Triglyceride-to-High-Density Lipoprotein Cholesterol Ratio and Systemic Inflammation in Patients with Idiopathic Pulmonary Arterial Hypertension

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Background: Idiopathic pulmonary arterial hypertension (IPAH) patients are characterized by elevated triglyceride (TG)-to-HDL cholesterol (HDL-C) ratio, which has been proposed to be an important prognostic factor in this population. The mechanism of this phenomenon remains unknown. We therefore investigated the potential determinants of increased TG/HDL-C ratio in IPAH patients.

Material/Methods: We prospectively recruited consecutive clinically stable IPAH patients between January 2016 and February 2017. Patients with diabetes or using statins were excluded. Anthropometric measurements included body mass index (BMI) and skinfold thickness; body fat mass was calculated using age and sex-specific equations. We assessed lipid profile, homeostatic model assessment of insulin resistance (HOMA-IR), serum adipokine levels (adiponectin, resistin, leptin, and visfatin), and circulating cytokines (IL-1β, IL-6, MCP-1, and TNF-α).

Results: We assessed 47 IPAH patients: 9 of them had been diagnosed with diabetes and 10 were treated with statins; therefore, were excluded them from further analysis. Age, sex distribution, and BMI were similar irrespectively of TG/HDL-C ratio. Patients with increased TG/HDL-C ratio (>3) as compared to patients with TG/HDL-C ≤3 were characterized by higher levels of IL-1β, MCP-1, and IL-6. TG level was correlated with IL-1β (R=0.76, p<0.001), IL-6 (R=0.52, p=0.005), TNF-α (R=0.62, p<0.001), and MCP-1 (R=0.63, p<0.001). IL-1β was also inversely correlated with HDL-C (R=−0.44, p=0.02). We found no differences in concentration of fasting glucose, insulin, HOMA-IR, body fat content, or adipokine levels between patients with higher and lower TG/HDL-C ratios.

Conclusions: In IPAH patients, elevated TG/HDL-C ratio is a marker of systemic inflammation.

MeSH Keywords: Hypertension, Pulmonary • Inflammation • Insulin Resistance • Lipid Metabolism

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Background

Idiopathic pulmonary arterial hypertension (IPAH) is a severe disease in which pulmonary vascular cells undergo uncontrolled hyperplasia, leading to narrowing and obliteration of small pulmonary arteries. This results in an increase of pulmonary vascular resistance, elevation of pulmonary artery pressure, and, eventually, heart failure [1]. The etiology of IPAH is considered to be multifactorial, but the exact mechanisms resulting in disease onset and progression are unclear. Most recently, IPAH has been considered as a systemic disease due to involvement of many organs and tissues, as well as inflammatory and metabolic pathways [2,3].

Recent clinical studies found alterations in lipid profile, such as elevated triglyceride (TG)-to-high-density lipoprotein cholesterol (HDL-C) ratio and lowered HDL-C, to be more prevalent in pulmonary arterial hypertension (PAH) patients than in age-matched controls [4,5]. Both of them were associated with poor survival [4] and worse clinical status in this population [6]. However, the mechanism of the increase in TG/HDL-C ratio in IPAH patients is not fully understood.

The mechanisms of increased TG and decreased HDL-C were investigated in different populations, including healthy subjects, patients with metabolic syndrome, and patients with chronic inflammatory disorders. In healthy adult and adolescent populations, elevated TG/HDL-C ratio was correlated with higher body weight and abdominal obesity [7,8]. Both increased TG and lower HDL-C concentrations were also associated with insulin levels and were described as characteristic lipid alterations associated with the defect in insulin action [9,10]. For this reason, TG/HDL-C was used as a marker of adiposity and insulin resistance in some populations. Patients with pulmonary hypertension, however, have similar or lower body mass index (BMI) than in the general population, and a recent study found that an increased TG/HDL-C ratio in this group was independent of the degree of obesity [4]. Therefore, the increased TG/HDL-C ratio cannot be simply explained by obesity or metabolic syndrome. Other studies show that multiple inflammatory cytokines can also increase serum TG levels [11] and decrease HDL-C concentration [12]. However, the mechanisms of increased TG/HDL-C ratio in the IPAH population have not yet been investigated.

