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The TG/HDL-c index, a marker of atherogenic dyslipidemia, is a significant factor in the contemporary epidemiological profile of Mexico

El índice TG/c-HDL, marcador de dislipidemia aterogénica, es un factor significativo en el perfil epidemiológico contemporáneo de México

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Palabras clave: *hipertrigliceridemia, índice TG/HDL, sociedad mexicana, perfil lipídico.*

ABSTRACT

Introduction: obesity/overweight (O/O) is the basis of the leading causes of general mortality in Mexico: ischemic heart disease and type 2 Diabetes Mellitus (2DM). The lipid triad, associated with O/O, is the most common type of dyslipidemia in our country. We analyzed the lipid profiles of a large sample of the contemporary urban population of Mexico City. **Material and methods:** sixty-eight thousand participants comprised this cohort. The clinical status, reason for the study, and whether the patient was being treated were not recorded. Total Cholesterol (TC), TriGlycerides (TG), and High-Density Lipoprotein cholesterol (HDL-c) levels were measured spectrophotometrically. Low-Density Lipoprotein (LDL-c) and non-HDL levels, and the risk ratios TC/HDL-c, LDL-c/HDL-c, and TG/HDL-c were calculated. The classification criteria were based on ATP III and European guidelines. The mean values and quartile distributions of all lipids and lipoproteins were estimated and stratified by sex. **Results:** the TC values were above the cut-off. The TG values were significantly higher than this. The HDL-c levels in both sexes remained close to the lower limit. The LDL-c levels were between 100 and 130 mg/dL in both men and women. Non-HDL-c levels never reached a cut-off of 160 mg/dL. The LDL-c/HDL-c index was below it. Interestingly, the TG/HDL-c values were above the cut-off limit. **Conclusions:** hypertriglyceridemia, caused by abdominal obesity, is the most critical lipid abnormality in the Mexican population. TG/HDL-c is a readily available, inexpensive risk marker that should be used routinely.

RESUMEN

Introducción: *la obesidad/sobrepeso (O/O) es la base de las principales causas de mortalidad general en México: cardiopatía isquémica y diabetes mellitus tipo 2 (DM2). La tríada lipídica, asociada con O/O, es el tipo más común de dislipidemia en nuestro país. Analizamos los perfiles lipídicos de una muestra amplia de la población urbana contemporánea de la Ciudad de México.* ***Material y métodos:*** *sesenta y ocho mil participantes conformaron esta cohorte. No se registró el estado clínico, el motivo del estudio ni si el paciente estaba recibiendo tratamiento. Se midieron espectrofotométricamente los niveles de colesterol total (CT), triglicéridos (TG) y colesterol unido a lipoproteínas de alta densidad (c-HDL). Se calcularon los niveles de lipoproteínas de baja densidad (c-LDL) y no HDL, y las razones de riesgo CT/c-HDL, c-LDL/c-HDL y TG/c-HDL. Los criterios de clasificación se basaron en el ATP III y las guías europeas. Se estimaron los valores medios y las distribuciones de cuartiles de todos los lípidos y lipoproteínas y se estratificaron por sexo.* ***Resultados:*** *los valores de CT estuvieron por encima del punto de corte. Los valores de TG fueron significativamente mayores que este. Los niveles de c-HDL en ambos sexos se mantuvieron cerca del límite inferior. Los niveles de c-LDL estuvieron entre 100 y 130 mg/dL tanto en hombres como en mujeres. Los niveles de c-no-HDL nunca alcanzaron un punto de corte de 160 mg/dL. El índice c-LDL/c-HDL estuvo por debajo de este. Curiosamente, los valores de TG/c-HDL estuvieron por encima del límite de corte.* ***Conclusiones:*** *la hipertrigliceridemia, causada por la obesidad abdominal, es la anormalidad lipídica más crítica en la población mexicana. TG/c-HDL es un marcador de riesgo fácilmente disponible y de bajo costo que debe usarse de forma rutinaria.*

