Molecular Biology

Inflammation increases MMP levels via PGE2 in human vascular wall and plasma of obese women

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Abstract

Background and objectives: Matrix metalloproteinases (MMPs) are involved in several inflammatory processes including obesity-related vascular diseases and graft failure of coronary artery (CA) bypass grafts [internal mammary artery (IMA), saphenous vein (SV)]. In these inflammatory conditions, the release of prostaglandin E2 (PGE2) is increased via the activity of inducible microsomal PGE synthase-1 (mPGES-1). Our aim was to investigate whether MMPs and their endogenous inhibitor (TIMPs) may be regulated by PGE2 under inflammatory conditions in human vasculature and perivascular adipose tissue (PVAT), as well as in plasma of obese patients.

Methods: MMP-1,-2 and TIMP-1,-2 densities were measured in human plasma (n = 68) as well as in supernatants of human vascular wall (IMA n = 16, SV n = 14, CA n = 13) and their PVAT. The effects of inflammation and mPGES-1 inhibitor (Compound III, 10 µM) on MMPs regulation were evaluated. The correlations between PGE2 and several parameters were calculated in plasma from patients with or without obesity.

Results: The vascular wall and PVAT from SV exhibited the greatest MMP-1,-2 release. An increase of MMP-1,-2 and/or a decrease of TIMP-1 quantities have been detected under inflammation only in vascular wall not in PVAT. These changes under inflammation were completely reversed by inhibition of mPGES-1. In obesity, C-reactive protein (CRP), biomarker of inflammation, and PGE2 levels were increased. PGE2 contents were positively correlated with some anthropometric parameters and plasmatic CRP in both genders, while the correlation with the plasmatic MMP-1 density was significant only in women.

Conclusions: The greater MMP activity observed in SV may contribute to the increased prevalence of graft failure. Under inflammation, the greater mPGES-1 and PGE2 levels lead to enhanced MMP activity in human vascular walls. The positive association between PGE2 and MMP-1 or CRP has been observed in plasma of women. We suggest that mPGES-1 inhibitors could prevent graft failure and obesity-related vascular remodeling mostly in women.

Introduction

Among prostanoids, prostaglandin (PG) E2 is involved in the control of vascular tone, remodeling, and inflammation. PGE2 is synthesized from arachidonic acid through cyclooxygenases (COXs) and three PGE synthases [1]. When human vascular cells are exposed to inflammatory cytokines such as interleukin-1β (IL-1β) and/or lipopolysaccharide (LPS), COX-2, and microsomal PGE synthase-1 (mPGES-1) are co-induced and thereby the release of PGE2 is strongly (tenfold) increased [2–5].

In many vascular diseases, such as atherosclerosis, aneurysm, or varicose veins, PGE2 regulates vascular remodeling through the regulation of matrix metalloproteinase (MMP) activity [6–8]. MMP activity is under the
control of tissue inhibitors of MMPs (TIMPs). MMP is involved in many physiological and pathological processes through degradation of extracellular matrix proteins. Studies performed on human vascular preparations have demonstrated that smooth muscle cells constitutively express MMP-2, TIMP-1, and TIMP-2, whereas endothelial cells express MMP-1, MMP-2, TIMP-1, and TIMP-2 [9]. Furthermore, some types of MMPs such as MMP-1, -2, -3, and -9 could be induced after inflammatory stimuli in human vascular cells probably via nuclear factor-kB [9, 10, 11–13].

Several studies indicated that human blood vessels such as internal mammary artery (IMA) and saphenous vein (SV) produced both MMPs and PGE2 [14–16]. These vessels are used as a graft material to bypass stenosed coronary arteries (CA) in CA bypass surgery. Our recent study demonstrated that mPGES-1 expression and PGE2 release were greater in SV than in IMA. Furthermore, inflammatory stimuli increased both mPGES-1 and PGE2 levels in these vessels [17]. On the other hand, several studies showed that MMP-2 levels were greater in SV than in IMA [14, 18]. However, the contribution of PGE2 on MMP release under inflammatory conditions has not been thoroughly evaluated in these human vessels.

