

Evaluation of relationship between hematocrit and lipid profile in adults

Avaliação da correlação entre o hematócrito e o perfil lipídico em adultos

Gabriel P. R. Lopes¹; Marcos A. G. Munhoz²; Leila Antonangelo^{1,2}

1. Faculdade de Medicina da Universidade de São Paulo (FMUSP), São Paulo, Brazil.

2. Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo (HCFMUSP), São Paulo, Brazil.

ABSTRACT

Introduction and objective: This study was carried out to analyze the relationship between hematocrit and lipid profile in adults. **Material and method:** A sample composed of complete blood counts and lipid profiles from the database of Hospital das Clínicas da Universidade de São Paulo (HCUSP), São Paulo, Brazil, was used in the analysis. Hematocrit was organized in five groups that were compared with total cholesterol (TC), low-density-lipoprotein cholesterol (LDL-C), non-high-density-lipoprotein cholesterol (NHDL-C) and high-density-lipoprotein cholesterol (HDL-C) by means of chi-squared and Kruskal-Wallis tests. **Results:** Both tests showed a relevant correlation between hematocrit and lipid profile, considering a p -value < 0.05 . Moreover, descriptive statistics revealed that the higher the hematocrit, the higher the proportion of people without recommended levels of each type of cholesterol, such TC, LDL-C, and NHDL-C. Just HDL-C showed an inverse association compared to the other variables, with an increased proportion of recommended levels along with rising of hematocrit. **Conclusion:** The relationship between hematocrit and lipid profile in all aspects of this study was more evident in women; nevertheless, the higher proportion of not recommended levels of HDL-C was shown in men. The reverse cholesterol transport probably plays an important role in the increase of cholesterol levels in blood in the presence of high hematocrit, by interaction of HDL-C and erythrocytes. Thus, further studies are necessary to elucidate these findings and to describe more aspects of the reverse cholesterol transport and its relationship with hematocrit and lipid profile.

Key words: cholesterol; hematocrit; erythrocytes; lipoproteins.

INTRODUCTION

Blood is a complex fluid, responsible for delivering nutrients to most body tissues and for collecting metabolic wastes, avoiding tissue accumulation and toxicity. It is composed of an extracellular fluid rich in proteins – plasma – and cells, such as erythrocytes, leukocytes and platelets⁽¹⁾.

Erythrocytes, or red blood cells, the main blood components, are non-nucleated cells that contain great amount of hemoglobin, a protein responsible for O₂ and CO₂ transport. Under normal conditions, erythrocytes do not leave the circulatory system: they always remain within blood vessels⁽²⁾, actively participating in homeostasis maintenance. Although their primary function is the transport of gases bound to hemoglobin, it is evident that

erythrocytes have other interactions, such as the capacity of diffusional exchange of cholesterol, but with low capacity for cholesterol storage⁽³⁾. This function makes us suppose there is a possible correlation between circulating erythrocytes and transport of cholesterol and its fractions.

This activity of erythrocytes in cholesterol mobilization highly depends on hematocrit concentration. The higher the hematocrit, the larger the volume occupied by the red cells in whole blood, and consequently, the smaller the plasma volume to comprise other elements, a fact that also contributes to the increased concentration of lipoproteins in this smaller plasma volume⁽⁴⁾. Moreover, the higher the hematocrit, the greater the quantity of erythrocytes contributing to the diffusional transport of cholesterol to plasma lipoproteins. This transport is possibly mediated by the cholesterol reverse transport promoted by the

