High leptin and low blood adiponectin, TNF-alpha and irisin blood concentrations as factors linking obesity with the risk of atrial fibrillation among inpatients with cardiovascular disorders

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Short title: Adipocytokines and atrial fibrillation

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What’s New?

Blood concentrations of adipocytokines, hormones secreted by adipose tissue, are considered an explanation for associations between obesity and cardiovascular disorder (CVD) but, in our study, were only weakly related to the risk of atrial fibrillation (AF). We also only found weak associations between blood adipocytokine concentrations and both body composition and echocardiographic parameters. Circulating irisin, a substance secreted by skeletal muscles, showed a stronger relationship than those of adipocytokines with the risk of AF and the values of echocardiographic parameters. The weak associations between parameters of body composition and circulating adipocytokines and irisin suggest the existence of disturbances in the regulation of their secretion among patients with AF and other CVDs.

Abstract

Background: The endocrine function of adipose tissue and skeletal muscles mediates the risk of cardiovascular complications of obesity.

Aim: The aim of this study was to determine the relationships between leptin, adiponectin, TNF-alpha and irisin and the risk of atrial fibrillation (AF) diagnosis on admission to hospital and parameters of transthoracic echocardiography among inpatients with cardiovascular disorders (CVDs).

Methods: The following were assessed in 80 consecutive patients hospitalized due to paroxysmal or persistent AF and a control group of 165 age- and sex-matched individuals admitted due to exacerbation of chronic CVD: serum leptin, adiponectin, TNF-alpha and irisin concentrations, body composition determined by bioelectrical impedance analysis, and transthoracic echocardiographic parameters.
Results: Compared to the control group, patients with AF had greater fat mass (FM), higher serum leptin concentrations and, when indexed to body surface area, FM and visceral adiposity, lower values of adiponectin, TNF-alpha and irisin. Hyperleptinemia slightly increased the risk of AF occurrence (OR; 95% CI: 1.02; 1.01-1.03; P<0.01) but being indexed to FM amplified this association (1.34; 1.01-1.81; P<0.05). The coefficients of significant correlations of parameters of transthoracic echocardiography with irisin were stronger than those of adipocytokines and amounted to 0.16-0.35 and 0.12-0.22, respectively.

Conclusions: Adipocytokines and irisin exert a significant but weak effect on heart chamber size and affect the risk of AF occurrence. Blood concentration of these substances does not seem to be related simply to body composition, but probably depends on interpersonal variations in adipocytokine and myokine secretion as a result of many factors.

Key words: adiponectin; atrial fibrillation; irisin; leptin, TNF-alpha

Introduction

There is evidence of an association between nutritional status and increased risk of cardiovascular disorder (CVD), including atrial fibrillation (AF) [1-6]. However, among patients with CVD, overweight and class I obesity is also related to better prognosis, which is referred to as the “obesity paradox” or “lean paradox” [1-3]. Recently discussed issues concerning the relationships between nutritional status and the risk of CVD, including AF, are the limitations of body mass index (BMI) for cardiometabolic risk stratification, the importance of individual variance in adipose tissue distribution, and the concepts of “metabolically healthy obesity” and the “fat but fit” phenomenon [1-4, 7]. One potential pathomechanism linking body composition with CVD risk is inflammation [1-5, 8, 9] and an imbalance in the secretion of various adipocytokines and myokines produced in adipose tissue and skeletal muscles, respectively [10, 11]. However, the results obtained thus far in the
literature provide ambiguous conclusions concerning the role of the endocrine function of adipose tissue and skeletal muscle in relation to AF risk [4-30]. For example, adiponectin (ADP) is shown to have anti-diabetic, anti-atherogenic, and anti-inflammatory properties in experimental studies [11-15]. Nevertheless, the outcomes of clinical studies concerning the relationship between blood ADP concentration and CVD risk are ambiguous [13-18]. Leptin presents, i.a., pro-inflammatory and pro-fibrotic activity [19, 21, 24], which can affect AF risk, causing electrical and structural heart remodeling and disturbances in cardiac and vascular function [10, 19, 21, 30, 31], although not all studies confirm these effects of leptin [20, 21, 24, 25]. Similarly, no evidence of negative CVD consequences of increased blood tumor necrosis factor alpha (TNF-alpha), a cytokine with pro-inflammatory and pro-fibrotic activity that is secreted mainly through adipose tissue [19], is found in the studies available [22]. Irisin, a myokine, potentially exerts a favorable effect on the cardiovascular (CV) system [9, 23]; however, data concerning its relationships with CVD and AF risk are scarce.