The graft materials, SV and IMA, are surrounded by perivascular adipose tissue (PVAT), which is also able to synthesize PGE2 and MMPs [15, 19]. In humans, the quantity of PVAT strongly correlated with obesity, anthropometric measures including waist circumference (WC), body weight, and body mass index (BMI) [20]. In addition, when the patients divided according to quartiles based on increasing peri-aortic adipose tissue, a gradual increase in the estimated cardiovascular risks and more severe systemic inflammation in terms of higher C-reactive protein (CRP) level were observed [20]. In fact, several studies demonstrated that inflammation observed in PVAT could contribute to vascular inflammation in obesity, which is defined as a low-grade inflammatory disease [19, 21–23]. One recent study emphasized the impairment of beneficial effects of PVAT in obese patients. Furthermore, loss in weight in these patients contributes to reduction of pro-inflammatory mediators released from PVAT, a decrease in macrophage number and restoration of PVAT beneficial effect on vascular tone [24]. In line with human studies, animal models of obesity revealed the increased PVAT mass and adipocytes size, and also greater release of pro-inflammatory cytokines have been observed [25, 26]. In subjects with cardiovascular diseases or undergoing bypass surgery, increased CRP, PGE2, and MMP plasma levels have been well established [27–33]. However, in the plasma of obese patients where PVAT produces more pro-inflammatory cytokines [23, 34], the association between these inflammation-induced mediators has not yet been studied.

The aim of the study was to investigate whether MMPs and TIMPs may be regulated by PGE2 under inflammatory conditions related to obesity. This regulation was determined both in vitro with human vessels and their PVAT and in vivo with plasma from obese patients.

Methods

Human vascular preparations

The study was performed on isolated segments of human IMA (n = 16, 12 males and 4 females aged 73 ± 3 years) and SV (n = 14, 9 males and 5 females aged 65 ± 5 years), and their isolated PVAT obtained from patients who had undergone CA bypass surgery. Moreover, CA and their isolated PVAT (n = 13, 10 males and 3 females aged 46 ± 7 years) were obtained after cardiac transplantation from the patients with non-occlusive cardiomyopathy. Vascular preparations used in this study were macroscopically without atherosclerotic lesions of fatty streaks. The Ethics Committee of INSERM (the French National Institute for Health and Medical Research) approved the study plan (approval number: 11–101). These tissues are considered as surgical waste in accordance with French ethical laws (L.1211-3-L.1211-9). All experiments with human subjects were performed in accordance with the Declaration of Helsinki.

Organ cultures

The IMA, SV, and CA were dissected free from PVAT, cut into rings of 2–4 mm width. “Control condition” indicates that the preparations presented few or no inflammatory markers [35–37], these vessels and their isolated PVAT were placed immediately into 12-well plates containing RPMI supplemented with PSA (penicillin 1000 IU/ml, streptomycin 100 µg/ml, amphotericin 0.25 µg/ml). In addition to RPMI and PSA, some vessels and their isolated PVAT were incubated with both IL-1β (100 ng/ml) and LPS (100 µg/ml) [3, 17, 38]. Both inflammatory agents were suspended in RPMI supplemented with PSA and this condition corresponds to “Inflammation.” Some preparations were incubated in the presence of mPGES-1 inhibitor (compound III, C3, 10 µM, [39]) under inflammatory condition and named as “Inflammation + mPGES-1 inhibitor.” The volume of the culture medium was adjusted to 1 ml for 70 mg of tissue. All tissue incubations were performed at 37 °C in a humidified atmosphere of 5% CO2 in air using a culture incubator [17]. After 24 h incubation, supernatants were kept at −80 °C for MMPs and TIMPs measurements.
Human plasma samples

In the present study, we recruited 68 randomly selected subjects, included 21 non-obese (healthy lean) subjects with BMI between 18.5 and 25 kg/m² and 47 obese subjects with BMI ≥ 30 kg/m². Patients characteristics are presented in Table S1. All participants gave written informed consent and the study was approved by Farhat Hached Hospital Ethics Committee for research on humans (approval number: 11–2011). Information on each participant’s life style and health status was obtained through an interview, including questions regarding smoking history, prescription medicines for diseases such as dyslipidemia, arterial hypertension, or cardiovascular diseases. Subjects with a history of cardiovascular disease, liver, renal, or thyroid disease, smoking habit, malignancy, diseases responsible for microvasculopathy, and subjects using medications that might affect lipid and glucose metabolism or alter the endothelial or smooth muscle dependent responses were excluded from the study. Other exclusion criteria were women in the menstrual cycle and pregnant women.

Anthropometric measurements and biochemical analyses in human plasma

Participants were first examined anthropometrically. Height (m) and weight (kg) were taken with participants dressed in light weight clothing without shoes and BMI was calculated (kg/m²). The WC was measured at the midpoint between the lower rib margin and the crest of the ileum in a horizontal plane at standing position (cm) and hip circumference was measured by placing a tape measure around the patient's hip at the level of the prominences over the greater trochanters of both femurs (cm). After we calculated waist-to-hip ratio (WHR) and waist-to-height ratio (WHtR). Blood samples were collected from subjects in tubes after 12 h overnight fast, the blood was maintained at 4 °C then centrifuged (4000 × g for 10 min). Plasma was distributed in aliquots and stored at −80 °C until the batched measurements of parameters. Total cholesterol and triglycerides were determined by the cholesterol oxidase and the glycerol oxidase methods (Elitech Diagnostic, France). High-density lipoprotein cholesterol was measured by the Friedwald formula. Apolipoprotein A1, ApoB and high-sensitivity CRP were also measured. All biochemical parameters were determined on an automated Synchron CX7 Clinical System (Beckman, Fullerton, CA).

