Characterization of adipokines serum levels in osteoarthritis mouse models STR/ort before the onset of the pathology and correlation between adiponectin serum levels and disease severity.

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It has long been recognized that excess body weight may lead to cartilage degeneration by increasing the mechanical forces across weight-bearing joints. However, several studies have reported the association between obesity and OA also in non-weight-bearing joints (fingers and wrists).

In obese patients many physiological parameters are dysregulated, in particular, adipocyte-derived hormones produced by white adipose tissue called adipokines. These adipokines, in particular leptin and adiponectin, may be responsible for the high prevalence of OA among overweight people. Leptin serum levels are higher in obese compared to healthy people, on the contrary, adiponectin serum levels decrease with increasing weight.

Many publications have provided clear evidence for a role of leptin in cartilage homoeostasis, showing that high levels of leptin induce the synthesis of metalloproteases involved in cartilage degradation(1).

On the contrary several studies reported a controversial role of adiponectin in the OA progression. This adipokine seems to have a negative correlation with disease severity while in other reports was observed an opposite correlation. Moreover in a recent clinical study in overweight OA patients (characterized by BMI ≥40) a weight loss induced by gastric surgery was associated with increased adiponectin serum levels and reduced loss of tibial and femoral cartilage volume suggesting a protective role of adiponectin in OA(2).

STR/ort mice are an animal model of spontaneous OA characterized by early disease development (at about 20 weeks) and dysregulated metabolism. Notably, these mice have lower adiponectin serum levels compared to those found in control mouse strains(3).

The aim of our study was to evaluate adiponectin and leptin serum levels in STR/ort mice before the onset of OA (at 8, 14 and 20 weeks of age), and in age-matched CBA control mice. Then, to assess a possible relationship between OA development, Body Mass Index (BMI), and adiponectin serum levels in STR/ort mice, we performed histopathological analysis of 26-week-old animals, which are known to have established OA.

First, we performed the time course of adipokine serum levels of STR/ort and CBA mice at 8-20 weeks. Blood samples were collected from caudal vein (time course) or from vena cava at sacrifice. For the histopathological analysis STR/ort and CBA mice were recruited at 26 weeks of age and euthanized. Knee joints were collected, processed for histology, and blindly scored according to both Mankin's and OARSI methods.

Adiponectin serum levels in STR/ort mice at 8, 14 and 20 weeks were significantly lower than in age-matched CBA mice (20.2±0.7 vs 9.2±0.3 μg/mL, 16.0±0.4 vs 7.3±0.2 μg/mL and 14.5±0.3 vs 6.0±0.2 μg/mL, respectively). Instead, leptin serum levels in STR/ort mice were higher than in CBA strain at 14 and 20 weeks (2.5±0.3 vs 8.7±1.3 ng/mL and 3.1±0.4 vs 7.9±1.1 ng/mL, respectively).

In STR/ort mice (but not in CBA mice) at 26 weeks of age, we observed a significant negative correlation ($p=0.007$) between adiponectin serum levels and BMI. Moreover there was a negative correlation between adiponectin levels and disease severity (as measured by OARSI score), reaching statistical significance ($p=0.04$) when considering the less damaged knee. Conversely, we observed a positive correlation between BMI and OARSI scores both in the less and in the more damaged knees, reaching statistical significance when considering the less damaged knees.

In conclusion, this study confirmed that adiponectin serum levels in STR/ort mice are significantly lower than in a normal strain like CBA at the same age, and showed that leptin serum levels in STR/ort mice are higher than in control mice. Notably, this adipokine dysregulation occurs before OA onset.

Moreover, we showed for the first time a significant negative correlation between adiponectin levels and disease severity in STR/ort mice. These findings suggest that decreased adiponectin levels may be associated with OA development and/or progression in this animal model.

References

1. Bao J.P. et all. Mol Biol Rep. 2010

2. King L.K. et al. Osteoarthritis and Cartilage, 2015

3. Uchida K. et al. Experimental Animals, 2009