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The Burden of Lipoprotein (a) in Türkiye: What We Know and What We Need to Learn

Türkiye'de Lipoprotein (a) Yükü: Bildiklerimiz ve Öğrenmemiz Gerekenler

EDITORIAL COMMENT
EDİTÖRYAL YORUM

In Türkiye, atherosclerotic cardiovascular diseases (ASCVD) are a significant cause of mortality and morbidity, emerging approximately 10 years earlier compared to European countries.[1] When evaluating ASCVD risk factors, the prevalence of hypercholesterolemia stands at 29.1%, with familial hypercholesterolemia being much more common than the global average.[2,3] The high incidence of familial hypercholesterolemia in Türkiye is a major factor underlying the high prevalence of early atherosclerosis.[4] Lipoprotein (a) [Lp (a)] is another lipoprotein similar to low-density lipoprotein (LDL), but with an additional protein called apolipoprotein (a). Lp (a) is accepted as a significant risk factor for both ASCVD and early-onset ASCVD.[5] Unlike other lipoproteins, Lp (a) levels are not significantly affected by diet, exercise, or lifestyle changes and are determined 90% by genetics. Moreover, Lp (a) levels seem to be slightly higher in women, and particularly increase with menopause. Current guidelines recommend measuring Lp (a) levels for all populations once in a lifetime to determine ASCVD risk.[6] Therefore, many countries have addressed the burden of high Lp (a) levels and its threat to their populations.[7,8] However, the prevalence of elevated Lp (a) levels in Türkiye remains largely uncharted, with only limited data currently available on this subject.

In this issue of the Archives of the Turkish Society of Cardiology (TSC), Güngör et al.[9] present a comparative analysis of Lp (a) levels in men and women, based on their evaluation of 1,381 consecutive patients with ASCVD from a single center. This study revealed a mean Lp (a) level of 28.2 mg/dL and a median of 16 mg/dL with an interquartile range (IQR) of 7 mg/dL and 39 mg/dL. Notably, 18.7% of patients had Lp (a) levels ≥ 50 mg/dL, 10.8% had levels ≥ 70 mg/dL, and 5.8% had levels ≥ 90 mg/dL. Lipoprotein (a) levels were significantly higher in females compared to males [mean 35.3 mg/dL vs. 26.1 mg/dL: median 21.5 mg/dL (IQR 8-52 mg/dL) vs. median 16 mg/dL (IQR (7-36 mg/dL), respectively, ($P < 0.01$)]. In males, the prevalence of Lp (a) < 30 mg/dL was significantly higher than in females (70.8% vs. 61.5%, $P < 0.01$). Conversely, the proportion of females with Lp (a) levels ≥ 90 mg/dL was significantly higher compared to males (11.4% and 1.4%, respectively, $P < 0.01$). The retrospective, single-center design of this study may introduce selection bias, and the findings may not be generalizable to the entire Turkish population. Additionally, measuring Lp (a) in mg/dL rather than nmol/L poses a limitation for comparison with international guidelines and studies. However, this study provides important insights into the burden of Lp (a) levels and the prevalence of high Lp (a) in Türkiye.

Table 1 depicts all available studies presenting Lp (a) levels either in the general population or in patients with ASCVD in Türkiye. In the Turkish Adult Risk Factor (TEKHARF) study by Onat et al.,[10] which included 124 high-risk Turkish individuals (98 men, 116 women), Lp (a) concentrations in serum ranged from 2.3 to 131 mg/dL. The median value was 11.0 mg/dL, with an IQR of 4.2 to 24.9 mg/dL. Lipoprotein (a) values > 30 mg/dL, considered the upper limit of normal, were found in 22% of the individuals. The geometric mean Lp (a) levels were 9.6 ± 2.8 mg/dL in men and 12.1 ± 3 mg/dL in women ($P < 0.001$). In contrast, Örem et al.[11] observed median Lp (a) values of 16 mg/dL in healthy individuals ($n = 65$) and 24 mg/dL in those with coronary artery disease (CAD) ($n = 60$). Additionally, the prevalence of high Lp (a) levels (> 30 mg/dL) was 27% in healthy subjects and 60% in patients with CAD.