Enzyme-linked immunosorbent assays

MMP-1, MMP-2, MMP-3, MMP-9, TIMP-1, and TIMP-2 levels in plasma or supernatants of human vessels and PVAT were determined by enzyme-linked immunosorbent assays (ELISA) using commercially available kits according to the manufacturer’s instructions. The concentration of PGE2 was measured in plasma using an EIA kit according to the manufacturer’s instructions. The PGE2, MMPs, and TIMPs concentrations were expressed as ng/ml of plasma or ng/mg of wet weight tissue. Technical replicates were used to ensure the reliability of single values.

Statistical analysis

All results obtained from different patients (n) were expressed as a mean ± SEM. Depending on data distribution (normal or non-normal), statistical analysis was performed by Mann–Whitney rank sum test, Student’s t-test (paired data derived from the same patient or unpaired), one-way analysis of variance with Bonferroni’s correction for multiple comparisons post hoc tests, and Pearson’s or Spearman’s correlations analysis were performed. P-value < 0.05 indicates that data are significantly different. Statistical analyses were performed using GraphPad Prism (Version 7, La Jolla California, USA).

Drugs and materials

The protease inhibitor cocktail, IL-1β, LPS, antibiotics, and antifungal were purchased from Sigma-Aldrich (St. Louis, MO, USA). PGE2 EIA kit was obtained from Cayman Chemical (Ann Arbor, MI, USA). Human MMP-1 (DY901), human MMP-2 (DY902), human MMP-3 (DY513), human MMP-9 (DY911), human TIMP-1 (DY970), and human TIMP-2 (DY971) were from R&D Systems (Duoset ELISA). RPMI was obtained from Gibco Invitrogen (Paisley, UK). C3 [Compound III; [1-(1-isopropyl -5,6 -dimethyl-1H- benzimidazol-2-yl)-piperidine-4-carboxylic acid cyclopentylamide] was a generous gift from NovaSAID AB and Dr. Per-Johan Jakobsson (Karolinska Institutet, Stockholm, Sweden).

Results

The effect of inflammation on the release of MMP and TIMP in vascular preparations

The MMP-1 and MMP-2 levels were significantly increased under inflammatory conditions in IMA, SV, and CA, whereas TIMP-1 content was lower in IMA and CA.
On the other hand, TIMP-2 levels remain unchanged under inflammation (Fig. 1d). The release of MMP-1 and MMP-2 from SV was greater vs. IMA and CA, respectively (Fig. 1a, b). The levels of TIMP-1 were significantly higher in CA vs. other vessels, whereas TIMP-2 levels were lower in CA as compared with SV (Fig. 1c, d).

The effect of mPGES-1 inhibitor on the release of MMP and TIMP in vascular preparations

The increased levels of MMP-1 and MMP-2 observed under inflammatory conditions were reversed by an mPGES-1 inhibitor (C3, 10 µM) (Fig. 1a, b). On the other hand, the decreased levels of TIMP-1 under inflammation, as well as TIMP-2 levels were restored in the presence of mPGES-1 inhibitor in CA (Fig. 1c, d).

The role of obesity on CRP, PGE$_2$, MMP-1, and MMP-9 levels in human plasma

CRP and PGE$_2$ levels were significantly increased in human plasma from obese patients (BMI $\geq$ 30 kg/m$^2$) vs. non-obese group (BMI between 18.5 and 25 kg/m$^2$) in both women and men (Fig. 3a, b). MMP-1 and MMP-9 contents were increased only in human plasma from obese women patients vs. non-obese women, whereas it was not modified in obese men patients (Fig. 3c, d).

The correlations between PGE$_2$ levels and MMP or CRP levels in human plasma

PGE$_2$ levels were significantly positively correlated with CRP levels in both men and women (Fig. 4a, b). Furthermore, there was also a positive correlation between MMP-1 levels and PGE$_2$ or CRP levels only in women but not in men (Fig. 4c–f). Moreover, PGE$_2$ contents were also measured in the supernatants of organ culture after 24 h incubation. The release of MMP and TIMP was expressed as ng/mg of wet weight tissue. *P < 0.05 indicates significantly different. Values are means ± SEM derived from [n values: 3–16 (IMA), 3–14 (SV), 3–13 (CA)] different patients.

