# Triglycerides (TG) to High-Density Lipoprotein (HDL-c) Ratio (TG/HDL-c Ratio) as a Marker of Cardiometabolic Risk

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## Contents



**Abstract**

Cardiovascular diseases represent the main cause of mortality and morbidity worldwide. Several metabolic conditions, as obesity, diabetes, metabolic syndrome, hypertension, and hypercholesterolemia, seem to play a pivotal role in the pathogenesis of cardiovascular diseases.

During the last 20 years, different surrogate markers have been proposed as possible tools not only to identify and to evaluate the progression of cardiovascular disease but also to recognize precocious stages of different cardio-metabolic diseases in general population.

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One of the most promising biomarker is the triglyceride-to-high-density lipoprotein cholesterol (TG/HDL-c) ratio that has been proposed as a new emerging marker able both to reflect the cardio-metabolic status and to predict the increased risk of developing metabolic and cardiovascular complications in adults as well as in children. In fact, several evidences demonstrated the TG/HDL-c ratio is well related not only with current cardio-metabolic diseases, but it seems to be able to predict the risk to develop cardiovascular accidents.

The goal of this book chapter is to describe the potential role of TG/HDL-c ratio as a marker to evaluate and to predict cardiovascular and metabolic diseases in adults and in children.

**Keywords**

TG/HDL-c ratio • Lipid profile • Cardiovascular risk • Cardio-metabolic diseases • Triglycerides • HDL cholesterol

**Abbreviations**

| | |
|---|---|
| AD | Atherogenic dyslipidemia |
| CHD | Cardiovascular heart diseases |
| cIMT | Carotid intima-media thickness |
| CVD | Cardiovascular diseases |
| HDL-c | High-density lipoprotein cholesterol |
| HOMA-IR | Homeostasis model assessment |
| IR | Insulin resistance |
| LDL-c | Low-density lipoprotein cholesterol |
| TC | Total cholesterol |
| TG | Triglycerides |
| TG/HDL-c | Triglyceride-to-high-density lipoprotein cholesterol |
| WBISI | Whole-body insulin sensitivity index |

## Key Facts of the Triglycerides (TG) to High-Density Lipoprotein (HDL-c) Ratio (TG/HDL-c ratio) as a Marker of Cardio-Metabolic Risk

- TG/HDL-C ratio represents a good surrogate marker to define the cardiovascular risk related to the atherogenic dyslipidemia.
- Several evidences have clearly demonstrated that TG/HDL-C ratio represents a key metabolic marker of metabolic and cardiovascular complications in obese subjects.
- TG/HDL-C ratio is directly related to IR status both in adult and children.
- In adult subjects, TG/HDL-C ratio is associated with the severity of coronary arterial stenosis.
- In obese children and adolescent, TG/HDL-C ratio is related to early signs of atherosclerosis as cIMT, left ventricular hypertrophy, arterial stiffness, and brachial distensibility.

## Definitions

**Arterial stiffness** Is an age-related process that occurs when the elastic fibers within the arterial wall (elastin) begin to fray due to mechanical stress. Increased arterial stiffness is associated with an increased risk of cardiovascular events.

**Arteriosclerosis** Is the thickening, hardening, and loss of elasticity of the walls of arteries. It should not be confused with atherosclerosis, which is a specific form of arteriosclerosis caused by the buildup of fatty plaques and cholesterol in the artery.

**Atherosclerosis** Is a specific form of arteriosclerosis in which an artery wall thickens as a result of invasion and accumulation of white blood cells, remnants of dead cells, cholesterol, and triglycerides. Atherosclerosis is therefore a syndrome affecting arterial blood vessels due to a chronic inflammatory response of white blood cells in the walls of arteries. This is promoted by low-density lipoproteins (LDL-c, plasma proteins that carry cholesterol and triglycerides) without adequate removal of fats and cholesterol from the macrophages by functional high-density lipoproteins (HDL-c). It is commonly referred to as a "hardening" or furring of the arteries. It is caused by the formation of multiple athermanous plaques within the arteries.

**Atherogenic dyslipidemia** Is a risk-conferring lipid/lipoprotein profile characterized by a higher proportion of small LDL particles, reduced HDL-C levels, and increased values of triglycerides.

**Carotid intima-media (cIMT)** Also called intimal-medial thickness, is a measurement of the thickness of tunica intima and tunica media, the innermost two layers of the wall of an artery. The measurement is usually made by external ultrasound and occasionally by internal, invasive ultrasound catheters; see intravascular ultrasound. Measurements of the wall thickness of blood vessels can also be done using other imaging modalities.