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INTRODUCTION

Due to profound socioeconomic and cultural changes, Mexico has undergone a rapid epidemiological transition, with its impact being uneven across different regions.[1-3] One of the most significant consequences of this transition is the alarming rise in the prevalence of overweight and obesity (O/O), now the country's foremost public health issue.[3] These conditions affect nearly four-fifths of the adult population and contribute to the onset, progression, and complications of other cardiometabolic disorders, particularly the two leading causes of mortality in Mexico, ischemic heart disease and diabetes mellitus (DM).[4] This growing health crisis has placed a considerable burden on the national healthcare system, undermining workforce productivity and economic competitiveness.[5-7]

Regretfully, neither the Mexican State nor society has responded adequately to the threat posed by these lethal epidemics The combination of limited and poorly managed governmental health spending, the absence of adequate preventive public policies, insufficient training of a significant proportion of healthcare personnel in managing cardiovascular risk factors, and the widespread adoption of lifestyle and dietary habits foreign to traditional Mexican culture, particularly the high consumption of junk and processed foods,[8-11] among many other contributing factors, has led to the explosive rise in the prevalence and lethality of O/O, DM, and Atherosclerotic Cardiovascular Diseases (ASCVD).[12]

Among the main risk factors for ASCVD, dyslipidemia is overlooked by Mexican health decision-makers, who do not consider it a national public health priority.[13] As a result, many patients, including those at the highest risk, fail to achieve their therapeutic goals due to inadequate diagnosis and treatment.

In a population with such a high prevalence of O/O, it is unsurprising that one of the most common lipid disorder phenotypes is atherogenic dyslipidemia, also known as the lipid triad,[14] which is pathophysiologically and epidemiologically linked to obesity and type 2 diabetes mellitus (DM2).[15,16] This condition appears to be the most prevalent lipid disorder associated with myocardial infarction in Mexico.[16] Unfortunately, Mexican physicians often ignore or underestimate this reality, including lipid experts, who uncritically adhere to guidelines based on populations that are significantly different from ours.[17] In this context, the triglyceride/high-density lipoprotein cholesterol (TG/HDL-c) ratio,[18,19] a simple, reliable, and excellent marker of cardiovascular risk and insulin resistance,[20] which aligns well with the metabolic profile of Mexicans, is widely overlooked by most treating physicians despite substantial evidence supporting its clinical usefulness.[21]

Therefore, our study presents the results of a lipid profile analysis, including the TG/HDL-c index, in a sample of the general urban population from the middle and lower-middle economic classes.

MATERIAL AND METHODS

The study followed Good Clinical Practice guidelines, the principles outlined in the Declaration of Helsinki, and the Mexican federal regulations established in the General Law of Health.[22-24] Participants were recruited through invitations, with no specific inclusion criteria. Any individual who accepted the invitation and provided informed consent (or whose parents or guardians did so on their behalf in the case of minors) was included in the study. As a result, the cohort consisted of a non-probabilistic sample of 68,000 participants of both sexes.

Blood samples were collected from individuals referred by private physicians for clinical laboratory testing between 2012 and 2022. However, the specific reasons for these medical evaluations, whether routine check-ups, diagnostic workups, or follow-ups, remain unknown. Additionally, no data were available on participants' clinical conditions or pharmacological treatments.

Lipid and lipoprotein levels were measured using standard spectrometric laboratory methods. The analyses included total cholesterol (TC), triglycerides (TG), HDL-c, and low-density lipoprotein cholesterol (LDL-c). LDL-c was estimated using the Friedewald formula [LDL-c = TC - HDL-c - (TG/5)].[25] Non-HDL

cholesterol (non-HDL-c),[26] which represents all atherogenic lipid fractions containing apolipoprotein B100, was calculated by subtracting HDL-c from TC.

