

# Insulin Stimulates IL-23 Expression in Human Adipocytes: A Possible Explanation for the Higher Prevalence of Psoriasis in Obesity

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**Purpose:** Psoriasis is a chronic systemic inflammatory disease involving the production of many pro-inflammatory cytokines derived from immune cells and interacting with different tissues leading to the typical skin lesions. Psoriasis shows a higher prevalence and a worse progression in obese than in lean subjects. The IL-23/IL-17 immune axis has a pivotal role in the pathogenesis of psoriasis and anti-IL-23 monoclonal antibodies are highly effective in its treatment. Since obesity is frequently associated with elevated insulin plasma levels, we have investigated the ability of in vitro differentiated human adipocytes to produce IL-23 at basal conditions and after insulin stimulation.

**Material and Methods:** In vitro differentiated human adipocytes were incubated in the absence and presence of different insulin concentrations and the expression of IL-23 was analyzed by real-time PCR and Western blotting.

**Results:** The results of this study show that in vitro differentiated human adipocytes spontaneously express IL-23 mRNA and protein being stimulated by insulin in a dose-dependent manner. The stimulatory effects of insulin on IL-23 expression were specific since it did not stimulate the expression of other well-known cytokines involved in psoriasis pathogenesis such as IL-22 nor IL-37. Furthermore, lipopolysaccharide did not stimulate IL-23 expression in human adipocytes, thus highlighting the specific effects of insulin in the stimulation of IL-23 expression in human adipocytes.

**Conclusion:** Here we show that human adipocytes spontaneously express IL-23 and that insulin stimulates IL-23 production by these cells in a specific manner as other stimuli, known to be involved in psoriasis pathophysiology, are ineffective. These observations could explain the association between psoriasis and obesity, a condition frequently characterized by a state of insulin hypersecretion.

**Keywords:** adipocyte, human, IL-23, insulin, obesity, psoriasis

## Introduction

Psoriasis is a chronic systemic immune-mediated inflammatory disease with a prevalence of 1–3% worldwide. Although the etiology of this disease is still not precisely known, its pathogenesis, albeit incompletely, has been clarified and in particular the role of many pro-inflammatory cytokines derived from immune cells and interacting with different tissues leading to the typical lesions affecting the skin. The interleukin-23/interleukin-17 (IL-23/IL-17) immune axis is considered to have a pivotal role in the pathogenesis of psoriasis and in line with this, IL-17- and IL-23 are highly effective targets of psoriasis therapeutic strategies.<sup>1</sup>

Psoriasis may be associated with several comorbidities such as psoriatic arthritis, mood disorders including depression, and a range of cardio-metabolic disorders that include myocardial infarction, hypertension, obesity, type 2 diabetes mellitus and non-alcoholic fatty liver disease (NAFLD).<sup>2</sup>

In particular, a significant number of cross-sectional studies have shown that psoriasis is independently associated with obesity.<sup>3–5</sup> Recently, increasing evidence from prospective studies showed that obesity precedes psoriasis occurrence, with a clear dose–response association between body mass index (BMI), waist circumference (WC), and waist-to-hip ratio (WHR), and weight gain with psoriasis risk.<sup>3</sup> Accordingly, recent Mendelian randomization studies (based on genome-wide association) identified a causal link between obesity and psoriasis in European and Japanese populations, showing that genetically higher BMI increases the odds of psoriasis occurrence.<sup>4,6</sup>

Several studies have also shown that weight loss in obese psoriatic patients improves psoriasis, with a linear dose–response association, with more weight loss being related to higher improvements in psoriasis severity.<sup>2,5,7–9</sup> Moreover, weight loss following lifestyle interventions such as diet and/or physical exercise may also prevent de novo psoriasis in obese subjects.<sup>10</sup>

While the relationship between obesity and psoriasis is well ascertained, the precise pathophysiologic link between obesity and psoriasis is not established although different explanations have been hypothesized such as pro-inflammatory mediators stemming from inflamed adipose tissue leading to systemic inflammation,<sup>11</sup> promotion of the development of Th17 cells induced by adipose tissue,<sup>12</sup> and increased leptin production by adipose tissue leading to the modulation of the immune response.<sup>13</sup> Most of these hypotheses are based on animal models or on indirect evidence derived from observational studies and compelling direct evidence of a mechanism explaining the obesity-psoriasis link in humans is missing. Since obesity is a well-known disease characterized by hyperinsulinemia,<sup>14</sup> in the present study we aimed to investigate the ability of human adipocytes to produce IL-23, one of the main cytokines involved in psoriasis pathogenesis.

