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*Review article*

# Concise Review of Common Non-Traditional Dyslipidemic Indices in Clinical Practice

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**ABSTRACT**

*Lipids are transported to a variety of target organs and tissues to be used for the synthesis of steroid hormone, the production and storage of energy, the synthesis of bile, vitamin absorption, and signalling molecules for cellular communication. Some unhealthy practices may derange levels of lipid, skewing them away from their individual reference ranges. If any type of lipid gets imbalanced, whether secondary to a chemical defect in lipid pathway handling or to unhealthful practices, a clinical situation called dyslipidemia will ensue. Dyslipidemia is a risk factor for the development of cardiovascular adverse events. Dyslipidemia identification, as early as possible, reduces cardiovascular events. Traditionally, the screening tools for dyslipidemia are the fasting lipid panel and lipid ratios from which several "atherogenic indices" have been proposed to predict cardiovascular risk. In this article, a quick review of the untraditional dyslipidemic parameters will be explained.*

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## INTRODUCTION

After being absorbed from the intestine, the lipids are transported by circulating blood to a variety of target organs and tissues using lipoproteins as vehicles. After being transported, lipids are used for diverse physiological purposes, including the synthesis of steroid hormone, the production and storage of energy, the synthesis of bile, the signalling molecules in cellular communication, and vitamin absorption [1]. In general, lipids in the body are fractionated into triglycerides (TGs), cholesterol, and various lipoproteins. Being hydrophilic compounds, both cholesterol and TGs are incorporated into different sized lipoprotein particles in order to be transported by the blood. These lipoproteins are divided into five major types, in order of decreasing size and cholesterol/ protein ratio, as follows: high-density lipoproteins (HDLc), low-density lipoproteins (LDLc), intermediate-density lipoproteins (IDLc), very-low-density lipoproteins (VLDLc), and chylomicrons [2]. Some unhealthy practices like smoking, consuming alcohol with no moderation, may derange levels of lipid, skewing them away from their individual reference ranges. If any type of lipid gets imbalanced, whether secondary to a chemical defect in lipid pathway handling or to unhealthful practices, a clinical situation called dyslipidemia will ensue [3].

Dyslipidemia is a very strong modifiable and independent risk factor that expedite the development of cardiovascular adverse events, including acute coronary syndrome (ACS), peripheral arterial disease (PDA), and cerebrovascular accidents (CVAs) [4]. Traditionally, dyslipidemia was designated as the disease of economically privileged societies, but nowadays, it finds its way among the underprivileged population [5]. Therefore, the identification of dyslipidemia as early as possible is a valuable measure to reduce cardiovascular events in such a population [6]. The primary screening tools for dyslipidemia are the fasting lipid panel, which consists of the conventional lipid parameters (i.e., total cholesterol "TC", LDLc, HDLc, and TGs), and lipid ratios from which several "atherogenic indices" have been proposed

to predict cardiovascular risk. In this article, a quick review of the latter untraditional dyslipidemic parameters will be dealt with [7].

***Classification of dyslipidemic parameters***

The main atherogenic parameters of dyslipidemia are classified into the following: A). Traditional (conventional) lipid parameters: these are simply the isolated lipid types, and they include the following, total cholesterol (TC), LDLc, HDLc, and triglycerides (TGs) [7]. B). Non-traditional lipid parameters (lipid ratios): these are derived from equations that utilize the isolated lipid types and involve the following; Castelli`s risk indices, the atherogenic index of plasma, non-HDLc, atherogenic coefficient, cholesterol index, cholesterol remnants, TG/HDL ratio, lipoprotein combine index, and ApoB/Apo-1 [9]. The lipid ratios can be applied for cardiovascular risk stratification by general practitioners or researchers, especially in cases where isolated lipid values are misleadingly normal, or in clinical situations of elevated levels of TG, or when the LDLc is below the target value [10]. The non-traditional lipid indices provide more robust predictive ability of cardiovascular risk (CVR) compared to the more isolated (conventional) lipid values, thus justifying their increased use in clinical research and medical practice. Furthermore, many under-developed countries with low economic resources have difficulties providing relatively sophisticated medical equipment like magnetic resonance imaging (MRIs) devices, echocardiographic machines, and so on. This makes the accessibility and the running cost of such techniques routinely used for CVR assessment, such as Doppler scanning of carotid arteries for example, difficult. Hence, the markers of atherogenicity are good alternatives in such circumstances of lacked resources [11].

