use of blood pressure lowering medications	**2.85 (2.35-3.46)*** **			**1.48 (1.18-1.86)****
Use of lipid lowering medications	**3.28 (2.66-4.05)*** **			**2.35 (1.83-3.01)*** **

Data were presented as odds ratio (95% confidence interval). HDL: High density lipoprotein; LDL: low density lipoprotein. * $p \leq 0.05$; ** $p \leq 0.01$; *** $p \leq 0.001$.

Table 2

Variables associated with aortic arch calcium in the univariate and multivariate analysis. ELSA-Brasil, 2015-2016. (N=2,424)

VARIABLES	MODEL 0 (Univariate)	MODEL 1	MODEL 2	MODEL 3 (Final)
Age (years)	**1.13 (1.12-1.15)*** **	**1.13 (1.12-1.14)*** **	**1.13 (1.11-1.14)*** **	**1.12 (1.11-1.14)*** **
Women	0.97 (0.83-1.15)	0.91 (0.76-1.10)	0.91 (0.75-1.10)	0.99 (0.80-1.22)
Educational level				
University degree	1.00	1.00	1.00	1.00
Complete secondary	**1.28 (1.05-1.55)***	**1.31 (1.06-1.62)***	1.20 (0.97-1.49)	1.17 (0.94-1.46)
Complete elementary	**3.25 (1.93-5.46)*** **	**2.08 (1.21-3.60)** **	**1.83 (1.05-3.19)***	**1.78 (1.02-3.11)***
Incomplete elementary	**2.83 (1.65-4.85)*** **	1.73 (0.97-3.06)	1.63 (0.91-2.92)	1.62 (0.90-2.92)
Smoker				
Never	1.00		1.00	1.00
Past	**1.98 (1.64-2.41)*** **		**1.27 (1.02-1.58)***	**1.29 (1.03-1.60)***
Current	**2.48 (1.81-3.41)*** **		**2.05 (1.45-2.90)*** **	**2.02 (1.43-2.87)*** **
Body mass index (kg/m^2)	**1.06 (1.04-1.08)*** **		**1.06 (1.04-1.09)*** **	**1.05 (1.02-1.07)*** **
Family history of CVD	**1.55 (1.30-1.86)*** **		**1.39 (1.14-1.70)** **	**1.39 (1.13-1.70)***
HDL-cholesterol (mg/dl)	1.00 (0.99-1.00)			**0.99 (0.98-1.00)***
LDL-cholesterol (mg/dl)	1.00 (1.00-1.00)			**1.00 (1.00-1.01)***
Use of blood pressure lowering medications	**2.80 (2.32-3.38)*** **			**1.66 (1.34-2.06)*** **

Data were presented as odds ratio (95% confidence interval). CVD: cardiovascular disease; HDL: High density lipoprotein; LDL: Low density lipoprotein. * $p \leq 0.05$; ** $p \leq 0.01$; *** $p \leq 0.001$.

Table 3

Variables associated with descending thoracic aortic calcium in the univariate and multivariate analysis. ELSA-Brasil, 2015-2016. (N=2,407)

VARIABLES	MODEL 0 (Univariate)	MODEL 1	MODEL 2	MODEL 3 (Final)
Age (years)	**1.12 (1.11-1.13)*** **	**1.12 (1.11-1.13)*** **	**1.13 (1.11-1.14)*** **	**1.10 (1.09-1.12)*** **
Women	0.87 (0.74-1.04)	**0.81 (0.67-0.97)***	**0.78 (0.64-0.95)***	0.85 (0.69-1.04)
Educational level				
University degree	1.00	1.00	1.00	1.00
Complete secondary	1.12 (0.91-1.37)	1.19 (0.96-1.48)	1.10 (0.88-1.37)	0.97 (0.77-1.22)
Complete elementary	**1.70 (1.13-2.56)***	1.15 (0.74-1.79)	1.03 (0.66-1.61)	0.88 (0.56-1.40)
Incomplete elementary	**2.93 (1.89-4.53)*** **	**2.06 (1.29-3.30)** **	**1.90 (1.18-3.06)***	**1.57 (0.96-2.59)**$^{+}$
Smoker				
Never	1.00		1.00	1.00
Past	**1.49 (1.23-1.80)*** **		0.98 (0.79-1.21)	0.95 (0.76-1.19)
Current	**1.85 (1.39-2.46)*** **		**1.73 (1.27-2.38)** **	**1.78 (1.29-2.47)*** **
Body mass index (kg/m^2)	**1.05 (1.03-1.07)*** **		**1.07 (1.05-1.09)*** **	**1.04 (1.02-1.06)** **
Hemoglobin A1c (%)	**1.51 (1.36-1.67)*** **			**1.17 (1.05-1.30)***
Systolic blood pressure (mmHg)	**1.04 (1.03-1.04)*** **			**1.02 (1.01-1.03)*** **
Use of blood pressure lowering medications	**3.19 (2.67-3.82)*** **			**1.80 (1.46-2.22)*** **
Use of lipid lowering medications				**1.36 (1.08-1.71)***

Data were presented as odds ratio (95% confidence interval). * $p \leq 0.05$; ** $p \leq 0.01$; *** $p \leq 0.001$; + p=0.075.

9. CONSIDERAÇÕES FINAIS

As diferenças entre as associações do CAC e do TAC com os fatores de risco cardiovascular sugerem mecanismos distintos de formação da calcificação nestes territórios vasculares. O aspecto multifatorial, a complexidade dos mecanismos de formação do cálcio na parede da aorta torácica e a extensão da aorta apontam para a necessidade de sua avaliação por segmentos. Entretanto, os achados encontrados não sustentam a inclusão do arco aórtico no mesmo escaneamento do escore de cálcio coronariano. A alta prevalência de cálcio no arco aórtico e a semelhança entre as associações dos fatores de risco com cada segmento da aorta, parecem não justificar o estudo do arco aórtico. Entretanto, estudos longitudinais serão fundamentais para avaliar a progressão das calcificações e confirmar as semelhanças ou apontar as diferenças entre os segmentos da aorta torácica, principalmente em relação ao potencial de predizer o risco de morbidade e mortalidade CV e não CV na nossa população.

É importante ainda considerar que todas as variáveis respostas, CAC, TAC, ATAC, AAC e DTAC, foram analisadas como variáveis dicotômicas. Não se conhecem os resultados das análises com as variáveis respostas tratadas de forma quantitativa. Além disso, a categorização das variáveis e a interação de CAC com o TAC por segmentos ainda merecem ser exploradas, o que nos proporciona uma infinidade de perguntas e hipóteses a serem testadas com os dados que já coletamos neste estudo.

Por fim, uma pergunta desafiadora seria sobre “o que o radiologista deveria escrever no laudo sobre as calcificações?”. Não há respaldo científico para sugerir, definir ou orientar qualquer propedêutica baseada na presença de calcificação na aorta. Entretanto, uma sugestão para o radiologista geral seria descrever além da presença de calcificação, em qual segmento aórtico ela está localizada. Há evidências de que a presença de calcificação somente no arco aórtico tem um significado diferente da presença de calcificação na porção ascendente,

independente de ter ou não calcificação nos demais segmentos. Oferecer este dado no laudo pode contribuir para pesquisas futuras, além de despertar a atenção do clínico para possíveis correlações com os dados clínicos e laboratoriais dos pacientes.

10. CONCLUSÕES

O presente estudo mostrou que a prevalência de TAC foi maior do que a prevalência de CAC para todas as faixas etárias e em ambos os sexos na população de indivíduos do ELSA-Brasil em Minas Gerais. Além disso, as prevalências de TAC e CAC aumentaram com a idade e foram maiores em homens do que mulheres até a menopausa. As prevalências de TAC, apesar de não terem sido estatisticamente diferentes entre homens e mulheres em nenhuma faixa etária, apresentaram valores um pouco maiores em homens entre 38 e 64 anos (exceto entre 45-49 anos), passando a apresentar valores um pouco maiores em mulheres acima de 65 anos. Em relação às prevalências de CAC, foi observada uma redução significativa das diferenças entre os sexos a partir de 65 anos. Até os 64 anos as prevalências de CAC em homens eram no mínimo o dobro das prevalências de CAC em mulheres, enquanto a partir de 65 anos as prevalências de CAC nas mulheres passam a representar mais de 70% das prevalências de CAC em homens. Estas diferenças entre as prevalências de CAC e TAC de acordo com o sexo e a faixa etária apontam para um fator de proteção associado ao sexo feminino para doenças cardiovasculares na pré-menopausa, provavelmente relacionado aos níveis hormonais de estradiol e estrogênio nesta faixa etária.

Em relação às prevalências de CAC e TAC total, houve diferenças significativas quanto ao sexo, raça e as variáveis associadas a diabetes. Enquanto CAC apresentou maiores prevalências em homens e na raça branca, TAC não apresentou diferenças significativas entre as prevalências em homens e mulheres, nem entre as raças. Além disso, na análise multivariada,

TAC não permaneceu associado ao uso de medicamentos antidiabéticos, nem aos níveis séricos de HbA1c.

No estudo da aorta torácica por segmentos, observou-se maior prevalência de cálcio no arco aórtico, seguida pela aorta descendente, e por fim, a aorta ascendente. As associações com os fatores de risco CV foram semelhantes para todos os segmentos da aorta, porém a maior prevalência de cálcio no arco aórtico pode ter enfraquecido as associações neste segmento. Destaca-se ainda a não associação do uso de medicamentos antidiabéticos com nenhum segmento aórtico estudado, aliado a associação dos níveis de HbA1c com ATAC e DTAC e não com AAC. Diferentemente do CAC que apresentou associação apenas com o uso de medicamentos antidiabéticos e não com os níveis de HbA1c no modelo final da análise multivariada.

