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ABSTRACT

Adipocytokine, including leptin and adiponectin, may play an important role in the pathophysiology of osteoarthritis (OA). Spa therapy is one of the most commonly used non-pharmacological approaches for OA, but its mechanisms of action are not completely known. The aim of the present study was to assess whether spa therapy modified plasma levels of leptin and adiponectin in thirty patients with knee OA treated with a cycle of a combination of daily locally-applied mud packs and bicarbonate-sulphate mineral bath water. Leptin and adiponectin plasma levels were assessed at baseline and after two weeks, upon completion of the spa treatment period. The concentrations of leptin and adiponectin were measured by ELISA.

At basal time, plasma leptin levels were significantly correlated with body mass index (BMI) and gender, but no significant correlation was found with patient age, duration of disease, radiographic severity of knee OA, VAS score or Lequesne index.

There was no correlation between plasma adiponectin level and BMI, gender and age, duration of the disease, radiographic severity of knee OA, and VAS score. A significant correlation of plasma adiponectin levels was found only with the Lequesne index.

At the end of the mud-bath therapy cycle, serum leptin levels showed a slight but not significant increase, while a significant decrease ($p<0.05$) of serum adiponectin levels was found. However, leptin and adiponectin concentrations after treatment were not correlated with other clinical parameters.

In conclusion, our data show that spa therapy can modify plasma levels of the adipocytokines leptin and adiponectin, important mediators of cartilage metabolism. Whether this effect may play a potential role in OA needs further investigations.

Key words: osteoarthritis, leptin, adiponectin, spa therapy

INTRODUCTION

Leptin is a peptidic molecule synthesized almost exclusively by adipocytes, which regulates appetite and energy expenditure at the hypothalamic level [1]. In the past few years, additional actions have been attributed to this molecule, specifically, modulating the immune response and affecting the bone and cartilage metabolism [2,3].

Adiponectin is also synthesized by adipose tissue, and one of its main actions is to improve insulin sensitivity [1]. In skeletal joints, adiponectin may act as a pro-inflammatory agent and may be involved in matrix degradation [4]. In patients with osteoarthritis (OA), leptin and adiponectin are detected in both synovial fluid and in plasma [5]. The adipokines exhibit different patterns of distribution in the joint and the circulating compartment: plasma levels of adiponectin exceed those in the paired synovial fluid, whereas leptin concentrations in synovial fluid are higher than their plasma counterparts [5].

Spa treatments have been applied for therapeutic purposes in rheumatic diseases since ancient times [6].

The mechanism by which mud-packs and/or balneotherapy improves the symptoms of rheumatic diseases is still not fully understood [6]. The effects of thermal baths are, in part, related to temperature [7] , and balneotherapy also induces a neuroendocrine reaction which causes an increase in serum levels of corticosteroids and catecholamines [8,9] and a reduction in circulation levels of tumour necrosis factor α (TNF-α) and Interleukin-1β (IL-1 β) [10].

Since serum levels of leptin and adiponectin are influenced by temperature [11,12], catecholamines [13], corticosteroids [14] and TNF-α and IL-1 β [15,16], we evaluated whether Spa therapy modify plasma levels of leptin and adiponectin in patients with OA treated with a cycle of a combination of daily locally-applied mud packs and bicarbonate-sulphate mineral bath water.

MATERIALS AND METHODS

Patients

As a part of a recently-published randomized single-blind controlled clinical trial [17] on the efficacy of spa therapy in knee OA, we included thirty patients of both sexes with knee OA fulfilling the ACR criteria [18]. Radiological staging was carried out using the Kellgren method [19]; patients with a radiological score of I– III were included in the study (Table I).

Exclusion criteria for the study were previously presented [17]. In addition, for the purposes of this study, we excluded patients with history of diabetes mellitus, instable weight history, those treated with medications known to affect body weight and heavy smokers.

All selected patients resided in the area near the spa at Rapolano Terme (Siena, Italy) and continued to live at home and go about their normal daily routines.

Treatment

The patients were treated daily at the spa centre at Rapolano Terme with a combination of mud packs applied on both knees for 20 min at an initial temperature of 45°C and with bicarbonate-sulphate mineral bath water at 38°C for 15 min, for a total of 12 applications carried out over a period of 2 weeks. [17] .