Given the fact that lipopolysaccharide (LPS), a complex molecule of gram-negative bacteria cellular wall, can stimulate an inflammatory response in adipocytes<sup>15</sup> and keratinocytes,<sup>16</sup> we have compared the effects of insulin on adipocyte expression of IL-23 with those of LPS.

## Materials and Methods

### Isolation of Human Pre-Adipocytes and in vitro Differentiation to Mature Adipocytes

Subcutaneous adipose tissue (SAT) samples were obtained from five subjects (3 females and 2 males) undergoing abdominoplasty after bariatric surgery and important weight reduction and who were otherwise healthy (in particular with no history of skin nor autoimmune diseases) and not taking any drug. At the time of abdominoplasty, the patients showed a BMI of  $36.2 \pm 7.3$  kg/m<sup>2</sup>, with a percentage total body weight loss (TBWL) of  $28.5 \pm 8.8\%$ . One set of cell culture experiments was performed from each subject. The stromal vascular fraction (SVF) was isolated from SAT by collagenase type II digestion (1 mg/mL; Sigma-Aldrich, St. Louis, MO) in DMEM/F12 at 37 °C for 1 hour. Cell suspension was centrifuged ( $350 \times g$  for 8 min), and pellet containing stromal cells was resuspended in erythrocyte-lysing buffer, washed, and seeded in DMEM/F12 supplemented with 10% fetal bovine serum ( $0.7 \times 10^6$  cells per well in 24-well plates). After 16–20 hours for cell attachment, cultures were refed with a serum-free adipogenic medium containing DMEM/F12 supplemented with 33  $\mu$ M biotin, 17  $\mu$ M pantothenate, 10  $\mu$ g/mL human transferrin, 66 nM insulin, 100 nM dexamethasone, 1 nM T3, 0.25 mM 3-isobutyl-1-methylxanthine and 10  $\mu$ M rosiglitazone were supplemented for 72 hours then the medium was changed three times per week. After 12 days of differentiation, adipocytes were stimulated for 24 hours with the low and high insulin concentration (0.1 and 5  $\mu$ M insulin dissolved in saline, respectively) and lipopolysaccharide at a dose intended to mimic a low-grade inflammation (LPS, 1.0 ng/mL). Control experiments were performed adding vehicle only (saline). A complete set of five experiments (one for each patient) that were run in triplicate was performed from each patient.

### RNA Isolation

Total RNA was extracted from adipocytes after acute treatment with LPS, different concentration of insulin and vehicle using an affinity column-based method (RNEasy Kit, Qiagen GmbH, Germany) following the manufacturer's protocol. The amount of RNA recovered by eluting the column was evaluated with a spectrophotometer (DS-11 Denovix), while

the quality of the same was evaluated by a Bioanalyzer (Agilent 2100). RNA samples after extraction were placed at  $-80^{\circ}\text{C}$  for the subsequent analysis of gene expression.

## Quantitative RT-PCR

First-strand cDNAs were synthesized from 0.5  $\mu\text{g}$  of total RNA using 150 ng random primers and 200 U M-MLV reverse transcriptase (Promega Corporation, Madison, WI, USA). cDNA was used to quantify gene expression levels of specific markers of inflammation, IL-23 and LL-37; each reaction was carried out in a final volume of 20  $\mu\text{L}$  containing 10 ng cDNA, 10  $\mu\text{L}$  of SYBR select master mix (Life-Technologies), 300 nM forward and reverse primers, specific for each gene (IL23: sense – AGAGAAGAGGGAGATGAAGAGACT, antisense – TCCTTTGCAAGCAGAACTGAC; LL37: sense – CCCAGGCCACGATGGATG, antisense – CTGTCCCCATACACCGCTTC). Each reaction provided the following protocol: Taq polymerase activation ( $95^{\circ}\text{C}$  for 2 minutes) and  $45 \times (30\text{ s } 95^{\circ}\text{C}; 30\text{ s } 60^{\circ}\text{C})$ . The change in fluorescence at every cycle was monitored and a threshold cycle above background for each reaction was calculated. A melt curve analysis was performed following every run to ensure a single amplified product for every reaction. Each sample was run in duplicate, and the mean value of the duplicate was used to calculate the relative amount of individual mRNAs. Each mean value was normalized to that of the Small Subunit 18 ribosomal ribonucleic acid (18S rRNA) as housekeeping (internal consistent control gene) using the comparative the  $2^{-\Delta\Delta\text{Ct}}$  method.

