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PII: S0196-9781(15)00146-1
DOI: http://dx.doi.org/10.1016/j.peptides.2015.05.001
Reference: PEP 69473

To appear in: Peptides

Received date: 30-3-2015
Revised date: 4-5-2015
Accepted date: 5-5-2015

Please cite this article as: Sanchis-Gomar F, Alis R, Rampinini E, Bosio A, Ferioli D, La Torre A, Xu J, Sansoni V, Perego S, Romagnoli M, Lombardi G, Adropin and apelin fluctuations throughout a season in professional soccer players: Are they related with performance?, Peptides (2015), http://dx.doi.org/10.1016/j.peptides.2015.05.001

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Title: Adropin and apelin fluctuations throughout a season in professional soccer players: Are they related with performance?

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Manuscript Type: Short Communication

Word count: 2310

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Abstract

Myokines are likely to be involved in the whole-body metabolic adaptive changes that occur in response to regular exercise. We aimed to investigate the association of the two myokines (adropin and apelin) with physical performance in professional soccer players. To this purpose, we analyzed the fluctuations of circulating levels of both adropin and apelin in professional soccer players during a season and evaluated the possible association of these myokines with the performance level. Creatine kinase (CK) and lactate dehydrogenase (LDH) activity as well as iron, transferrin and high-sensitivity C-Reactive protein (hsCRP), ferritin, soluble transferrin receptor (sTfR), free testosterone/cortisol ratio (FTCR), total iron binding capacity (TIBC) were also determined. Fifteen male professional soccer players from an Italian Serie A team were included in this study. Regarding the results of the biochemical analyses, the patterns of changes in the biomarkers of fatigue and inflammation, i.e., HsCRP, CK and LDH reflected the effects of the training throughout the season. No significant changes were observed in adropin, while apelin exhibited variations that seem not to be related with performance. In addition, both adropin and apelin did not represent valuable strategy to assist in the performance assessment of professional soccer players.

Keywords: skeletal muscle; performance; cytokines.
Introduction

Myokines are cytokines produced by skeletal muscles, especially induced by exercise, modulating different metabolic processes [6]. By influencing metabolism locally in the muscles, myokines are thought to be involved in the whole-body metabolic adaptive changes that occur in response to regular exercise like, for example, attenuation of fat accumulation [2]. Skeletal muscle and pancreas act in a synergistic manner to monitor systemic glucose homeostasis, and it has been suggested that myokines mediate the cross-talk between insulin-sensitive tissues [17]. Striated skeletal muscle is one of the body’s largest tissues. However, it is unclear how contracting skeletal muscles transmit metabolic positive effects on health. One of the possible explanations for the health benefit of exercise can be that regular muscle contractions produce important messengers such as myokines [5]. Released circulating myokines may explain how normal muscle activity influences mood, physical performance and cognitive function [14].

It has been shown that exercise up-regulates the expression of the newly described myokine apelin in patients with type 2 diabetes [11]. In addition, apelin expression is induced by exercise and secreted in vitro in human primary myotubes, and may behave as a novel exercise-regulated myokine with autocrine/paracrine action [4]. Apelin is also up-regulated by insulin, contributing thus to glucose homeostasis [19]. Finally, apelin is highly implicated in cardiovascular function [10].

Adropin is also a recently described myokine involved in the regulation of lipid metabolism. It was first isolated in 2008 by Kumar et al. in liver and brain tissues [12]. In mice, adropin regulates physical activity (locomotion and coordination) via the \( NB-3/Notch \) signaling pathway [20]. Elevated circulating levels of adropin reduce insulin
resistance and glucose intolerance that arise in response to metabolic stress [7]. In this case, there is no clear evidence about whether exercise can regulate circulating levels of this myokine.

Therefore, because myokines are clearly involved in exercise-associated metabolic and cardiac changes, and hence could be potentially implicated in performance improvements throughout a soccer season, we aimed to analyze the fluctuations of circulating apelin and adropin levels in professional soccer players during a season. In addition, we also evaluated the possible association of both myokines with the performance level.

**Material and methods**

**Subjects**

Fifteen male professional soccer players from an Italian Serie A team (age (mean±SD) 27±5 years, weight 76.9±4.1 kg, height 1.82±0.05 m, body fat 8.7±2.4 %) were included in this study. Goalkeepers were not considered in this study since their physical load during soccer games is different from the other field players and as such their training programs are also different. All participants were informed of the purpose, protocol, and procedures of the study before agreeing to participate. The study complies with the World Medical Association Declaration of Helsinki regarding ethical conduct of research involving human subjects and/or animals and was approved by the ethics committee of University of Valencia, and by the soccer clubs involved.