Conclui-se que o presente estudo apresenta suas limitações, porém representa uma primeira análise das calcificações na aorta torácica e nas coronárias e de suas associações com os fatores de risco CV na população do ELSA-Brasil em Minas Gerais. Os resultados obtidos geraram inúmeras perguntas, propostas de metodologias de análises dos dados e, ainda proporcionou dados basais para o acompanhamento destes participantes ao longo do tempo. Portanto, este foi o primeiro estudo de uma linha de pesquisa repleta de possibilidades sobre a análise tomográfica das calcificações vasculares no ELSA-Brasil.

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ANEXO 1 - Aprovação da Emenda pelo COEP da UFMG

UNIVERSIDADE FEDERAL DE MINAS GERAIS
COMITÊ DE ÉTICA EM PESQUISA - COEP

Projeto: CAAE – 47125015.4.1001.5149

Interessado(a): Profa. Sandhi Maria Barreto
Departamento de Medicina Preventiva e Social
Faculdade de Medicina - UFMG

DECISÃO

O Comitê de Ética em Pesquisa da UFMG – COEP aprovou, no dia 10 de dezembro de 2015, a emenda, abaixo relacionada, do projeto de pesquisa intitulado **"Estudo longitudinal de saúde do adulto – ELSA Brasil UFMG"**:

- Inclusão da avaliação do escore de calcificação das artérias coronárias, arco aórtico e artérias carótidas, por meio de imagens de tomografia computadorizada do coração, do arco aórtico e artérias carótidas.

O relatório final ou parcial deverá ser encaminhado ao COEP um ano após o início do projeto através da Plataforma Brasil.

Telma Campos Medeiros Lorentz

Profa. Dra. Telma Campos Medeiros Lorentz
Coordenadora do COEP-UFMG

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Telefax: (031) 3409-4592 - e-mail: coep@prpq.ufmg.br

ANEXO 2 - Termo de Consentimento Livre e Esclarecido

Estudo Longitudinal de Saúde do Adulto ELSA BRASIL

ESTUDO LONGITUDINAL DE SAÚDE DO ADULTO (ELSA-Brasil)

Mensuração do escore de calcificação das artérias coronárias, arco aórtico e artérias carótidas por meio de imagens de tomografia computadorizada

Termo de Consentimento Livre e Esclarecido (TCLE)

Apresentação do estudo

O Estudo Longitudinal de Saúde do Adulto (ELSA - Brasil) é uma pesquisa sobre doenças crônicas que acometem a população adulta, incluindo as doenças cardiovasculares, o diabetes e a demência. É um estudo pioneiro no Brasil por acompanhar os adultos estudados por um longo período de tempo, em várias etapas. O ELSA - Brasil é desenvolvido por seis Centros de Investigação pertencentes a instituições públicas de ensino e pesquisa, localizados em seis estados brasileiros (BA, ES, MG, RJ, RS e SP)[1] e coordenado por representantes de cada centro, do Ministério da Saúde e do Ministério da Ciência e Tecnologia, tendo sido aprovado pelos Comitês de Ética em Pesquisa dos seis centros. Em Belo Horizonte, o estudo está sob a responsabilidade da Universidade Federal de Minas Gerais, sob a coordenação do Hospital das Clínicas.

No Centro de Investigação ELSA de Minas Gerais (CI-MG), os participantes do ELSA - Brasil realizarão exames de tomografia computadorizada do coração, do arco aórtico e artérias carótidas para a avaliação da presença de calcificação das lesões ateroscleróticas. Para garantir a qualidade das imagens de tomografia computadorizada realizadas ao longo do ELSA - Brasil, a técnica para obtenção das imagens foi padronizada.

Objetivo

Mensurar o escore de calcificação das artérias coronárias, arco aórtico e artérias carótidas por meio de imagens por tomografia computadorizada no ELSA - Brasil.

Instituições envolvidas

O exame de tomografia computadorizada do coração, do arco aórtico e artérias carótidas será realizado no Centro de Tecnologia em Medicina Molecular da Faculdade de Medicina da

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[1] Universidade Federal da Bahia (UFBA), Universidade Federal do Espírito Santo (UFES), Universidade Federal de Minas Gerais (UFMG), Fundação Osvaldo Cruz (FIOCRUZ), Universidade Federal do Rio Grande do Sul (UFRGS) e Universidade de São Paulo (USP).

UFMG, localizado no Campus Saúde, Av. Alfredo Balena, nº190, Bairro Santa Efigênia, atrás do Hospital São Geraldo, em frente ao Banco Sicoob Credicom, próximo a uma guarita dos seguranças do Campus Saúde.

Participação no estudo

O(a) Sr(a) está sendo convidado(a) a participar como voluntário(a) para mensuração do escore de calcificação das artérias coronárias, arco aórtico e artérias carótida por meio de imagens de tomografia computadorizada realizado no ELSA - Brasil.

O exame de tomografia computadorizada têm duração média de 20 minutos e não há necessidade do uso de meio de contraste e nem de jejum para a realização do exame. As contra indicações para a realização deste exame são suspeita de gravidez, puérperas, mulheres amamentando até 6 meses após o parto, pessoas em tratamento radioterápico atual, exposição frequente à radiação em ambiente de trabalho (se este for o seu caso, favor informar à equipe ELSA), utilização de marcapasso, stent cardíaco, clip cirúrgico metálico intracraniano ou qualquer tipo de metal na região do coração, pescoço e crânio. A dose efetiva de radiação recebida durante a tomografia computadorizada é pequena (4,9 milisievert - mSv). Por exemplo, os limites de dose efetiva para indivíduos que estão em exposição frequente à radiação no ambiente de trabalho são de até uma média de 20 mSv por ano em 5 anos consecutivos, ou até 50 mSv em um único ano.

Seus direitos como participante

Sua participação neste estudo é inteiramente voluntária. Se quiser, poderá deixar de participar da pesquisa a qualquer momento.

Não será feito qualquer pagamento pela sua participação, e o resultado do escore de cálcio coronariano será fornecido gratuitamente. Os voluntários poderão ter acesso aos resultados das análises realizadas no estudo por meio de publicações científicas e do *website* oficial da pesquisa (www.elsa.org.br).

As imagens de tomografia computadorizada neste estudo não têm como objetivo o diagnóstico de nenhuma doença. Entretanto, elas podem contribuir para o (a) senhor (a) conhecer melhor sua saúde e podem indicar a necessidade de acompanhamento com o seu médico. Portanto, o escore de cálcio coronariano lhe será entregue, e o (a) Sr (a) será orientado (a) a procurar as unidades da rede SUS, ou outro serviço de saúde de sua preferência, quando elas indicarem alguma alteração em relação aos padrões considerados normais.

Todas as informações obtidas do (a) senhor (a) serão confidenciais, identificadas por um número e sem menção ao seu nome. Elas serão utilizadas exclusivamente para fins de análise científica e serão guardadas com segurança. Somente terão acesso a essas informações os pesquisadores envolvidos no projeto. Em nenhuma hipótese será permitido o acesso a informações individualizadas a qualquer pessoa, incluindo empregadores, superiores hierárquicos e seguradoras.

Uma via deste Termo de Consentimento Livre e Esclarecido lhe será entregue. Se houver perguntas ou necessidade de mais informações sobre o estudo, ou qualquer intercorrência, o(a) Sr(a) pode procurar a coordenadora do ELSA - Brasil em Minas Gerais, Professora

Sandhi Maria Barreto, Faculdade de Medicina, no endereço: Av. Alfredo Balena, n° 190, Santa Efigênia. Telefone: (31) 3409-9140.

O Comitê de Ética em Pesquisa da Universidade Federal de Minas Gerais (COEP/ UFMG) pode ser contatado em caso de dúvidas éticas no seguinte endereço:
Av. Antônio Carlos, 6627, Unidade Administrativa II – 2º andar – Sala 2005 - Campus Pampulha - Belo Horizonte, MG. E-mail: coep@prpq.ufmg.br, ou pelo telefone: (31) 3409-4592.

Sua assinatura a seguir significa que o(a) Sr(a) leu e compreendeu todas as informações e concorda em participar da mensuração do escore de calcificação das artérias coronárias, arco aórtico e artérias carótidas por meio de imagens de tomografia computadorizada do ELSA - Brasil.

Nome do(a) participante:

_____

Documento de identidade:_____

Data de nascimento:_____/_____/_____

Endereço_____

_____CEP_____

Telefones para contato:_____

Declaro que compreendi as informações apresentadas neste documento e dei meu consentimento para participar da mensuração do escore de calcificação das artérias coronárias, arco aórtico e artérias carótidas por meio de imagens de tomografia computadorizada, realizada pelo Centro de Investigação ELSA de Minas Gerais.

Assinatura: _____

Data: _____/_____/_____

Assinatura do pesquisador: _____

Local: _____ Data: _____/_____/_____

APÊNDICE 1 – Cópia da publicação do Artigo de Resultados 1

ARTICLE IN PRESS

Relation of Thoracic Aortic and Coronary Artery Calcium to Cardiovascular Risk Factors (from The Brazilian Longitudinal Study of Adult Health [ELSA-Brazil])

Jesiana F. Pedrosa, MD[a], Antonio Luiz P. Ribeiro, MD, PhD[b], Priscila C. Santana, PhD[a], Larissa F. Araújo, PhD[c], and Sandhi M. Barreto, MD, PhD[d,*]

Thoracic aortic calcium (TAC) and coronary artery calcium (CAC) are associated with an increased risk of cardiovascular disease (CVD) and death. However, risk factors associated with arterial calcium may vary across vascular beds. We verified whether TAC is associated with the same risk factors as is CAC in adults without established CVD. Cross-sectional analysis including 2,433 participants (aged 38 to 78 years) of ELSA-Brasil cohort in Minas Gerais, Brazil. Nonenhanced ECG-gated multislice computed tomography were performed to detect calcium in the thoracic aorta and the coronaries (2015 to 2016). Multivariate logistic regression evaluated the associations of both TAC and CAC with CVD risk factors (smoking, body mass index, physical activity, alcohol intake, family history of CVD, low-density lipoprotein- and high-density lipoprotein-cholesterol, HbA1c, blood pressure, antidiabetic, antihypertensive, and lipid lowering medications). Overall prevalence of TAC and CAC were 69% and 43%, respectively. CAC prevalence was lower among women (31%) than men (56%) (Adjusted odds ratio [OR] 0.30; 0.24 to 0.38). After adjustments, black individuals were less likely to have any CAC as compared with whites (OR 0.63; 0.47 to 0.86). Neither sex, nor race/skin color were statistically associated with TAC. Use of antidiabetic medications remained associated with CAC (OR 1.80; 1.23 to 2.631.01), but not with TAC. All other risk factors, except education, alcohol, physical activity and HbA1c, persisted statistically associated with both TAC and CAC in the final analysis, with small differences in the magnitudes of the ORs. In conclusion, the only disagreements seen in the risk factors associated with CAC and TAC were sex, race/skin color, and use of antidiabetic medications. **(Am J Cardiol 2019;00:1–7)**

