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Letter to Editor

Does HTLV-1 Infection Lead to Increased Intima-Media Thickness (IMT)? "Evidences form Human Clinical Studies"

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Dear Editor. Coronary artery disease (CAD) is on the list of top causes of human death, with 30% (nearly 7.6 million cases) of coronary heart disease (CHD) occurring annually (1).

Atherosclerosis is the most important risk factor for cardiovascular diseases.

Atherosclerosis is a chronic inflammatory disease that results in damaging the intima of the arteries and the formation of fatty plaques on the walls of the arteries, and it accounts for one-fifth of deaths worldwide (2-3). There are several factors involved in the atherosclerosis immunopathogenesis, among which the role of viral infection is quite prominent (4).

It was first observed in the late 1970s that the atherosclerotic lesions in chickens infected with the Marek's disease virus (as a herpes virus) is very similar to the human atherosclerosis (5). The researchers then indicated the role of cytomegalovirus (CMV), herpes simplex virus type I (HSV-1), hepatitis C virus (HCV), human immunodeficiency virus (HIV), and Epstein-Barr virus (EBV) in inducing atherosclerosis in humans. (4,6). It has recently been suggested that HTLV-1 infection may also induce and exacerbate the process of atherosclerosis in humans (7).

HTLV-1 is an RNA of the human oncogenic virus that was first isolated and introduced by Gallo et al. in 1980 from the skin lymphoma (8). HTLV-1 has infected about 15-20 million people worldwide and is endemic in Japan, Caribbean Islands, Latin America, Saharan Africa, Australia and Iran (8-9). The virus is considered as the cause of adult etiological T-cell leukemia / lymphoma (ATLL), HTLV-1associated myelopathy / tropical spastic (HAM / TSP), infectious dermatitis (ID), uveitis, alveolitis, Sjogren's syndrome, autoimmunity thyroiditis, Behcet autoimmunity disease and cardiovascular disorders such as arthropathy and polymyositis (10).

HTLV-1 can infect vascular endothelial cells. Moreover, there are several evidences indicating that HTLV-1 may play a role in the pathogenesis of cardiovascular disorders. For instance, HTLV-1 leads to carotid intimamedia thickness. Moreover, cardiovascular conflicts, myocardial calcification, and cardiac valves conflicts in the lymphoma patients, and also cardiovascular autonomic dysfunction in the patients infected with HTLV-1, and cardiac symptoms in people infected with HTLV-1 are about 3 times more than in the healthy individuals (4,6). Intima-media thickness is one of the most reliable indicators of atherosclerosis diagnosis (11). In this study, we assessed the possible role of HTLV-1 infection and increased intima-media thickness, for the first time, to provide a novel document for the possible role of HTLV-1 in atherosclerosis development in human.

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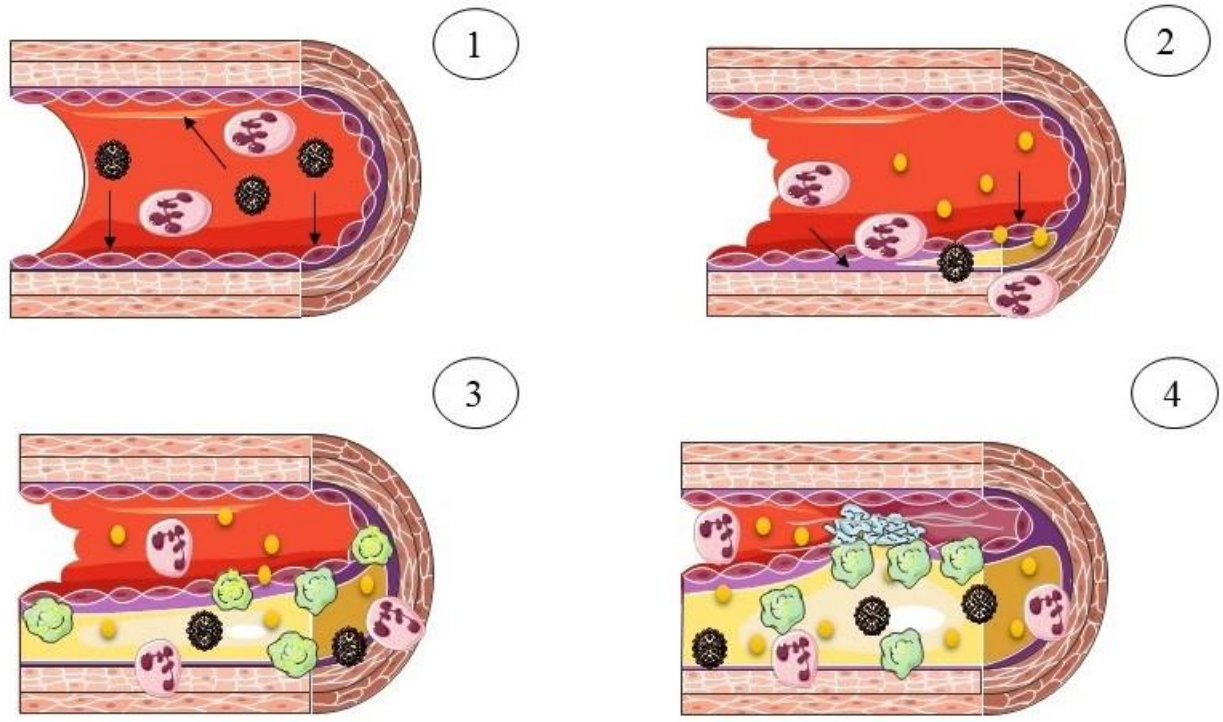

