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Araştırma

Determination of Reference Ranges of Four Lipid Parameters in Elderly Individuals

Yaşlı Bireyler için Dört Lipit Parametresinin Referans Aralıklarının Belirlenmesi

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ABSTRACT

Aim: The present study aimed to determine the reference range values for four lipid parameters associated with chronic diseases that were routinely examined in our laboratory in elderly individuals aged ≥65 years.

Materials and Methods: We determined the reference ranges for TC, HDL -C, LDL -C, and TG in individuals aged ≥65 years using samples from 268 individuals, including 139 women and 129 men, between June 20th, 2019, and August 8th, 2020, who met the inclusion criteria.

Results: The average age of the individuals included in the study was 74.8 years. The average age of the men was 74.7 years, and the average age of the women was 74.9 years. The reference range values of lipids (mg/dL) for the entire group (male-female), male, and female individuals, respectively, were as follows: TC: 116–295 mg/dL,105–280 mg/dL, and 141–287 mg/dL; HDL-C:30–79 mg/dL, 28–65 mg/dL, and 31–77 mg/dL; LDL-C: 59–200 mg/dL, 50–193 mg/dL, and 76–195 mg/dL; and TG: 45–298 mg/dL, 45–272 mg/dL, and 53–242 mg/dL.

Conclusion: As with children, determining reference range values specific to elderly individuals is important for an accurate and appropriate assessment of their health status.

Key Words: *elderly, lipid, reference range*

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ÖZET

Amaç: Laboratuvarımızda rutin çalıştığımız, kronik hastalıklarla ilişkilendirilen 4 lipit parametresinin 65 yaş ve üzeri yaşlılarda referans aralık değerlerinin oluşturulması.

Materyal ve Metod: 20.06.2019-07.08.2020 tarihleri arasında belirlenen kriterlere uygun olan, 139 kadın 129 erkek, 268 bireyden aldığımız numunelerde 65 yaş ve üzeri kişilerde total kolesterol, HDL kolesterol, LDL kolesterol, trigliserit referans aralıklarını belirledik.

Bulgular: Çalışmaya dahil edilen kişilerin yaş ortalaması 74.8, erkeklerin yaş ortalaması 74,7, kadınların yaş ortalaması ise 74,9 olarak hesaplandı. Lipitlerin referans aralık değerleri(mg/dL) tüm grup, erkek ve kadınlar sırasıyla, total kolesterol:116-295,105-280,141-287; HDL kolesterol:30-79, 28-65,31-77;LDL kolesterol:59-200,50-193,76-195; trigliserit:45-298, 45-272, 53-242 olarak bulundu.

Sonuç: Yaşlı bireylerde, aynı çocuklarda olduğu gibi, kendilerine özgü referans aralık değerlerinin oluşturulması yaşlı bireylerin sağlık durumlarının doğru ve uygun değerlendirilebilmesi için önemlidir.

Anahtar kelimeler: yaşlı, lipit, referans aralık

INTRODUCTION

The International Federation of Clinical Chemistry (IFCC) and the National Committee on Clinical Laboratory Standards (NCCLS) recommend that each laboratory should set its own reference values (1). Reference intervals are the most widely used diagnostic tool, and it is vital for patient health that the laboratory provides results with reference ranges specific to the relevant patient group that conform to test conditions (2). Age and gender are the most commonly used criteria for subgrouping reference ranges (3). Reference ranges can be either established directly by taking samples from a specific healthy group established for the reference range or indirectly based on laboratory records and values (4, 5).

Aging is a natural process associated with physiological, mental, and social regression in the individual (6). Although there are different approaches to determining when chronological old age begins, the World Health Organization (WHO) recommends that the age group of individuals ≥65 years be considered the old age period. According to the Turkish Statistical Institute (TUIK) 2019 data, the proportion of the elderly population in Turkish society is calculated to be 9.1%. Population projections predict that this proportion will be 12.9% in 2030 and 16.3% in 2040 (7). Among the physiological changes that occur with aging, those related to the cardiovascular and respiratory systems receive the most attention (6). The levels of laboratory tests change in tandem with age. Older individuals are more likely to have abnormal glucose patterns compared to younger individuals (8). Similarly, certain differentiations in lipid metabolism occur as people age. TC, LDL-C, HDL-C, and TG levels tend to change/increase with age (9-11). However, the reference ranges used in laboratories often do not reflect age-related changes. In Turkey, there is little information on the reference intervals and levels developed specifically for the elderly.