Many studies have demonstrated that the presence of either coronary artery calcium (CAC) or thoracic aortic calcium (TAC), detected by computed tomography (CT), are markers of subclinical atherosclerosis and are associated with an increased risk of cardiovascular events.[1,2] Allison et al (2012) followed up 4,544 individuals who underwent whole body CT to ascertain, and found after about 7.8 years, that the calcium in thoracic aorta, carotids, and iliac arteries were associated with total mortality, whereas the presence of CAC was associated with cardiovascular disease (CVD) mortality.[3] Knowledge on the association of particular cardiovascular risk factors to the presence of calcium in thoracic aorta and/or coronary arteries may contribute to understand the different mechanisms of atherosclerosis. We performed a cross-sectional study to assess the prevalence of TAC and CAC and verify if TAC is associated with the same cardiovascular risk factors as is CAC in participants from Minas Gerais Investigation Center of ELSA-Brasil Study without overt CVD.

Methods

The study is embedded in the ELSA-Brasil Study, a multicenter cohort designed to investigate the determinants of CVD and diabetes.[4] The study started in 2008 and included 15,105 civil servants. Eligibility criteria included active and retired employees of 6 institutions, aged 35 to 74 year.[5] The present study was conducted in the Minas Gerais

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See page 6 for disclosure information.

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Investigation Center. Multislice Computed Tomography (MSCT) was performed in 2015 to 2016 after the second visit (2012 to 2014), which enrolled 2,923 participants. Exclusion criteria for MSCT scan was pregnancy, postpartum, breast-feeding (until 6 months post childbirth), exposure to radiation at work, any piece of metal in the chest (e.g., pacemaker and coronary stent), current radiotherapy, nonparticipation in second visit to Investigation Center and refusal to perform MSCT scan. A total of 2,638 participants were scanned. Of these, 63 reported a history of CVD at second visit and were excluded from this analysis. History of CVD was defined as medical history of myocardial infarction (n = 15), congestive heart failure (n = 21), stroke (n = 24) or cardiac surgery (n = 13). Additionally, in 142 participants measurements of both CAC and TAC were not available due to use of different scan protocol, in which the aortic arch was not included. Thus, 2,433 participants were included in the present study.

Written informed consent was obtained from each participant included in the study. The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki and our protocol has been priorly approved by the Universidade Federal de Minas Gerais's ethics committee on research in humans.

Sociodemographic, behavioral, and medical history factors were obtained by face-to-face questionnaires. Race/skin color were self-reported and participants could choose from a fixed set of categories based on Brazilian Census classification: white; brown or "pardo"; black and others (Indigenous and Asian were grouped in the same category because its smaller participants number).[5] Educational level was categorized into university degree, complete secondary school, complete elementary school, and incomplete elementary school. Smoking was assessed by the following questions: "Are you or have you ever been a smoker, that is, have you smoked at least 100 cigarettes (5 cigarette packs) throughout your life?" and "Do you currently smoke cigarettes?" (never smoker, former smoker, and current smoker).[6] Never smoker were the reference group. Physical activity was assessed by the short version of the International Physical Activity Questionnaire and participants were classified as insufficient (<600 metabolic equivalent-min/week), moderate (600 to 3000), and vigorous (≥3000).[7] Excessive use of alcohol was defined as ≥210 g of ethanol per week for men and ≥140 g for women.[5] Family history of premature CVD was defined as "positive" if the participant reported a case of acute myocardial infarction, myocardial revascularization or sudden death in first-degree relative (men aged ≤55 and women ≤65 years old).[4]

Body mass index (BMI) was calculated by dividing the participant's weight in kilograms by height in meters squared. Blood pressure was measured 3 times in the seated position after 5 minutes of rest, automatically (Omron 765CP; Omron, Kyoto, Japan) in the left arm, 2 cm above the cubital fossa, and the average of the second and third measurements was considered to obtain systolic and diastolic blood pressure as continuous variables in mm Hg.[8] Blood samples were collected in after 12-hours overnight fast to measure hemoglobin A1c (HbA1c), high-density lipoprotein (HDL)-cholesterol and low-density lipoprotein (LDL)-cholesterol.[4] The use of antidiabetic, antihypertensive, and lipid lowering medications was self-reported. All participants were asked about the use of continuous medication in the previous 2 weeks and were instructed to bring prescriptions and/or drugs used to the study clinic.[9]

Imaging was performed with a 64-slice MSCT scanner (*Lightspeed*, General Electric). The scanogram encompassed all thoracic aorta, and the heart, from 1 cm above the top of the aortic arch to the heart apex as is shown in Figure 1. The scan consisted of 56 to 88 images. Before performing the scan, the participants exercised breath holding. Within a single breath hold consecutive nonoverlapping 2.5 mm thick slices were acquired with 20 × 0.62 mm collimation, 120 kVp, 100 mAs and prospective electrocardiogram triggering at 70% of the cardiac cycle. The media of effective dose calculated was 1.75 mSv.

Calcium was identified and scored by only one experienced radiologist, using semiautomatic software (*Smart Score 4.0*). Correlation study was performed with a second experienced radiologist. A random sample of 50 participants was scored twice by the observer and once by the other radiologist, who has only participated in this correlation study. Intraclass correlation coefficients for all arteries scored were higher than 0.99 for intraobserver and interobserver analysis.

The software highlighted in green all calcium based on a threshold of 130 Hounsfield Unit (HU).[10] Then, the observer went over every axial image and clicked on the green lesions to turn them another codified color as is shown in Figure 1. CAC presence consisted of any calcified lesions identified within left main, left anterior descending, left circumflex, and right coronary artery. The presence of TAC was defined as any calcium on the aortic arch, ascending, and descending aorta wall, from the sinutubular junction until the last image of heart apex. Calcium from Valsalva sinus and aortic valve was not included.

Descriptive statistics was based on mean and standard deviation for continuous variables and frequency distribution for categorical variables. Continuous variables were compared with Student *t* test and categorical variable with Pearson's chi-square test. TAC and CAC were dichotomized as present (Agatston score >0) or absent (=0). The independent association of sociodemographic, lifestyle, laboratory, and clinical risk factors with TAC and CAC were assessed using multivariate logistic regression analyses. The analysis consisted of 4 stages for TAC and CAC separately: model zero (univariate analysis); Model 1 was adjusted for sociodemographic factors (age, gender, race/skin color, and education); Model 2 added lifestyle factors (smoking, physical activity, and alcohol intake), BMI, and family history of CVD; Model 3 included the remaining risk factors (LDL- and HDL-cholesterol, HbA1c, blood pressure, antidiabetic, antihypertensive, and lipid lowering medications). All associated covariables with $p < 0.20$ in the univariate analysis were considered in the multivariate models, but only the variables that remained statistically associated at the level of $p < 0.05$ remained in the final analysis (Model 3) of TAC or CAC. The confidence interval corresponded to 95%. Statistical analyses were performed with Stata/MP 14.0 for MAC (StataCorp LP, College Station, Texas).

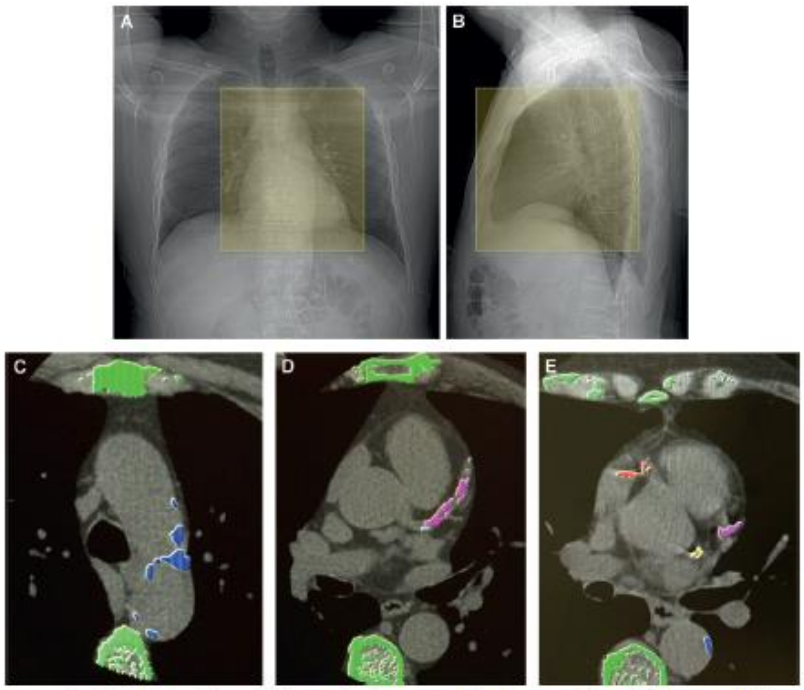

Figure 1. (*A* and *B*) Scanogram: frontal and lateral views. Yellow rectangles represent the tomographic acquisition area. (*C, D* and *E*) Screens obtained by "Smart Score" software showing any calcium area highlighted in green. Calcium in different vascular beds are shown according to codified colors: blue, aortic arch (*C* and *E*); pink, anterior descending artery (*D* and *E*); light blue, left main coronary artery (*D*); red, right coronary artery and yellow, circumflex artery (*E*).