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Table 1. All Available Epidemiologic or Atherosclerosis-Related Studies in Türkiye That Report Lipoprotein (a) Levels

Study	Year	Population	Sample Size	Lp (a) unit	Lp (a) Levels	Lp (a) Levels According to Sex	High Lp (a) Prevalence	LDL-C Levels (mg/dL)	Comments - Study Results
Mahley et al.[12]	1995	Turkish population from different regions of Türkiye	800	mg/dL	12.54 ± 14.12	Men: 11.9 ± 13.7 (Range: 0-76), Women: 13.7 ± 14.8 (Range: 0-86)	NA	Whole study population: 117.5 ± 2.5 Men: 118 ± 1.70 Women: 116 ± 3.77	Lp (a) levels did not differ between men and women, nor did they vary between different regions of Türkiye.
Orem et al.[11]	1995	Patients with CAD from a single center	CAD = 60 Controls = 65	mg/dL	CAD Group mean: 4 ± 21, median: 24 Controls mean: 21 ± 17, median: 16	(NA)	> 30 mg/dL CAD - 60% Controls - 24.7%	CAD: 175 ± 41 Controls: 139 ± 39	The Lp (a) level was higher in CAD patients; Lp (a) level of the study population was higher than those reported for the US population at the time this article was released.
Hergenç et al.[14]	1998	Healthy people from Marmara Region	132	mg/dL	Mean: 23.9 ± 26.3 Median: 14.3	NA	NA	106.1 ± 37.8	The mean Lp (a) level is higher than the previous studies of the Turkish population.
Adam et al.[15]	1999	Healthy people from Black Sea Region	1,348	mg/dL	NA	Geometric mean with range Men: 25 (3-275), Women: 22 (3-216)	NA	Men: 105 ± 33 (range: 40 - 170) Women: 111 ± 34 (range: 42 - 180)	The Lp (a) level of the study population is higher than those reported for Finns & North Americans according to publications available at the time this article was released.
Onat et al.[10]	2004	Turkish population with high ASCVD risk	214	mg/dL	Median: 11 IQR: 4.2-24.9)	Geometric mean Men: 9.6 ± 2.8, Women: 12.1 ± 3	> 30 mg/dL - 22%	125 ± 34	While the Lp (a) level was not related to other risk factors in women, in men it was positively correlated with LDL levels and negatively correlated with BMI, waist circumference, and insulin levels.
Onat et al. [13]	2008	Turkish adult population > 33 years old from all geographical regions of Türkiye	1,309	mg/dL	NA	Median Men: 9.23 (IQR: 3.85 - 9.75) Women: 11.4 (IQR: 4.81 - 24.4)	NA	Men: 115 ± 34 Women: 122 ± 36	The Lp (a) level was related to CAD in women; mid-tertile Lp (a) level was inversely related to metabolic syndrome and triglyceride levels.
Yurtseven et al.[16]	2024	Patients admitted to cardiology and internal medicine outpatient clinics from a single center	1,858	mg/dL	Median: 12 (IQR: 5-29)	Median Men: 9.23 (IQR: 4-25) Women: 13 (IQR: 6-32)	Whole study population ≥ 30 mg/dL - 22.9% ≥ 50 mg/dL - 11.7% Men ≥ 30 mg/dL - 20.6% ≥ 50 mg/dL - 10.1% Women ≥ 30 mg/dL - 25.6% ≥ 50 mg/dL - 13.5%	Men: 128 ± 45 Women: 136 ± 46	While an Lp (a) cutoff of ≥ 50 mg/dL was associated with CAD in both sexes, an Lp (a) level of ≥ 30 mg/dL was associated with CAD only in women.
Güngör et al.[9]	2024	Patients with ASCVD from a single center	1,381	mg/dL	Average: 28.2 Median: 16 (IQR: 7-39)	Men mean: 26.1, median: 16 (IQR: 7-36) Women: mean: 35.3, median: 21.5 (IQR: 8-52)	≥ 50 mg/dL - 18.7% ≥ 70 mg/dL - 10.8% ≥ 90 mg/dL - 5.8%	Whole study population: 132 ± 47 Men: 130 ± 46 Women: 139 ± 51	Women had higher Lp (a) levels. Lp (a) level was weakly correlated with LDL and total cholesterol levels.

ASCVD, Atherosclerotic Cardiovascular Disease, BMI; Body Mass Index, CAD; Coronary Artery Disease, IQR; Interquartile Range; LDL-C, Low-Density Lipoprotein Cholesterol; Lp (a), Lipoprotein (a); NA, Data Unavailable.