high-density-lipoprotein cholesterol (HDL-C) fraction^(5, 6). Due to the activity of ATP-binding cassette protein A1 (ABCA1) and lecithin cholesterol acetyltransferase (LCAT), HDL-C associated to Apo-A1 (LCAT cofactor) withdraws the free cholesterol present in the membrane of erythrocytes and esterifies it^(6, 7). Later, by activity of cholesterol ester transfer protein (CETP), the esterified cholesterol contained in the HDL-C is transferred to the very-low-density-lipoprotein (VLDL) and the chylomicrons, receiving their triglycerides in exchange and contributing to the increased density of both. The process helps in the formation of intermediate-density-lipoprotein (IDL) and low-density-lipoprotein cholesterol (LDL-C) from VLDL⁽⁷⁾ and clearance of chylomicrons⁽⁸⁾. This cholesterol transport cycle possibly contributes to an influx of esterified cholesterol of cellular membranes for lipoproteins of blood plasma. This mechanism is plausible since the efflux of cholesterol from erythrocytes to HDL-C is greater than the influx of free cholesterol from lipoproteins to erythrocyte when the system relies on the presence of LCAT⁽⁶⁾.

Considering the mechanism of diffusional transport of cholesterol between erythrocytes and plasma lipoproteins, we can suppose that the levels of total cholesterol (TC) and fractions, as well as that of related lipoproteins depend, at least in part, on the quantity of erythrocytes present at an individual's blood, and therefore, on the percentage occupied by them in relation to the total blood volume.

This hypothesis is reinforced when we verify that in both extremes of the hematocrit we can observe alterations in the lipid profile of individuals. In anemic individuals, whose hematocrit values are low and there is decreased quantity of erythrocytes in the blood, we can notice a considerable decrease in TC and fractions, as well as associated lipoproteins, characterizing the presence, in some cases, of hypocholesterolemia^(9, 10), which has a tendency towards normalization with the resolution of the anemic process⁽¹¹⁾. On the other hand, individuals with increased hematocrit levels, and consequently with increased number of circulating erythrocytes, can have higher levels of non-high-density-lipoprotein cholesterol (NHDL-C)⁽⁵⁾.

In the cases of increased TC, we must pay attention to the risks this altered lipid profile poses to an individual. Hypercholesterolemia is known to be a great risk factor for the development of complications in the cardiovascular system, such as atherosclerotic disease and acute myocardial infarction⁽⁷⁾. Besides, there is evidence that a higher hematocrit value also contributes to a higher risk of involvement of the cardiovascular system, because with larger amounts of erythrocytes in the blood a bigger loss of energy would occur by cell-cell contact,

mainly in microcirculation, leading to increased apparent blood viscosity⁽¹²⁻¹⁴⁾. This increased viscosity provides higher resistance to blood passage through the circulatory system, demanding stronger force from the cardiac pump to dislocate this mass downstream. Thus, we can consider that the increased blood viscosity is also a risk factor for the development of alterations of the cardiovascular system, as for instance, systemic arterial hypertension⁽¹⁵⁾, a disease that can evolve to left ventricular hypertrophy⁽¹⁶⁾.

OBJECTIVE

Considering that the increase of hematocrit can be related to a cascade of hemodynamic and metabolic alterations that contribute to higher cardiovascular risk, this study aims at assessing the correlation between hematocrit and variations of TC, its fractions and associated lipoproteins in a population of individuals treated at a tertiary care hospital.

MATERIAL AND METHOD

This study is a retrospective cohort, approved by the Research Ethics Committee (Cappesq) under CAAE 68643017.6.0000.0068, whose objective is to evaluate the possible correlation between levels of hematocrit and cholesterol. From the data bank of the clinical laboratory of Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo (HC/FMUSP) (system SIGH), a total of 69,408 blood counts and respective lipid profiles referring to the period of January to August 2017 were analyzed. We excluded cases in which data of blood count or lipid profile were incomplete.

After this step, tests of adult individuals aged 20 years or older (age group 20-100 years) were kept in the sample body. Such a measure was adopted to avoid a possible bias in data analysis, once the adopted normal reference values of lipid profile were taken from the V Diretriz Brasileira de Dislipidemias e Prevenção da Aterosclerose⁽⁷⁾, making just individuals older than 20 years eligible for analysis. Due to the interference that triglycerides high rates (lipemia) can cause in the evaluation of parameters of blood cell indices⁽¹⁷⁾, we opted for excluding data from patients whose triglyceride levels were equal or greater than 500 mg/dl.