Results

The overall prevalences of TAC and CAC were 69% and 43%, respectively. Figure 2 shows a Venn diagram with the intersection of all study participants according to the presence or absence of CAC and/or TAC. About 24% of participants were free from both TAC and CAC, while 37% had TAC and CAC, simultaneously. Almost all participants with CAC also had TAC (94%).

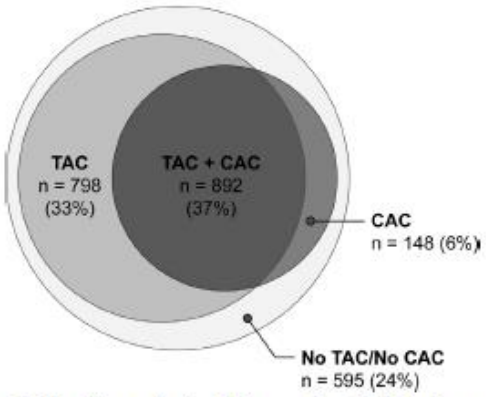

Figure 2. Venn diagram showing the intersection of individuals according to presence or absence of coronary artery calcium (CAC) and thoracic aortic calcium (TAC). Percentages refer to the overall population (n = 2,433). ELSA-Brasil, 2015-2016.

Figure 3 shows the prevalences of TAC and CAC according to gender and age category. The prevalence of CAC was significantly lower in women than in men at all age groups, whereas the prevalence of TAC was quite similar between genders throughout age groups.

Table 1 shows the distribution of the study population characteristics in total and according to presence or absence of TAC and CAC. Overall, the mean age was 55.6 ± 8.7 years; 54% women; nearly half were whites (49%); about 67% had university degree. Thirty-eight percent were either current or former smoker; and 33% had a family history of CVD. In all the factors included in Table 1, only gender, race/skin color, physical activity, excessive use of alcohol, and HDL-cholesterol were not statistically associated with the presence of TAC at the level of $p < 0.05$. Whereas only physical activity and LDL-cholesterol had nonsignificant association with CAC in the univariate analysis. The results of the multivariate analysis for cardiovascular risk factors associated with the presence of TAC and CAC are shown in Tables 2 and 3, respectively. Increasing age, current smoking, family history of CVD, higher BMI, LDL-cholesterol and systolic blood pressure, lower HDL-cholesterol, use of lipid and blood pressure lowering medications, all remained associated with greater odds ratio (OR) for TAC and CAC, with small differences in the magnitude of the associations. The chance of having CAC was lower in women than men,

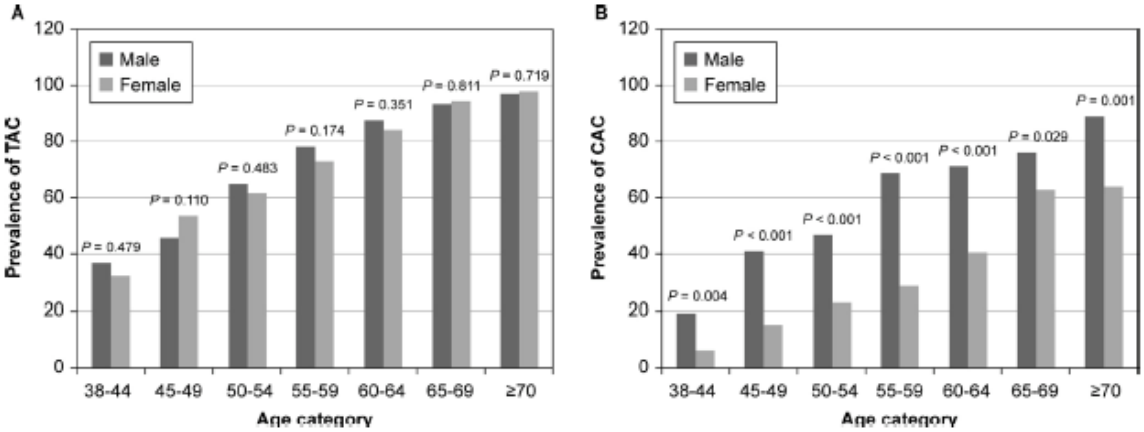

Figure 3. (*A* and *B*) Prevalences of thoracic aortic calcium (TAC) and coronary artery calcium (CAC) according to gender and age category, respectively. ELSA-Brasil, 2015-2016.

Table 1
Characteristics of all population and according to presence or absence of thoracic aortic calcium (TAC) and coronary artery calcium (CAC). ELSA-Brasil, 2015-2016

Variables	Population N = 2,433 (100%)	TAC = 0 N = 743 (30.5%)	TAC >0 N = 1,690 (69.5%)	p Values	CAC = 0 N = 1,393 (57.3%)	CAC >0 N = 1,040 (42.7%)	p Values
Age (years)	55.6 ± 8.7	50.2 ± 6.8	58.0 ± 8.4	**<0.001**	52.9 ± 8.0	59.2 ± 8.3	**<0.001**
Women	1,314 (54.0%)	400 (53.8%)	914 (54.1%)	0.910	903 (64.8%)	411 (39.5%)	**<0.001**
Race/skin color				0.378			**<0.001**
White	1,169 (48.6%)	337 (46.2%)	832 (49.7%)		625 (45.4%)	544 (53.1%)	
Brown	850 (35.4%)	276 (37.8%)	574 (34.3%)		501 (36.4%)	349 (34.0%)	
Black	319 (13.3%)	97 (13.3%)	222 (13.3%)		208 (15.1%)	111 (10.8%)	
Others (Asian, Indigenous)	65 (2.7%)	20 (2.7%)	45 (2.7%)		44 (3.2%)	21 (2.1%)	
Educational level				**<0.001**			**<0.001**
University degree	1,627 (66.9%)	540 (72.8%)	1,087 (64.4%)		958 (68.8%)	669 (64.4%)	
Complete secondary school	616 (25.3%)	174 (23.4%)	442 (26.2%)		354 (25.5%)	262 (25.2%)	
Complete elementary school	102 (4.2%)	17 (2.3%)	85 (5.0%)		42 (3.0%)	60 (5.8%)	
Incomplete elementary school	86 (3.5%)	11 (1.5%)	75 (4.4%)		38 (2.7%)	48 (4.6%)	
Smoker				**<0.001**			**<0.001**
Never	1,494 (61.5%)	539 (72.6%)	955 (56.5%)		961 (69.1%)	533 (51.3%)	
Past	705 (29.0%)	161 (21.7%)	544 (32.2%)		318 (22.8%)	387 (37.3%)	
Current	232 (9.5%)	42 (5.7%)	190 (11.3%)		113 (8.1%)	119 (11.4%)	
Physical activity				0.078			0.064
Insufficient	1,732 (71.2%)	543 (73.2%)	1,189 (70.4%)		1,016 (73.0%)	716 (68.9%)	
Moderate	498 (20.5%)	132 (17.8%)	366 (21.7%)		263 (18.9%)	235 (22.6%)	
Vigorous	201 (8.3%)	67 (9.0%)	134 (7.9%)		113 (8.1%)	88 (8.5%)	
Excessive use of alcohol	254 (10.4%)	69 (9.3%)	185 (10.9%)	0.220	109 (7.8%)	145 (14.0%)	**<0.001**
Family history of CVD	807 (33.2%)	202 (27.2%)	605 (35.8%)	**<0.001**	409 (29.4%)	398 (38.3%)	**<0.001**
Body mass index (kg/m^2)	27.0 ± 4.7	26.1 ± 4.4	27.4 ± 4.8	**<0.001**	26.6 ± 4.6	27.5 ± 4.8	**<0.001**
LDL-cholesterol (mg/dl)	115.0 ± 30.3	112.2 ± 28.7	116.3 ± 30.9	**0.002**	115.0 ± 29.3	115.1 ± 31.6	0.926
HDL-cholesterol (mg/dl)	53.6 ± 13.4	54.3 ± 13.7	53.3 ± 13.3	0.113	55.2 ± 13.3	51.4 ± 13.4	**<0.001**
Hemoglobin A1c (%)	5.5 ± 0.9	5.3 ± 0.7	5.5 ± 1.0	**<0.001**	5.3 ± 0.7	5.6 ± 1.1	**<0.001**
Systolic blood pressure (mm Hg)	120.5 ± 15.5	116.2 ± 13.4	122.4 ± 15.9	**<0.001**	117.6 ± 14.6	124.4 ± 15.8	**<0.001**
Diastolic blood pressure (mm Hg)	77.6 ± 9.7	76.4 ± 9.1	78.1 ± 9.9	**<0.001**	76.7 ± 9.5	78.8 ± 9.8	**<0.001**
Use of lipid lowering medications	525 (21.7%)	87 (11.8%)	438 (26.1%)	**<0.001**	194 (14.0%)	331 (32.0%)	**<0.001**
Use of antidiabetic medications	191 (7.9%)	26 (3.5%)	165 (9.8%)	**<0.001**	56 (4.0%)	135 (13.0%)	**<0.001**
Use of blood pressure lowering medications	861 (35.4%)	145 (19.5%)	716 (42.4%)	**<0.001**	374 (26.9%)	487 (46.9%)	**<0.001**

Data were presented as mean ± standard deviation, or n (%). CVD = cardiovascular disease; HDL = high density lipoprotein; LDL = low density lipoprotein.