Therefore, we undertook our study in order to determine the associations between blood concentrations of selected adipocytokines (leptin, ADP, and TNF-alpha), one myokine (irisin) and the risk of AF diagnosis at admission to hospital, parameters of body composition and transthoracic echocardiography. We also evaluated the risk of AF on admission associated with blood leptin, ADP, TNF-alpha and irisin concentrations among patients with CVD.

**Methods**

**Patients**

This observational study was performed with 80 consecutive patients hospitalized due to paroxysmal or persistent AF and a control group containing 165 consecutive inpatients with no history of AF and no indication of it in the ECG on admission, hospitalized because of exacerbation of several forms of CVD, such as a shortening claudication distance, angina
pectoris and hypertension. The exclusion criteria for both groups were: history or clinical signs of inflammatory processes or neoplasm; lack of informed consent for participation in the study; and/or an implanted mechanical valve, cardioverter or cardiotransmitter. At least one year following discharge, the patients (or their relatives) in the control group and AF group took part in a standardized telephone interview with the same physician.

Adipocytokines and irisin determination

Serum leptin determination was performed using an enzyme-linked immunosorbent assay (ELISA) kit from ALPCO (cat. no. 11-LEPHU-E01); serum ADP determination was also performed using an ELISA kit from ALPCO (cat. no. 80-ADPHU-E01); and serum TNF-alpha was assessed using an ELISA kit from CUSABIO (cat. no. CSB-E04740h). Serum irisin was analyzed using the ELISA method and a kit produced by BioVendor (cat. no. RAG018R). All parameters were determined in accordance with the manufacturer’s instructions.

Parameters of nutritional status assessment

A nutritional status assessment was performed for all the study participants. Body composition was determined using the bioelectrical impedance analysis (BIA) method and a TANITA BC-420 MA device (TANITA Corporation, Japan). The following BIA parameters were analyzed: fat mass (FM) (%; kg); visceral adipose tissue (VAT) score (in the range 1-59); fat-free mass (kg); and skeletal muscle mass (SMM) (%; kg).

Parameters of transthoracic echocardiography

Echocardiography was performed on admission for all the patients who participated by the same, experienced cardiologist, using an Aplio transthoracic ultrasound device (TOSHIBA, Canon, USA) and a 2-5 MHz radial probe. The following echocardiographic parameters were analyzed: left ventricular end-diastolic dimension (LVEDD); interventricular septum
thickness (IVST) at end-diastole; posterior wall thickness (PWT); left ventricular ejection fraction (LVEF); left ventricular mass (LVM); and left atrium area (LAA) and left atrium volume (LAV) in apical four- and two-chamber views (LAA4, LAV4 and LAA2, LAV2, respectively). LVM, LAA2, LAA4, LAV2 and LAV4 were indexed to body surface area (BSA). In this way, LVM index (LVMI), LAA index (LAAI), and LAV index (LAVI) were obtained. LVEF was assessed using the biplane, two-dimensional method of disks (modified Simpson's rule) in apical four- and two-chamber views. Left ventricular mass was calculated using the following formula: 
\[ \text{LVM (g)} = 0.8 \times \{1.04 \times [(\text{LVEDD} + \text{IVST} + \text{PWT})^3 - \text{LVEDD}^3] \} + 0.6. \]

Body surface area was calculated using the following formula:
\[ \text{BSA (m}^2) = 0.01666667 \times \text{height}^{0.5} \times \text{body mass}^{0.5} \]

**Bioethics**

The investigation was conducted in compliance with the Declaration of Helsinki for medical research, after receiving permission from local Bioethical Committee No. 389/2015. Each patient gave written consent to participate in the study.

**Statistics**

Statistical analysis was conducted using a licensed version of statistical software STATISTICA version 13.1 (a data analysis software system) developed by StatSoft, Inc. (2017). The normal distribution of the study variables was checked using the Shapiro-Wilk test. The results were mainly presented as the mean (standard deviation, SD), median (interquartile range, IQR) or n, %. The statistical significance of differences between groups was verified using the Student’s t-test, the Mann-Whitney U-test and the two-tailed Chi² test. A logit model using the Generalized Linear/Nonlinear Models module was used to determine
the odds ratio (OR) and 95% confidence interval (CI) as parameters of the risk of AF occurrence associated with unitary changes (e.g. per 1 pg/ml) in blood adipocytokine and myokine concentrations. Spearman’s correlations were checked to determine the relationships between adipocytokines and irisin and the parameters of transthoracic echocardiography and body composition. The statistical significance level was set at a P value < 0.05.