In the present study we investigated the potential determinants of increased TG/HDL-C ratio in patients with IPAH. Based on the current literature, we analyzed body fat content and its endocrine function, insulin resistance, and β-cell function, as well as systemic inflammation.

Material and Methods

Study population

We prospectively recruited consecutively hospitalized IPAH patients from a single pulmonary hypertension reference center between January 2016 and February 2017. All hospitalizations were for diagnostic purposes. We included patients with precapillary pulmonary hypertension with elevated pulmonary vascular resistance (>3 Wood units) without other known causes of PAH or chronic thromboembolic pulmonary hypertension [1]. Patients included in the study were clinically stable. Due to the known significant interactions with TG/HDL-C ratio or anthropometric measurements, we excluded subjects with heart failure decompensation, signs of peripheral edema or infection, patients with diabetes, and those treated with antidiabetic drugs or lipid-lowering drugs. All patients signed an informed consent before participation in the study. The local ethics committee revised and approved the study protocol, which conforms to the guidelines of the Declaration of Helsinki.

Evaluation of patients and anthropometric measurements

Patient assessment, laboratory tests, and anthropometric measurements were performed on the same day at our center. We collected a medical history, including use of statin, fibrates, niacin, and estrogen hormonal therapy. Diabetes was diagnosed according to current guidelines [13]. Anthropometric measurements included weight, height, and body fat mass (FM). Body weight was measured by using an electronic scale (WPT 60/150 OW, RADWAG, Radom, Poland). BMI was calculated by indexing body mass to the square of body height. Subjects with BMI of ≥25 kg/m^2 were considered as overweight and those with a BMI ≥30 kg/m^2 as obese.

Body FM was calculated according to Equation 1 [14]:

$$FM = weight \frac{495}{(BD-450)} \qquad (1)$$

where BD is the body density.

BD was calculated using skinfold thickness measurements with age- and sex-specific Durnin and Womersley equations [14]. Skinfold thickness was measured using the Harpenden Skinfold Caliper (Baty International, West Sussex, UK) at 4 sites: biceps, triceps, subscapular, and suprailiac. Each measurement was performed 3 times and the final outcome was calculated as an average of the readings.

Fat mass index (FMI) was obtained by indexing FM to the square of body height [15]:

$$FMI = \frac{FM}{height^2} \qquad (2)$$

Fat-free mass index (FFMI) was calculated:

$$FMI = BMI - FM \tag{3}$$

Laboratory tests

We collected venous blood from each participant after 12 h of fasting on the day of hemodynamic assessment. Complete lipid profile was assessed using the direct colorimetric method, as described previously [5]. Insulin concentration was assessed using electro-chemiluminescence immunoassay (Roche, Switzerland). The homeostatic model assessment of insulin resistance (HOMA-IR) was calculated using Equation 4 as the product of fasting glucose (mmol/l) and fasting insulin (mU/l) [16]:

$$HOMA-IR = \frac{fasting\ insulin \times fasting\ glucose}{22.5} \tag{4}$$

The β cell function (%B) was calculated as shown in Equation 5 [16]:

$$\%B = \frac{20 \times fasting\ glucose}{fasting\ glucose - 3.5} \tag{5}$$

The function of adipose tissue was assessed by measurement of serum adipokine levels: adiponectin, resistin, leptin (ELISA, Wuhan Fine Biotech, China), and visfatin (ELISA, Elabscience, USA). Systemic inflammation was assessed by measuring serum markers: IL-1β, IL-6, MCP-1, and TNF-α (ELISA, Wuhan Fine Biotech, China). The TG/HDL-C ratio was previously used as a surrogate measure of insulin resistance and a predictor of poor prognosis in numerous studies. Individuals with TG/HDL-C ratio >3 were described as insulin-resistant [4]. In our study, we used this threshold to compare patients with elevated TG/HDL-C ratio to other subjects.