Table 2
Variables associated with thoracic aortic calcium (TAC) in the univariate and multivariate analysis. ELSA-BRASIL, 2015-2016. (N = 2,419)

Variables	MODEL 0 (Univariate)	MODEL 1	MODEL 2	MODEL 3 (Final)
Age (years)	**1.14 (1.12-1.15)*** **	**1.14 (1.12-1.15)*** **	**1.14 (1.12-1.15)*** **	**1.12 (1.11-1.14)*** **
Women	1.01 (0.85-1.20)	0.93 (0.77-1.13)	0.92 (0.75-1.12)	1.10 (0.88-1.39)
Smoker				
Never	1.00		1.00	1.00
Past	**1.91 (1.55-2.34)*** **		1.19 (0.94-1.49)	1.21 (0.95-1.53)
Current	**2.55 (1.80-3.62)*** **		**2.19 (1.51-3.18)*** **	**2.16 (1.48-3.14)*** **
Body mass index (kg/m^2)	**1.06 (1.04-1.08)*** **		**1.07 (1.05-1.09)*** **	**1.04 (1.02-1.07)*** **
Family history of CVD	**1.49 (1.24-1.81)*** **		**1.29 (1.04-1.59)***	**1.25 (1.01-1.55)***
LDL-cholesterol (mg/dl)	**1.00 (1.00-1.01)** **			**1.01 (1.00-1.01)*** **
HDL-cholesterol (mg/dl)	0.99 (0.99-1.00)			**0.99 (0.98-0.99)***
Systolic blood pressure (mm Hg)	**1.03 (1.02-1.04)*** **			**1.01 (1.00-1.02)***
Use of blood pressure lowering medications	**3.03 (2.47-3.72)*** **			**1.67 (1.31-2.12)*** **
Use of lipid lowering medications	**2.64 (2.06-3.39)*** **			**1.37 (1.03-1.82)***

Data were presented as odds ratio (95% confidence interval). CVD = cardiovascular disease; HDL = high density lipoprotein; LDL = low density lipoprotein.
* $p \leq 0.05$; ** $p \leq 0.01$; *** $p \leq 0.001$

Table 3
Variables associated with coronary artery calcium (CAC) in the univariate and multivariate analysis. ELSA-Brasil, 2015-2016. (N = 2,388)

Variables	MODEL 0 (Univariate)	MODEL 1	MODEL 2	MODEL 3 (Final)
Age (years)	**1.10 (1.08-1.11)*** **	**1.11 (1.09-1.12)*** **	**1.10 (1.09-1.12)*** **	**1.09 (1.07-1.10)*** **
Women	**0.35 (0.30-0.42)*** **	**0.28 (0.23-0.34)*** **	**0.27 (0.23-0.33)*** **	**0.30 (0.24-0.38)*** **
Race/skin color				
White	1.00	1.00	1.00	1.00
Brown	**0.80 (0.67-0.96)** **	0.97 (0.79-1.18)	0.94 (0.77-1.15)	0.87 (0.70-1.07)
Black	**0.61 (0.47-0.79)*** **	0.77 (0.58-1.03)	**0.70 (0.53-0.94)***	**0.63 (0.47-0.86)** **
Others (Asian, Indigenous)	**0.55 (0.32-0.93)***	0.69 (0.39-1.24)	0.75 (0.42-1.34)	0.69 (0.38-1.26)
Smoker				
Never	1.00		1.00	1.00
Past	**2.19 (1.83-2.63)*** **		**1.39 (1.13-1.71)** **	**1.41 (1.14-1.75)** **
Current	**1.90 (1.44-2.51)*** **		**1.74 (1.28-2.37)*** **	**1.67 (1.22-2.30)*** **
Body mass index (kg/m^2)	**1.04 (1.02-1.06)*** **		**1.06 (1.04-1.08)*** **	**1.03 (1.01-1.05)** **
Family history of CVD	**1.49 (1.26-1.77)*** **		**1.43 (1.18-1.74)*** **	**1.35 (1.10-1.64)** **
HDL-cholesterol (mg/dl)	**0.98 (0.97-0.98)*** **			**0.99 (0.98-0.99)***
LDL-cholesterol (mg/dl)	1.00 (1.00-1.00)			**1.01 (1.00-1.01)*** **
Systolic blood pressure (mm Hg)	**1.03 (1.02-1.04)*** **			**1.01 (1.00-1.02)** **
Use of antidiabetic medications	**3.57 (2.58-4.93)*** **			**1.80 (1.23-2.63)** **
Use of blood pressure lowering medications	**2.40 (2.03-2.85)***			**1.47 (1.19-1.82)*** **
Use of lipid lowering medications	**2.89 (2.37-3.53)***			**2.01 (1.58-2.56)*** **

Data were presented as odds ratio (95% confidence interval). CVD = cardiovascular disease; HDL = high density lipoprotein; LDL = low density lipoprotein.
* $p \leq 0.05$; ** $p \leq 0.01$; *** $p \leq 0.001$

but there was no statistical differences between genders regarding TAC. Race/skin color differences were also observed only for CAC, with blacks being less likely to have any CAC compared with whites. Similarly, the use of antidiabetic drugs remained associated only with CAC in the final Model.

Discussion

The present study showed a much higher prevalence of TAC compared with CAC. After full adjustments, the chances of CAC were higher in men and lower in black individuals as compared with white ones. However, there were no differences in TAC chances regarding gender and race/skin color. All other cardiovascular risk factors but the use of antidiabetic medication, were statistically associated with both TAC and CAC with subtle differences in the OR.

Considering the few studies that compared the overall prevalences of TAC and CAC and that have also included the aortic arch in TAC analysis, our results contrast with those of Craiem et al as they found similar prevalences of TAC (64%) and CAC (62%) in a sample of 970 adults (77% men), aged 57± 9 years.[11] In contrast, our results agree with Jacobs et al findings concerning the greater prevalence of TAC (97%) than CAC (75%), even though their prevalences were much higher than ours, possibly because they studied a high-risk population of heavy smokers, 83% men.[12]

Even though extensive evidences exist that men are more likely to have CAC,[12–15] the absence of gender differences in the chances of having TAC remains controversial.

Some studies found greater prevalence of TAC in men and others in women. Nasir et al studied 8,549 individuals (69% men, mean age: 52 ± 9 years) and demonstrated slightly higher prevalence of TAC in women,[16] while the Heinz Nixdorf Study analyzed 4,025 participants (47% men, mean age: 59 ± 9 years) and showed higher TAC prevalence in men.[13] However, the CT scan protocols of these latter studies did not include the aortic arch and, hence their prevalences cannot be directly compared with ours as this may impact gender differences in the prevalence of TAC. Reports including the aortic arch are scarce, but some show that women concentrate more calcium in this segment than men,[11,17,18] even though the inclusion of the aortic arch in the analysis will increase the prevalence of TAC in both genders. Craiem et al investigated a population of asymptomatic subjects at increased cardiovascular risk, and showed that TAC prevalence doubled from 31% to 64% after using the scan method covering the aortic arch.[11]

Our study found an absence of race/skin color difference in the prevalence of TAC, whereas CAC was 40% lower in black individuals as compared with white ones, and this difference was not explained by cardiovascular risk factors. Our results on CAC are in accordance with the MESA study, as they also found lower chance of CAC (OR 0.78; 95% confidence interval 0.74 to 0.82) in blacks as compared with whites.[19] However, they disagree with MESA concerning the prevalence of TAC, as they reported lower prevalence of TAC in African Americans (27%) than in whites (42%).[20] Such differences might be related to the inclusion of the aortic arch in our study, as there appear to be race differences concerning the distribution of calcium along the aorta. In the MESA cohort, blacks had higher prevalence of calcium in the ascending portion of the aorta than whites, whereas they showed lower calcium in the descending aorta segment.[21] Unfortunately, studies comparing TAC prevalence in different race/skin color are scarce, indicating an important gap to be pursued in future research, and do not know whether race differences also exist regarding the aortic arch that could account for the absence of race/skin color difference in TAC prevalence that we found. Finally, race/skin color findings in the Brazilian population must be interpreted considering 2 important facts (1) self-referred race/skin color does not equate biological ancestry information[22]; (2) different from other multiethnic populations, the Brazilian population has not only intrapopulation ethnic diversity, but also intraindividual ancestry variety.[23]

The finding of no statistical association between variables related to diabetes and TAC in the present study may reflect a true weaker association of diabetes and calcification in the aortic territory, when compared with coronary arteries. Indeed, in the MESA Study insulin resistance, evaluated by the homeostasis model assessment index, was associated with the presence of CAC, but not TAC in individuals without diabetes, even though significant associations were seen between insulin resistance and TAC in individuals in the 3rd tertile of subcutaneous and visceral fat areas.[24] In contrast, a recent study showed that higher HbA1c and the presence of diabetes were associated with thoracic aorta calcium after adjustment for several risk factors.[25] However, we cannot discard that our finding of no association reflect differences in diabetes contribution to the pathophysiologic pathways of atherosclerosis in distinct arterial territories.

The race/skin color and gender differences in TAC and CAC prevalences found here may also express different underlying pathophysiologic processes relevant to different diseases. There are 2 mechanisms of vascular calcium: intimal (atherosclerotic) and medial (arteriosclerotic).[26] Whereas CAC is mostly intimal, medial calcium is common in the aorta and uncommonly reported in the coronary arteries.[27] Abramowitz et al posit that TAC can be the result of both atherosclerotic and nonatherosclerotic processes, with the former occurring in the tunica intima of the vessel wall and the latter occurring in the tunica media.[28] Thomas et al suggested that medial calcium may reflect biological aging.[29]

The present study has limitations. It is cross-sectional analysis and the temporality of the associations cannot be stablished. The prevalences found cannot be extrapolated to the Brazilian population, given that ELSA-Brasil is a cohort of civil servants in urban areas, and in this study they come from just one Brazilian state.[4] To counterbalance these limitations, the strengths of our study include a large multiethnic well-characterized sample; measurements of calcium from aortic arch, ascending, and descending thoracic aorta segments for which there is very limited literature; the comparison with CAC, and simultaneous adjustments for most risk factors for CVD.

In conclusion, we found differences between TAC and CAC prevalences in genders and race/skin color that might be related to the mechanisms of calcium formation across different vascular beds. Further studies using similar protocols, including aortic arch and the analysis of each segment of the aorta separately, might shed some light in the potential contribution of TAC in the classification of cardiovascular risk and whether it varies by gender, race/skin color or diabetes status.

Disclosures

The authors have no conflicts of interest to disclose. The funding sources had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit for publication.