In this study, we aimed to determine the reference range limits of TC, HDL-C, LDL-C, and TG levels in people aged ≥65 years in our region.

MATERIALS AND METHODS

Permission was obtained from the Ethics Committee of Adnan Menderes University (Date:April26, 2019; No. E.7260) for the study. The study protocol, informed consent form, and questionnaire form were approved by the Ethics Committee of Adnan Menderes University, Faculty of Medicine. Consent forms were obtained from each individual, and they were fully informed about the study upon request.

People aged ≥65 years who applied to the outpatient clinics of Nazilli State Hospital (a district hospital with 520 beds) were included in the study. The selection of individuals started on June 20, 2019 and continued until August 8, 2020. The IFCC's

recommendations were used to select individuals and establish the exclusion criteria. The exclusion criteria were as follows: individualson steroids, thiazides, beta blockers,or anticonvulsant drugs; those who consumed alcohol regularly; those with diabetes mellitus, hypothyroidism, or hyperthyroidism; those with a previous history of chronic kidney disease, hepatitis, or acute trauma (surgery); and those who had an infection.

Over the course of 14 months, 129 men and 139 women were recruited to our study based on the mentioned criteria. Overnight fasting blood samples were collected in the morning and allowed to clot before being centrifuged for 10 min at 4000 rpm to separate the serum. The serum samples were then stored at −20°C until further examination. The samples were wait to reach room temperature before working the samples, then the tubs were slightly shaked. All lipid tests worked simultaneously (on August 15, 2020).

The measurements were taken with the Beckman 680 (Beckman Coulter INC., USA) device that was available in our laboratory, as well as the original kits of the device. The calibrations of the tests were performed using the same company's calibrators. Each day, a dual control methodology was used, with Beckman Coulter's original control and internal quality control. The desired analytical variations (CVAs) between days were compared to the half-value of biological variation identified by Ricos et al. and reported on Westgard's site (12, 13). None of the analytes had inter-day analytical variations of CVAs outside the desired limits (Table 1). The BIO-RAD (EQAS) sample was used for external quality control, with which we continue to agree on our routine external quality assessment protocol. External quality control results were then acceptable within the same peer-to-peer group.

Statistical Analysis

Statistics Package for Social Sciences" (SPSS) statistical program was used for all calculations and statistical analysis. When the normal distribution hypothesis was confirmed, the t test was used to determine whether there was a significant difference in the TC, HDL-C, and LDL -Clevels by gender. For gender and TG data that did not meet the normal distribution hypothesis, the Mann–Whitney U test was used (Table 2).

The extreme values adversely affect the distribution in the reference range studies. Boxplot were used to calculate the extreme values (based on the principle of excluding the values in the data set outside the interquartile range, i.e., 25^{th}–75^{th} percentile). The Kolmogorov–Smirnov test was used to test the normality hypothesis. The TG values of men and women were found to be not distributed normally. A logarithmic transformation was performed on variables that did not show a normal distribution. The reference range values obtained by parametric methods after logarithmic transformation are included in Table 3. İlçöl and Aslan argued in their studies that non-parametric methods were more feasible compared to the parametric methods (14). Accordingly, the TG reference intervals in men and women were recalculated using non-parametric methods. The results are shown in Table 3. The combined reference ranges for men and women are shown in Table 3.

RESULTS

The average age of our group was 74.8 years. The results of the analysis showed no statistically significant difference between TG values ($p=0.615>0.05$). When TC, HDL-C, and LDL-C values were examined in terms of gender, a significant difference was found ($p=0.000<0.05$) (Table 2). The average age of men was 74.7 years, whereas that of women was 74.9 years. The reference range values of lipids (mg/dL) for the entire group (male-female), male, and female individuals, respectively, were as follows: TC: 116–295 mg/dL,105–280 mg/dL, and 141–287 mg/dL; HDL-C:30–79 mg/dL, 28–65 mg/dL, and 31–77 mg/dL; LDL-C: 59–200 mg/dL,50–193 mg/dL, and 76–195 mg/dL; and TG: 45–298

mg/dL, 45–272 mg/dL, and 53–242 mg/dL (Table 3).