## Western Blotting Analysis for IL-23 in Human Adipocytes

After 24 hours of treatment, mature adipocytes were homogenized in RIPA Lysis Buffer with phosphatase and protease inhibitors cocktail (Sigma-Aldrich, Milan, Italy) for protein analysis. Thirty  $\mu\text{g}$  proteins were separated on precast 4–12% SDS-polyacrylamide gel (NuPage Bis Tris mini Gels, Life Tech) and then transferred to a Hybond ECL nitrocellulose membrane. This was blocked with 5% (w/v) dried non-fat milk in TBS buffer with 0.1% Tween 20 and then incubated with 1:500 diluted rabbit polyclonal anti-human IL-23 (#ab45420, Abcam, Cambridge, MA) and 1:1000 diluted mouse monoclonal anti-human  $\beta$ -actin (# SAB1305546, Sigma Aldrich, Milan, Italy). For IR detection of two proteins, blots were incubated by IRDye 680RD Goat anti-rabbit IgG (#926-68071, LI-COR Biosciences GmbH, Bad Homburg, Germany) and IRDye 800CW Goat anti-mouse IgG (#926-32210 LI-COR Biosciences GmbH, Bad Homburg, Germany) for IL-23 and  $\beta$ -actin, respectively. Blots were evidenced with the Odyssey Infrared System (LI-COR Biosciences GmbH, Bad Homburg, Germany) at both 700 and 800 nm channels in a scan at 169  $\mu\text{m}$  resolution.

## Statistical Analysis

Statistical analysis was performed using GraphPad Prism software (version 9.5.1, GraphPad Software Inc., San Diego, CA, USA). Results from five separate experiments were considered and expressed as mean values  $\pm$  standard deviation (SD). Data comparisons from two samples were analyzed with the Student's "*t*-test". Comparisons of means from multiple groups were conducted by ANOVA analysis. The variables were tested for normality using the Shapiro–Wilk test. Differences between groups were considered statistically significant at P value  $<0.05$ .