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APÊNDICE 2 – Cópia da publicação do Artigo de Revisão

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EVIDENCE-BASED MEDICINE, CLINICAL TRIALS AND THEIR INTERPRETATIONS (L. ROEVER, SECTION EDITOR)

Anatomical References to Evaluate Thoracic Aorta Calcium by Computed Tomography

Jesiana Ferreira Pedrosa [1] · Sandhi Maria Barreto [1] · Márcio Sommer Bittencourt [2] · Antonio Luiz Pinho Ribeiro [1]

Abstract

Purpose of Review Thoracic aortic calcium (TAC) has received some interest in recent studies as an important subclinical marker of atherosclerosis. Besides that, using computed tomography (CT) scans performed with cardiac or chest protocols, ECG-gated, or non-gated, TAC can be easily evaluated with no addition in radiation dose. This review discusses the particularities of the aortic wall calcium formation, as well as the differences between the aortic segments and summarizes the current status of TAC evaluation, mainly concerning the anatomical references used in the studies.

Recent Findings The studies have evaluated TAC considering different anatomical references. It was identified two different study groups. In the first one, researchers have analyzed the aorta as the sum of calcium in the ascending aorta (ATAC), aortic arch (AAC), and descending thoracic aorta (DTAC). The second group has used cardiac CT scans to assess TAC; therefore, they did not include AAC; however, the aortic root calcium (ARC) was added in the analysis. So, caution is advisable when interpreting and comparing studies that used different TAC anatomical references.

Summary The broad methodological variability, in addition to the variations in the population characteristics of the studies on TAC, may be in part contributing to the differences between results of different studies. Currently TAC does not have a role in clinical decisions, so it is necessary to create a standard protocol for the aortic calcium research as well as exists for the coronary artery calcium evaluation.

Keywords Computed tomography · Thoracic aorta · Vascular calcification · Cardiovascular disease · Aortic Atherosclerosis · Aortic Arteriosclerosis

Introduction

Atherosclerosis is a systemic, progressive, and chronic condition that can affect the entire vascular tree [1]. Calcium in the artery wall is considered a direct marker of atherosclerotic disease [1] and can be easily evaluated through computed tomography (CT) [2]. There are remarkable mass of robust data supporting the prime role of coronary artery calcium (CAC) in cardiovascular risk assessment of the intermediate-risk population, as well as specific subgroups, as patients with diabetes and family history of premature coronary heart disease (CHD) [3]. Several studies have shown that thoracic aortic calcium (TAC) is also a marker of subclinical atherosclerosis [4]. Distinct associations of TAC arouse interest in its particularities compared with CAC analysis. TAC also impacts the CV system, as aortic wall calcium worsen arterial stiffening [5], which is associated with several implications for end-organ damage [6]. CAC and TAC prevalence also seem to differ between men and women and race/skin color [7–11], though results are inconsistent. Moreover, unlike CAC, TAC has not been evaluated through standard CT protocol, mainly with regard to TAC anatomical extension [12–14] and the use of ECG synchrony during exam [15].

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Because differences in TAC definition and acquisition might impair the evaluation of study's results on the predictive value of TAC both at individual and population levels, our aim was to review recent studies about TAC, discussing the particularities of the aortic wall calcium formation and the differences between the aortic segments. And, finally, emphasize the anatomical references and the extension of the aorta included in the TAC studies.

Mechanisms Related to the Calcium Formation in the Thoracic Aorta Wall

The distribution of calcium along the aorta is usually very heterogeneous. It is possible to identify coarse calcium in one segment, while there is no calcium in another segment from the same individual, as shown in Fig. 1. In the first case (images 1a and 1b), there was calcium in large amount in the arch and descending thoracic segments, while there was no calcium in the ascending aorta. In the second case (images 1c and 1d), the calcium concentration was much higher in the aortic arch compared with ascending and descending thoracic portions.

The variation in the distribution of calcium across aorta segments may be in part associated with different embryonic origin of the vascular smooth muscle cells colonizing the aorta, which in the aortic arch derives from cardiac neural crest cells, whereas the calcium found in the descending aorta derives from the mesoderm [16]. The Leroux-Berger et al. study found correlation between the embryonic origin of vascular smooth muscle cells and the timing of the appearance of calcium [16]. Thus each aortic segment differs in their embryonic origin and is subject to different hemodynamic stress, which also appears to affect susceptibility to calcium [16], as the rate of calcium seems to differ among individuals [17]. Therefore, the calcium found in each aortic segment may be associated differently to cardiovascular risk factors [18] and probably has distinct predictive value for cardiovascular (CV) and non-CV morbidity and mortality, as suggested in some studies [12, 13, 19, 20•, 21•].

Another important particularity refers to the molecular mechanism of plaque calcium in the aortic wall, which is mainly composed by two mechanisms:

1) Intimal calcium: atherosclerosis, inflammatory response of tunica intima;
2) Medial calcium: occurs independently of intimal calcium in the tunica media.

The intimal layer consists of endothelial cells that eventually form atheromatous plaques which can rupture and cause thromboembolic events, whereas the medial layer consists of smooth muscle cells and elastic fibers that are associated with blood flow and arterial pressure regulation [2]. Medial

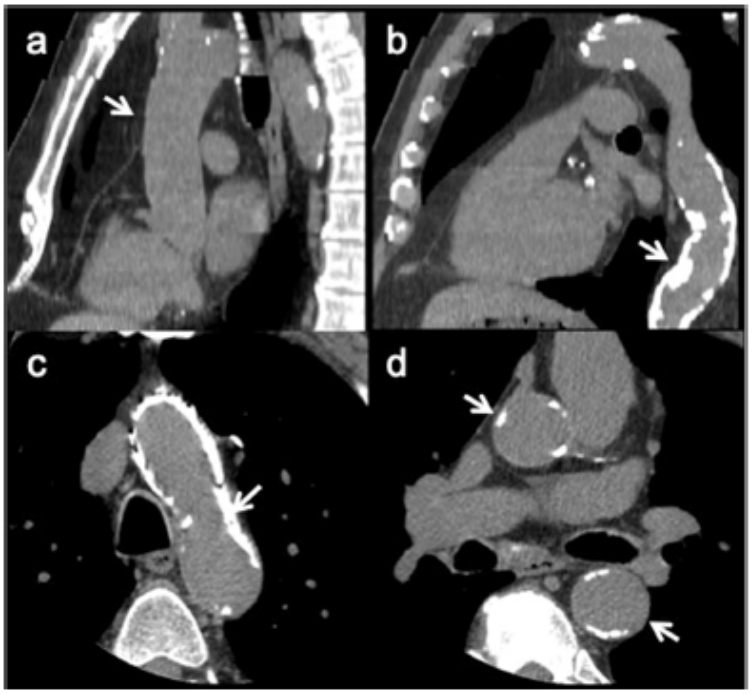

Fig. 1 Heterogeneous distribution of calcium along the aorta. a, b CT reconstructions in the parasagittal plane. In this case, ascending aorta had no calcium (arrow in a), whereas in the arch and descending portions (arrow in b) there were circumferential plaques covering almost all aortic wall. c, d CT reconstructions in the axial plane. The most calcium concentration was in the aortic arch (arrow in c), while in ascending (superior arrow in d) and descending (inferior arrow in d) segments calcium were coarse, but sparse

calcium is thought to cause arterial stiffening, reduce compliance, and limit distensibility [2]. Actually the way to distinguish intimal and medial calcium is through ex vivo histological analysis [22]. Then CT scans cannot define if the calcium is in the intimal or medial layer of aortic wall [2].

However, the patterns of calcium distribution observed in CT scans may suggest the predominance of intimal or medial calcium. Intimal calcium usually has a patchy distribution within atherosclerotic lesions and is most commonly amorphous without distinct architecture [23•]. On the other hand, vascular medial calcium is generally concentric, appears more circumferential, and has a diffuse distribution [23•]. Figure 2 shows schematically the patterns of calcium distribution in the tunica intima and media.

Frequently, medial calcium is associated with uremia, radiotherapy, or vascular inflammation which induces a phenotypic change of vascular smooth muscle cells into osteoblasts, a process of metabolite-induced (toxic) vascular changes in the absence of lipid deposits [24•]. However aging, chronic kidney disease, diabetes mellitus, and mediastinal radiation are also associated with accelerated intimal atherosclerosis [24•]. Therefore, the overlap of these two processes in the aortic wall might explain some differences in findings on cardiovascular risk factors associated with calcium in different vascular beds, and mainly between distinct aorta territories.

Differences in the Anatomical References Used at TAC Evaluation

The differences in TAC evaluation can impact both the identification of calcium as well as its quantification either in volume or using the Agatston score. So, caution is advisable when interpreting and comparing studies that used different TAC extensions. Table 1 shows selected studies published in the last 5 years evaluating calcium in the thoracic aorta. They were grouped based on the aortic segments included in the analysis. The first group evaluated calcium in three segments: ascending thoracic aorta (ATA), aortic arch, and descending thoracic aorta (DTA). The aortic root calcium was not included in this group. The second group represents the largest one, and evaluated TAC in the ATA, DTA, and in the aortic root, but not in the aortic arch. The third, fourth, and fifth groups included each a single study that used distinct anatomical references, respectively: the extended versions of ATA plus DTA, aortic arch, and aortic root. These studies shown in Table 1 also differ with respect on how they measured or analyzed the presence of calcium: yes/no [11], and/or Agatston [4, 12, 13, 25•,26–32] and/or volume [5, 33–35, 36••], and/or density [19, 20•, 21•], and/or semi-qualitative evaluation [14].