**Experimental Protocol**

The players were sampled 3 times during the last part of a competitive season (in January, in March, in May). The competitive season finished at the end of May.
Thereafter, all players took a vacation and returned to the team discipline at the beginning of July, when the players included in the study were sampled again (just before preseason training beginning). At all sampling points, both mokines were assessed along with the physical performance determinations. An extensive biochemical and hematological profile study was also performed at all time-points but at May.

**Physical performance determinations**

At all time-points, the players were subjected to three physical performance tests, a continuous running test (Mognoni’s Test) [8], a high-intensity intermittent test (HIT) [18] and a counter-movement jump (CMJ) test.

During the Mognoni’s Test, blood lactate (La) concentration was determined immediately after a single 6-min run at 13.5 km·h⁻¹ while the mean heart rate (HR) of the last minute of running was considered for the analysis. After 10-min of passive recovery, subjects completed, following an acoustic signal, a HIT protocol (total duration = 5 min) consisting of 10 x 10 s shuttle running at 18 km·h⁻¹ over a 25-m course with an 180° direction change from run to run and 20s of passive recovery between runs. Immediately after the HIT protocol, blood La⁻ concentration was determined and the mean HR of 5-min run was considered for the analysis.

During both tests, blood La⁻ accumulation was measured using a portable amperometric microvolume lactate analyzer (Lactate Plus, Nova Biomedical, Waltham, MA, USA). Capillary blood samples (0.7 µl) were collected from the earlobe. Before the tests, the analyzer was calibrated following the instructions of the manufacturer. HR data was collected using Polar Team² Pro system (Kempele, Finland).
The CMJ test was performed using a portable force platform (Quattro Jump, Kistler, Switzerland). In short, after a standardized warm-up, the subjects performed 6 single CMJ and jump height and peak power output (PPO), averaged from the 3 best jumps were recorded.

In addition, the body fat percentage was estimated at all time points by the skin-fold technique, based on the Jackson and Pollock formula [9].

**Blood sampling**

Blood collection and sample management before analysis was carried out strictly following the good laboratory practice for pre-analytical phase of sports biochemistry and hematology tests [3]. The samples were drawn by venipuncture in the antecubital vein in fasting conditions. For hematological determinations, blood was collected in K$_3$EDTA vacuum tubes (Vacutainer, BD, Franklin Lakes, NJ, USA) and for biochemical tests, in vacuum plain tubes without additives (Vacutainer). The former were allowed to coagulate, then centrifuged at 3000 g for 10 min at room temperature and after centrifugation, serum was separated into aliquots. Whole blood tubes were immediately kept refrigerated at 4°C and assayed within 24 hours. Serum aliquots were frozen at -80°C until the assay.

**Laboratory Methods**

Adropin and apelin were determined in serum samples using available commercial competitive enzyme-linked immunosorbent assay kits (CSB-EL007669HU, Cusabio, Wuhan, China and EIA-APC, RayBiotech, Norcross, GA, USA; respectively). Both assays were performed in duplicate following manufacturer’s instructions. Intra-assay coefficients of variation were 13.92% for adropin and 4.52% for apelin determinations.
Full blood cell count was carried out on the automated analyzer XE-2100L (Sysmex, Kobe, Japan). Creatine kinase (CK) and lactate dehydrogenase (LDH) activity as well as iron, transferrin and high-sensitivity C-Reactive protein (hsCRP) concentration were determined on the automated clinical chemistry platform ADVIA 1800 (Siemens Healthcare Diagnostics, Erlangen, Germany), employing proprietary reagents. Cortisol and testosterone were immunoassayed on the automated analyzer Elecsys 1010 (Roche Diagnostics, Mannheim, Germany) using the dedicated electro-chemiluminescence immunoassay kits. Ferritin was assayed on automated immunoassay system (ADVIA Centaur) and soluble transferrin receptor (sTfR) on a fully automated immunonephelometer (BN ProSpec), both provided by Siemens Healthcare Diagnostics and by using proprietary immunoassays. For calculation of the testosterone/cortisol ratio (FTCR), free testosterone was assumed as 2% of the total testosterone, and the formula previously validated was adopted [1]. Also the total iron binding capacity (TIBC) was estimated by applying the formula \[ \text{TIBC (µg/dL)} = \text{transferrin (g/L)} \times 140 \] derived from the stoichiometric relationship between divalent transferrin and iron.