**Results**

**Clinical characteristics**

Compared to the control group, patients with AF were significantly less likely to smoke cigarettes and less likely to suffer from coronary artery disease, were more likely to be obese, especially in terms of an abdominal distribution of adiposity (increased waist-to-height ratio), and to have a greater FM, VAT score and lower SMM (Table 1). Moreover, they were more likely to have a greater LVEDD, IVST, LAV, LAVI (left atrium volume index calculated as a ratio of LAV to body surface area), LVM, LVMI, and lower LVEF (Table 1). Patients with AF were significantly more likely to use beta-blockers and anticoagulants, and less likely to take statins compared to their counterparts in the control group.

**Parameters of endocrine function of adipose tissue and skeletal muscle**

Compared to the control group, patients with AF were more likely to have a greater blood leptin concentration and a higher blood leptin concentration adjusted for to BSA (Table 2). Compared to individuals without arrhythmia, patients with AF were also more likely to have lower ratios for concentrations of ADP to leptin and ADP to C-reactive protein (CRP), lower values for ADP concentrations when indexed to BSA, FM and VAT score, as well as a lower value of TNF-alpha concentration when indexed to BSA, FM, and VAT. Indexing of blood
adipocytokine and irisin concentrations was performed in order to adjust for the effect of differences in body composition between the AF and control groups (Table 1).

Adipocytokines, irisin, body composition and echocardiographic parameters

We found some significant correlations of blood adipocytokine and irisin concentrations, both in relation to their crude and adjusted values, with parameters of transthoracic echocardiography and body composition in BIA (data not presented). The correlations were mostly positive for blood leptin concentration and negative for adiponectin, irisin and TNF-alpha, expressed as crude values and as values indexed to BSA and FM. However, the blood concentrations of the adipocytokines and irisin measured explained no more than 12.3% of the variance in the echocardiographic parameters (the values of correlations coefficients amounted to 0.12-0.22 and 0.16-0.35, respectively). Of the indexed values of the adipocytokines measured, the strongest relationships concerned leptin and TNF-alpha indexed to BSA. Of the indexed values of irisin, the strongest relationship was for irisin indexed to FM. However, parameters of body composition explained, on average, only 25% of the variance in the adipocytokines and myokine measured.

Adipocytokines, irisin and the risk of AF

Using a logistic regression model, we confirmed statistically significant relationships between the risk of AF on admission and the adipocytokines measured and irisin (Figure 1). The level of AF risk increased the higher the blood leptin concentration (by 2%), the greater the blood leptin concentration indexed to BSA (by 2%), and the higher the blood leptin concentration indexed to FM expressed as a percentage of whole body mass (by 34%). A statistically significant reduction in AF risk on admission was linked with increased ratios of ADP to leptin (by as much as 61%), ADP to CRP (by 4%), ADP to FM expressed in kg (by
50%), and ADP to VAT (by 28%). However, these associations were weaker than the relationships between the risk of AF and the indexed values of irisin. The risk of AF decreased with an increase in the ratio of blood irisin concentration to FM expressed in kg (by 81%) and irisin to VAT (by 67%). No significant relationship was found between the crude value of TNF-alpha concentration and AF risk, but the ratios of TNF-alpha to FM and TNF-alpha to VAT appear to have a significant inverse relationship with AF risk (Figure 1).