We used the lipid and lipoprotein classification criteria from the ATP III guidelines and selected risk thresholds from the European Society of Cardiology/European Atherosclerosis Society to define the risk cut-offs.[27,28] In both genders, TC and TG levels of 200 and 150 mg/dL, respectively, were considered reference points. For LDL-c, the ATP III guidelines consider an optimal value to be less than 100 mg/dL and «near optimal/above optimal», a value between 100 and 129 mg/dL.

For non-HDL-c, given that its concentration should be 30 mg/dL above LDL-c, the recommended threshold for pharmacological intervention is 130 mg/dL. In comparison, levels below 160 mg/dL were classified as «near optimal».[28] The ATP III HDL-c cut-offs for metabolic syndrome were applied to both genders. According to the National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP III) criteria, hypoalphalipoproteinemia is diagnosed when HDL-c is < 40 mg/dL in men and < 50 mg/dL in women.[29]

Atherogenic ratios, including TC/HDL-c,[30] LDL-C/HDL-c,[31] and TG/HDL-c,[18] were calculated based on lipid and lipoprotein measurements. The cut-off value for the TC/HDL-c ratio was derived from the 1999-2014 National Health and Nutrition Examination Surveys (NHANES), where a ratio of ≥ 4.22 was positively correlated with cardiovascular mortality.[31] The LDL-C/HDL-c ratio cut-off of 2.7 was determined by averaging results from multiple studies.[32-34]

We considered findings from various studies on the TG/HDL-c ratio, which indicated average cut-off values of 2.7 for women and 3.4 for men.[35] However, given that this index varies significantly across ethnicities and clinical conditions, we also incorporated quartile values from a previous study[36] conducted on a sample of the urban middle class in Mexico City. These interquartile ranges were < 3.3, [3.3-4.6], [4.7-6], and > 6, corresponding to the four classical risk categories defined by the American Heart Association/American College of Cardiology (AHA/ACC): low, borderline, intermediate, and high risk.[37]

Finally, all lipid, lipoprotein, and ratio values were stratified by sex and plotted across decades of age, ranging from 10 to 90 years or older.

RESULTS

Table 1 summarizes the data on lipids and lipoproteins, expressed as mean and standard deviation, and categorized into quartiles. As

Table 1: Mean and standard deviation of the main lipids and lipoproteins.

Gender	TC mg/dL	TG mg/dL	HDL-c mg/dL	LDL-c mg/dL	Non-HDL-c mg/dL
Women, mean ± SD	205.5 ± 47.3	188.5 ± 149.7	50.4 ± 13.9	120 ± 56.5	147.9 ± 47.8
Percentile					
Quartile 25	171	111	41	86.53	115
Quartile 50	200	157	49	116.8	143
Quartile 75	233	219	59	152.6	176
Men, mean ± SD	199.5 ± 47.8	211.9 ± 187	46.5 ± 12.5	111.7 ± 62.1	135.2 ± 45.3
Percentile					
Quartile 25	168	115	38	84.75	104
Quartile 50	194	166	45	110.8	132
Quartile 75	226	244	52.7	139.2	162

HDL-c = high-density lipoprotein cholesterol. LDL-c = low-density lipoprotein cholesterol. Non-HDL-c = non-HDL cholesterol. SD = Standard Deviation. TC = Total cholesterol. TG = Triglycerides.

Table 2: Mean and standard deviation of atherogenic indexes, along with quartile values (N = 68,000).

Gender	TC/HDL-c mg/dL	LDL/HDL-c mg/dL	TG/HDL-c mg/dL
Women, mean ± SD	4.45 ± 1.70	2.45 ± 1.18	3.63 ± 4.93
Percentile			
Quartile 25	3.29	1.68	1.792
Quartile 50	4.17	2.31	2.838
Quartile 75	5.26	3.03	4.429
Men, mean ± SD	4.53 ± 1.62	2.64 ± 1.08	4.62 ± 9.98
Percentile			
Quartile 25	3.42	1.89	1.936
Quartile 50	4.22	2.58	3.243
Quartile 75	5.26	3.27	5.257

HDL-c = high-density lipoprotein cholesterol. LDL = low-density lipoprotein. SD = Standard Deviation. TC = Total cholesterol. TG = Triglycerides.

expected, given the nature of the survey, the data showed a considerable dispersion. When analyzing the mean and median values of lipids, lipoproteins, and their ratios, TC was found to be close to or precisely at the cut-off limit in both sexes. In contrast, both the mean and median TG values were significantly elevated, with higher levels observed in men compared to women.