Fig. 1. the schematic scheme of the crucial role of HTLV-1 infection in atherosclerosis pathogenesis; 1) HTLV-1 entered into endothelial cells and triggered innate immunity; 2) intima is disrupted after HTLV-1 infection and LDL particles are precipitate in sub-endothelial layers; 3) LDL particles converted to oxidized-LDL caused by innate immunity and lead to formation of foam cells; 4) maturation of atherosclerotic plaques and thrombosis.

For this purpose, all the studies related to the effect of HTLV-1 infection on intima-media thickness changes were investigated and retrieved using the keywords "HTLV-1", "Intima-media thickness", "Atherosclerosis" and "Coronary artery disease" in PubMed databases, Scopus and Google scholar. The search was done up to April 2020 with no date limitation. However, the duplicates were excluded from the study. Then, the titles and abstracts of all the identified records were evaluated, and studies that supported our purpose were included in our analysis. Possible relationship of the infection with HTLV-1 and changes in intima-media thickness were measured using the odds ratio statistical index.

The statistical analysis was performed using Comprehensive Meta-Analysis (CMA) software (Ver. 2.2 -Biostat, Englewood, NJ).

The studies with low heterogeneity were used by applying the fixed effect models, and the high heterogeneity cases (I^2 index> 25%; Cochrane Q statistic p <0.005) were used by applying the random effect models (12). The Egger's regression method index was also used to determine the publication bias.

Seven studies were included in the present meta-analysis. The included studies, fulfilled within 2010-2020, were conducted in Iran (n = 3), Japan (n = 3) and Brazil (n = 1).

In the present study, the data from 5,818 people were evaluated. About 63.2% of the study population were women and the rest were men. Also, the mean age of the study population was about 64.7 ± 2 years. The included studies were of the case-control, cross-sectional, and prospective type. The other key data of the included were listed in Table 1 (Table 1).

Based on the results of statistical analysis, we observed a significant relationship between HTLV-1 infection (HTLV-1 infection) and the increased intima-media thickness (OR: 2.26; 1.17-4.35 with 95% CIs; I^2: 24.52%; df (Q): 6; Q-value: 7.95; p-value: 0.014). Based on the symmetric nature of the funnel-plot and the Egger's intercept (bias studies), the publication bias was not observed in the included studies (Egger's intercept: 1.164).

Thus, we have shown that HTLV-1 infection with the increased intima-media thickness (IMT) causes the onset of atherosclerosis and leads to disruption of the integrity of sub-layers of arteries and through various mechanisms,

Table 1. Characteristics of included study

First author	Publication year	Location	Female/Male Age	Type of study	HTLV-1 infected	Intima-media thickness			Ref
						HTLV-1	Control	*P*-value	
Layegh et al	2014	Iran	77/36 42.9 ± 1	Case-control	58	0.57 ± 0.16 mm	0.48 ± 0.12 mm	p = 0.005	13
Yamanashi et al	2018	Japan	1374/810 72.5	Case-control	401	0.74 ± 0.14 mm	0.72 ± 0.13 mm	P = .020	14
Dória et al	2015	Brazil	NA NA	Prospective	54	9	45	NA	15
Mozayeni et al	2020	Iran	21/21 63.5	Case-control	42	29	13	NA	16
Mohammadi et al	2019	Iran	NA 65.64 ± 7	Case-control	22	14	8	NA	17
Shimizu et al	2019	Japan	1223/702 79	cross-sectional	163	1.17 ± 0	0.84 ± 0	NA	18

is considered a risk factor for the cardio-vascular diseases. According to the review of the literature, the role of intima disruption in atherosclerosis pathogenesis is critical, such that the circulating low-density lipoprotein (LDL) is dissociated after the disruption of the intima vascular layer in the sub-endothelial layer of arteries, and the innate immune response converts LDL to oxidized-LDL (oxLDL) (20). OxLDL formation leads to the increased expression of adhesion molecules at the level of arteries, which leads to the recruitment of macrophages in the endothelial layer of arteries (21-22).

Foamy cells are formed following phago-cytosis of oxLDL particles and the athero-sclerotic plaque gradually expands and matures by the deposition of circulating cholesterol crystals to this lesion (23-24).

HTLV-1 can play a direct role in increasing the mass of the atherosclerotic plaques directly (infecting endothelial cells of the vascular wall and disruption of intima) or indirectly (recur-rent of innate immune cells and launching chronic inflammation in the vascular wall) and develop into atherosclerosis (Fig. 1).

Briefly, based on the previous evidence and the results of the present study, it seems that infection with HTLV-1 by destruction of sub-layers of arteries, especially the intima layer, causing the sub-layer's destruction, increasing the intima-media thickness, changing the lipid profile, and development of atherosclerotic plaques, both directly and indirectly.

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Conflict of interest

The authors have no conflict of interest.

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