Table 4 includes the reference intervals of the current study; reference interval values found in the reference interval study in people aged ≥85 years (15) that we previously conducted using the indirect method with the same regional population; the reference interval values of people aged ≥65 years (16) reported by Özarda et al. in their multicenter study across Turkey; the reference interval values reported by Yeşim Özarda et al. of healthy and young individuals in Bursa (14); reference interval values reported by Motor et al. in individuals aged ≥40 years in Ankara (17); reference interval values (18) reported by Köseoğlu et al. in healthy individuals aged 20–50 years; and reference interval values (19) of individuals aged 18–85 years reported by Bakan et al. in Erzurum. The aforementioned studies were performed using a direct methodology, except for our previous study in individuals aged ≥85 years (15).

Ryden et al. determined the reference intervals of 31 laboratory tests in 75-year-old elderly individuals (20). Millan–Calenti et al. conducted a reference interval study in individuals aged ≥65 years in Spain and compared their findings with younger individuals in Spain (21). The study carried out abroad by means of a direct method is also shown in Table 4.

Also, the results of the present study were compared with those of Bayram et al., who investigated dyslipidemia and associated risk factors in Turkish adults (22). Table 4 shows the means of TG, LDL cholesterol, and HDL cholesterol levels in men and women aged >70 years in the study by Bayram et al. and the means of TG, LDL-C, HDL-C levels in elderly men and women in the present study.

Table 1. Analytical and methodological characteristics of analytes together with CV_A data
Tablo 1. CV_A verileriyle birlikte analitlerin analitik ve metodolojik özellikleri

Analyte	Unit	Method	N	Between-day CV_A		Analyticalsystem/ Kit Version
				C1	C2	
TG	mg/dL	Enzymatic, endpoint	20	2,43	2,59	BECKMAN COULTER 680 OSR 61118
TC	mg/dL	Cholesteroloxidase, esterase, peroxidase	20	0,89	0,86	BECKMAN COULTER 680 OSR 6216
HDL-C	mg/dL	Direct measure, Immunoinhibition	20	1,94	1.98	BECKMAN COULTER 680 OSR 6287

CV_A :Analyticalvariation
C1: Control 1C2: Control 2

Table 2. Mean of females andmales lipids
Tablo 2. Kadınların ve erkeklerin lipit ortalamaları

Analyte (Unit)	Female		Male		P
	N	Mean±SD	N	Mean±SD	
HDL –C (mg/dL)	139	54±12	129	47±12	P<0,05
LDL –C (mg/dL)	139	135±32	129	122±38	P<0,05
TG (mg/dL)	139	123±52	129	127±77	P=0,615
TC (mg/dL)	139	213±41	129	194±47	P<0,05

Table 3. Males, Females and total reference intervals for parametric and nonparametric (mg/dL)
Tablo 3. Erkek, kadın ve iki cins birarada parametrik ve nonparametrik olarak referans aralıkları (mg/dl)

Analyte (Unit)	Sex	PARAMETRIC				NONPARAMETRIC			
		N	Lower – Upper limits	%90 Confidence interval lower limits	%90 Confidence interval upper limits	N	Lower – Upper limits	%90 Confidence interval lower limits	%90 Confidence interval upper limits
TC	Male	128	105-280	94-116	269-292	265	116-295	100-133	282-304
	Female	136	141-287	131-150	278-296				
TG	Male	125	45-272	40-51	242-305	125	51-322	45-60	228-355
	Female	135	53-242	48-58	220-266	135	57-239	45-62	215-252
						260 (male+female)	45-298	41-56	250-355
HDL-C	Male	122	28-65	26-31	63-68	265	30-79	25-32	75-82
	Female	137	31-77	28-34	74-79				
LDL-C	Male	127	50-193	41-60	184-202	265	59-200	53-70	194-213
	Female	136	76-195	68-83	187-202				

Table 4. Comparison of the male and female lipid mean levels between Nazilli study and other study; comparison of the reference intervals of the serum lipid levels of the Nazilli study with those of other studies
Tablo 4. Nazilli çalışması ile diğer çalışmanın erkek ve kadın lipit ortalamalarının karşılaştırılması; Nazilli çalışmasının referans aralıklarının diğer çalışmaların referans aralıkları ile karşılaştırılması