**Discussion**

Our observational prospective study was performed with a cohort of consecutive inpatients with AF and a high prevalence of cardiometabolic risk factors (Table 1) matched in relation to age and gender with individuals suffering from mildly exacerbated CV non-arrhythmic disorders. Compared to the non-arrhythmic patients, we found that individuals with AF had, i.a., a significantly higher FM (Table 1), blood leptin concentration and leptin-to-BSA ratio (Table 2). Although an increase in crude blood leptin concentration by 1 pg/ml increased AF risk by 2% on average (Figure 1), indexing blood leptin concentration to FM, expressed as a percentage of whole body mass, increased the risk of AF by, on average, 34% (Figure 1). This may suggest that the evidenced pro-arrhythmic effect of obesity [4-6, 32] does not simply depend on body composition and the level of adipocytokines, but mainly on an individually differentiated imbalance in the secretive activity of adipose tissue and skeletal muscles (e.g. 1kg of FM produced more leptin and less adiponectin in patients with AF than in control group). These variations may be related to genetic factors (e.g. gene polymorphism), physical activity, adipose distribution (e.g. higher VAT score), sensitivity of adipocytokine receptors, insulin resistance, which is an important factor leading to hyperleptinemia and cross-talk between adipose tissue, skeletal muscles and the liver [1-4, 9, 23, 32]. Our study did not confirm the importance of adipose tissue distribution on pro-arrhythmic effect of visceral
obesity, because the measured adipocytokines and irisin indexed to VAT were associated non-
significantly (leptin) or with a lower reduction in the risk of AF on admission (ADP, TNF-
alpha, irisin) than those parameters indexed to FM (Figure 1). Nonetheless, our results suggest
that higher blood leptin concentration and lower values of ADP and irisin indexed to FM and
VAT may be recognized as markers of a pro-arrhythmic effect of obesity and an imbalance in
the endocrine function of adipose tissue and skeletal muscles, which corroborates the outcomes reported by other researchers, although those authors did not analyze indexed values of adipocytokines [1-6, 10, 11, 16-18, 21, 23, 24-32, 33]. By contrast, in studies by
Kim et al. [13], Kawada [12], Macheret et al. [15] and Barnett and Piccini [27], high circulating adiponectin was independently associated with an increased risk of AF. In addition, Ermakov et al. [30] did not find any significant associations between plasma leptin and adiponectin concentrations and the risk of AF.

Our study shows that the adipocytokines and irisin measured were weakly associated with heart enlargement and body composition. This finding indirectly corroborates the outcomes of other authors. For example, after incubation of isolated rabbit left atrial myocytes, Lin et al. [31] found that leptin modulates electrophysiological characteristics and isoproterenol-
induced arrhythmogenesis in atrial myocytes, which suggests that hyperleptinemia may favor AF occurrence. A similar conclusion was drawn by Fukui et al., who, in ob/ob mice [24] and Sprague-Dawley rats [25], showed that leptin may take part in the pathogenesis of atrial fibrosis. However, in contrast to the results of our study, Kamimura et al. [34] found that higher blood leptin concentration was associated with lower LVM. In addition, in a study by Shimano et al. [17], adiponectin exerted beneficial effects on ventricular and atrial remodeling in patients with AF, and Ybarra et al. [35] found an inverse relationship between adiponectin and left atrium size independent of age, gender, insulin resistance and LVM.

Study limitations
Although numerous analyses performed in our study reached statistical significance, we were unable to avoid shortcomings that could decrease the strength of our conclusions. First, our control group did not consist of healthy individuals, as in the majority of studies on the effect of nutritional status on CV risk. However, in our study, we tested the hypothesis that patients with AF differ from other CVD patients with regard to the severity of inflammation status mediated by adipocytokines (leptin, ADP, TNF-alpha) and myokine (irisin). Second, not all potential confounding factors were balanced between patients with AF and the control group (Table 1). We enrolled consecutive patients with a diagnosis AF on admission to hospital and, despite subject matching, differences between the groups were impossible to avoid. To decrease the effect of these differences, we not only analyzed crude values, but also the indexed values of the adipocytokines and irisin measured. Third, we only determined blood irisin concentration after patients had received a night’s rest, but it is known that myokines are secreted after exercise. Moreover, physical activity was not assessed in our study but is a more significant element of a patient’s prognosis than an increased BMI value [1-4, 33]. Fourth, we enrolled our patients to the control group on the basis of their having no history of AF and a diagnosis of sinus rhythm in ECG at the moment of recruitment, without the exclusion of silent AF cases possible through long-term ECG monitoring prior to the patients’ allocation to the study groups [36]. This may be the source of an important bias because it is well known that AF may include clinically occult arrhythmia and incidence of AF increases with age and comorbidities, such as smoking habit and a history of myocardial infarction, which were more prevalent in the control group.

In conclusion, compared to patients with non-arrhythmic CVD, patients with AF were more prevalently obese, had higher crude and indexed concentrations of blood leptin, and lower indexed values of adiponectin, TNF-alpha and irisin. These parameters were significantly associated with an increased risk of arrhythmia. The adipocytokines and irisin
measured were statistically significant but only weak mediators of the obesity effect on heart remodeling in patients with CVD. As blood adipocytokine and irisin concentrations were only weakly related to body composition, the individual variance in their secretion seems to be a potential pathomechanism explaining the heterogeneous pro-arrhythmic effect of obesity.