Fig. 1 The effects of inflammation and microsomal prostaglandin E synthase-1 (mPGES-1) inhibitor (C3, 10 µM) on the release of matrix metalloproteinases (MMP-1, -2) and tissue inhibitors of MMP (TIMP-1, -2) from internal mammary artery (IMA), saphenous vein (SV), and coronary artery (CA). The productions of MMP and TIMP were measured in the supernatants of organ culture after 24 h incubation. The release of MMP and TIMP was expressed as ng/mg of wet weight tissue. *P < 0.05 indicates significantly different. Values are means ± SEM derived from [n values: 3–16 (IMA), 3–14 (SV), 3–13 (CA)] different patients.
correlated with TIMP-1 levels in women (Table 1). On the other hand, there was no significant correlation between PGE2 and MMP-2, MMP-3, MMP-9, or TIMP-2 in both genders (Table 1).

The correlations between PGE2 levels and anthropometric parameters in human plasma

A positive correlation was found between PGE2 levels and WHR values in human plasma independently of gender status. Moreover, in men, PGE2 levels were positively correlated with all anthropometric parameters (BMI, WHtR, WHR, and WC) (Table 2).

Discussion

Increased MMP activity is involved in vascular remodeling observed in several inflammatory processes [9, 10, 12] such as CA bypass graft failure or obesity-related vascular diseases. In the present work, we studied in vitro vascular inflammation with graft materials (IMA, SV) and CA, as well as in vivo inflammation with plasma of obese patients. Our results showed that PGE2 increases MMP levels via mPGES-1 enzyme under inflammation. Our study suggests that mPGES-1 inhibitor could be a novel approach to decrease inflammation-induced MMP activity for prevention of obesity-related diseases and graft failure.

In control conditions, we have demonstrated that higher MMP-1 and MMP-2 contents were released from SV vs. IMA and CA, respectively (Figs. 1a, b). In accordance with our results, several studies showed greater MMP levels in SV vs. IMA [14, 18]. Regulation of MMP activity is one of the key events in the development of intimal hyperplasia, which could be the reason of graft failure after bypass surgery [16]. The greater MMP levels observed in SV vs. IMA (Fig. 1a, b) could be responsible for the increased prevalence of SV graft failure through intimal hyperplasia [40, 41]. In addition, intra- and postoperatively, the bypass grafts are exposed to inflammatory conditions, graft failure could become more obvious because of increased MMP levels in this condition (Fig. 1a, b).

In our previous studies [15, 17], we have measured and compared PGE2 levels in IMA, SV, and CA in both control and inflammatory conditions. Inflammation significantly increased PGE2 levels via inducible mPGES-1 enzyme in these vessels. SV produced approximately fivefold more PGE2 amount when compared with IMA either from their...
vascular wall or their respective PVAT [15, 17]. This difference was even more obvious when these vascular preparations were submitted to inflammatory conditions [2, 17]. As in the cases of MMP levels, IMA released similar amount of PGE2 as CA and when CA derived from atherosclerotic patients they had a greater capacity to synthesize PGE2 in comparison with patients without atherosclerosis [35].

Under inflammatory conditions, both PGE2 and MMP-1,-2 releases were positively associated in human vessels [17] (Fig. 1a, b). This association has been reported in vascular preparations derived from patients (atherosclerosis, aneurysm), in vascular models of inflammation [7, 8, 42]. In non-pathological conditions, this association has also been detected. In SV without inflammation, the MMP-1/(TIMP-1 or TIMP-2) ratio was significantly decreased in the presence of a selective PGE2 receptor antagonist (GW62768X) [6, 7]. Our results presented in Fig. 1 demonstrate that the upregulation of MMP-1/2 by endogenous PGE2 is also detectable in IMA and CA. Unlike other studies, here we demonstrated that the regulatory role of endogenous PGE2 on MMP synthesis is supported by the use of a selective inhibitor of mPGES-1 (C3, 10 µM). C3 reversed the inflammation-increased MMP levels in these three different human vessels (Fig. 1).

Measuring only MMPs levels is not considered sufficient to interpret MMP activity, as MMP activity is mostly determined as a ratio between MMPs and their endogenous inhibitors, TIMPs [43]. Therefore, we also quantified TIMPs levels in this study. Our results indicated that TIMP-1 was downregulated by inflammation in both IMA and CA (Fig. 1c). When we calculated our results as an MMP-1/TIMP-1 or MMP-2/TIMP-2 ratio (data not shown), we observed that in vitro inflammation induced more pronounced enhancement in IMA and CA vs. SV. That could be explained by the lower increase in PGE2 production under inflammation by SV (1.3-fold) as compared with IMA (2-fold) and CA [17].