It was recommended to patients that they should continue their established non-pharmacological treatments (physical exercise) and non steroidal anti-inflammatory drugs (NSAIDs) (150 mg Diclofenac tablets, 20 mg Piroxicam tablets, 750 mg Naproxen tablets, 200 mg Aceclofenac tablets) and/or analgesics (500 mg acetaminophen tablets), which were to be consumed liberally and noted daily in a diary. Furthermore, we advised patients not to utilize corticosteroids or hyaluronic acid infiltrations.

Leptin and Adiponectin measurements

Leptin and adiponectin plasma levels were assessed at baseline time and after 2 weeks, upon completation of the spa treatment period.

Baseline blood samples (6 ml) were drawn from an antecubital vein, in the supine position in the morning after an overnight fast, and again after two weeks under the same conditions. The blood was immediately centrifuged and serum was stored at -80°C.

Plasma leptin levels were determined by enzyme-linked immunosorbent assay method using ready kits of Quantikine® human Leptin Immunoassay (R&D Systems Europe, Abingdon, United Kingdom) [20].

Sensitivity of undiluted samples was 7·8 pg/ml. Inter- and intra-assay coefficients of variation were 5·4% and 3·3%, respectively.

Plasma adiponectin levels were detected by enzyme-linked immunosorbent assay method using ready kits of Quantikine® human Adiponectin Immunoassay (R&D Systems) [20]. Sensitivity of undiluted samples was 0·246 ng/ml. Inter- and intra-assay coefficients of variation were 6·9% and 4·7%, respectively.

Assessment parameters

All the patients were evaluated on a 0 to 100 mm visual analogue scale (VAS) with 0 for the absence of pain, as well as the Lequesne Index of severity of knee OA [21].

Acetaminophen consumption was calculated by the number of daily tablet intake. The NSAID consumption score was expressed as mg equivalence of diclofenac, according to a previously validated and published scale [22].

The clinical assessments were performed before and at the end of the period of spa therapy.

Statistical analysis

All the parameters of this study are expressed as mean and standard deviation (SD). For all tests, a p value less than 0.05 was considered as statistically significant.

The difference in clinical parameters (VAS, Lequesne Index, NSAID and analgesic consumption) and the plasma leptin and adiponectin levels before and after spa therapy were assessed using the Student's paired t-test.

Correlation analysis was performed using Pearson's correlation coefficient or Spearman's rank correlation coefficient

For all analyses, SAS System v. 9.0 statistical software (Carry, USA Inc.) was used.

RESULTS

The baseline recorded variables in this series of 30 OA patients treated with spa therapy are shown in Table I.

At basal time, plasma leptin levels were significantly correlated with BMI ($r=0.41$, $p<0.001$) and gender ($r=0.61$, $p<0.001$). However, no significant correlation was found between serum leptin and patient age at the time of the study ($r= 0.04$, $p=$ NS) , duration of the disease ($r= 0.07$, $p=$ NS), radiographic severity of knee OA according to Kellgren and Lawrence's score ($r=0.18$, $p=$NS), VAS score ($r=0.20$, $p=$NS) or Lequesne index ($r=0.15$, $p=$NS).

There was no correlation between the plasma adiponectin level and BMI ($r= -0.30$, $p=0.06$), gender ($r=0.04$, $p=0.82$), age ($r=0.20$, $p=0.22$), duration of the disease ($r= 0.05$, $p=$ NS), radiographic severity of knee OA ($r=0.21$, $p=$NS) or VAS score ($r=0.19$, $p=$NS). However, a significant correlation of plasma adiponectin levels with Lequesne index ($r=0.34$, $p=0.03$) was found.

After spa treatment (two weeks), we observed a statistically significant reduction ($p<0.001$), in spontaneous pain and in the Lequesne index score for gonarthrosis (Table II). This symptomatic effect was confirmed by the significant reduction of NSAID consumption.

At the end of the cycle of mud-bath therapy, serum leptin levels showed a slight, but not significant increase, while we found a significant decrease ($p<0.05$) in serum adiponectin levels (Table II). However, leptin and adiponectin concentrations after the treatment were not correlated with other clinical parameters (VAS and Lequesne index score) described in Table II (data not shown).