Statistical analysis

We used median (interquartile range) to present continuous variables and counts (%) for categorical variables. Comparison of continuous variables between groups was performed using the *t* test or Mann-Whitney U test, according to data distribution. Comparison of categorical variables was performed using the chi-squared test. To assess correlations between continuous variables, we used Spearman rank-correlation. The alpha level was set as 0.05. Statistical analysis was performed with the use of the Dell Statistica data analysis software system (2016) version 13 (software.dell.com).

Results

Study population

Between January 2016 and February 2017, we assessed 47 clinically stable caucasian IPAH patients. Nine of them had been previously diagnosed with diabetes or received antidiabetic drugs and 10 patients were treated with statins; therefore, were excluded them from the study, as shown in the study flowchart (Figure 1). From the group of 28 patients included in the final analysis, 22 (79%) were treated with PAH-specific therapy: 9 (32%) with monotherapy, 9 (32%) with dual therapy, and 4 (14%) with triple combination therapy. Four (14%) patients were treated with calcium channel blockers. Daily activities of study patients were significantly limited, as half (n=14) of them were in the World Health Organization functional class III. At the time of diagnosis, all patients were told to avoid excessive physical activity, which could lead to distressing symptoms. Further details of the study group are shown in Table 1.

After dividing the study population using TG/HDL-C ≤3 and >3 cutoff levels, we found significant differences in TG (1.0 *vs.* 1.7 mmol/l, p<0.001, respectively) and HDL-C (1.6 *vs.* 0.9 mmol/l, p<0.001, respectively) levels between groups. We found no differences in LDL-C levels (3.0 *vs.* 3.4mmol/l, p=0.6 respectively). Patients with TG/HDL-C >3 had similar age (44.0 *vs.* 42.0 years, p=0.6) and proportion of female sex (94 *vs.* 73%, p=0.1) compared with patients with lower TG/HDL-C. We found no differences in established clinical, laboratory, and hemodynamic markers of disease severity between patients with TG/HDL-C ≤3 and those with TG/HDL-C >3: the N-terminal pro-brain natriuretic peptide concentration was 867 (84–1731) *vs.* 704 (97–1428) pg/ml; p=0.8, the proportion of WHO Functional Class III was 59 *vs.* 36%; p=0.3, the six-minute walk distance was 405 (360–500) *vs.* 440 (400–513) m; p=0.2, the mean pulmonary arterial pressure was 48 (35–61) *vs.* 47 (43–60) mmHg; p=0.7, the right atrial pressure was 4 (3–6) *vs.* 4 (3–9) mmHg; p=0.6, the cardiac index was 2.4 (2.1–2.9) *vs.* 2.11 (2.0–2.7) l/min/m^2; p=0.5), and the mixed venous saturation was 67.7 (64.2–71.9) *vs.* 68.5 (65.8–70.1)%; p=0.6.

TG/HDL-C ratio and body fat

TG/HDL-C in IPAH patients was not associated with parameters of body composition, including BMI (R=0.14, p=0.5) and FMI (R=0.03, p=0.9), as shown in Table 2. Additionally, no association between fat tissue function and TG/HDL-C ratio was found. BMI and FMI were, however, associated with higher HOMA-IR (R=0.55, p=0.003 and R=0.7, p<0.001, respectively). Overweight patients (n=15) were characterized by higher HOMA-IR than patients with normal BMI (3.5±2.2 *vs.* 1.67±0.96, p=0.008). Additionally, we noted a strong association between HOMA-IR and adipokines: visfatin (R=0.8, p<0.001) and leptin (R=0.76,
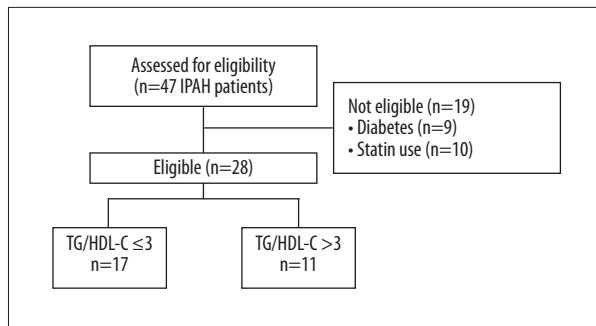
Figure 1. Study flowchart of participant selection.
IPAH – idiopathic pulmonary arterial hypertension;
TG/HDL-C – triglyceride-to-high-density lipoprotein
cholesterol ratio.

p<0.001). We found no correlation between HOMA-IR and inflammatory cytokines.