**Dyslipidemia** Is an abnormal elevation of plasma total cholesterol, triglycerides (TGs), or low high-density lipoprotein level that contributes to the development of atherosclerosis. Causes may be primary (genetic) or secondary.

## Introduction

Cardiovascular diseases (CVD) represent the main cause of mortality and morbidity worldwide. Several metabolic conditions such as obesity, diabetes, metabolic syndrome, hypertension, and hypercholesterolemia seem to play a pivotal role in the pathogenesis of cardiovascular accidents (Go et al. 2013). Despite considerable improvements in medical care over the past 25 years, CVD remain one of the major public health challenges. In fact, the World Health Organization estimates

that more than six million of deaths are due to cardiovascular diseases every year worldwide, and this number seems to rise to more than 20 million during the next decades (Lozano et al. 2012). In addition, a recent National Vital Statistical Report calculates that CVD are in the top of the list of the 15 leading causes of death in the USA, with an annually total cost of 108.9 billion of dollars each year for health-care services, medications, and lost productivity (Murphy et al. 2013). In the same way, in Europe, CVD are responsible for nearly 50 % of all deaths, and they are the main cause of all disease burdens, with management costs estimated at 192 billion euro annually (The World Health Organization 2012). Most importantly, several studies underline that this burden is projected to escalate dramatically not only in USA and in Europe but also in underdevelopment countries (Mahmood et al. 2014).

More alarming are the data regarding the increase of cardiovascular disease in pediatric population. In fact, recently considering the important rise of obesity and different obesity-related complications, the spectrum of cardiovascular diseases is becoming more relevant already in children and adolescents (Cote et al. 2013). Many studies, as the Bogalusa Heart Study and Framingham Study, have convincingly shown that childhood obesity is not only an important risk factor for obesity during adult age, but it also increases the risk to develop precociously CVD, metabolic syndrome, and atherosclerosis (Li et al. 2012; Mahmood et al. 2014).

In order to contain this important growth of cardiovascular accidents in adult population, during the last 20 years different surrogate markers have been proposed as tools to evaluate the progression of CVD but also to recognize in general population precocious stages of different cardio-metabolic diseases, when they are still silent. However, up to now, there are a series of uncertainties on the possibility to obtain a single biomarker that could identify and predict early signs of cardio-metabolic diseases (Cohn 2004).

Recently, one of the most used biomarkers is the triglyceride-to-high-density lipoprotein cholesterol (TG/HDL-c) ratio, which has been proposed as a new emerging marker able both to reflect the cardio-metabolic status and to predict the increased risk of developing metabolic and cardiovascular complications in adults as well as in children (Arca et al. 2012; Salazar et al. 2012).

The goal of this book chapter is to describe the potential role of TG/HDL-c ratio as a marker to evaluate and to predict cardiovascular and metabolic diseases in adults and in children.

## The Role of Atherogenic Dyslipidemia and Cardiovascular Diseases

In 1959, the Framingham Heart Study identified cholesterol levels as one of the most important risk factors for the development of cardiovascular (Dawber et al. 1959). Confirming these results, during the last decades, several prospective studies have clearly demonstrated that high levels of low-density lipoprotein cholesterol (LDL-C) and low levels of high-density lipoprotein cholesterol (HDL-c) represented the most important lipid abnormalities involved in the pathogenesis of atherosclerosis. In fact,

these prospective observations described this lipid profile as a predictor factor for the risk to develop CVD (Castelli 1996; Rosenson 2005).

With the increasing prevalence of obesity and its related complications, there is a new interest to define the role of other lipid molecules involved in the pathogenesis of atherosclerosis (Fig. 1). In 1990, for the first time, Austin et al. described "atherogenic dyslipidemia" (AD) or "atherogenic lipoprotein phenotype," as a major lipid abnormalities implicated in the pathogenesis of obesity-related complications. These authors proposed a risk-conferring lipid/lipoprotein profile characterized by a higher proportion of small LDL particles, reduced HDL-C levels, and increased values of triglycerides (Austin et al. 1990). This spectrum of lipid abnormalities is normally evaluable in patients with obesity and with obesity-related complications, as metabolic syndrome, insulin resistance, and type 2 diabetes mellitus (Kannel et al. 2008; Wu and Parhofer 2014; Gasevic et al. 2014). In particular, diabetic dyslipidemia is a widespread condition in which insulin resistance seems to be the driving force for the genesis of the characteristic lipid abnormalities (Kannel et al. 2008). After the definition proposed by Austin, different studies underlined that this spectrum of lipid abnormalities could represent an important factor for CVD risk also in general populations. In fact, in these studies considering the diabetic dyslipidemia as a risk factor for CVD, it was more highly associated with incident CVD events (hazard ratio of 1.22 per 1 standard deviation) than single value of LDL-c (hazard ratio of 1.10 per 1 standard deviation) (Musunuru 2010). In addition, in a separate post hoc analysis of two large and different clinical trials conducted in subjects with stroke while receiving a statin and otherwise best medical therapy, those having atherogenic dyslipidemia had a higher residual cardiovascular risk than those without AD (Sirimarco et al. 2014). Therefore, it is easily understandable that these lipid abnormalities seem to be strictly associated with cardiovascular risk. In