Finally, it should be noted that no changes whatsoever were made in terms of diet or physical activity levels, and no modifications in body weight were observed.

DISCUSSION

This preliminary report was designed to investigate the possible effect of spa therapy on plasma levels of leptin and adiponectin in OA patients treated with mud-packs and balneotherapy. Our results demonstrated only a slight, but not significant, increase in plasma leptin after 2 weeks of spa therapy with no evident correlation with parameters of clinical efficacy.

Leptin induces the expression of growth factors such as IGF-1 and TGF-β1, stimulates proteoglycan and collagen synthesis, and increases the stimulatory effects of proinflammatory cytokines on nitric oxide (NO) production in chondrocytes [23-26]. Leptin may also trigger cartilage destruction by increasing matrix metalloproteases (MMP)-9 and MMP-13 [26]. The present study shows for first time that there is no significant change in leptin concentration following a cycle of spa therapy. However, leptin concentration, measured after the treatment, did not correlate with the clinical parameters (VAS, Lequesne Index).

In our study, spa therapy produced a significant decrease ($p<0.05$) in serum adiponectin levels in patients with knee OA.

There is some evidence that adiponectin in skeletal joints may have proinflammatory effects and may be involved in cartilage degradation [4,27].

Lago et al recently demonstrated that adiponectin induced the expression of type-2 nitric oxide synthase (NOS) and stimulated IL-6, MMP-3, MMP-9 and monocyte chemoattractant protein-1 (MCP-1) release [4]. In view of these recent findings, the decrease of adiponectin after spa therapy demonstrated in our study may play a protective role in OA.

However, adiponectin presents metabolic properties as it increases insulin sensitivity, improves glucose metabolism and decreases plasma triglycerides, and has antiatherogenetic actions [28,29]. Furthermore, plasma levels of adiponectin are low in obese individuals and in those with cardiovascular disease [2,28,29]; obesity and cardiometabolic syndrome are frequently associated with OA [30]. Thus it is important to study the effects of spa therapy on certain cardiovascular risk factors.

Finally, it remains to be clarified which of the mechanisms of action of spa therapy [11-16] may have determined the changes in plasma levels of leptin and, above all, adiponectin that we observed. One possible hypothesis is that local application of heat, by causing an increase in the internal temperature of the knee, may determine a change in serum adipocytokine levels, probably due to localized production thereof [5]. Nevertheless, our study and other currently available data do not allow for specific identification of any specific mechanism of action.

In conclusion, our data show that spa therapy can modify plasma levels of the adipocytokines leptin and adiponectin, important mediators of cartilage metabolism.

Further studies on larger numbers of cases are needed to evaluate the effects of spa therapy on adipocytokines and the mechanisms with which said therapy may modify production thereof, as well as whether such modifications may have repercussions on cardiovascular risk factors.

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Table I: Baseline characteristics in 30 patients with knee OA treated with spa therapy

Variable		
Age (years) (m±SD)		69.10±7.90
Gender (M/F)		14/16
BMI (Kg/m^2) (m±SD)		26.05±5.23
Desease duration (years) (m±SD)		7.50±4.53
Radiological score	I	8
	II	12
	III	10

F = female; M =male; BMI = body mass index; OA = osteoarthritis

Table II Assessment and biochemical parameters before and after spa therapy in our cohort of patients

Measures	**T0**	**T1**
VAS (mm) (m±SD)	41.18±15.6	29.42±14.36**
Lequesne Index (m±SD)	10.13±2.95	7.68±3.14**
Leptin (ng/ml) (m±SD)	14.338.±9.725	16.320±10.788
Adiponectin (ng/ml) (m±SD)	13.715±4.566	11.215±4.068*
Drugs consumption (m±SD)		
NSAIDs +	7.13±4.87	4.29±1.60**
Acetaminophen ++	0	0

VAS= Visual Analogue Scale for spontaneous pain

+ NSAIDs = non-steroidal anti-inflammatory drugs (daily consumption as score);

++ Acetaminophen (daily consumption as tablets).

*p<0.05; **p<0.001 vs basal time