TG/HDL-C ratio, systemic inflammation, and insulin resistance

Patients with elevated TG/HDL-C had higher levels of IL-1β, MCP-1, and IL-6 than found in other individuals (Table 3). Graphic representation of the correlation between TG/HDL-C and inflammatory cytokines is shown in Figure 2.

Similar to TG/HDL-C ratio, TG level was correlated with IL-1β (R=0.76, p<0.001), IL-6 (R=0.52, p=0.005), TNF-α (R=0.62, p<0.001), and MCP-1(R=0.63, p<0.001). IL-1β was also correlated with HDL-C (R=-0.44, p=0.02). There were no significant differences in concentration of fasting glucose, insulin, HOMA-IR, or %B between patients with TG/HDL-C >3 and those with TG/HDL-C ≤3 (Table 4).

Table 1. Group characteristics.

Age (y)	43	(39.0–54.0)
Sex (female)	24	(86%)
WHO-FC (II/III)	14 (50%)/14 (50%)	
NT-proBNP [pg/ml]	785.5	(85.5–1723.0)
6-MWD [m]	422.5	(370.0–505.0)
mPAP [mmHg]	47.5	(37.0–60.5)
CI [l/min/m2]	2.3	(2.0–2.8)
PVR [WU]	9.85	(6.43–13.1)
PAH-specific therapies		
ERA	9	(32%)
PDE5i	17	(61%)
Prostacyclin	9	(32%)
ERA+ PDE5i	4	(14%)
PDE5i + prostacyclin	5	(18%)
Triple therapy	4	(14%)

Continuous variables are presented as median (interquartile range). 6-MWD – six-minute walk distance; CI – cardiac index; ERA – endothelin receptor antagonists; NT-proBNP – N-terminal pro-brain natriuretic peptide; mPAP – mean pulmonary artery pressure; PAH – pulmonary arterial hypertension; PDE-5i – phosphodiesterase type 5 inhibitors; PVR – pulmonary vascular resistance; WHO-FC – WHO Functional Class.

Discussion

The present study shows for the first time that in a selected population of clinically stable IPAH patients without diabetes

Table 2. Adipose tissue content and function in patients with TG/HDL-C >3 and TG/HDL-C ≤3.

	TG/HDL-C ≤3 (n=17)		TG/HDL-C >3 (n=11)		p
Sex (Female)	16	(94%)	8	(73%)	0.1
Age (y)	44.0	(39.0–54.0)	42.0	(38.0–54.0)	0.6
BMI (kg/m²)	23.6	(22.0–27.5)	26.5	(23.2–29.4)	0.1
FMI (kg/m²)	7.7	(7.0–9.7)	8.7	(8.1–9.7)	0.5
FFMI (kg/m²)	16.3	(15.0–17.9)	17.5	(16.9–20.9)	0.1
% of fat	33.4	(31.9–35.0)	33.1	(27.8–36.0)	0.8
Resistin (ng/ml)	4.0	(3.5–6.6)	6.6	(5.1–17.5)	0.03
Leptin (ng/ml)	14.1	(8.5–26.9)	17.6	(6.9–27.0)	0.9
Adiponectin (ng/ml)	448.0	(360.0–519.0)	334.0	(259.0–463.0)	0.1
Visfatin (ng/ml)	61.1	(45.7–113.1)	101.4	(23.0–136.9)	1.0

Continuous variables are presented as median (interquartile range). BMI – body mass index; FFMI – fat-free mass index; FMI – fat mass index; TG/HDL-C – triglyceride-to-high-density lipoprotein cholesterol ratio.