	NAZİLLİ	**Reference 22***	**NAZİLLİ**	**Referance 15****	**Referance 16*****	**Referance 14 ******	**Referance 17******	**Referance 18 *******	**Referance 19********	**Referance 20*********	**Referance 21**********
	Lipid Mean ±SD	**Lipid Mean** ±SD	**Refence Range**	**Refence Range**	**Refence Range**	**Refence Range**	**Refence Range**	**Refence Range**	**Refence Range**	**Reference Range**	**Reference Range**
MALE+ FEMALE KOLESTEROL			116 –295	122-284		102-256	130-279	121-269			135-309
MALE+ FEMALE HDL-C			30 – 79	29-74							35-90
MALE+ FEMALE LDL-C			59 – 200	62-180			61-192				73-212
MALE+ FEMALE TG			45 – 298	55-230							62-354
MALE TC			105– 280	119-275	132-267				116-258	124-286	
FEMALE TC			141– 287	127-288	151-292				112-252	151-305	
MALE HDL-C	47±12	48,9 ±14,5	28 – 65	26-72	31-60	30-54	27-64	31-66	21-50	30-88	
FEMALE HDL-C	54±12	53± 14,3	31 – 77	30-77	34-76	31-65	34-74	35-78	28-78	39-107	
MALE LDL-C	122±38	121,6 ±39,2	50 – 193	57-178	63-170				58-192	54-208	
FEMALE LDL-C	135±32	129,1± 40,9	76 – 195	65-187	68-180				56-173	69-208	
MALE TG	127±77	143 ±109,8	45– 272	55-196	58-383	35-299	38-277	50-313	52-276	57-278	
FEMALE TG	123±52	147 ±77,5	53 – 242	56-239	63-347	24-220	42-271	39-199	56-240	53-271	

* Prevalence of dyslipidemia and associated risk factors in Turkish adults,** indirect reference study, over 85 years , *** direct reference studyover 65 years, multicenter study, ****direct reference study18-40 years, Bursa study, *****direct reference studyover 40 years, Ankara study, ******direct reference study20-50 years, İzmir study, *******direct reference study18-85 years, Erzurum study, ********direct reference study75 years, Sweden, *********direct reference studyover 65years, Spain

DISCUSSION

One of the most important starting points of this study was to determine the reference range values of four important biochemical tests associated with chronic diseases in elderly individuals in Turkish society. For this purpose, 268 people aged ≥65 years who presented to the Nazilli State Hospital for routine control tests between 2019 and 2020 were included in the study and this study were compared with other studies. When the reference range studies in the literature were examined, it was observed that the age ranges were kept fairly broad, ranging from 18 to 60 years (23, 24, 25). The inclusion of only individuals aged ≥65 years and the sufficient sample size enabled the use of parametric methods and strengthened our study.

The lower limits of TC in female–male group in the indirect reference range study of elderly individuals aged ≥85 years were higher than the lower limits of the present study (5%). The upper limit in the current study was slightly higher than the upper limit in the other study (4%). In the current study, the lower limits of HDL –C were similar between male-female group, and the upper limits of HDL-C between male-female group were slightly higher (7%). In the present study, the lower limit of the male-female TG levels was low (22%) and the upper limit was significantly higher (30%). In our study and the multicenter study conducted by Özarda et al. across Turkey, the lower and upper limit values of HDL-C levels in male group and female group were similar. When comparing a study in Bursa with our study, although the HDL-C levels for lower limit values were similar in the male group and female group in both studies, the upper limit of these values were different. Our study and the study by Motor et al. had similar upper and lower limit values for LDL –C levels in the male- female group. Also, upper and lower limit values for HDL –C had similar in the male group and female group too. In the Izmir study, HDL –C levels were similar to our results.

In the Izmir study, HDL –C levels were similar to our results. Erzurum study, the lower and upper limits of TG in men were close to the results of the present study but slightly higher. In female group, the lower limit was slightly higher, while the upper limit was similar. In male group, HDL –C levels were lower compared to the present study in terms of both the lower and upper limits, whereas the lower and upper limits were similar in female group. When we compared the HDL –C values in our studies to the values found in the overseas studies, we observed that our HDL–C upper limits were significantly lower than the values found in both the overseas studies. In the domestic studies, lipids other than HDL–C differed overall, which could be attributed to age, region, and eating and drinking habits.