**Statistical analysis**

All data were analyzed for normality by Shapiro-Wilk test. Since the majority of the variables were not normally distributed, non-parametric tests were adopted. The effect of training and detraining (sampling time: January, March, May and July) on the parameters tested was analyzed with the Friedman’s test (\( \chi^2 \)) and paired comparisons were performed with the Wilcoxon’s test (z). The Spearman’s coefficient (\( \rho \)) was used to explore the correlation between adropin and apelin levels as well as with the other parameters determined. The statistical analyses were performed using SPSS, version 21 (IBM Corporation, Armonk, NY, USA). The results were considered statistically significant at \( p \leq 0.05 \). Data were expressed as median (10\textsuperscript{th}-90\textsuperscript{th} percentile).
**Results**

The aerobic endurance, assessed by post-exercise La− levels in Mognoni’s and HIT tests changed at the end part of the competitive season and by the detraining period [Mognoni $\chi^2(3)=19.53$, p<0.001; HIT $\chi^2(3)=15.53$, p=0.001; see Figure 1]. In the Mognoni’s test, La− levels in January [3.50(2.55-6.82) mM] were higher than in March [2.85(2.02-5.33) mM, z=-2.552, p=0.011] and in May [3.02(2.08-4.66) mM, z=-2.601, p=0.009]. In the same line, La− levels in the HIT test in March [2.47(1.37-6.21) mM] were lower than in January [4.40(1.65-8.35) mM, z=-2.045, p=0.041] and May [3.65(1.52-6.07) mM, z=-2.090, p=0.002]. This data would indicate a progressive adaptation with training. However, the July La− values were higher in both tests (see Figure 1) which would reflect the detraining occurring during the vacation period between the end of the season and the beginning of the next pre-season. Accordingly, the cardiovascular implication was higher after the detraining period in both Mognoni’s $[\chi^2(3)=13.00$, p=0.005] and HIT $[\chi^2(3)=11.44$, p=0.010] tests (see Figure 1). Nevertheless, we failed to find any significant effect of training and detraining on either jump height $[\chi^2(3)=5.23$, p=0.156] or PPO $[\chi^2(3)=1.46$, p=0.692] in the CMJ test.

Figure 2 shows a significant increase in the apelin concentration from 341.8(283.0-444.8) ng/mL in January to 433.3(373.4-677.5) ng/mL in March. Nonetheless, no statistically significant changes were found in either May or July compared to the previous time points. No significant changes were observed in adropin at any time.

A full blood cell panel along with several biochemical parameters was performed in January, March and July sampling times, but it could not be performed in May. These data are displayed on Table 1. The detraining period induced some alterations in erythrocyte indices. The mean corpuscular volume decreased while mean corpuscular
hemoglobin increased in July in comparison with the previous sampling points (Table 1). The red blood distribution width was slighter lower in July compared with January levels ($z = -2.284$, $p = 0.022$, Table 1). HsCRP, an inflammatory marker, was found to be lower in July compared to January ($z = -2.528$, $p = 0.011$). After detraining, levels of both biomarkers of muscle damage CK and LDH, were significantly lower compared with the previous time points (see Table 1).

Players’ weight [January 77.0 (69.8-82.3) kg, March 77.0(69.0-83.5) kg, May 76.5(68.0-84.8) kg and July 77.6(70.1-86.9) kg)] and percentage of body fat [January 8.4(5.8-13.1) %, March 8.1(6.5-12.0) %, May 8.2(5.5-12.0) %, July (9.2(7.0-12-4) %] did not significantly change at the end of the competitive season or after the detraining period [$\chi^2(3) = 6.126$, $p = 0.106$; $\chi^2(3) = 4.576$, $p = 0.206$; respectively].

Finally, no correlation was found between adropin or apelin concentrations and performance parameters at all time points measured (Supplementary Table 1). On the other hand, significant correlations were found between adropin and apelin levels and other hematological and biochemical parameters measured (Supplementary Table 2), although those correlations did not provide additional insights.

**Discussion**

No significant changes were observed in adropin levels, while apelin exhibited variations that seem not to be related with performance. On the other hand, the patterns of changes in the biomarkers of fatigue and inflammation, i.e., HsCRP, CK and LDH reflected the effects of the training throughout the season.

While apelin levels showed a significant increase only in the first time point, possibly linked to an increased effort, fluctuations in adropin levels did not reach statistical
significance. In both cases, however, the distribution widths within the study cohort were large: this was particularly true in the case of adropin but was also evident for apelin at the end of the season and after the rest period. It thus seems that the use of these two markers is not useful to assist in the performance assessment of professional soccer players. It should be also mentioned that, while other myokines seem to be relatively stable within person [13-16] thereby allowing longitudinal analyses, there is paucity of such data on apelin and adropin.