***The non-traditional lipid-ratios***

The commonly used lipid parameters of atherogenicity in this category include the following:

***1. Castelli Risk Indices (CRIs):***

The CRIs are eligible predictors of cardiovascular risk with a superior predictive ability compared to individual lipid parameters like total cholesterol, HDLc, and so on [12]. Castelli risk indices include two different parameters, CRI-I and CRI-II:

***A. Castelli Risk Index I (CRI-I):***

This is alternatively called “Cardiac Risk Ratio (CRR)”. It is calculated based on the following formula [14]:

$$\text{CRI-I} = (\text{Total cholesterol} / \text{HDLc})$$

The CRI-I reliably determines the total cholesterol level and is highly useful as a screening tool for the buildup of atherosclerotic plaque within coronary arteries. The significance of CRI-I as a tool in dyslipidemic screening was gained from the minimal overlap shown by it when assessing CVR within populations, with or without, cardiovascular risk and with a normal or relatively high lipoprotein balance [14]. The cut-off value for CRI-I is 5.0 for males and 4.5 for females, above these values, the CVR increases [15].

***B. Castelli Risk Index II (CRI-II):***

This is also known as the “Atherosclerosis Index (AI)”. It is calculated based on the following formula [16]:

$$\text{CRI-II} = (\text{LDLc}/\text{HDLc})$$

CRI-II is extremely powerful in predicting cardiovascular risk, especially in predicting acute myocardial infarction (AMI). It also has a significant correlation with resistance to insulin action and the atherogenic index. Several studies have found that the CRI-II is an outstanding monitor for the effectiveness of lipid lowering therapies. The cut-off value for CRI-II is 3.5 in males and 3.0 in females, if the ratio of CRI-II is increasing, then the risk is more [17].

***2. Non-high density lipoprotein cholesterol (non-HDLc):***

The calculation of non-HDLc is done without paying attention to the individual`s fasting state. It is the difference between total cholesterol and HDLc as follows [18]:

$$\text{Non-HDL} = \text{Total cholesterol} - \text{HDL}$$

This parameter represents the sum of the body`s bad cholesterol that is carried by the lipoproteins of atherogenic potential, namely; very low-density lipoprotein cholesterol (VLDLc), intermediate density lipoprotein cholesterol (IDLc), low-density lipoprotein cholesterol (LDLc), lipoprotein (a), and chylomicrons. In other words, non-HDLc represents the sum of all contributors to arterial plaque formation [18]. Non-HDLc is believed to be more accurate in

predicting CVR-based mortality especially from AMI [20]. The lipid reducing medications target LDLc as the second measure be controlled as recommended by Adult Treatment Panel-III (ATP-III), especially if the serum TGs levels were elevated. Hence, non-HDLc can replace the HDLc for monitoring therapy [21]. While interpreting the non-HDLc, one should pay attention to the fact that the index varies greatly with patient`s age. In patients aged less than 19 years, the index shouldn't exceed 120 mg/dl. Meanwhile, for those 20 years of age and older, the index shouldn't exceed 130 mg/dl [22].

***3. Atherogenic coefficient (AC):***

This is also known as the "atherogenic index (AI)", not to be confused with the atherogenic index of plasma (AIP). The AC measures the ratio of atherogenic "bad" cholesterol present in LDLc, VLDLc, and IDLc with respect to the anti-atherogenic "good" cholesterol, i.e., the HDLc [23]. This parameter is calculated by the following formula [24]:

$$AC = (\text{Total cholesterol} - \text{HDL})/\text{HDL}$$

or

$$AC = (\text{Non} - \text{HDL})/\text{HDL}$$

An atherogenic coefficient of more than 3.0 is regarded as a criterion for increased CVR [25]. Atherogenic coefficient is regarded as a significant index that is used to predict risk factors for CAD and stroke [26]. In essence, the AC, being inclusive of all the atherogenic lipids in the lipoprotein family, relates closely to the apo-B serum levels [27]. Some studies reported the superiority of AC over LDLc in predicting adverse cardiovascular events [28,29].