References


Table 1. Clinical characteristics of the studied patients with and without atrial fibrillation

<table>
<thead>
<tr>
<th>Feature</th>
<th>Atrial fibrillation (n=80)</th>
<th>Control group (n=165)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>69.50 (8.87)</td>
<td>69.21 (9.29)</td>
<td>0.81</td>
</tr>
<tr>
<td>Male gender, n, %</td>
<td>41 (51.3)</td>
<td>88 (53.33)</td>
<td>0.88</td>
</tr>
<tr>
<td>Smoking habit, past / current, n, %</td>
<td>8 (10.0) /</td>
<td>56 (33.94) /</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td></td>
<td>Values</td>
<td>p-Value</td>
<td></td>
</tr>
<tr>
<td>------------------------------------</td>
<td>-----------------</td>
<td>---------</td>
<td></td>
</tr>
<tr>
<td><strong>Diabetes mellitus, n, %</strong></td>
<td>30 (37.5)</td>
<td>77 (46.67)</td>
<td>0.58</td>
</tr>
<tr>
<td><strong>Dyslipidemia, n, %</strong></td>
<td>70 (87.50)</td>
<td>146 (88.48)</td>
<td>0.82</td>
</tr>
<tr>
<td><strong>Hypertension, n, %</strong></td>
<td>68 (85.00)</td>
<td>141 (85.45)</td>
<td>0.92</td>
</tr>
<tr>
<td><strong>History of myocardial infarction, n, %</strong></td>
<td>8 (10.0)</td>
<td>50 (30.30)</td>
<td>0.02</td>
</tr>
<tr>
<td><strong>CHA2DS2VASc score</strong></td>
<td>3.16 (1.56)</td>
<td>4.09 (1.61)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td><strong>BMI, kg/m²</strong></td>
<td>31.26 (6.07)</td>
<td>27.32 (4.91)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td><strong>BMI range according to WHO ranges kg/m²: n, %</strong></td>
<td>0 / 10 (12.5) / 25 (31.25) / 45 (56.25)</td>
<td>0 / 45 (27.27) / 79 (47.88) / 41 (24.85)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td><strong>Central adiposity in reference to WHtR, n, %</strong></td>
<td>54 (67.50)</td>
<td>80 (48.48)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td><strong>FM, %</strong></td>
<td>36.20 (9.56)</td>
<td>30.55 (9.37)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td><strong>FM, kg</strong></td>
<td>32.59 (12.46)</td>
<td>23.65 (10.02)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td><strong>SMM, kg</strong></td>
<td>36.15 (5.34)</td>
<td>39.40 (5.44)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td><strong>VAT, score</strong></td>
<td>15.43 (4.87)</td>
<td>12.25 (3.82)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td><strong>LVEDD, mm</strong></td>
<td>50.65 (7.34)</td>
<td>46.61 (9.50)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td><strong>IVST, mm</strong></td>
<td>12.01 (1.82)</td>
<td>11.19 (1.81)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td><strong>LVEF, %</strong></td>
<td>53.44 (10.42)</td>
<td>59.77 (10.15)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td><strong>LAV, mm³</strong></td>
<td>106.16 (36.02)</td>
<td>70.86 (24.94)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td><strong>LAVI, mm³/m²</strong></td>
<td>52.86 (19.45)</td>
<td>37.78 (12.20)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td><strong>LVM, g</strong></td>
<td>246.50 (81.27)</td>
<td>196.09 (69.29)</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>
LVMI, g/m² & 121.22 (35.54) & 104.51 (32.43) & <0.01 \\
ACEI, n, % & 49 (61.25) & 112 (67.88) & 0.67 \\
Beta-blockers, n, % & 71 (88.75) & 125 (75.76) & <0.01 \\
Statin, n, % & 52 (65.0) & 165 (100.0) & <0.01 \\
Anticoagulant (vitamin K antagonist / or new oral anticoagulants), n, % & 42 (52.50) / 38 (47.50) & 1 (0.61 / 2 (1.21) & <0.01 \\

Data presented as median (SD), n, %; Mann-Whitney U-test or two-tailed Chi² test. 
Abbreviations: ACEI = angiotensin-converting enzyme inhibitors; BMI = body mass index; FM = fat mass; IVST = interventricular septum thickness at end-diastole; LAV = left atrium volume calculated in four-chamber view; LAVI = left atrium volume index calculated as a ratio of LAV to body surface area; LVEDD = left ventricular end-diastolic dimension; LVEF = left ventricular ejection fraction; LVM = left ventricular mass; LVMI = left ventricular mass index; SMM = skeletal muscle mass; VAT = visceral adipose tissue; WHO = World Health Organization; WHtR = waist-to-height ratio.