The main limitation of our study is the low number of subjects included on each experimental group that can decrease the power of the statistical analyses performed. Since season openings in Europe are regularly at mid/late August, we did not have a first season's start sample to compare. In addition, the specific design of this study with only professional athletes recruited limits the generalizability of its results in less trained individuals. Moreover, due to a problem of samples conservation, the hematological and biochemical panel could not be determined at May. Nevertheless, this study needs to be evaluated in both larger and different cohorts before they can be translated into clinical practice.

In conclusion, a one-season follow-up of professional soccer player's training did not lead to observe changes in circulating apelin and adropin levels. Accordingly, neither apelin nor adropin were associated with changes in performance level.


Competing financial interests
The authors declare no competing financial interests.

Acknowledgements
This research has been supported by grant DEP2012-37494 from the Spanish Government and by grants 2013-168-002 and 2012-011-001 from Catholic University of Valencia. RA is predoctoral fellow of Catholic University of Valencia. A special thanks to the athletes involved in the study, to Cedal laboratory and Dr Alberto Dolci for the support in the data collection.

References


Table and Figures Legends

**Table 1.** Players’ hematological and biochemical parameters in January, March, and July (i.e., at the beginning of the next pre-season).

**Figure 1.** Blood lactate (La') and heart rate (HR) in the Mognoni and HIT protocols, and height jump and peak power output in the counter-movement jump test (CMJ) during the competitive season (January, March and May) and in the next pre-season stage (July). During the Mognoni’s Test, La’ concentration was determined immediately after the test, while the mean HR of the test’s last minute of running was considered. During the HIT protocol La- concentration was determined just after the test and the mean HR of 5-min run was considered. CMJ height and peak power output was averaged from the 3 best of 6 jump repetitions. Data represented as median (horizontal line), 1st to 3rd quartile (box) and 10th to 90th percentile (whiskers). Significant comparisons are indicated.