After this refinement, 39,843 and 29,237 blood counts and respective lipid profiles were recorded in female and male patients,

respectively, amounting to a sample of 69,080 paired tests. The assessment of the correlation proposed between hematocrit and TC and fractions was applied separately for both sexes, avoiding interference in comparison because of different average values of lipid profile that are observed between men and women, besides different levels of plasma apolipoproteins, what also alters mean values of lipid profile between sexes⁽¹⁸⁾.

Regarding hematocrit levels, normality limits were not considered in men and women in the division of groups for analysis, since the study proposes analyzing primarily alterations of TC and fractions. Thus, the total sample was allocated into five groups of hematocrit, as follows:

- group A (< 30%) – composed of 1,172 tests of female patients and 900 of male patients;
- group B (30%-35.9%) – composed of 7,499 tests of female patients and 2,675 of male patients;
- group C (36%-40.9%) – composed of 21,299 tests of female patients and 7,634 of male patients;
- group D (41%-45.9%) – composed of 9,335 tests of female patients and 13,914 of male patients;
- group E (46%-50.9%) – composed of 538 tests of female patients and 4,114 of male patients.

Hematocrit values above these levels were not considered due to the limited number of available blood counts for analysis.

Regarding lipid profile, we analyzed the percentage of tests of men and women with alterations in the variables TC, LDL-C, HDL-C, and NHDL-C in each proposed hematocrit group. Lipid variables were classified as normal or altered, with the latter being composed of values borderline + altered or just altered, according to the classification of V Diretriz Brasileira de Dislipidemias e Prevenção da Aterosclerose⁽⁷⁾. Triglycerides and VLDL were not analyzed separately, as those parameters can undergo alterations in patients under inadequate fasting^(19, 20).

Statistical analysis

Comparisons between lipid profiles and hematocrit groups were done by chi-squared test and by Kruskal-Wallis test, the latter being responsible for analysis of distribution of lipid values in the several hematocrit ranges. The adopted significance level was $p < 0.05$. The obtained results are graphically presented for better visualization of the proposed correlation between hematocrit and TC and fractions.

RESULTS

Chi-squared and Kruskal-Wallis tests revealed statistically significant correlation between hematocrit and TC and fractions

The chi-squared test showed a significant correlation ($p < 0.05$) between values of hematocrit and TC and fractions, for all analyzable variables: TC, LDL-C, HDL-C, and NHDL-C in both sexes (**Table 1**).

By means of the Kruskal-Wallis test, we observed that the distribution of lipid values among the proposed hematocrit ranges is significantly different ($p < 0.0001$), suggesting that hematocrit has influence on lipid values in the analyzed samples.

TABLE 1 – Number of men and women with normal and altered values for each lipid variable in the several hematocrit ranges

	TC		LDL-C		HDL-C		NHDL-C	
	Men	Normal	Altered	Normal	Altered	Normal	Altered	Normal
Group A	814	86	824	76	355	545	820	236
Group B	2,316	359	2,387	288	1,443	1,232	2,388	756
Group C	6,205	1,429	6,53	1,104	4,56	3,074	6,522	2,487
Group D	10,565	3,349	11,026	2,888	8,064	5,85	11,08	4,982
Group E	2,882	1,232	3,057	1,057	2,33	1,784	3,062	1,661
<i>p</i>	< 0.0001*		< 0.0001*		< 0.0001*		< 0.0001*	
	TC		LDL-C		HDL-C		NHDL-C	
	Women	Normal	Altered	Normal	Altered	Normal	Altered	Normal
Group A	928	244	1,009	163	706	466	997	175
Group B	5,548	1,951	6,226	1,273	5,907	1,592	6,33	1,169
Group C	14,121	7,178	16,433	4,866	17,974	3,325	16,904	4,395
Group D	5,33	4,005	6,482	2,853	7,814	1,521	6,656	2,679
Group E	293	245	371	167	435	103	370	168
<i>p</i>	< 0.0001*		< 0.0001*		< 0.0001*		< 0.0001*	

* $p < 0.05$ for the variables total cholesterol, LDL-C, HDL-C and NHDL-C.