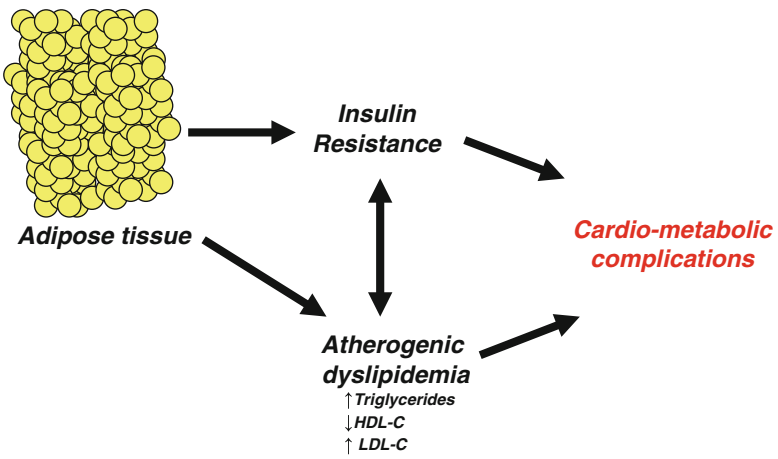


**Fig. 1** Cardiovascular complications related to obesity and obesity-related metabolic complications

**Table 1** LDL-C and atherosclerosis

| Small dense LDL particles in athero/vasculo activities |
|---|
| Easily trapped in arterial wall |
| Easily oxidized |
| Pro-inflammatory activity |
| Pro-thrombotic activity |

**Table 2** Triglycerides and atherosclerosis

| Triglycerides in athero/vasculo activities |
|---|
| Constitute core of the triglyceride-rich lipoproteins (remnant cholesterol) |
| Easily trapped in arterial wall |
| Increase binding and lipolysis at the artery wall |
| Pro-inflammatory activity |
| Pro-thrombotic activity |
| Impaired vasodilatory activity |

fact, it is well known that small dense, lipid-poor LDL particles have greater susceptibility to oxidation, and these molecules seem to be able to penetrate in the arterial wall earlier than LDL-C, generating the inflammatory processes in vascular endothelium (Preiss and Sattar 2009) (Table 1).

Although triglycerides (TG) are not directly circulating, they represent the core of the triglyceride-rich lipoproteins (remnant cholesterol). Remnant cholesterol molecules are simply trapped in arterial wall for their size attaching to extracellular proteoglycans. In this context, lipoprotein-lipase activity induces the release of free fatty acids, monoacylglycerols, and other components of triglycerides that induced a local injury, activating the production of inflammatory factors and promoting the thrombin generation (Chapman 2010; Chapman et al. 2011; Nordestgaard and Varbo 2014) (Table 2). The other component of atherogenic dyslipidemia is HDL-c. Normally HDL-c is considered an athero-protective factor. In fact, several evidences underline a very important relevant role of HDL-c in the athero/vasculo-protection process. These molecules seem able to play an important anti-inflammatory and antioxidant activity stimulating different mechanisms that control endothelial repair system or endothelial vasodilator activity. In addition, it is well known that HDL-c controls the cellular cholesterol efflux and cholesterol homeostasis. In fact, it is able to acquire additional lipids and apolipoproteins derived from the hydrolysis of triglyceride-rich lipoproteins and reduce the peripherally presence of triglycerides. Subsequently, these "new and mature" HDL-c molecules are metabolized or directly by liver uptake or by steroidogenic tissues via different and specific tissue receptors/enzyme. This complex and intriguing efflux process seems to be able to partly account for the strong inverse relation between TG and HDL-c (Rader and Hoving 2014) (Table 3).

Although, all these studies have underlined the role of the single components of atherogenic dyslipidemia and the correlation with several cardiovascular diseases, new evidences reported that sometimes the single components of the atherogenic dyslipidemia cannot reflect their overall cardiovascular risk, whereas their

**Table 3** LDL-c and atherosclerosis

| HDL in athero/vasculo-protection activities |
|---|
| Control cellular cholesterol efflux |
| Anti-inflammatory activity |
| Antioxidative activity |
| Endothelial repair |
| Vasodilatory activity |
| Anti-thrombotic activity |

combination in a single ratio seems to have a better predictive power for both cardiovascular and metabolic diseases (Salazar et al. 2012).