Table 3. Comparison of inflammatory markers between patients with TG/HDL-C >3 and TG/HDL-C ≤3.

	TG/HDL-C ≤3 (n=17)		TG/HDL-C >3 (n=11)		p
IL-1β (pg/ml)	7.8	(5.9–12.9)	32.3	(15.8–48.0)	<0.001
MCP-1 (pg/ml)	51.5	(43.3–75.0)	103.9	(52.4–135.8)	0.01
TNFα (pg/ml)	66.1	(57.7–89.5)	142.4	(71.6–218.5)	0.03
IL-6 (pg/ml)	5.8	(4.7–14.4)	22.4	(12.9–36.0)	0.009

Continuous variables are presented as median (interquartile range). Il-1β – interleukin 1β; Il-6 – interleukin 6; MCP-1 – monocyte chemoattractant protein 1; TG/HDL-C – triglyceride-to-high-density lipoprotein cholesterol ratio; TNFα – tumor necrosis factor α.

Figure 2. Association between TG/HDL-C and inflammatory cytokines. Il-1β – interleukin 1β; Il-6 – interleukin 6; MCP-1 – monocyte chemoattractant protein 1; TG/HDL-C – triglyceride-to-high-density lipoprotein cholesterol ratio; TNFα – tumor necrosis factor α.
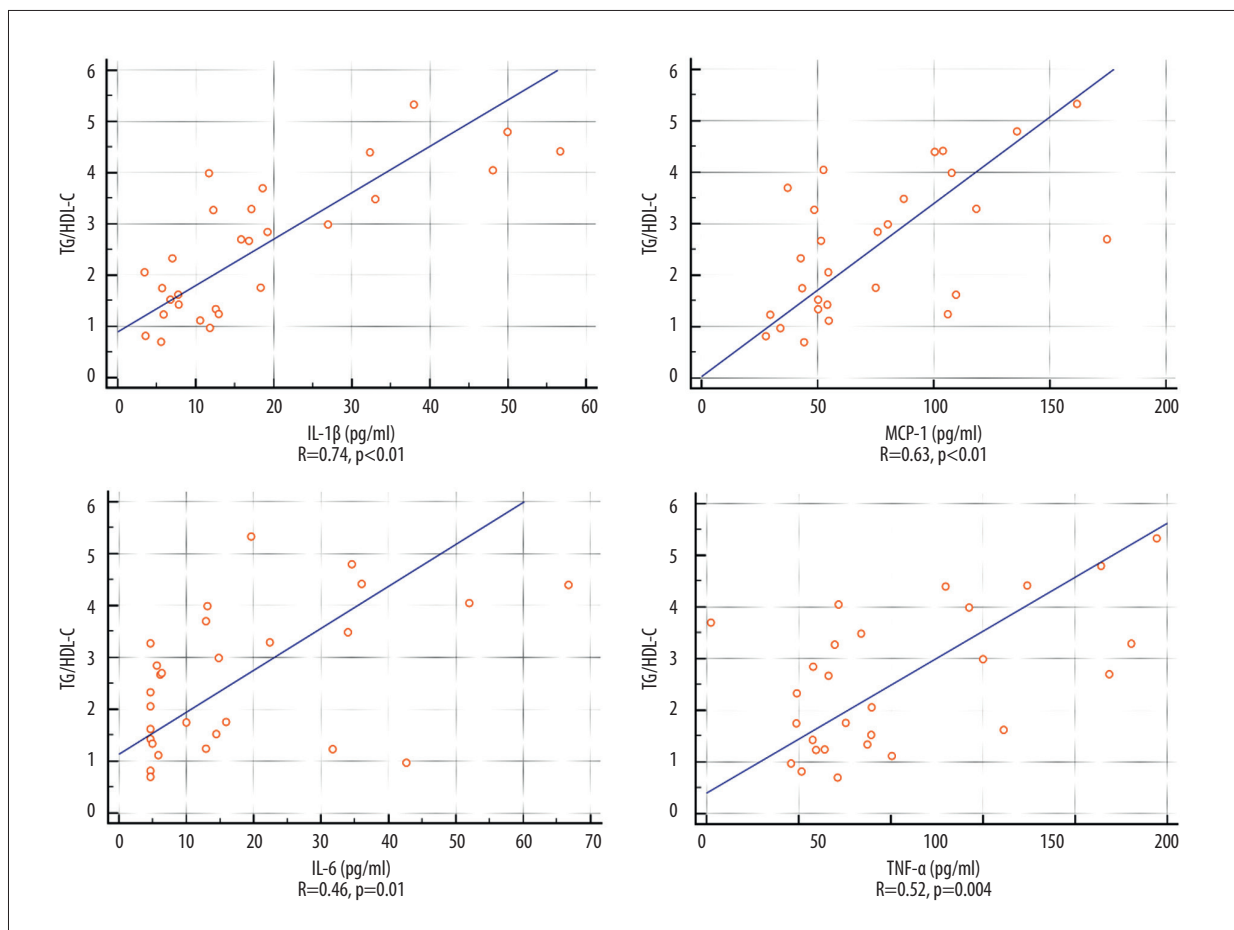
or lipid-lowering therapies, TG/HDL-C ratio was strongly associated with systemic inflammation. Inflammatory cytokines were correlated with higher TG and lower HDL-C. However, we did not find any link between TG/HDL-C ratio and body fat content and function, or between TG/HDL-C ratio and HOMA-IR or beta cell function.