TC: total cholesterol; LDL-C: low-density-lipoprotein cholesterol; HDL-C: high-density-lipoprotein cholesterol; NHDL-C: non-high-density-lipoprotein cholesterol.

Increasing hematocrit values concomitant with changes in the pattern of lipid variables

We observed that increased hematocrit involves increased percentage of individuals with altered TC, LDL-C, and NHDL-C and decreased percentage of individuals with altered values of HDL-C, a fact observed for both sexes (**Table 2**).

The percentages of individuals of both sexes and the respective alterations of lipid profile according to hematocrit ranges can be better visualized in **Figures 1** and **2**.

TABLE 2 – Percentage of men and women with altered lipid variables in comparison with normal individuals in the same hematocrit range

Men	Group A	Group B	Group C	Group D	Group E
TC	9.56%	13.42%	18.72%	24.07%	29.95%
LDL-C	8.44%	10.77%	14.47%	20.76%	25.69%
HDL-C	60.56%	46.06%	40.27%	42.04%	43.36%
NHDL-C	8.89%	10.73%	14.57%	20.37%	25.57%
Women	Group A	Group B	Group C	Group D	Group E
TC	20.82%	26.02%	33.7%	42.9%	45.54%
LDL-C	13.91%	16.98%	22.85%	30.56%	31.04%
HDL-C	39.76%	21.23%	15.61%	16.29%	19.14%
NHDL-C	14.93%	15.59%	20.63%	28.7%	31.23%

One notices the increased percentage of individuals with altered lipid value while there is hematocrit increase (from group A to group E).

TC: total cholesterol; LDL-C: low-density-lipoprotein cholesterol; HDL-C: high-density-lipoprotein cholesterol; NHDL-C: non-high-density-lipoprotein cholesterol.

A higher percentage of women with altered lipid values is observed in the several hematocrit groups

In all hematocrit groups, a higher percentage of women with altered lipid values was observed (except HDL-C, which will be considered in the next item) in comparison with the percentage of men in the same group.

Considering group A, approximately 20% of women presented altered TC values; and 15%, altered LDL-C and NHDL-C, while just 10% of men presented alterations in the three variables. Considering group E, approximately 45% of women presented altered TC versus 30% of men. These comparisons exemplify the general pattern observed when we compare women and men in the several hematocrit ranges regarding a certain lipid variable (Figures 3, 4 and 5).

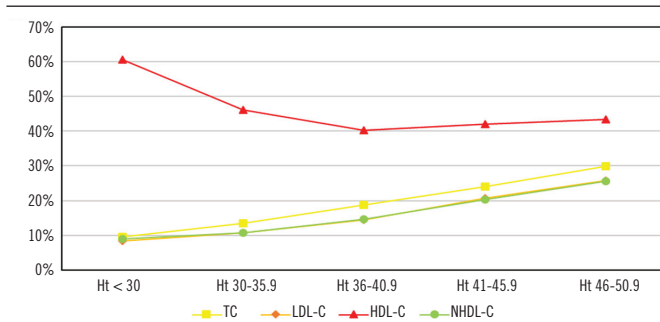


FIGURE 1 – Percentage of men with altered lipid variables (y-axis) in each range of hematocrit analyzed (x-axis). Observe the change of lipid variables between the groups in the different hematocrit ranges

TC: total cholesterol; LDL-C: low-density-lipoprotein cholesterol; HDL-C: high-density-lipoprotein cholesterol; NHDL-C: non-high-density-lipoprotein cholesterol.