## Potential Applications to Prognosis: TG/HDL-c Ratio as a New Marker for Cardio-Metabolic Diseases in Adult Subjects

Several evidences demonstrated that the traditional cholesterol measurements tend to be most accurate in predicting cardiovascular risk only for those at the lower and higher ends of the risk spectrum, while they seems to be not so strongly related to the cardiovascular risk for those patients that are in the middle part of lipid profile (Chapman et al. 2011; Preiss and Sattar 2009). Therefore, there has been a growing focus of research on the possibility to identify a surrogate marker of lipid abnormalities that could be able to define the cardiovascular risk in the general population. Recent data demonstrated that the ratio between different components of lipid profile represents one of the most specific predictors of cardiovascular risk (Preiss and Sattar 2009). At the beginning of this century, several groups showed that LDL-c/HDL-c or total cholesterol (TC)/HDL-c could be considered as good markers of cardiovascular disease. In fact, changes in this ratio have been shown to be a better indicator of a successful CHD risk reduction compared to changes in absolute levels of lipids or lipoproteins. In particular, many studies conducted in population with different cardiovascular risk have clearly reported that LDL-c/HDL-c ratio is significantly more robust predictor of CVD than the individual levels of LDL-c or HDL-c (Kannel et al. 2008; Manninen et al. 1992). However, both LDL-c/HDL-c and TC/HDL-c ratio seems to be well related only with CVD, while it is poorly linked to metabolic diseases implicated in the pathogenesis of CVD (Wu and Parhofer 2014).

Therefore, recently there has been a growing interest on the possibility to identify a new ratio between different component of lipid profile that is better related to cardiovascular and metabolic diseases and that could represent also a good predictor for the future risk to develop cardio-metabolic diseases. One of the most promising factors that seems to have the previously noted characteristics is the ratio between TG and HDL-c. In fact, it is well known that TG, low-density, and HDL-c are mainly deregulated in different metabolic diseases (as type 1 diabetes, insulin resistance, type 2 diabetes, etc..), and they seem directly related to risk of cardiovascular diseases (Wu and Parhofer 2014). However, several studies underlined that the combination of TG and HDL-c in a single ratio confers a good power not only to

define the current cardio-metabolic status but also to predict the future cardiovascular risk (Kannel et al. 2008; Sirimarco et al. 2014; Gasevic et al. 2014; Salazar et al. 2012).

For the first time, in 2008, Kannel et al. confirmed the role of the TG/HDL-c ratio as a positive predictor of cardiovascular and metabolic risk in the large cohort of adult obese subjects included in the Framingham offspring study. In this paper, the authors analyzed the relationship between TG/HDL-c ratio not only with insulin resistance (IR) but also with the risk to develop cardiovascular events longitudinally. Therefore, considering a large study population of 3,014 patients (mean age 54 years; 55 % women), the authors demonstrate that in the spectrum of the several considered lipid markers, TG/HDL-c ratio represented the best parameters correlate with IR. In addition, the authors showed that IR prevalence increased across the tertiles of lipid ratios ($p < 0.0001$); also the area under curves for predicting IR on the base of TG/HDL-c ratio confirmed a strong correlation between IR and the ratio in this large population. In order to evaluate the power of the ratio to predict possible cardiovascular events, the authors continued to monitor the enrolled population. In particular, during a follow-up period of mean 6.4 years, a group of 112 patients experienced a first CHD event. In this longitudinal arm of the study, the authors demonstrated that even after adjustment for lipid variables (including TG/HDL-c ratio), IR was significantly and strongly associated with CHD risk. Interestingly, these prospective analyses suggested that TG/HDL-c ratio is a good surrogate index of IR (multivariable-adjusted hazards ratio 2.71, 95 % confidence interval 1.79–4.11). In conclusion, these observations recommend a role of TG/HDL-c ratio as a surrogate marker for IR. In addition, this parameter seems to be a good predictor of potential cardiovascular risk related to insulin resistance. This study represents a milestone to use the TG/HDL-c ratio as a marker of cardio-metabolic disease (Kannel et al. 2008).