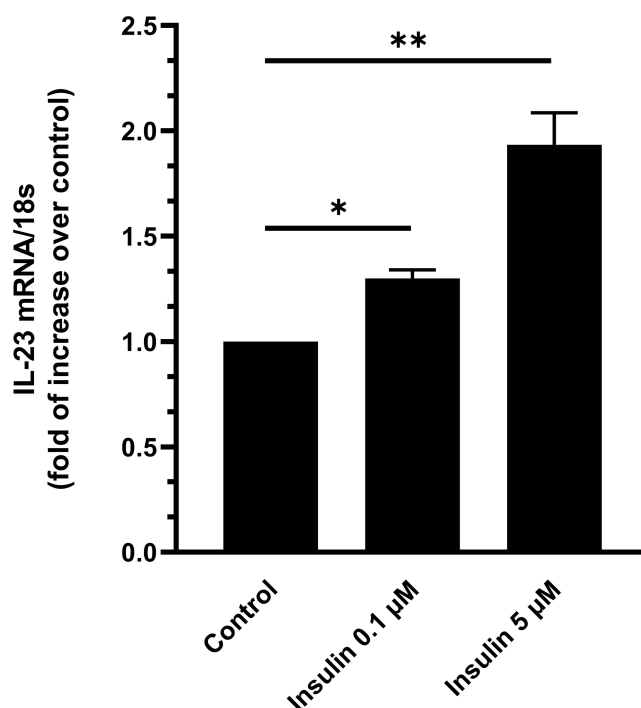
## Results

### Insulin Stimulates IL-23 mRNA Expression in Human Adipocytes

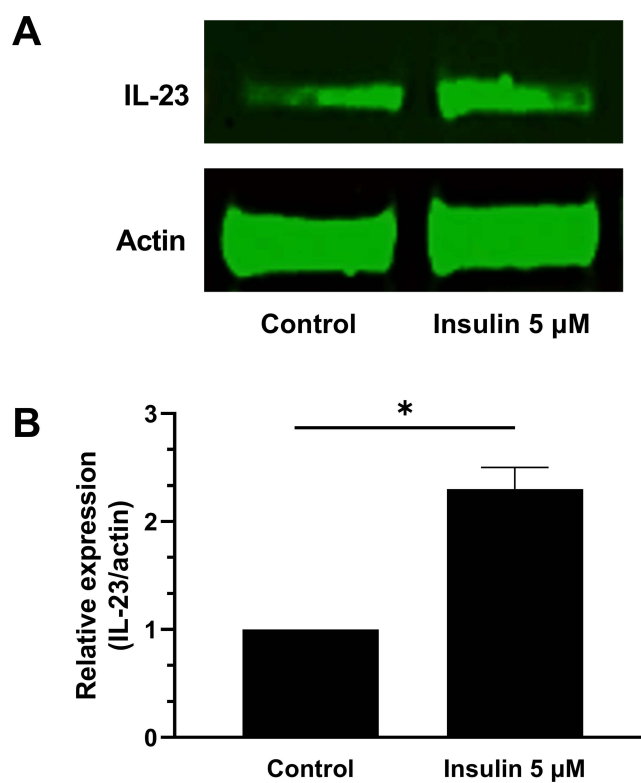
As shown in Figure 1, insulin induced a dose-dependent increase in the expression of IL-23 mRNA in human adipocytes in vitro with a 1.3- and 1.9-fold increase of IL-23 mRNA expression at 0.1 ( $P<0.05$ ) and 5  $\mu\text{M}$  ( $P<0.01$ ), respectively (Figure 1). Given the effects observed at the highest insulin concentration tested (5  $\mu\text{M}$ ), successive experiments were performed with this insulin concentration.

### Insulin Stimulates IL-23 Protein Expression in Human Adipocytes

As shown in Figure 2, insulin stimulation of human adipocytes for 2 hours induced a significant increase in the expression of IL-23 also at protein level ( $P<0.01$ , Figure 2).



**Figure 1** Dose-dependent effects of insulin on IL-23 expression in human adipocytes. In vitro differentiated human adipocytes were incubated for 24 hours with saline (control), low-dose (0.1  $\mu$ M) and high-dose (5  $\mu$ M) insulin and then PCR analysis of IL-23 mRNA expression was performed. Data are expressed as means  $\pm$  SD of five independent experiments. \* $P$ <0.05; \*\* $P$ < 0.01.



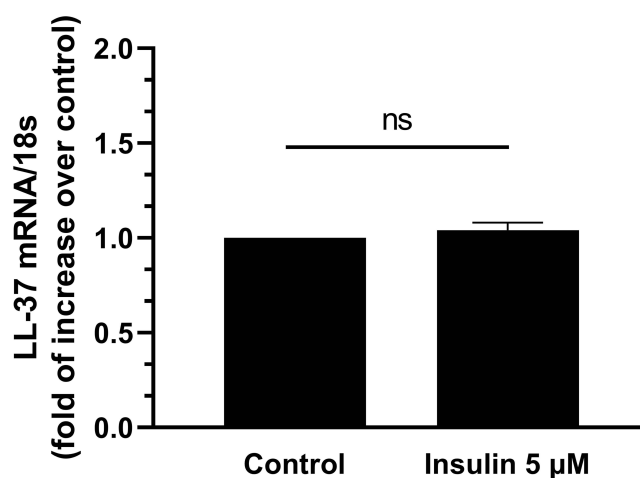
**Figure 2** Insulin upregulates the IL-23 protein expression in human adipocytes. In vitro differentiated human adipocytes were incubated for 24 hours with saline (control) and insulin (5  $\mu$ M). **(A)** Representative western blot analysis showing IL-23 protein expression. **(B)** Western blot densitometric quantification of IL-23 protein expression as normalized to  $\beta$ -actin. Control = saline. Values are expressed as mean  $\pm$ SD from five independent experiments. \* $P$ <0.01.