The Turkish Heart Study, which included 800 participants from six regions of Türkiye, reported a mean Lp (a) level of 12.9 mg/dL, ranging from 11 to 15 mg/dL with no significant regional differences. When comparing men (n = 526) and women (n = 274), mean Lp (a) levels were 11.9 ± 13.7 mg/dL (range: 0-76 mg/dL) and 13.7 ± 14.8 mg/dL (range: 0-86 mg/dL), respectively. However, the difference was not significant (P < 0.05). The distribution of Lp (a) levels was shifted towards lower values with a quarter of the population having levels ≤ 3 mg/dL, including a high percentage with levels < 1 mg/dL. The 75th percentile value was 19 mg/dL, while the 90th percentile was 30 mg/dL for both sexes.[12] In a study of the Turkish population that included 1,309 subjects, Onat et al.[13] reported median Lp (a) levels of 9.23 mg/dL (IQR: 3.85-19.75) for men (n = 698) and 11.4 mg/dL (IQR: 4.81-24.4) for women (n = 701). The 5th and 95th percentile values in men were 1.60 mg/dL and 52.2 mg/dL, respectively, while for women, these percentiles were 2.02 mg/dL and 57.8 mg/dL, respectively. Another study, which included 132 participants from the Marmara Region of Türkiye, reported a mean Lp (a) level of 23.9 ± 26.3 mg/dL, with a median of 14.3 mg/dL, and found that 24% of the study population had Lp (a) levels above 30 mg/dL.[14] Adam et al.[15] conducted a study involving healthy individuals from the Black Sea Region of Türkiye and found a geometric mean of Lp (a) of 22 mg/dL (range: 3-216 mg/dL) for women and 25 mg/dL (range: 3-375 mg/dL) for men.

In a new study by Yurtseven et al.,[16] which analyzed Lp (a) levels in 1,858 patients admitted to cardiology and internal medicine outpatient clinics with non-urgent complaints in a single center, the median Lp (a) level for the whole study population was 12 mg/dL (IQR: 5-29 mg/dL). The median Lp (a) level was 9.23 mg/dL (IQR: 4-25 mg/dL) in men (n = 978) and 13 mg/dL (IQR: 6-32 mg/dL) in women (n = 880). The 75th percentile for the whole population was 29 mg/dL. Among men, 20.6% (n = 201) had Lp (a) levels ≥ 30 mg/dL and 10.1% (n = 99) had Lp (a) levels ≥ 50 mg/dL. Meanwhile, 25.6% of women (n = 225) had Lp (a) levels ≥ 30 mg/dL and 13.5% (n = 119) had Lp (a) levels ≥ 50 mg/dL.

These limited studies with small sample sizes indicate an average Lp (a) level of 18.88 mg/dL, ranging from approximately 0 to 275 mg/dL, with an IQR of 11.4 to 22 mg/dL. The prevalence of high Lp (a), defined as > 30 mg/dL, is on average 28.93% in the Turkish population. In a UK Biobank study, the white population had a median of 19 nmol/L, South Asians had a median of 31 nmol/L, and the black population had 75 nmol/L Lp (a) levels.[17] Accordingly, Turkish individuals seem to have higher Lp (a) levels (approximately 47.2 nmol/L) than the white and South Asian populations in the UK, but lower than the black population.

While analyzing these Turkish data, it must be considered that there are discrepancies between the Lp (a) levels detected in recent studies compared to older studies, whose Lp (a) measurements may have been less accurate due to the lack of standardized Lp (a) measurement methods previously. However, although both are recent studies, the median Lp (a) levels were also different in Güngör et al.'s[9] and Yurtseven et al.'s[16] studies. This difference most likely depends on differences in the study populations. Güngör et al.'s[9] study included individuals with ASCVD with a median Lp (a) level of 16 mg/dL, while Yurtseven et al.'s study included both CAD and non-CAD individuals with a median Lp (a) level of 12 mg/dL. Notably, in Yurtseven et al.'s[16] study, the median Lp (a) level for CAD patients was 15 mg/dL, similar to the median Lp (a) level in Güngör's[9] study.

Despite current guidelines recommending measuring Lp (a) levels in nmol/L, no Lp (a) measurements in Türkiye have been reported in nmol/L.[18] The nmol/L unit is preferred because it accounts for the number of Lp (a) particles, which is more relevant for assessing ASCVD risk. Mass unit measurement can cause underestimation or overestimation of the number of Lp (a) particles. Preferably, clinical assays should use an antibody for a unique non-repetitive epitope in apolipoprotein (a), ensuring that all Lp (a) particles are recognized once, and the levels are accurately reported in nmol/L.

It is evident that more comprehensive and higher-quality studies using standardized measurement methods for Lp(a) levels are needed in Türkiye to better understand the high Lp(a) burden. This may, in turn, help to explain the high prevalence of premature ASCVD events in our population and lead to the development of more effective prevention and treatment strategies.

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