Moreover, also a new recent study confirms that obese subjects with a high TG/HDL-c values have a considerably increased risk of CHD and CVD. In this study, the authors considered a population of 54,061 patients from the Swedish National Diabetes Register, and they showed that obese and prominently obese subjects with TG/HDL-c $\geq$1.9 had an hazard ratios around 1.7 for fatal/nonfatal CHD and 1.6 for CVD ($p < 0.001$), while obese and prominently obese patients with TG/HDL-c ratio $<$1.9 presented hazard ratios of 1.2 for CHD and 1.3 for CVD ($p < 0.005$). However, it is important to remark that in all these studies, the authors demonstrated the relation between the lipid ratio and insulin resistance; nevertheless, they did not prove a direct relationship between TG/HDL-c ratio and direct signs of CVD (Eeg-Olofsson et al. 2014).

In order to evaluate the direct influence of TG/HDL-c ratio on CVD, Yang et al. designed a study to explore the relationship between different lipids ratio and the degree of coronary artery stenosis, defined according to Gensini score. For this study, the authors enrolled 207 patients divided in four groups according to the severity of coronary stenosis: group 1 or control group (34 patients), group 2 with a score less than 30 score (84 patients), group 3 with a score from 31 to 90 score (66 patients), and group 4 scored greater that 90 (23 patients). These authors

demonstrated that the coronary lesions increased moving across tertiles of TG/HDL-c, but also with the increase of other lipid parameters taking into account, as LDL-c/HDL-c, levels of TC, LDL-c, triglycerides, TC/HDL-c, and reduction of HDL-c. In particular, the authors showed that patients with a higher coronary artery stenosis (groups 2, 3, and 4) presented significantly increased values of ratio compared to group 1 ($p < 0.05$); however, when they compared the values of ratio across the groups 2, 3, and 4, no differences in terms of TG/HDL-c were found. In addition, also the Pearson correlation analysis revealed that only LDL-c/HDL-c ($r = 0.54, p < 0.05$) and TC/HDL-c ($r = 0.50$, $p < 0.05$) were significantly and positively correlated with the coronary artery lesions. The results suggested that the severity of coronary artery lesions were correlated with abnormal lipid metabolism; however, the predictive value of TG/HDL-c was not confirmed in this study (Yang et al. 2011).

At the same time, a different group investigated the association between lipid levels, specifically TG/HDL-c, and a direct sign of cardiovascular disease, as the extent of coronary disease. In this study, the authors enrolled a group of 374 high-risk patients (220 males and 154 females, age 57.2 ± 11.1 years) admitted to their attention to perform coronary angiography. In all patients, lipid parameters were measured, and they were scored according to the coronary disease extent using the Friesinger index. The main results of this study show that the severity of coronary disease (dichotomized by a Friesinger index of 5) is directly related to triglycerides [odds ratio of 2.02 (1.31–3.1; $p = 0.0018$)], HDL-c [odds ratio of 2.21 (1.42-3.43; $p = 0.0005$)], and TG/HDL-c [odds ratio of 2.01(1.30–3.09; $p = 0.0018$)]. After categorizing subjects according to quartiles of the Friesinger score, the authors demonstrated that the frequency and the severity of coronary disease increased progressively moving from the lower to the upper tertiles of the ratio (47.9 vs. 63 vs. 66 vs. 75.3; $p = 0.0018$). In addition, the odds ratio for the extent of coronary disease between the lower and the upper quartiles and TG/HDL-c was 3.31, (95 %CI 1.78–6.14, $p = 0.0002$), suggesting that across the TG/ HDL-c quartiles, the increase of the ratio led to a 30 % increase in disease extent. In addition, in order to investigate the potential independent contribution of the TG/HDL-c ratio on severity of atherosclerotic lesions, a multivariate analysis by logistic regression was performed, and these analysis revealed that the TG/HDL-c ratio showed a strongest association with extent of coronary disease (0.779 ± 0.074, $p = 0.0001$). Finally a ROC curve was calculated to individuate a value of the TG/HDL-c ratio able to identify subjects with Friesinger score in the upper quartile of the ratio. An AUC-ROC value of 0.63 for TG/HDL-c ($p = 0.0001$) can identify subjects with high risk for cardiovascular events. It is important to show that although this study demonstrated for the first time a direct relationship between the ratio and direct signs of cardiovascular disease, it present same points that should be addressed. In particular, it might be noted that the authors did not include in their study population a control group; therefore, the results of this study could be apply only in subjects with high cardiovascular risk (da Luz et al. 2008).

Considering all these studies demonstrating the power of TG/HDL-c ratio as a useful biomarker able to reflect the cardio-metabolic status and to predict subjects at increased risk of developing cardiovascular complications, a recent guideline for the

clinical approach to obese patients recommends that the TG/HDL-c ratio should be used to define the impaired metabolic status and chronic inflammation in these subjects. This guideline is intended as a useful guide that can be used by health-care professionals in everyday clinical practice in order to easily detect obese subjects with increased cardio-metabolic risk. The authors of this guideline proposed that a value of the TG/HDL-c ratio major than 2 seems to reflect the current metabolic status, and it is able to predict the future risk of cardiovascular diseases (Lau et al. 2007).