Regarding HDL-c, both men and women exhibited borderline values, with women showing approximately 5 mg/dL higher levels, as expected. LDL-c concentrations in women were at the pharmacological treatment threshold, whereas in men, they were slightly lower, but still near the cut-off. The mean and median non-HDL-c values exceeded the minimum desirable limit for both sexes.

Table 2 presents the results for the atherogenic ratios. The mean and median TC/HDL-c values exceeded the cut-off of 4.2 in both sexes. For the LDL-c/HDL-c ratio, both the mean and median values were slightly below the risk threshold but remained close in both sexes. In contrast, the mean TG/HDL-c index was above the cut-off in both men and women. However, although the median value was elevated in women, it was slightly below the threshold in men. When applying the quartile values from our previous study, the overall mean TG/HDL-c ratio corresponded to the 50th percentile, with higher values observed in men compared to women.

Figures 1 to 5 present the lipid, lipoprotein, and index values analyzed in the study population stratified by age.

The data showed that TC levels *(Figure 1)* were slightly higher in women than in men. In both sexes, the highest values were observed between the ages of 40 and 70 years, when the mean values were barely above the 200 mg/dL limit, followed by a modest decline in the oldest age group.

Throughout life, from youth to old age, TG values remained similar in both sexes and consistently above the cut-off limit of 150 mg/dL, with no significant changes in the oldest groups. Notably, TG levels were higher in men than in women of all ages *(Figure 2)*.

As expected, the plasma HDL-c concentration *(Figure 3)* was slightly higher in women than in men, with no significant variations across age groups. In women, HDL-c levels remained consistently around the 50 mg/dL cut-off, while in men, differences across decades were minimal, with slightly higher values in the older groups.

LDL-c levels *(Figure 4)* remained between 100 and 130 mg/dL in both sexes across most age groups, except in the youngest and oldest

groups, where values dropped below 100 mg/dL. A decline was observed in the oldest age group, which was more pronounced in men.

Non-HDL-c levels *(Figure 5)* followed a similar pattern in both sexes. While values never reached the 160 mg/dL cut-off, women aged 40-79 years and men aged 30-69 years had levels above 130 mg/dL. Sustained decline was observed in the oldest age group.

The TC/HDL-c atherogenic ratio *(Figure 6)* was slightly above the 4.22 cut-off in women aged 30-90 years and men aged 20-80 years.

The LDL-C/HDL-c ratio *(Figure 7)* remained below the 2.7 cut-off in women; in men, it exceeded this threshold between the ages of 30 and 50. As observed with the other parameters, a decline occurred in the oldest age groups, starting at 69 years in women and 59 years in men.

Finally, the TG/HDL-c ratio *(Figure 8)* exceeded the 2.7 cut-off in women across all age decades, except for those older than 80 years. In men, the values remained above the 3.4 threshold between 20 and 80 years old. Using the quartile distribution from a Mexican population as a reference, most women in this study fell within the first and second quartiles (low and borderline risk). In contrast, most men, except for the youngest and oldest age extremes, had values corresponding to the second and third quartiles (intermediate and high risk).

DISCUSSION

This study analyzed the lipid profile of a non-probabilistic segment of the urban middle class in Mexico City, providing insight into the alarming metabolic reality of a society that has undergone a drastic shift in dietary habits over the past few decades. The widespread adoption of a Westernized diet, characterized by excessive consumption of

Figure 1:

Total cholesterol concentrations by age and gender. The dotted line expresses the cut-off value of this variable.

Figure 2:

Triglyceride concentrations according to age and gender. The dotted line expresses the cut-off value of this variable.