## Insulin Induced Expression of IL-23 in Human Adipocytes are Specific

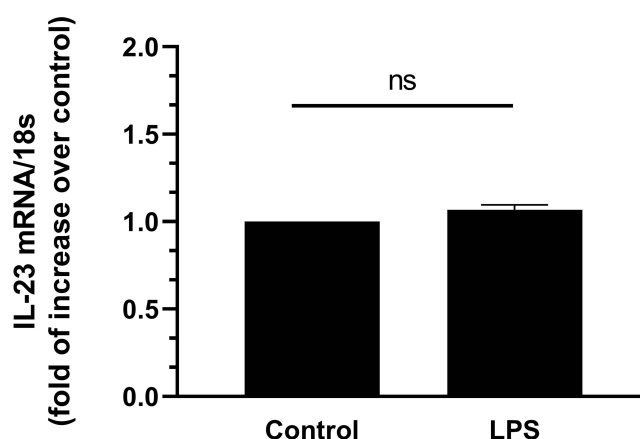
Many different cytokines have been involved in psoriasis pathogenesis. To verify that the effects of insulin were not aspecific, we evaluated the expression of another well-known cytokines involved in psoriasis such as IL-22 and Leucine–Leucine 37 (LL-37).<sup>17,18</sup> As shown in Figure 3, insulin did not stimulate the expression of LL-37, a peptide involved in skin inflammation in psoriasis.<sup>17</sup> Similarly, we did not detect any stimulatory effect of insulin on the expression of another cytokine involved in the development and pathogenesis of psoriasis such as IL-22,<sup>18</sup> that was undetectable (under the limit of detection of the technique) (data not shown).

## Lipopolysaccharide Does Not Stimulate IL-23 Expression in Human Adipocytes

Finally, lipopolysaccharide (LPS), a component of the gram-negative bacterial wall that is known to induce inflammatory cytokine secretion by adipocytes and involved in keratinocyte stimulation in psoriasis,<sup>15,16</sup> did not stimulate any increase of IL-23 expression in human adipocytes in vitro (Figure 4). All these results further suggest that the stimulatory effect of insulin on IL-23 expression by human adipocytes is selective and specific.



**Figure 3** Insulin does not stimulate LL-37 mRNA expression in human adipocytes. In vitro differentiated human adipocytes were incubated for 24 hours with saline (control) and insulin (5  $\mu$ M) and then PCR analysis of LL-37 mRNA expression was performed. Data are mean  $\pm$  SD of five independent experiments.



**Figure 4** LPS does not stimulate IL-23 mRNA expression in human adipocytes. In vitro differentiated human adipocytes were incubated for 24 hours with saline (control) and LPS (1 ng/mL) and then PCR analysis of IL-23 mRNA expression was performed. Data are expressed as mean  $\pm$  SD of five independent experiments.

## Discussion

In this study we showed that insulin directly stimulates an increase of IL-23 expression in human adipocytes. IL-23, belonging to the IL-12 cytokine family, together with IL-12, IL-27 and IL-35, is a heterodimeric cytokine composed of the unique p19 subunit linked with the p40 subunit, which is in common with IL-12.<sup>19</sup>

IL-23 is produced by Langerhans cells,<sup>20</sup> dendritic cells,<sup>21</sup> and monocytes/macrophages (ie, antigen-presenting cells),<sup>22</sup> in response to an inflammatory or biochemical insult, specifically at barrier sites such as the skin, gut and entheses. Moreover, keratinocytes are a skin-specific source of IL-23,<sup>23</sup> and very recently it has been demonstrated that also ex-vivo human subcutaneous adipose tissue expresses IL-23.<sup>24</sup>

The present study provides the first evidence that insulin stimulates IL-23 in in vitro differentiated human adipocytes derived from subcutaneous adipose tissue. Intriguingly, these cells were fully differentiated adipocytes and did not require the presence of dendritic cells or other cell types to produce IL-23.

Previous studies reported that in obese women and in patients with metabolic syndrome IL-23 plasma levels were higher than in lean controls.<sup>25,26</sup> Our finding could potentially help to explain the association between psoriasis and obesity, a condition characterized by quite elevated insulin plasma levels, with adipocytes directly producing IL-23, which could contribute to the higher plasma levels observed in obese subjects and then to the development of psoriatic plaques and possibly of other conditions such as psoriatic arthritis (PsoA). Noticeably, if subcutaneous adipose tissue is able to secrete IL-23, its local cutaneous concentrations in obese subjects could be several orders higher than those after dilution within blood. Indeed, obesity is a well-known risk factor for the development of psoriasis in the general population.<sup>3–5,27,28</sup> Furthermore, several prospective studies showed that BMI is associated with an increased risk of PsoA development,<sup>29</sup> and a higher PsoA severity.<sup>30</sup> In particular, the development of enthesitis, which is arguably the primary lesion of PsoA and is pathogenetically related to IL-23, has been shown to be strongly associated with a higher BMI.<sup>31</sup>