## Potential Applications to Prognosis: TG/HDL-C Ratio as a New Marker for Cardio-Metabolic Diseases Already in Pediatric Population

According to these previously findings, recently some evidences have proposed that even in the pediatric population, the TG/HDL-c ratio is related to IR, chronic inflammation, and cardiovascular risk (Quijada et al. 2008; Giannini et al. 2011; Musso et al. 2011). With regard to the pediatric population, Giannini et al. proposed for the first time in obese children and adolescents that the TG/HDL-c ratio could represent a good marker of IR also in this population. In this study, the authors enrolled a group of 1,452 obese and multi-ethnic children and adolescents, and they evaluated lipid profile and insulin sensitivity. In particular, it is important to note that in this study, Giannini et al. measured insulin sensitivity not only using surrogate indices of insulin sensitivity, as whole-body insulin sensitivity index (WBISI) and homeostasis model assessment (HOMA)-IR, but in a subgroup of 146 obese youths, they also defined insulin sensitivity by the hyperinsulinemic-euglycemic clamp. As main results, the authors showed that across rising tertiles of TG/HDL-c ratio, WBISI progressively decreased, whereas 2-h glucose and the AUC-glucose progressively increased. In addition, this group using a receiver operating characteristic (ROC) curve analysis proposed a threshold of TG/HDL-c ratio able to identify subjects in the upper quartile of WBISI. The estimated cutoff for TG/HDL-c ratio was 2.27, and the odds of presenting with IR, in youths with TG/HDL-c ratio higher than the cutoff, was 6.023 (95 % CI 2.798–12.964; $p = 0.001$) in white girls and boys, whereas for both Hispanics and African Americans, the AUC-ROCs were not significant. Therefore, this study showed in a large multi-ethnic cohort that the TG/HDL-c ratio is associated with IR mainly already in pediatric population and thus may be used as risk factor to identify subjects at increased risk of IR (Giannini et al. 2011).

Subsequently an Italian group demonstrated that this lipid ratio is not only directly related with IR status, but it also represents a good marker to evaluate possible preclinical signs of cardiovascular diseases in obese children and adolescent. The authors evaluated in a large population of normal-weight and obese children and adolescents (884 subjects) a possible correlation between TG/HDL-c ratio and early signs of cardiac remodeling, such as left ventricular hypertrophy. In line with previously reported results in adult subjects, Di Bonito et al. demonstrated a correlation between increasing values of ratio and well-known cardio-metabolic

parameters, as insulin resistance, liver enzymes, or other indexes of metabolic impairment status, already during childhood. In addition, for the first time, this study reported not only that left ventricular hypertrophy increased across tertiles of the TG/HDL-c ratio in children and adolescents but also that pediatric subjects with a TG/HDL-c ratio major than 2.0 had a two to threefold higher risk of concentric LV hypertrophy compared to those with a TG/HDL-c ratio lower than 2.0 (Di Bonito et al. 2012).

In addition a new recent study reported the role of this lipid ratio in the pathogenesis of vascular remodeling evaluated by arterial stiffness and brachial distensibility in obese youth. In this population, the authors described a progressive rise in arterial stiffness across TG/HDL-c ratio. In addition, the ratio seemed to be an independent determinant of brachial distensibility in CV risk factor. These results confirmed that a high TG/HDL-c ratio is related not only with specific cardiometabolic profile but also with preclinical signs of cardiac abnormalities already in pediatric population. Moreover, also these data confirmed that a value of TG/HDL-c ratio major than 2.0 could be considered a useful clinical marker to detect children with high cardio-metabolic risk (Urbina et al. 2013).