***4. TGs/HDLc ratio:***

This is calculated by dividing the TGs levels in mg/dl by the HDLc in mg/dl. A ratio of 2:1 or less is considered ideal. A ratio of 4:1 is considered high, and a ratio of 6:1 or more is considered extremely high and indicates an elevated risk of heart attack and stroke [30].

Recent research showed that the TGs/HDLc ratio can predict the development of metabolic syndrome, cardiovascular disease. Additionally, the TGs/HDLc ratio can predict insulin resistance and diabetes where it can be used as a surrogate marker of Insulin resistance (TG/HDL). As a result, the TG/HDL ratio might be a superior predictor of CVR than the LDLc/HDLc ratio [31].

***5. Atherogenic index of plasma (AIP):***

AIP uses the logarithmic relation of TGs with HDLc. This ratio focuses on the diverse interactions of different lipid types, the protective as well as the promoters of atherogenicity, and is highly predictive for the CVR [32]. Research conducted by the Action to Control Cardiovascular Risk in Diabetes (ACCORD) concluded that the ability of AIP to predict CVR was more robust in diabetes mellitus patients, hypertensive patients, and obese patients [33]. The marker also can be utilized for estimating the risk for metabolic syndrome and stenosis of the carotid artery [34, 35].

The AIP calculation is as follows, where the TGs and HDLc are expressed in mmol/l:

$$AIP = \log(\text{TGs}/\text{HDLc})$$

The reference range for AIP is < 0.11, where the CVR is minimal. CVR is moderate when the AIP ranges from 0.11-0.21 and high when the marker exceeds 0.24 [36, 37].

***6. Cholesterol index (CHOLindex):***

As a novel lipid index, the CHOLIndex is applicable owing to its simplicity and was validated as CVR assessment tool especially for coronary arterial disease (CAD) with high accuracy [38]. The formula used to calculate CHOLindex is as below:

- When the TGs level is below 400 mg/dl:

$$\text{CHOLIndex} = \text{LDLc} - \text{HDLc}$$

- When the TGs level is higher than 400 mg/dl:

$$\text{CHOLIndex} = (\text{LDLc} - \text{HDLc}) + \text{TG}/5$$

The cutoff value of CHOLIndex is 2.07. Higher figures are associated with an increased CVR [39].

***7. Lipoprotein combine index (LCI):***

This index, which may also be referred to as the "comprehensive lipid tetrad index", also determines the balance between

the good and bad lipids. Recently, the LCI was found to be a better predictor of coronary artery disease (CAD) [40]. This is calculated according to the following equation:

$$LCI = (TC \times TGs \times LDL)/HDL$$

The cutoff point for LCI is 16.0. A previous report showed a superior ability of the LCI over other lipid ratios to detect atherosclerosis [41].

***8. ApoB/ApoA-1 ratio:***

ApoB is a protein found in high concentrations in LDLc. Since LDLc is "bad cholesterol", hence higher serum levels of apo-B increase the risk of cardiovascular damage. Alternatively, apolipoprotein A-I (apoA-I) is the major constituent of HDLc "the good cholesterol". Therefore, apo-B represents the spectrum of the atherogenic lipids, while apo- A1 represents the lipid components with an antiatherogenic potential. Hence, the apoB/apoA1 ratio denotes the state of balance between the atherogenic lipids, and their counterpart, the anti-atherogenic lipids and their ratio correlates well with CVR [42]. The reference values for the normal and abnormal apoB/apoA1 ratio are given in table (1). [43]