Table 2. Blood adipocytokine and irisin concentrations and their selected indexed values for inpatients with and without atrial fibrillation

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Atrial fibrillation (n=80)</th>
<th>Control group (n=165)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leptin, pg/ml</td>
<td>36.94; 18.26-86.61</td>
<td>18.34; 8.84-45.22</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Leptin-to-BSA ratio</td>
<td>19.20; 8.78-40.86</td>
<td>9.77; 5.00-24.75</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td></td>
<td>Min-Max</td>
<td>Min-Max</td>
<td>Min-Max</td>
</tr>
<tr>
<td>--------------------------</td>
<td>---------</td>
<td>---------</td>
<td>---------</td>
</tr>
<tr>
<td>Leptin-to-FM ratio</td>
<td>1.17; 0.64-2.10</td>
<td>0.91; 0.48-1.91</td>
<td>0.88</td>
</tr>
<tr>
<td>Leptin-to-VAT ratio</td>
<td>2.57; 1.12-5.61</td>
<td>1.51; 0.76-4.40</td>
<td>0.14</td>
</tr>
<tr>
<td>ADP, pg/ml</td>
<td>4.86; 1.60-12.64</td>
<td>5.76; 3.16-10.95</td>
<td>0.18</td>
</tr>
<tr>
<td>ADP-to-BSA ratio</td>
<td>2.29; 0.85-6.12</td>
<td>3.03; 1.67-5.47</td>
<td>0.11</td>
</tr>
<tr>
<td>ADP-to-leptin ratio</td>
<td>0.11; 0.03-0.30</td>
<td>0.28; 0.10-0.71</td>
<td>0.01</td>
</tr>
<tr>
<td>ADP-to-CRP ratio</td>
<td>1.29; 0.21-5.63</td>
<td>2.17; 0.65-6.75</td>
<td>0.02</td>
</tr>
<tr>
<td>ADP-to-FM ratio</td>
<td>0.15; 0.05-0.39</td>
<td>0.25; 0.14-0.53</td>
<td>0.04</td>
</tr>
<tr>
<td>ADP-to-VAT ratio</td>
<td>0.29; 0.10-0.85</td>
<td>0.49; 0.26-0.93</td>
<td>0.03</td>
</tr>
<tr>
<td>TNF-alpha, pg/ml</td>
<td>22.61; 6.04-45.71</td>
<td>30.83; 7.57-63.72</td>
<td>0.77</td>
</tr>
<tr>
<td>TNF-alpha-to-FM ratio</td>
<td>0.72; 0.21-1.64</td>
<td>1.31; 0.47-2.84</td>
<td>0.01</td>
</tr>
<tr>
<td>TNF-alpha-to-VAT ratio</td>
<td>1.52; 0.44-3.60</td>
<td>2.57; 0.83-4.90</td>
<td>0.04</td>
</tr>
<tr>
<td>Irisin, µg/ml</td>
<td>10.92; 7.90-13.86</td>
<td>11.15; 7.38-16.82</td>
<td>0.17</td>
</tr>
<tr>
<td>--------------</td>
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</tr>
<tr>
<td>Irisin-to-BSA ratio</td>
<td>5.43; 3.85-7.24</td>
<td>6.05; 3.94-8.82</td>
<td>0.02</td>
</tr>
<tr>
<td>Irisin-to-FM ratio</td>
<td>0.35; 0.24-0.48</td>
<td>0.54; 0.33-0.81</td>
<td>0.01</td>
</tr>
<tr>
<td>Irisin-to-VAT ratio</td>
<td>0.79; 0.47-0.98</td>
<td>0.93; 0.60-1.51</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Irisin-to-SMM ratio</td>
<td>0.34; 0.24-0.48</td>
<td>0.40; 0.26-0.61</td>
<td>0.03</td>
</tr>
</tbody>
</table>

Data presented as median; interquartile range; Mann-Whitney U-test.

Abbreviations: ADP = adiponectin; BSA = body surface area; CRP = C-reactive protein; TNF-alpha = tumor necrosis factor alpha; for the remaining abbreviations, see Table 1.
Figure 1. Risk of atrial fibrillation on admission associated with selected crude and indexed blood adipocytokine and irisin concentrations.

Data are presented as odds ratio (OR), 95% CI for changes per one unit (e.g. per 1 pg/ml) of variable.

Abbreviations: LEP - leptin, for remaining abbreviations see Table 1 and Table 2.