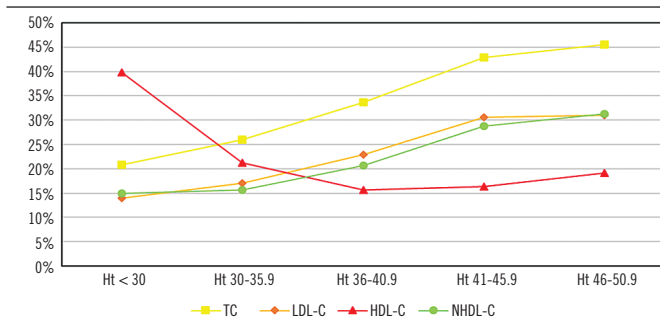


FIGURE 2 – Percentage of women with altered lipid variables (y-axis) in each range of hematocrit analyzed (x-axis). Observe the change of lipid variables between groups in the different hematocrit ranges

TC: total cholesterol; LDL-C: low-density-lipoprotein cholesterol; HDL-C: high-density-lipoprotein cholesterol; NHDL-C: non-high-density-lipoprotein cholesterol.

Regarding the HDL-C variable, the variation showed itself contrary to the hematocrit values, with the percentage of women with altered HDL-C being 39.76% (group A) to 19.14% (group E) and from 60.56% (group A) to 43.36% (group E) in men.

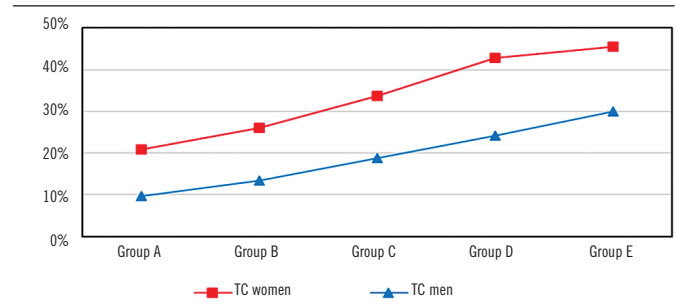


FIGURE 3 – Percentage of men and women with altered TC in the different hematocrit ranges (groups A to E)

TC: total cholesterol.

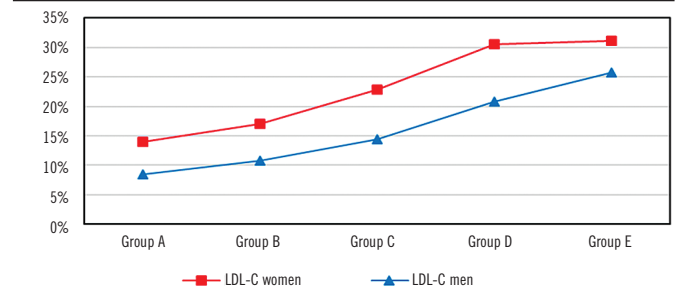


FIGURE 4 – Percentage of men and women with altered LDL-C in the different hematocrit ranges (groups A to E)

LDL-C: low-density-lipoprotein cholesterol.

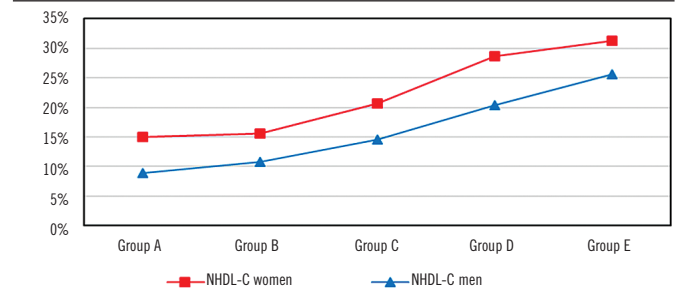


FIGURE 5 – Percentage of men and women with altered NHDL-C in the different hematocrit ranges (groups A to E)

NHDL-C: non-high-density-lipoprotein cholesterol.

HDL-C is an exception to the last topic

We observe that the percentage of women with altered lipid variables is higher than that of men in the several hematocrit groups. However, this finding does not apply to HDL-C values. In this variable, the percentage of men with altered values is higher than that of women. In group A, just 40% of women had this lipid variable below desirable levels versus 60% of men; in group E we had around 20% of women versus 43% of men. This reveals the peculiarity of HDL-C in relation to the obtained data (Figure 6).