The role of fat accumulation in psoriasis manifestations is further supported by different retrospective and prospective studies and by many meta-analyses showing that weight loss in patients suffering from psoriasis lowered the activity of the disease, even without an active treatment for psoriasis.<sup>2,5–9,32–34</sup> Moreover, obesity in psoriatic patients may be a predictor of lower response to antitumor necrosis factor $\alpha$  (TNF $\alpha$ ) agents and biologic treatment discontinuation.<sup>35,36</sup> Accordingly, weight loss is associated with a better response to treatment with systemic therapies.<sup>37</sup>

Heretofore, several hypotheses have been proposed to explain the association between obesity and psoriasis,<sup>11</sup> although not completely clear.

The ability of subcutaneous adipocytes to directly produce IL-23 without the need of an interaction with immune cells may represent the molecular basis of the dangerous liaison between fat tissue and psoriasis. On the other hand, the role of locally produced IL-23 in promoting in situ proliferation of skin Th17 cells has been recently demonstrated, thus confirming the therapeutic efficacy of IL-23 blockade in the treatment of psoriasis.<sup>38</sup>

Intriguingly, IL-23 production was stimulated by insulin. Obesity is frequently characterized by elevated insulin plasma levels.<sup>39</sup> Therefore, we can speculate that hyperinsulinemia in obese patients may be able to directly enhance the inflammatory pathway characterizing psoriasis via the secretion of IL-23 directly from adipocytes. To this respect, Wu et al reported that diabetic subjects are at risk to develop first-time psoriasis and that the frequent use of insulin is associated with a dose-dependent increase in the risk of psoriasis.<sup>40</sup> On the contrary, the use of oral antidiabetic drugs, such as metformin and thiazolidinediones, synthetic ligands for the peroxisome proliferator-activated receptor- $\gamma$  (PPAR $\gamma$ ) receptor is associated with a lower risk to develop psoriasis, in particular if those diabetic subjects had never used insulin.<sup>41,42</sup> However, these studies do not exclude the fact that the insulin dose-dependent increase in psoriasis may be due to a common inflammatory pathway between diabetes and psoriasis instead of a direct action of insulin per se on the effector cells involved in immune response in psoriasis. In support of the latter hypothesis, it has been reported that insulin exacerbates psoriasis in diabetic patients,<sup>43</sup> and induction of new psoriasis plaques at insulin injection site has been described.<sup>44</sup> Furthermore, it has been reported that psoriasis may worsen after the development of insulinoma.<sup>45</sup>

The link between insulin and psoriasis induction or exacerbation has not been precisely clarified yet although it has been suggested an involvement of the well-known mitogenic effects of insulin via its receptor or via the activation of the insulin-like growth 1 factor receptor, thus promoting keratinocyte proliferation.<sup>46</sup>

The demonstration of direct effects of insulin on IL-23 secretion by human adipocytes might open new avenues to tailor and improve the treatment of obese subjects with psoriasis pointing primarily to body weight reduction as the first strategy to improve the clinical results of psoriasis treatment protocols. A limitation of the present study could be that this is an in vitro study which results should be transferred to the patients, thus to definitely demonstrate that hyperinsulinemia represents the link between psoriasis and obesity.

## Conclusion

In conclusion, the demonstration that insulin stimulates IL-23 expression in human adipocytes might be potentially important to unveil the complex relationship between obesity and psoriasis. In fact, since adipose tissues is well represented within the skin dermis, our observations suggest that these dermal adipocytes might possibly participate in the pathogenesis of psoriatic plaques, particularly in subjects with obesity, a condition frequently characterized by elevated insulin plasma levels.

## Data Sharing Statement

The raw data supporting the conclusions of this article will be made available by the corresponding author upon justified request, without undue reservation.

## Ethical Approval

The study was conducted according to the guidelines of the Declaration of Helsinki and approved by the Ethics Committee of the University Hospital of Padova (approval n. RF-2016-02363566). Informed consent was obtained from all subjects involved in the study.

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## Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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## Disclosure

The authors report no conflicts of interest in this work.

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