Figure 3:

HDL-c concentrations by age and gender. The dotted lines indicate the cut-off points, by gender, for this variable.

Figure 4:

LDL-c concentrations according to age and gender. Dotted lines indicate the cut-off values described in the ATP III document for the optimal level (< 100 mg/dL) and for values close to or above the optimal level (between 100 and 130 mg/dL).

junk and processed products, as well as foods rich in calories, cholesterol, and saturated fat, has been compounded by a sedentary lifestyle, contributing to the exponential rise in obesity (O/O) and its associated cardiometabolic consequences.[3,38]

Although the study design did not allow us to determine the clinical conditions of the participants, the reasons for their biochemical evaluations, or whether they were undergoing lipid-lowering treatment, the data revealed a clear pattern of dyslipidemia. Elevated TG levels were observed across all age groups, along with consistently high TG/HDL-c ratios, which were more pronounced in men than in women. Even if a proportion of participants were receiving lipid-lowering therapy, the persistence of these abnormalities suggests that current interventions do not effectively modify the underlying dyslipidemia profile of this population.

These findings highlight a concerning scenario: a population at significant cardiometabolic risk, where dyslipidemia remains prevalent despite potential medical interventions. The combination of high TG concentrations, atherogenic lipid ratios, and the increasing burden of O/O underscores the urgent need for more effective public health strategies. Addressing this issue requires comprehensive policies that promote healthier dietary habits, encourage physical activity, and improve the early detection and treatment of dyslipidemia to mitigate the long-term impact on cardiovascular health.

Certainly, LDL-c is not a primary concern in contemporary Mexican lipid epidemiology. Instead, hypertriglyceridemia and the TG/

HDL-c index, markers of insulin resistance generally associated with O/O, are of greater significance. The link between insulin resistance syndrome and lipid abnormalities is well documented.[39-42] This syndrome is strongly associated with hyperinsulinemia, which persists as long as pancreatic function is maintained. The binomial of insulin resistance and hyperinsulinemia is a significant factor in the development and progression of traits that define Metabolic Syndrome (MS).[43]

The clinical and epidemiological significance of MS lies in its predictive value for (DM2), its frequent association with this disease, and, even before diabetes manifests, its role as a cluster of cardiometabolic risk factors that contribute to severe, disabling, and potentially fatal cardiovascular and metabolic complications.[44,45]

Atherogenic dyslipidemia, also known as the lipid triad, is one of the most critical consequences of insulin resistance. Elevated TG concentrations, concomitant reduction in HDL-C mass, and increased LDL-C levels characterize this dyslipidemic profile.[46-48] However, the most concerning aspect is the significant rise in small, dense LDL particles, the most atherogenic lipid fraction.[49,50] This dyslipidemia poses a substantial threat to the health of the Mexican population, which underscores the importance of our research in understanding and addressing this issue.

The role of TG as a significant atherogenic risk factor has been debated for decades.[51-59] Although epidemiological evidence supporting this association is robust, hypertriglyceridemia is often omitted or minimized in the USA and European Dyslipidemia Risk Scores designed to estimate cardiovascular morbidity and mortality. Unfortunately, most Mexican lipid

Figure 5:

Non-HDL cholesterol concentrations according to age and gender. Dotted lines indicate the cut-off values for this variable, which is 30 mg higher than the LDL-c values.

Figure 6:

TC/HDL-c ratio according to age and gender. The dotted line expresses the cut-off from the 1999-2014 National Health and Nutrition Examination Surveys (NHANES), with a positive correlation with mortality, where a ratio of ≥ 4.22 was positively correlated with mortality.

Figure 7: LDL-c/HDL-c index according to age and gender. The dotted line indicates de LDL-C/HDL-c ratio of 2.7, determined by averaging results from multiple studies (see text).