*Table 1: the normal value of apoB/apoA1 ratio in both genders with the respective cardiovascular risk corresponding each abnormal value.*

| ***ApoB/apo A1*** | ***Adult males*** | ***Adult females*** |
|---|---|---|
| ***Ideal ratio*** | <0.77 | <0.63 |
| ***Moderate risk*** | 0.77-0.95 | 0.63-0.78 |
| ***High risk*** | >0.95 | >0.78 |

***8. Remnant cholesterol (RC):***

Different apoproteins transport TGs and cholesterol in the circulation. ApoB48 is dominant in the chylomicrons that transport endogenous TGs (from intestinal absorption), whereas exogenous TGs (from hepatic synthesis) are carried using VLDLc. Lipoprotein lipase hydrolyses both, the chylomicrons to decrease TG size and VLDLc to yield VLDLc remnants [44]. The cholesterol that remains in both after hydrolysis is referred to as remnant cholesterol. Remnant cholesterol can be calculated as follows:

- Calculated directly from related lipids, and here it is called the "RC-direct" as follows [45]:

$$RC\text{-}direct = TC - (HDLc + LDLc)$$

- Calculated utilizing TG, and here it is denoted as "RC-calculated" as follows:
  In the case of TGs (in mg/dl), RC-calculated = TGs/5.
  In the case of TGs (in mmol/l), RC-calculated = TGs/2.2.

The cutoff value for the RC is 30 mg/dl above which the RC is regarded as abnormally high and the CVR is elevated [46].

## CONCLUSION

All of the non-traditional lipid ratios (CRI-I, CRI-II, non-HDLc, AC, TG/HDLc ratio, AIP, CHOLindex, and ApoB/apoA1 ratio) corelate well with CVR, even with a stronger correlation compared to the traditional indices. They can be used in predicting adverse cardiovascular events, stroke, and insulin resistance. After reviewing many literatures, the LCI and the CHOLIndex might be the atherogenic parameters of higher accuracy among others. Apart from AIP, the calculation of eventually all such indices is relatively easy to perform without the need for sophisticated software making them suitable for every day practice.

***Conflict of Interest***

There are no financial, personal, or professional conflicts of interest to declare.

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# مراجعة موجزة لمؤشرات عسر شحميات الدم الشائعة غير التقليدية في الممارسة السريرية

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**المستخلص**

يتم نقل الدهون إلى مجموعة متنوعة من الأعضاء والأنسجة المستهدفة لاستخدامها في تخليق هرمون الستيرويد ، إنتاج وتخزين الطاقة ، تخليق الصفراء ، امتصاص الفيتامينات ، وتخليق جزيئات الاشارة في الاتصال الخلوي. قد تؤدي بعض الممارسات غير الصحية إلى إفساد مستويات الدهون ، مما يؤدي إلى انحرافها بعيدًا عن نطاقاتها المرجعية الفردية. إذا حدث خلل في أي نوع من الدهون ، سواء كان ذلك ثانويًا لعيب كيميائي في معالجة مسار الدهون أو لممارسات غير صحية ، فسوف يترتب على ذلك حالة سريرية تسمى عسر شحميات الدم. عسر شحميات الدم هو عامل خطر لتطور الأحداث السلبية القلبية الوعائية. ان تحديد عسر شحميات الدم ، في أقرب وقت ممكن ، يقلل من أحداث القلب والأوعية الدموية.تقليديا, إن أدوات الفحص الخاصة بخلل شحميات الدم هي لوحة الدهون أثناء الصيام ونسب الدهون التي تم من خلالها اقتراح العديد من "مؤشرات تصلب الشرايين" للتنبؤ بمخاطر الإصابة بأمراض القلب والأوعية الدموية. في هذه المقالة ، سيتم شرح مراجعة سريعة لمعلمات خلل شحميات الدم غير التقليدية.

**الكلمات الدالة**. عسر شحميات الدم ، مؤشرات تصلب الشرايين ، نسب الدهون ، مخاطر القلب والأوعية الدموية.