In the general population, elevated TG/HDL-C ratio is used as an accessible and easy to apply marker of insulin resistance, and was associated with age and the degree of obesity [17]. Increased TG/HDL-C ratio was also found in PAH patients but not in age-matched healthy adults, and was established as an important prognostic marker. In this group of patients, increased TG/HDL-C ratio independent of BMI was able to predict worse clinical outcome and poor survival [4]. The mechanisms

Table 4. Insulin resistance and beta cell function in patients with TG/HDL-C >3 and TG/HDL-C ≤3.

	TG/HDL-C ≤3 (n=17)		TG/HDL-C >3 (n=11)		p
Insulin (uIU/ml)	9.8	(5.4–14.6)	11.5	(4.4–16.2)	0.8
HOMA-IR	2.0	(1.3–3.6)	2.4	(1.0–4.2)	0.8
%B	126.7	(78.8–178.6)	141.7	(64.6–214.0)	0.6
Glucose (mmol/l)	5.2	(4.9–5.4)	5.1	(4.6–6.0)	0.8

Continuous variables are presented as median (interquartile range). %B – pancreatic β-cell function; HDL-C – high-density lipoprotein cholesterol; HOMA-IR – homeostatic model assessment of insulin resistance; LDL-C – low-density lipoprotein cholesterol; TG – triglyceride; TG/HDL-C – triglyceride-to-high-density lipoprotein cholesterol ratio.

of increased TG/HDL-C ratio in the PAH population are still not well understood, especially when one considers that PAH patients are not more obese than their healthy counterparts. Considering the distinct clinical characteristics of patients with IPAH, we reviewed potential determinants of elevated TG and decreased HDL-C levels in this population, including inflammation, body fat content, and altered insulin-glucose homeostasis.

Chronic inflammation was recently proposed as an important factor in the progression of pulmonary vascular disease. In experimental studies, upregulated inflammatory response precedes vascular remodeling and is considered to cause altered vascular cell metabolism and consequent smooth-muscle cells proliferation [3,18–21]. In IPAH patients, levels of circulating cytokines such as interleukin-1β, IL-2, IL-6, IL-8, IL-10, TNF-α, and MCP-1 are elevated and can predict poor prognosis, including increased mortality [22–24]. In our study, we found that in IPAH patients, inflammation is associated with elevated level of TG and decreased HDL-C. This kind of dyslipidemia was also described in other inflammatory diseases, including rheumatoid arthritis [25], lupus [26], and psoriasis [27]. It was shown that inflammatory cytokines or bacterial lipopolysaccharide increased TG levels by upregulated hepatic fatty acid synthesis and increase in adipose tissue lipolysis [11,28]. Inflammation also increased expression of the angiopoietin-like protein 4, an inhibitor of lipoprotein lipase activity, which further inhibited the metabolism of TG-rich lipoproteins [29]. In another study, modification of the TG lipases by cytokines decreased HDL-C concentration [12]. The causative role of inflammation in lipid abnormalities was confirmed by a study of rheumatoid arthritis patients treated with anti-TNFα antibodies, which resulted in a decrease of IL-6 and elevation of HDL-C, independent of other lipid fractions [30].