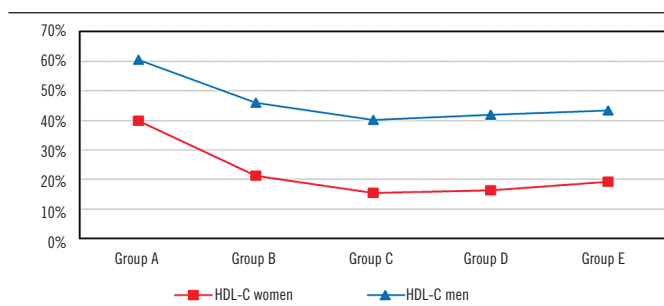


FIGURE 6 – Percentage of men and women with altered HDL-C in the different hematocrit ranges (groups A to E)

HDL-C: high-density-lipoprotein cholesterol.

DISCUSSION

In the current study we tried to highlight possible correlations between levels of hematocrit and those of TC and fractions. The obtained results suggest that hematocrit is directly related to alterations in the lipid profile of individuals, regardless of sex, with observed increase in the level of all lipid variables analyzed (TC, LDL-C, HDL-C, and NHDL-C), according to increased levels of hematocrit. One can notice the increased percentage of individuals with altered lipid values in the highest ranges of hematocrit, except HDL-C, which tends towards adequate values in these hematocrit ranges. Interestingly, the correlation between hematocrit and lipid profile was more expressive in women, for all ranges analyzed.

The correlation observed in the study can, at least in part, be attributed to reverse cholesterol transport, mediated by HDL-C, a lipoprotein that seems to play a central role in this process. Studies suggest that HDL-C levels are associated with the total number of erythrocytes present in the blood, and accordingly, with the hematocrit, regardless of age, race, ethnicity, gender, smoking habit or body mass index (BMI)⁽³⁾. HDL-C apparently promotes cholesterol efflux of erythrocyte membranes in the presence of LCAT, promoting a further transference of esterified cholesterol

to VLDL and chylomicrons, due to the action of CETP^(7, 8). The lipid metabolism evolves with the transformation of VLDL particles into IDL, and later, into LDL, accumulated in blood circulation⁽⁷⁾. Besides that, it is suggested that erythrocytes interact with lipoproteins for the metabolism of cholesterol and lipids associated with hemoglobin (Hb-Ch). Most part of these factors is incorporated by the HDL-C fraction, with parallel decrease in quantity of Hb-Ch⁽⁵⁾. All the cholesterol taken from erythrocytes can be attributed to the plasma lipoprotein metabolism, which can also be taken by other cells, by the liver or even excreted through the bile⁽²¹⁾.

This metabolism reflects that erythrocytes, although having low capacity to store cholesterol, take part in its diffusional exchanges and metabolism⁽³⁾. Erythrocytes apparently have the capacity to generate pre-beta-HDLs with cellular lipids when they interact with free lipoproteins (from the dissociation of HDL-C already formed in the circulation)⁽⁶⁾. Also, the stable membrane of these components appears to be related to circulating levels of LDL-C. Low cholesterol levels that exceed a critic limit culminate in instability of the membrane, increasing osmotic fragility and the hemolysis of red cells⁽³⁾.

Considering those pathways, we can presume several interactions, many already described, between erythrocytes and TC and fractions. Fessler *et al.* (2013)⁽³⁾ demonstrated that in the American population, larger quantities of circulating erythrocytes are involved with higher levels of NHDL-C. According to Temte (1996)⁽⁴⁾, TC levels seem to be linearly associated with hematocrit in low altitudes.