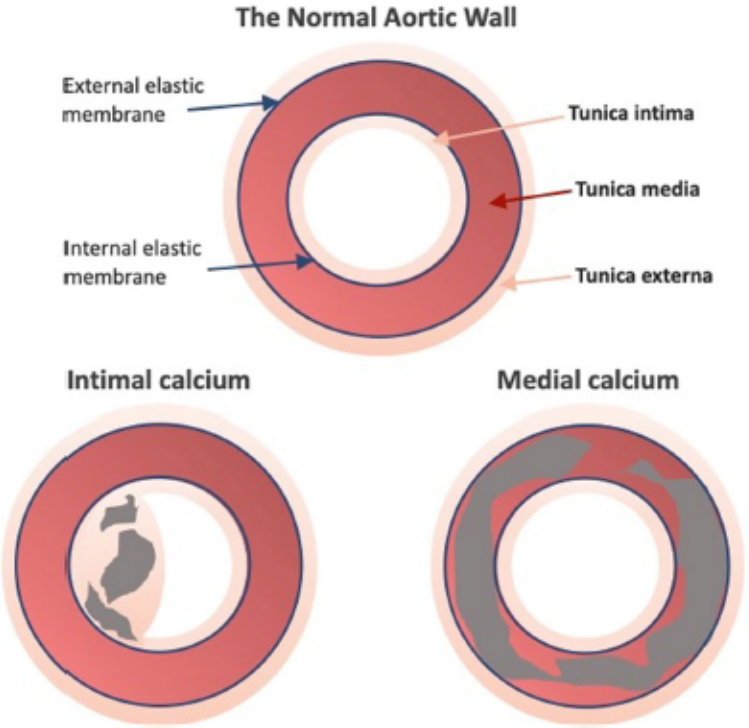

Fig. 2 Patterns of calcium distribution in the aortic wall. Intimal calcium has a patchy distribution in the atherosclerotic lesion and medial calcium is generally diffuse and circumferential

Table 1 Recent thoracic aorta calcium studies organized according to each group of thoracic aorta anatomical references used in the computed tomography evaluation

Anatomical references	Study reference (design)	Population	TAC analysis	Objective	Conclusion
Total TAC: from the apex of the heart until the top of the aortic arch. Total TAC = ATAC + AAC + DTAC ATAC: from the origin of left coronary artery to the lower edge of the pulmonary bifurcation AAC: above ATAC and DTAC DTAC: From the lower edge of pulmonary artery bifurcation to cardiac apex Obs.: ARC was not included.	Craiem et al. 2014 (cross sectional) [25•]	*n* = 970; 77% men; mean age 57 ± 9 years	Agatston	To investigate the prevalence and spatial distribution of TAC all along the thoracic aorta.	Aortic arch and proximal descending thoracic aorta concentrated most of the calcium. Middle-aged women were more prone to have calcium in those segments. TAC prevalence doubled from 31% to 64% comparing TAC evaluation without and with aortic arch, respectively.
	Craiem et al. 2016 (cross sectional)[26]	*n* = 1000; 78% men; mean age 57 ± 9 years		To assess TAC and CAC relations with non-CV events history in a cohort of subjects at risk for CVD and compare the findings between total TAC, partial TAC, and only aortic arch calcium	History of non-CV events was significant for total TAC, partial TAC, aortic arch, but not for CAC. But when entering total TAC and CAC together in the logistic regression as well as risk factors, of all covariates, OR was significant only for total TAC.
	Pedrosa et al. 2019 ELSA-Brasil (cross sectional)[11]	*n* = 2433; 54% women; mean age 56± 9 years	Calcium presence or absence	To assess the prevalence of TAC and CAC and verify if TAC is associated with the same cardiovascular risk factors as is CAC	Prevalence of TAC was much higher than CAC. Chances of CAC were higher in men and lower among blacks. There were no differences in TAC chances regarding gender and race/skin color.
	Rodríguez-Granillo et al. 2019 (longitudinal) [14]	*n* = 1250; women 55%; mean age 56.5 ± 10.1 years; Follow-up 3.7 years; Patients underwent clinically indicated chest CT scans for nonmalignant conditions.	Segment-involvement score	To explore the interplay and prognostic value of vascular calcifications and adipose tissue depots.	Age, pericardial fat volume upper tertile, and extensive CAC were independent predictors of all-cause death. Aortic calcium was not identified as predictor of death.
	Cho et al. 2015 (Longitudinal) [5]	*n* = 164; 100% men; mean age 73 years; Patients with hypertension	Volume	To investigate the relationship between TAC, arterial stiffening, left ventricular hypertrophy, and diastolic dysfunction	Heavy TAC and resultant arterial stiffening might underline left ventricular hypertrophy and diastolic dysfunction in elderly male patients with hypertension.
	Cho et al. 2016 (longitudinal) [34]	*n* = 702; 58% women; mean age 69 ± 4 years		To investigate the relationship of TAC and exercise SBP with all-cause death, (heart	TAC was related to SBP response during exercise and was an independent

Table 1 (continued)

Anatomical references	Study reference (design)	Population	TAC analysis	Objective	Conclusion
		Elderly individuals without obstructive CAD (luminal stenosis < 50%)		failure, obstructive CAD, and stroke)	predictor for outcomes, especially stroke, regardless SBP
TAC = ATAC + DTAC ATAC: from the aortic annulus to the lower edge of the pulmonary artery bifurcation Obs.: Aortic root was included. DTAC: from the lower edge of pulmonary artery bifurcation to apex of the heart. Obs.: Aortic arch was not included.	Ong et al. 2014 MESA (cross sectional)[27]	$n = 1632$; Participants without diabetes with valid data on homeostasis model assessment index.	Agatston	To investigate the association of insulin resistance with AAC, CAC and TAC, and whether it differs according to different levels of subcutaneous fat area and visceral fat area.	There was a modest association of insulin resistance with the presence but not extent of calcified atherosclerosis, especially CAC. For TAC, the association tended to be stronger in participants with abdominal obesity.
	Yeboah et al. 2014 MESA (longitudinal) [28]	$N = 5745$; Follow-up 9 years; Diabetics were excluded		To assess the improvement in discrimination afforded by the addition TAC, AVC, MVC, pericardial adipose tissue volume (PAT) and liver attenuation (LA) to FRFs plus CAC for incident CHD and CVD	CAC, TAC, AVC, MVC were independent predictors of incident CHD and CVD. When added to the FRFs, CAC has superior discriminative ability compared with TAC, AVC, MVC, PAT, or LA. Compared with FRFs plus CAC, the addition of TAC, AVC, MVC, PAT, or LA to the FRFs and CAC resulted in significant worsening of discrimination.
TAC = ATAC + DTAC ATAC: from the aortic annulus to the lower edge of the pulmonary artery bifurcation Obs.: ARC was included. DTAC: from the lower edge of pulmonary artery bifurcation to apex of the heart. Obs.: AAC was not included	Youssef et al. 2015 MESA (longitudinal) [29]	$n = 5886$; 52% women; mean age 62 years; Follow-up 2.4 ± 0.8 years	Agatston	To evaluate TAC progression.	Traditional CV risk factors were related to both TAC incidence and progression. Blacks had the lowest incidence and median changes across ethnic groups. The strongest risk factors for TAC incidence and progression were smoking, age, and hypertension.
	Kim et al. 2017 MESA (longitudinal) [30]	$n = 3415$; 63% women; median age 55 years; Follow-up 11 years; CAC = 0 at baseline		To study the association between TAC and incident CHD, CVD events and all-cause mortality.	TAC did not improve 10-year estimation of prognosis beyond traditional risk factors.
	Katz et al. 2016 MESA (cross sectional) [35]	$n = 6778$; 53% women; mean age 62 years (range 45–84 years); Follow-up 5 years	Agatston and volume	To examine the relation of the MetS, and each of its components, to the prevalence of TAC	MetS and diabetes are both independently associated with increased prevalence and severity of TAC after adjustment for age, gender, and ethnicity.
	Thomas et al. 2017 MESA	$n = 6811$; Follow-up 10 years	Density and volume	To test the hypothesis that ATAC volume and density predict	One-SD higher ATAC density was associated with a lower

Table 1 (continued)

Anatomical references	Study reference (design)	Population	TAC analysis	Objective	Conclusion
	(longitudinal) [19]			incident CVD events independently of CAC.	risk of CHD and CVD after full adjustment, while ATAC volume was not associated with outcomes after full adjustments
	Thomas et al. 2018 MESA (longitudinal) [20•]	$n = 5887$; Follow-up 2.4 years.		To evaluate changes in ATAC volume and density scores and incident atherosclerotic CVD.	After adjusting for CVD risk factors and baseline levels of ATAC volume and density, there were a significant association between an increase in ATAC volume over time and incident CHD, CVD, and ischemic stroke, while an increase in ATAC density over time was associated with a lower incidence of CHD and CVD, but not stroke.
	Thomas et al. 2018 MESA (longitudinal)[21•]	$n = 6765$; mean age 62 years Follow-up 12 years		To evaluate the association of DTAC with non-CV morbidity and mortality.	DTAC is associated with non-CV morbidity and mortality.
	Kälsch et al. 2017 Heinz Nixdorf Recall Study (longitudinal) [12]	$n = 3270$; 53% women; 45–74 years of age; Follow-up 5 ± 0.3 years	Agatston	To investigate associations of CV risk factors with incident TAC, of baseline TAC with incident CAC, and for baseline CAC with incident TAC.	TAC and CAC share similar major determinants for incidence and progression of calcification. High extent of TAC, especially ATAC, revealed considerably elevated risk of incidence and accelerated progression of CAC.
	Mahabadi et al. 2016 Heinz Nixdorf Recall Study (longitudinal) [31]	$n = 3630$; 54% women; mean age 59 ± 8 years; Follow-up of 10 ± 3 years		To determine whether noncoronary measures from cardiac CT may enhance the prognostic value of this diagnostic imaging tool.	Combined assessment of left ventricular and atrial axial area index, epicardial adipose tissue volume, and TAC from cardiac CT improves the prediction of incident hard CV events above CAC and established CV risk factors.
	Hoffmann et al. 2016 Framingham Heart Study (longitudinal)[32]	$n = 3486$; 51% women; mean age 50 ± 10 years; Follow-up 8 years		To determine whether TAC, CAC, AAC, MVC and AVC predict incident major CHD, CVD, and all-cause mortality independent of FRFs.	After adjustment for age and sex, FRFs, and CAC, TAC was not statistically significant for prediction of CHD events and major CVD. However, TAC remained significantly associated with all-cause

Table 1 (continued)