In a recent study, our group (de Giorgis et al. 2013) tried to extend this association between the TG/HDL-c ratio and early signs of cardiovascular disease in children, assessing the relationship between the ratio and carotid intima-media thickness (cIMT) that is a more feasible, direct, and noninvasive method, detecting preclinical signs of arterial wall dysfunction in obese pediatric population. In our study, obese children showed significantly higher values of the TG/HDL-c ratio ($1.9 \pm 1.1$ vs. $1.2 \pm 0.6$, $p = 0.002$) compared with controls. In addition, after dividing the population in tertiles of the TG/HDL-c ratio (<1.04, 1.04–1.67,>1.67), insulin resistance and marker of chronic inflammation progressively increased moving from the lower to the upper tertile (HOMA-IR $p = 0.0001$, WBISI $p = 0.0003$ and sRAGE $p = 0.05$). Interestingly, also cIMT progressively increased moving across tertiles ($p = 0.0003$) (Fig. 2). Additionally, a multiple linear regression analysis revealed a significant and positive correlation between the TG/HDL-c ratio and cIMT ($r = 0.493$, $P = 0.0005$). Considering this very interestingly relation between cIMT and the lipid ratio, a ROC curve analysis was calculated in order to estimate a threshold of TG/HDL-c ratio that was able to identify the subjects in the upper quartile of cIMT. A cutoff point for TG/HDL-c ratio of 1.12 had 81 % sensitivity and 49 % specificity in the identification of children with cIMT values in the upper quartile (de Giorgis et al. 2013). It needs to be acknowledged that in our study population, values of the TG/HDL-c ratio were lower compared to values proposed in previous studies (Giannini et al. 2011; Musso et al. 2011). However, this study population included only prepubertal and Caucasian children. Therefore, these aspects could explain the differences in terms of threshold of TG/HDL-c ratio, where also adolescents and a mixture of ethnic groups were studied. These data could also reflect the well-known influences of puberty and ethnicity on insulin sensitivity and cardio-metabolic parameters. In conclusion, in this study we showed that the TG/HDL-c ratio is an additional independent factor associated with cIMT; therefore, these data provided a further line of evidence for a role of the TG/HDL-c ratio in the cardiovascular risk.

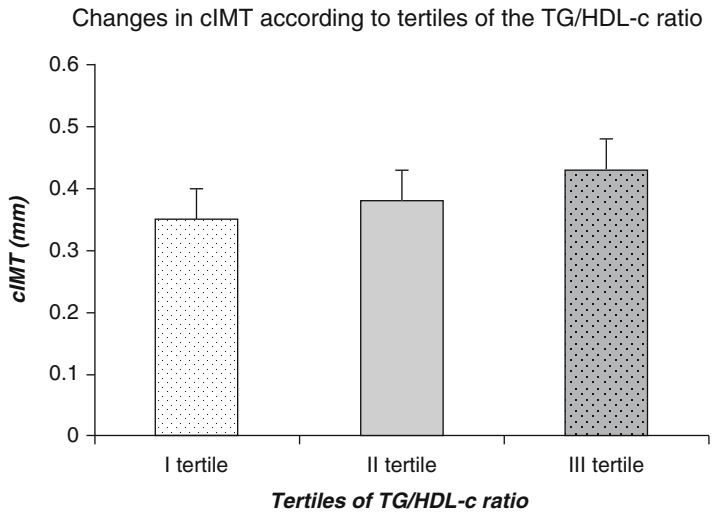


**Fig. 2** Changes in cIMT according to tertiles of the TG/HDL-c ratio

Taking together, all these findings support the role of the TG/HDL-c ratio as a useful marker able to define the cardio-metabolic status also in obese children and adolescents. Therefore, all these evidences underline the role of the ratio as a new emerging marker of cardiovascular disease in adult population as well as also in childhood.

## What Are the Limits of the TG/HDL-C Ratio as a Marker of Cardio-Metabolic Risk?

As previously showed, strong evidences support the role of the TG/HDL-c ratio as a reliable marker of cardiovascular disease in adults as well as also in children. However, a series of limits have been reported regarding the possibility to introduce this ratio as a single recommend marker for screening general population at increased risk for developing metabolic and cardiovascular complications.

The first limit is related to the possibility to identify a standardized cutoff point for the TG/HDL-c ratio above which subjects present an increased cardio-metabolic risk. Up to now, although several studies have been conducted, with the main aim to use the ratio as a marker of the cardio-metabolic status, there are a series of differences in proposed threshold (Di Bonito et al. 2012; Giannini et al. 2011; Salazar et al. 2012). Probably, these differences in terms of proposed threshold for TG/HDL-c could be related by the differences of characteristics in the populations included in these studies. In fact, it is well know that there are substantial differences in lipid profile and cardio-metabolic risk in adult population according to different ethnicity. In particular, these discordances seem to be more evident in pediatric population. In fact, there are a series of strong data indicating that in children more that in adult subjects, lipid profile is influenced by different parameters as age, gender, pubertal stage, and ethnicity.