Most recent studies have proposed the integrated theory of PAH pathogenesis, incorporating both the role of inflammation and metabolic alteration in vascular smooth-muscle cells proliferation [3,31]. In this theory, the central role is played by the altered bone morphogenetic protein type 2 receptor (BMPR2)/peroxisome proliferator-activated receptor γ (PPARγ)

signaling. Mutation of the BMPR2 gene is the most common cause of heritable PAH, and depressed BMPR2 expression was described in the lungs of patients with other forms of PAH as well [1,32]. Decreased activity of PPARγ can lead to increased inflammatory response and elevation of TG/HDL ratio [33–37] and thus at least partly explains the coexistence of inflammation and lipid abnormalities in our study patients.

In the general population, low plasma HDL-C and elevated TG traditionally have been associated with metabolic syndrome, increased adiposity, and insulin resistance. Visceral fat can supply the liver with free fatty acids, leading to changes in TG secretion [8]. Insulin is able to stimulate *de novo* synthesis of fatty acids, which is an important step in hepatic TG synthesis [38]. Hyperinsulinemia was also shown to stimulate hepatic TG secretion and apolipoprotein A1(ApoA1) catabolism, which results in decreased HDL-C levels [39].

In contrast to the abovementioned studies performed in the general population, lipid alterations in IPAH patients in our study were not associated with adiposity or elevated fasting glucose and insulin levels. Therefore, we conclude that the mechanisms of TG/HDL-C ratio alterations described in the general population may not play the leading role in IPAH patients. It seems possible that in this group, elevated TG/HDL-C ratio primarily reflects altered inflammation rather than the dysfunction of insulin-mediated signaling itself. In fact, in our study we did not found any association between TG/HDL-C and HOMA-IR or between TG/HDL-C and body fat content or levels of adipokines. Interestingly, a recent study by Heresi et al. showed that fasting insulin and HOMA-IR levels in IPAH patients were lower than in age-, sex-, and BMI-matched controls, which casts doubt on the role of fasting indices of insulin resistance in lipid abnormalities in this population. The higher prevalence of impaired glucose tolerance with decreased fasting indices of IR suggests a significant role of pancreatic β cell dysfunction, which may affect metabolic changes in IPAH patients [40].

The present study has several important strengths. For the first time we described an association between TG/HDL-C and

inflammatory cytokines in patients with IPAH. Second, we rigorously selected a subgroup of patients with stable disease without diabetes or statin use, which could potentially confound the study results. Third, understanding determinants of increased TG/HDL-C ratio in IPAH is clinically significant since it has been shown to be an important predictor of poor prognosis in this population. Additionally, our data provide potential targets for the therapy of lipid abnormalities in IPAH patients.

Our study has also some limitations. First, this was a single-center study and, due to strict patient selection, the number of enrolled patients was limited. Therefore, the present study may have lacked sufficient statistical power to reveal some less prominent associations between TG/HDL-C and other anthropometric or metabolic markers. We were also unable to adjust our association for potential confounders. We were, however, able to show that TG/HDL-C is strongly related to inflammation in IPAH patients. Second, due to the observational design of this study, we could not determine if the relationship between TG/HDL-C and inflammation is causal. Based on previous studies and experimental models, we were, however, able to propose potential mechanisms underlying the observed findings.

Conclusions

In IPAH patients, elevated TG/HDL-C ratio is a marker of systemic inflammation.

Conflicts of Interest

None.

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