Anatomical references	Study reference (design)	Population	TAC analysis	Objective	Conclusion
					mortality even after these adjustments.
	Brodov et al. 2015 EISNER (longitudinal) [4]	$n = 1648$; 54% men; mean age 52 ± 9; Follow-up 5 years; CAC = 0 at baseline		To evaluate the predictive value of TAC for CAC conversion.	TAC ≥ 100 Agatston is an independent predictor of CAC
TAC = ATAC + DTAC ATAC: above the origin of the right coronary artery to the end of scan range or up to the origin of the brachiocephalic artery. Obs.: ARC was not included. DTAC: distal from the origin of the left subclavian artery up to the diaphragm. Obs.: AAC was not included.	Dudink et al. 2018 (longitudinal) [13]	$n = 327$; 66% men; mean age 56 years; Follow-up 67 ± 12 months; Low-risk population	Agatston	To determine the feasibility of assessing ATAC and DTAC on standard CAC scans and their associations of with coronary events	In patients without CAC, the event rate was higher in the patients with DTAC than in those without, which is comparable with patients with CAC without DAC. The event rate in patients with both CAC and DTAC was the highest. DTAC appears to improve the identification of those patients that will experience coronary events. ATAC showed no significant association with the occurrence of coronary events.
ATAC = AC Aortic arch: from the slice on which the ascending and descending aorta merge into the inner curvature of the arch to the first centimeter of the common carotid arteries, vertebral arteries, and subclavian arteries beyond the origin of the vertebral arteries.	Bos et al. 2015 Rotterdam Study (longitudinal)[33••]	$n = 2408$; 52% women; mean age 69 ± 7; Follow-up 15775 person years	Volume	To investigate associations of CAC, aortic arch, extracranial and intracranial internal carotid arteries with mortality adjusting for age, sex, and CV risk factors	Independent of calcification elsewhere, aortic arch calcium was related to a higher risk of CV mortality and non-CV mortality.
TAC = ARC ARC: the region of ATAC between the aortic annulus and the sinutubular junction.	Tesche et al. 2017 (Longitudinal) [36••]	$n = 189$; 53% women; mean age 60 ± 11 years; Patients with intermediate pre-test probability of CAD	Volume and Agatston	To evaluate the correlation between ARC and CAC and their ability to predict obstructive CAD.	ARC is a strong and independent predictor of CAC and obstructive CAD.

AAC, abdominal aortic calcium; *ARC*, aortic root calcium; *AAC*, aortic arch calcium; *ATAC*, ascending thoracic aorta calcium; *AVC*, aortic valve calcium; *CAC*, coronary artery calcium; *CAD*, coronary artery disease; *CHD*, coronary heart disease; *CV*, cardiovascular; *CVD*, cardiovascular disease; *DTAC*, descending thoracic aorta calcium; *EISNER*, Early Identification of Subclinical Atherosclerosis by Noninvasive Imaging research; *FRFs*, Framingham risk factors score; *LA*, liver attenuation; *MVC*, mitral valve calcium; *MESA*, Multi-ethnic Study of Atherosclerosis; *MetS*, metabolic syndrome; *OR*, Odds ratio; *PAT*, pericardial adipose tissue; *SBP*, systolic blood pressure; *SD*, Standard Deviation; *TAC*, thoracic aortic calcium

Does the Aortic Arch Add Relevant Information to TAC?

As shown by Craiem et al., the inclusion of aortic arch in combination with ATA and DTA doubled the TAC prevalence, mainly in middle-aged women [25•]. Besides the impact on the overall and sex-specific prevalence of TAC, the inclusion of the aortic arch in TAC evaluation might also relate to TAC predictive value on morbidity and mortality. Bos et al., for instance, analyzed only the aortic arch and found that the volume of calcium in this segment was related to increased CV and non-CV mortality, after adjustment for many CV risk factors including CAC, intracranial, and extracranial internal carotids calcium [33••]. A recent study of Cho et al. used the same TAC extension described by Craiem et al. and followed 702 patients without obstructive coronary artery disease (CAD) during 64 months and also found TAC as an independent predictor for outcomes, especially stroke [34]. Thus, taking account these latter results, it appears that calcium in the aortic arch might contribute to TAC prediction, but we cannot rule out that it may be also a marker of calcium in other thoracic aorta segments.

What Do We Know About the Presence of Calcium in ATA and DTA?

The largest study group presented in Table 1 is the ones that assessed TAC using the same scan performed for CAC assessment. Thus, only the presence of calcium in the ascending thoracic aorta (ATAC) and descending thoracic aorta (DTAC) were evaluated. Eight studies are from Multi-ethnic Study of Atherosclerosis (MESA), and they measured calcium using Agatston, volume, and/or density [19, 20•, 21•, 27–30, 35]. The others are from Heinz Nixdorf Recall Study [12, 31], Framingham Heart Study [37], and EISNER [4], and all of them used Agatston to measure TAC. All these studies included the aortic root in the TAC and excluded the aortic arch. As demonstrated by Tesche et al., calcium in the aortic root is a stronger and independent predictor of CAC and of obstructive CAD [36••], suggesting that a similar process lead to calcium in these vascular beds. Thus, like the CAC [38], it is possible that calcium in aortic root reflects more localized than generalized atherosclerosis, differently from other thoracic aorta segments.

When taken together, results on ATAC plus DTAC associations and predictive value are controversial [27–32, 35]. However, when Thomas et al. and Kälsch et al. studied the ATAC and DTAC separately, they found that while greater ATAC volume predicted the incidence and progression of CHD and CVD [12, 21•], DTAC was associated with the occurrence of non-CV morbidity and mortality [20•]. These authors also showed that greater ATAC density, contrary to greater volume, was associated with lower risk of CAD [19, 21•], and explained such differences between aorta segments in terms of embryology, wall constitution and pathophysiologic mechanisms of calcium formation. It is thus, possible, that such differences in DTAC and ATAC also account for the controversial results reported by the other studies included in this group, as they are based on ATAC plus DTAC [27, 28, 30, 32]. In light of these recent findings, further research using the same anatomical references for each thoracic aorta segment should be stimulated.

Anatomical References for TAC Segmentation

Based on the current anatomical references used in some TAC studies, and understanding the possible value of studying each aortic segment separately, including the aortic arch, we created the video 1 to show each portion of the aorta slice-by-slice in axial CT images. Since aorta has an oblique path, some details are of importance. The following anatomical references were used for TAC segmentation:

1) ATAC: from the sinutubular junction to the lower edge of pulmonary artery bifurcation (Some caution with the first slices, because of the initial curvature of ascending aorta above aortic root, where there are some slices that both appear in the same axial slice).
2) Aortic arch calcium: from ascending to descending thoracic aorta at the same anatomical reference, which is the level of the lower edge of pulmonary artery bifurcation.
3) DTAC: from the lower edge of pulmonary artery bifurcation to the apex of the heart.

What Is the Best Way to Measure TAC?

In addition to anatomical definitions, other methodological TAC parameters deserve to be considered. Agatston method has been widely used; however, the quantification of TAC can vary considerably between different CT systems once the acquisition of CAC scans, usually used to measure TAC, was not created for this application [39]. Mori et al. in 2015 described and validated a new volume-rendering approach to quantify TAC that demonstrated an excellent agreement of the pixel-based TAC score with volumetric TAC score and observed that volume-based score was less influenced by slice thickness as compared with pixel-based score [40••]. Agatston score depends nonlinearly on the measured Hounsfield Unit density of each pixel in the calcium, which changes with different x-ray energies, while the calcium volume is only slightly affected by scanning at different energies [41]. Since TAC is in the early development phase, perhaps now is the time to think about more accurate measures of quantifying the TAC [39].

Is TAC Radiation Exposure Justified?

The last, but a very important consideration to be made, refers to the radiation dose involved in TAC extended exams (all segments). Although the increase in the radiation dose of extended CAC, necessary to include the aortic arch, is lower than that delivered for a bilateral mammogram [25•], its value remains uncertain. So far, there appear to be no doubt regarding the value of evaluating DTAC and ATAC on CAC scans, as CAC clinical indication is already established. Lung cancer screening trials [42] seem to offer some opportunity to evaluate the predictive value of all segments, especially the aortic arch.

Limitations

The current review of the literature is limited mostly due to the high variability across the studies included in the analysis. As previously detailed, there is no current standards to define which aortic segments to include or the most appropriate tool to quantify the presence and extent of TAC. Moreover, the outcomes included in each analysis are not similar. Collectively, those issues limit the comparison between studies and the potential to fully interpret those results in other populations or scenarios.

Future Directions

Future studies should focus on the standardization of image acquisition, areas of the thoracic aorta to be included and most appropriate tools to quantify TAC. Moreover, detailed investigation on the different role of each thoracic aorta segment for the prediction of different outcomes, including separate analysis for coronary artery disease events, cerebrovascular events, and incidence of acute aortic syndromes.

Additionally, more studies on the implications of such findings for clinical management are needed. Currently, TAC is understood to be atherosclerosis. However, the clinical management of asymptomatic individuals with atherosclerosis is currently based on the individual's clinical risk profile with the potential use of other diagnostic tools, such as CAC scores in selected individuals. Yet, not clear role for TAC in selecting the most appropriate management strategy for those individuals exist.

Conclusions

TAC has been considered as subclinical marker of atherosclerosis; however, the lack of standard protocol regarding the anatomical segments included and measurement analytical unit have contributed to controversial results and studies comparability. The accumulated evidences indicate that each aorta segment should be evaluated separately, as they differ in terms of structural characteristics, embryologic origin, and pathophysiologic mechanisms of calcium formation along the aorta and predictive value.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

Abbreviations AAC, abdominal aortic calcium; ATA, ascending thoracic aorta; ATAC, ascending thoracic aorta calcium; CAC, coronary artery calcium; CAD, coronary artery disease; CHD, coronary heart disease; CV, cardiovascular; CVD, cardiovascular disease; CT, computed tomography; DTA, descending thoracic aorta; DTAC, descending thoracic aorta calcium; MESA, Multi-ethnic Study of Atherosclerosis; TAC, thoracic aortic calcium

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