**Figure 2.** Apelin and adropin concentrations during the competitive season (January, March and May) and in the next pre-season stage (July). Data represented as median (horizontal line), 1st to 3rd quartile (box) and 10th to 90th percentile (whiskers). Significant comparisons are indicated.
Table 1.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>January</th>
<th>March</th>
<th>July</th>
<th>Friedman’s p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>RBC ($\times 10^6/\mu L$)</td>
<td>5.03(4.60-5.73)</td>
<td>5.12(4.78-5.45)</td>
<td>5.11(4.72-5.87)</td>
<td>0.247</td>
</tr>
<tr>
<td>Hemoglobin (g/dL)</td>
<td>15.1(13.8-16.0)</td>
<td>15.3(14.3-16.2)</td>
<td>15.3(13.7-16.7)</td>
<td>0.302</td>
</tr>
<tr>
<td>Hematocrit (%)</td>
<td>44.0(41.0-47.3)</td>
<td>44.5(42.0-46.8)</td>
<td>44.9(40.1-47.7)</td>
<td>0.591</td>
</tr>
<tr>
<td>MCV (fl)</td>
<td>87.2(81.9-89.6)***</td>
<td>85.9(83.0-91.2)***</td>
<td>84.7(80.9-88.4)*</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>MCH (pg)</td>
<td>30.0(27.9-31.2)*</td>
<td>30.1(27.9-31.1)***</td>
<td>29.5(27.8-30.9)*</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>MCHC (g/dL)</td>
<td>34.3(33.1-35.5)***</td>
<td>34.5(33.2-35.9)***</td>
<td>34.5(33.2-36.6)***</td>
<td>0.581</td>
</tr>
<tr>
<td>RDW (%)</td>
<td>13.0(12.5-13.5)*</td>
<td>12.9(12.4-13.5)</td>
<td>12.8(12.3-13.6)</td>
<td>0.011</td>
</tr>
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<td>0.581</td>
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<td>12.8(12.3-13.6)</td>
<td>12.8(12.3-13.6)</td>
<td>0.011</td>
</tr>
<tr>
<td>Reticulocytes (%)</td>
<td>0.67(0.51-1.02)**</td>
<td>0.66(0.43-0.88)**</td>
<td>0.82(0.57-1.33)*</td>
<td>0.005</td>
</tr>
<tr>
<td>IRF (%)</td>
<td>3.2(1.44-5.98)</td>
<td>2.8(0.94-6.28)</td>
<td>3.2(1.26-5.78)</td>
<td>0.721</td>
</tr>
<tr>
<td>Fe (µg/dL)</td>
<td>82.60-117)</td>
<td>96(58-131)</td>
<td>84(67-145)</td>
<td>0.627</td>
</tr>
<tr>
<td>Ferritin (ng/mL)</td>
<td>125.7(69.1-246.7)</td>
<td>130.2(48.7-244.7)</td>
<td>113.4(51.6-217.6)</td>
<td>0.070</td>
</tr>
<tr>
<td>Transferrin (mg/dL)</td>
<td>249(213-273)</td>
<td>242(211-290)</td>
<td>259(207-297)</td>
<td>0.085</td>
</tr>
<tr>
<td>TIBC (µg/dL)</td>
<td>349(299-383)</td>
<td>339(296-405)</td>
<td>363(290-416)</td>
<td>0.085</td>
</tr>
<tr>
<td>Transferrin saturation (%)</td>
<td>25(18-32)</td>
<td>26(18-41)</td>
<td>26(18-39)</td>
<td>0.349</td>
</tr>
<tr>
<td>sTfR (mg/L)</td>
<td>1.30(0.84-1.63)</td>
<td>1.15(0.90-1.49)</td>
<td>1.19(0.83-1.62)</td>
<td>0.591</td>
</tr>
<tr>
<td>WBC (x10^3/µL)</td>
<td>4.97(4.01-6.52)</td>
<td>4.70(3.89-7.5)</td>
<td>5.01(4.25-7.76)</td>
<td>0.516</td>
</tr>
<tr>
<td>Lymphocytes (x10^3/µL)</td>
<td>2.2(1.4-3.3)</td>
<td>2.1(1.5-2.9)</td>
<td>2.3(1.6-3.0)</td>
<td>0.272</td>
</tr>
<tr>
<td>Neutrophils (x10^3/µL)</td>
<td>2.3(1.4-2.9)</td>
<td>2.4(1.4-4.1)</td>
<td>2.3(1.5-3.9)</td>
<td>0.179</td>
</tr>
<tr>
<td>Monocytes (x10^3/µL)</td>
<td>0.4(0.3-0.6)</td>
<td>0.4(0.3-0.6)</td>
<td>0.4(0.3-0.6)</td>
<td>0.971</td>
</tr>
<tr>
<td>Eosinophils (x10^3/µL)</td>
<td>0.02(0.01-0.03)</td>
<td>0.02(0.01-0.04)</td>
<td>0.02(0.01-0.03)</td>
<td>0.928</td>
</tr>
<tr>
<td>Basophils (x10^3/µL)</td>
<td>0.1(0.1-0.4)</td>
<td>0.1(0.1-0.5)</td>
<td>0.2(0.1-0.5)</td>
<td>0.009</td>
</tr>
<tr>
<td>hsCRP (mg/L)</td>
<td>0.97(0.40-8.22)*</td>
<td>0.71(0.16-2.25)</td>
<td>0.30(0.13-2.49)</td>
<td>0.022</td>
</tr>
<tr>
<td>Creatine kinase (U/L)</td>
<td>392(240-2053)**</td>
<td>382(168-713)**</td>
<td>294(125-925)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Lactate dehydrogenase (U/L)</td>
<td>205(73-271)*</td>
<td>190(148-231)***</td>
<td>158(127-217)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Cortisol (ng/mL)</td>
<td>238.0(190.3-277.4)</td>
<td>214.9(183.9-271.7)</td>
<td>214.1(135.2-260.1)</td>
<td>0.165</td>
</tr>
<tr>
<td>Testosterone (ng/mL)</td>
<td>7.21(4.15-9.57)</td>
<td>7.61(5.39-9.34)</td>
<td>7.16(5.39-9.95)</td>
<td>0.766</td>
</tr>
<tr>
<td>FTCR</td>
<td>0.74(0.47-0.95)</td>
<td>0.82(0.58-0.99)</td>
<td>0.91(0.61-1.57)</td>
<td>0.241</td>
</tr>
</tbody>
</table>


*p<0.05, **p<0.01 and ***p<0.001 vs July.  p<0.05, **p<0.01 and ***p<0.01 vs January.
Highlights

- Myokines are involved in metabolic adaptive changes induced by regular exercise.

- We investigated the association of two myokines (adropin and apelin) with physical performance.

- No significant changes were observed in adropin.

- Apelin exhibited variations that seem not to be related with performance.

- Apelin and adropin levels are not related to performance in professional soccer players.