Figure 8: TG/HDL index according to age and gender. The gross dotted line indicates the cut-off values of 2.7 for women and 3.4 for men reported in various studies. The thinnest dotted lines signal the quartile values observed in a sample of the urban middle class in Mexico City (< 3.3, 3.4-4.6, 4.7-6, and > 6), which correspond to the classical risk categories (low, borderline, intermediate, and high risk) of the American Heart Association/American College of Cardiology (AHA/ACC): see text.

experts have adopted this approach. This uncritical stance is primarily due to the absence of a national risk scale that considers the anthropometric and metabolic characteristics of the Mexican population.

In previous studies,[36,60] we documented that the American College of Cardiology/American Heart Association Pooled Cohort Equations (ACC/AHA PCEs)[37] and the international GLOBORISK[61] tool fail to assess cardiovascular risk in the Mexican population accurately. These models overlooked two key pathogenic traits in our population: increased abdominal circumference and elevated TG concentrations. A more recent risk scale for primary prevention, developed by the American Heart Association, incorporates the body mass index (BMI), hemoglobin A1c, urine albumin-to-creatinine ratio, and a social deprivation index. However, surprisingly, it neglects the TG concentration and abdominal circumference, limiting its applicability.[62]

It is increasingly evident that TG are not directly atherogenic but contribute to cardiovascular risk primarily through the formation of small, dense LDL particles. These have a greater ability to infiltrate the arterial wall owing to their reduced size, increased

retention in the subendothelial proteoglycan network, and higher susceptibility to oxidation. Moreover, they are not efficiently cleared by hepatic LDL receptors and are more readily bound by arterial wall LDL receptors, exacerbating their atherogenic potential.[63,64]

Risk quotients (RQs) have long been used as valuable predictive tools.[65] The Castelli indexes or ratios[30,66] (TC/HDL-c and LDL-c/HDL-c) are based on the simple assumption that a higher numerator (LDL-c or TC, whose main component is LDL-c) combined with a lower denominator (HDL-c, the protective lipid fraction) indicates an increased coronary risk. Conversely, lower atherogenic fractions and higher HDL-c values suggest a lower risk.

Unlike these traditional ratios, the TG/HDL-c index is more complex, reflecting lipid imbalances secondary to the insulin resistance/hyperinsulinemia binomial, which is a characteristic feature of atherogenic dyslipidemia. This condition is highly prevalent in individuals with DM2, obesity, or both.[20,66] Although several recent studies have highlighted the clinical relevance of the TG/HDL-c index,[67-71] this tool has rarely been discussed in Mexican publications on lipid disorders. General practitioners and specialists use it less frequently in routine clinical practice.

The data presented here clearly demonstrate that hypertriglyceridemia is a prominent feature of the lipid profile of the contemporary Mexican population. However, unlike previous studies,[14,72-74] including some conducted by our group, the present findings did not show low HDL-c concentrations (hypoalphalipoproteinemia), the other key component of the lipid triad. There was no obvious explanation for the increased HDL-c level. Nonetheless, a recent national survey reported a similar pattern: while 48.9% of participants in a probabilistic sample had hypertriglyceridemia, only 28.3% had HDL-c levels < 40 mg/dL (21.6% of women and 35.5% of men).[75] These discrepancies warrant further investigation in future studies.

CONCLUSIONS

Even though the cohort reported in this study is not probabilistic, independent of the clinical status of the patients, and whether or not they were treated with agents that influence the concentration of serum lipids, the striking results showed an adverse lipid profile, clearly indicating an ominous picture of a population ravaged by a very severe epidemic of O/O. Hypertriglyceridemia is the most prevalent lipid disorder identified in this sample of contemporary inhabitants of Mexico City. In recent times, hypoalphalipoproteinemia (another component of atherogenic dyslipidemia) has been the most prominent lipid abnormality identified in several Mexican surveys and clinical trials; however, it was less prevalent in the present study. Nonetheless, the quotient of TG/HDL-c (a marker of insulin resistance/hyperinsulinism) was the most relevant CV risk marker. These results underline the urgent need to launch a campaign against O/O, the foundation of diabetes and ASCVD epidemics.

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