**Table 4** Advantages and disadvantages of TG/HDL-c ratio

| Advantages | Disadvantages |
|---|---|
| Not expensive | Not specific for a single disease |
| Easy to calculate | A single cutoff is not available |
| Correlated with direct and surrogate signs of cardio-metabolic diseases | Influenced by changes of different components of lipid profile according to age, gender, pubertal stage and infections |
| Correlated with insulin resistance | |

Some studies demonstrated that the relationship between the ratio and cardio-metabolic parameters is not confirmed when the studies included in their study population both obese African-American and non-Caucasian subjects. Therefore, these differences in the TG/HDL-c ratio according to different ethnic group could be related to the differences in genetic patterns that are able to influence the specific ethnic cardio-metabolic risk (Davis 2008). In addition, it needs to be acknowledged that the large difference for the proposed threshold of the TG/HDL-c ratio in pediatric group could be related to the pubertal characteristics of children included in the study population. In fact, the major part of these studies included in their study population both pubertal and prepubertal children, and only few of these studies performed a sub-analysis in order to define a specific value of ratio according to the pubertal stage of the population. Consequently, the variability in the proposed cutoff point of the TG/HDL-c across the different studies could be related to the well-known physiological changes in lipid profile, insulin resistance, and other cardio-metabolic parameters related to puberty (Radtke et al. 2012). It easy understandable that the possibility to apply of ratio as a markers of cardiovascular diseases in general pediatric population is strictly related to the chance to have percentiles of TG to HDL ratio for age, gender, pubertal stage, and ethnicity. Therefore, considering this limit, new studies should be performed in order to obtain a specific cutoff point.

The last limitation associated to the use of the TG/HDL-c ratio in the clinical practice is related to the absence of long-term follow-up studies evaluating the power of this marker during life. In fact, although we have sufficient data on the role of TG/HDL-c ratio as a marker able to measure the current cardio-metabolic status in adults as well in children (Di Bonito et al. 2012; Giannini et al. 2011; Salazar et al. 2012), there are no data regarding a possible role of the ratio as a factor able to predict the future cardio-metabolic risk. Therefore, longitudinal studies are needed in order to verify whether TG/HDL-C ratio could be the best marker able to reflect and predict the cardio-metabolic status during long life (Table 4).

## Conclusion

In conclusion, the TG/HDL-C ratio seems to represent a new and useful marker related to cardio-metabolic risk factors and early signs of vascular damage both in adults and in children (Giannini et al. 2011; Di Bonito et al. 2012; de Giorgis et al. 2013;

Eeg-Olofsson et al. 2014; Kannel et al. 2008). These data suggest that the use of TG/HDL-c may be helpful in identifying patient at high risk for cardiovascular diseases requiring aggressive intervention to prevent atherosclerotic CV diseases.

Although different studies confirm the important role of this marker in adult patients and in children with different metabolic and cardiovascular diseases, there are a series of limits that should be considered in particular when the ratio would be used in general population (Giannini et al. 2011; Di Bonito 2011; de Giorgis et al. 2013; Eeg-Olofsson et al. 2014; Kannel et al. 2008).

Therefore, other longitudinal and large studies are needed in order to validate also in adults as well as in pediatric population the power of the TG/HDL-C ratio as a marker able to reflect not only the current cardio-metabolic status but also the risk to develop cardio-metabolic disease later in life.

## Summary Points

- To contain the important increase of cardiovascular accidents in general population, during the last 20 years, different surrogate markers have been proposed as tools not only to evaluate the progression of diseases but especially to recognize early in general population a precocious stage of diseases, probably when they are still silent.
- Several studies have clearly demonstrated that atherogenic dyslipidemia, characterized by decreased levels of HDL-c associated with increased TG and normal or minimally elevated levels of LDL-c, seems to be directly implicated in the pathogenesis of atherosclerosis in obese subjects.
- Recently, one of the most promising biomarker is the triglyceride-to-high-density lipoprotein cholesterol (TG/HDL-c) ratio that has been proposed as a new emerging marker able both to reflect the cardio-metabolic status and to predict subjects at increased risk of developing metabolic and cardiovascular complications in adults.
- Considering the strong correlation between TG/HDL-c ratio and different surrogate markers of cardio-metabolic diseases in obese subjects, a recent guideline for the clinical approach to obese patients recommends that the TG/HDL-c ratio should be used to define the impaired metabolic status and chronic inflammation in these subjects.
- There has been growing interest on the role of the TG/HDL-c ratio as a new emerging marker able to reflect the cardio-metabolic status and to predict subjects at increased risk of developing metabolic and cardiovascular complications in pediatric population.
- Several evidences demonstrated that TG/HDL-c ratio represents a strong surrogate marker of insulin resistance and of early signs of cardiovascular diseases; therefore, it could be used as an important risk factor to develop cardiovascular diseases already in obese pediatric population.
- A series of limits should be consider regarding the possibility to introduce this ratio as a recommend marker for screening general population at increased risk of developing metabolic and cardiovascular complications.

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