According to the Adult Treatment Panel Criteria (ATP), the prevalence of dyslipidemia in people >70 years of age was found to be 30.8% for high TG levels, 45.4% for high LDL-C levels, and 32.4% for low HDL-C levels as observed by Bayram et al. In elderly individuals included in the present study, these rates were found to be 26% for high TG levels, 28% for high LDL-C levels, and 31% for low HDL-C levels. The lower rates of dyslipidemia prevalence in all the groups could be attributed to the fact that the elderly individuals in the present study were specifically selected to establish the reference range.

The HDL –C values in the study conducted by Bayram et al. and the HDL –C values in our study were similar in all the HDL-C parameters measured (Table 4). We determined that the similar results in both studies provide us with valuable information about the HDL–C levels of Turkey's elderly population.

It is stated in the literature that low HDL-C and high TG levels in the Turkish population increase the risk of cardiovascular events and myocardial infarction, especially in men (26, 27). Studies investigating the change in HDL-C levels with age have yielded inconsistent results. While some studies have found that HDL-C levels tend to decrease with age (28, 29), HDL-C levels have been

found to increase in some studies (30).In some studies, it has been shown that HDL-C levels do not change with age (31). In the Turkish studies consisting of different age groups that we have compared, the lower and upper limits of the reference ranges were generally close to each other. In the two overseas studies that we included in our study, the upper limits of HDL-C levels were found to be significantly higher than in our study. This apparent difference in the upper limits may be related to the lower HDL-C levels in Turkish society.

TC and LDL-C levels tend to increase with age (32, 33), and after a certain age, these levels tend to decline (11, 30). Although there is a risk of atherosclerosis associated with high TC levels in elderly individuals, certain publications suggest that high cholesterol levels in the elderly are not necessarily bad because they protect against infections and cancer, and higher TC levels might be beneficial for elderly individuals (34-37). For this reason, the question of how to use cholesterol-lowering drugs in the elderly is dependent on well-defined reference intervals. However, clinical decision limits for lipid parameters are well-defined. The American Heart Association (AHA) has predicted that statin therapy may benefit the following four large groups: 1) those with clinical signs of cardiovascular disease; 2) those with an LDL-C level of ≥190 mg/dL; 3) those aged 40–75yearswith diabetes and an LDL-C level of 70–189 mg/dL; and 4) those without cardiovascular disease and diabetes but with LDL-C levels between 70 and 189 mg/dL and a 10-year coronary artery disease risk calculation of ≥7.5 (38). Based on these clinical decision limits of AHA, a diagnosis is made and treatments are initiated. Based on these recommendations, antilipid drugs are increasingly used In Turkey and all over the world. However, it is critical to understand the reference ranges based on societal characteristics. Knowing the levels and reference intervals may be useful for making decisions when making a diagnosis and reaching a beneficial conclusion in drug use, especially in the elderly group, where we have very little data. In our study, the upper limit of the LDL-C reference range was 195 mg/dL for women and 193 mg/dL for men. The values we found in our group were slightly higher than the benchmark values specified by the AHA. We believe that the upper limits of LDL-C that we found should be used as a cutoff value for our region's elderly population.

CONCLUSION

Other than HDL-C, we found that the other three groups of lipids differed in different age groups and studies. Considering the regional characteristics of the place of residence, age groups, diets, and differences in methods, reference ranges specific to population and age should be obtained, as recommended by the IFCC. Elderly patients constitute a significant part of outpatient or inpatient treatment. The majority of evaluations for elderly groups are based on reference ranges for younger age groups. For this reason, it is extremely important to establish reference ranges for elderly groups, such as pediatric age groups, and clinical evaluations in the elderly should be made according to these reference limits. As a result, it would be much more beneficial to evaluate these reference ranges for lipid parameters as well as their levels and clinical decision limits before deciding to begin drug treatment.

Conflict of interest statement

Authors' conflict of interest disclosure: The authors state that there are no conflicts of interest regarding the publication of this article.

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