The correlation between the increased hematocrit and increased levels of circulating lipoproteins is based mainly on the mechanism of reverse cholesterol transport. In the current study, this was more evident in women, perhaps because of the fact that females present higher values of TC, HDL-C, and ApoAI, than males⁽¹⁸⁾, although there are data in the literature suggesting that women have lower levels of LDL-C in developed countries⁽¹⁰⁾. With larger quantities of HDL-C, women can have higher expression of reverse cholesterol transport pathways when in the presence of high levels of hematocrit, a fact that can explain the observation of higher percentages of women with altered lipid values in all hematocrit levels. Men, due to lower HDL-C levels, would not have this pathway so active, what would explain the lowest percentage of individuals with altered lipid profile. However, this hypothesis can be complemented when we observe that enrichment of chylomicrons with cholesterol, a factor that is important for removal of these particles from circulation, occurs rapidly with high levels of circulating HDL-C. So, women would count on a more rapid elimination of these particles than men, and their

accumulation would be associated with higher cardiovascular risk⁽⁸⁾, what would explain higher incidence of coronary events in male individuals.

Although there is evidence of other mechanisms of cholesterol transport associated with erythrocytes and independent from HDL-C⁽²¹⁾, transport dependent on this lipoprotein seems to be the base for us to understand physiopathology of the interactions that occur in lipid metabolism in vivo. Interactions of reverse cholesterol transport can explain the correlation between the increase of circulating lipoproteins in the presence of high values of hematocrit, mainly if we consider that cholesterol is stored in the plasma in its esterified form by this pathway⁽⁷⁾.

This study presents as limitation the use of a sample population taken from a tertiary care hospital, where lipid levels

or blood cell indices may not correspond to those of the population in general. The altitude of the location where the study was carried out (760 meters above the sea level) may also have influenced the obtained results, since altitude is related with blood cell indices and blood lipoprotein.

CONCLUSION

Although our findings reinforce the strict correlation between hematocrit levels and lipid profile, further studies are necessary for better comprehension of the obtained results, with major focus on the functioning mechanisms and on physiopathology of the described pathways.

RESUMO

Introdução e objetivo: Este estudo foi escrito com o objetivo de analisar a relação entre o hematócrito e o perfil lipídico em adultos. **Material e método:** Utilizou-se uma amostra composta por hemogramas e perfis lipídicos do banco de dados do Hospital das Clínicas da Universidade de São Paulo (HCUSP), São Paulo, Brasil. O hematócrito foi organizado em cinco grupos, sendo eles comparados com o colesterol total, o colesterol da lipoproteína de baixa densidade (LDL-C), o colesterol da lipoproteína de alta densidade (HDL-C) e o colesterol total não HDL (NHDL-C), por meio de análise estatística com os testes de qui-quadrado e Kruskal-Wallis. **Resultados:** Ambos os testes mostraram correlação relevante entre o hematócrito e o perfil lipídico, considerando um valor de $p < 0,05$. Além disso, a estatística descritiva forneceu uma visão de que, quanto maior o hematócrito, maior a proporção de indivíduos sem níveis recomendados de cada tipo de colesterol, como colesterol total, LDL-C e NHDL-C. Excepcionalmente, o HDL-C mostrou uma associação inversa em comparação com outras variáveis, com um aumento na proporção dos níveis recomendados juntamente com o aumento do hematócrito. **Conclusão:** A relação entre o hematócrito e o perfil lipídico em todos os aspectos deste estudo foi mais evidente nas mulheres; no entanto, a maior proporção de níveis não recomendados de HDL-C foi demonstrada nos homens. O transporte reverso de colesterol provavelmente tem um papel importante no aumento dos níveis de colesterol no sangue na presença de hematócrito alto, pela interação do HDL-C e dos eritrócitos. Assim, outros estudos são necessários para elucidar esses achados e descrever mais aspectos sobre o transporte reverso do colesterol e sua relação com o hematócrito e o perfil lipídico.

Unitermos: colesterol; hematócrito; eritrócitos; lipoproteínas.

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CORRESPONDING AUTHOR

Gabriel P. R. Lopes

Rua Teodoro Sampaio, 281; Cerqueira César; CEP: 05405-000; São Paulo-SP, Brasil; e-mail: gabriel.lopes@fm.usp.br



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