Several lines of evidence suggest that PVAT may contribute to improve graft patency whereas this beneficial effect may be lost in obese patients where PVAT released more pro-inflammatory cytokines [24, 25, 44–46]. For this reason, we have also measured and compared MMP activity between vascular wall and PVAT for each vessel both in control and inflammatory conditions. When we calculated our results as an MMP-1/TIMP-1 or MMP-2/TIMP-2 ratio, we found that these ratios were greater in PVAT than in vascular wall of the corresponding vessel (4–12-fold for MMP-1/TIMP-1 ratio; 2–4-fold for MMP-2/TIMP-2 ratio). These results suggested that not only vascular wall but also

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**Fig. 3** The CRP (C-reactive protein), PGE2 (prostaglandin E2), MMP-1 (matrix metalloproteinase-1), and MMP-9 levels in human plasma of non-obese (BMI between 18.5 and 25 kg/m²) or obese patients (BMI ≥ 30 kg/m²). *P < 0.05 indicates significantly different. Values are means ± SEM derived from different patients (n = 39 for men, n = 24 for women)
PVAT could provide MMPs and contribute to the vascular remodeling. Furthermore, greater MMP contents shown in vascular wall of SV vs. other vessels have been also detected in PVAT from SV vs. PVAT from other vessels (Figs. 1a, b, 2a, b).

Our in vitro results demonstrate that, in contrast to the MMP levels observed in the vascular wall (Fig. 1a, b), those in PVAT (Fig. 2a–d) were not enhanced under inflammatory conditions. In line with our results, in human adipocytes incubation with LPS did not modify MMP-2 levels [47]. However, in some rodent PVAT, inflammation was responsible for increased MMP-2/-9 levels [48, 49]. It is possible that these results could be due to a different regulation of MMPs between vascular wall and PVAT, as well as different species used in these studies.

Obesity is defined as a low-grade inflammatory disease [23], which is supported by increased CRP measurement, marker of inflammation [50], in plasma of obese patients (Fig. 3a). In these samples, we have investigated the interactions among inflammatory mediators (CRP, PGE\textsubscript{2}, and MMP). There was an upregulation of PGE\textsubscript{2} levels in plasma of obese patients (Fig. 3b) as well as in omental adipose tissue.
tissue [51] derived from obese vs. healthy patients. Moreover, in rodent obese models, the release of PGE2 in plasma or adipose tissue was usually greater than in the control group [52–55].

In our study, plasma PGE2 was positively correlated with some markers, such as CRP levels and anthropometric parameters such as BMI, WHR, WC, and WHtR (Fig. 4a, b, Table 2). In addition to PGE2, MMP-1 and MMP-9 levels were also increased in plasma of obese women (Fig. 3a, b, and Table 1) and there was a positive correlation between PGE2 and MMP-1 or TIMP-1 levels in women but not in men (Fig. 4c–f, Table 1). Taken together, these results (Fig. 4, Tables 1 and 2) showed that more pronounced correlations were found in women between MMP-1 and PGE2, while CRP release was higher in men. Even though MMP-9 has an important role in cardiovascular disease and obesity [56], there was no correlation between PGE2 and MMP-9 levels (Table 1). This result suggests that MMP-9 levels were not controlled by PGE2 in obese and non-obese patients, whereas it was the case in acute coronary syndrome [57].

In literature, several studies showed a gender difference in the regulation of MMPs [58, 59]. In accordance with our results, increased MMP-1 and MMP-9 levels have been shown in obese vs. normal-weight women, whereas in a mixed-gender study no difference of pro-MMP-1 contents was observed in obesity [56, 60–62]. Sex hormones could participate in MMP regulation in obesity, several studies emphasized a strong involvement of estrogen in adipose tissue metabolism and accumulation [63, 64]. In premenopausal women, estrogen levels and estrogen receptor-alpha quantities were significantly reduced in obesity [65, 66]. In vitro studies exhibited that estrogens significantly decrease MMP-1 levels in many human cells [67, 68]. These data with our results (Fig. 3c, Fig. 4d, f, and Table 1) suggest that reduced levels of estrogens could account for the elevated levels of MMP-1 measured in our premenopausal obese women. Therefore, with mPGES-1 inhibitor either for obesity-related vascular remodeling or prevention of graft failure could mediate more effective results in women. Furthermore, therapeutic approaches might be more urgent in women than in men since several studies exhibited a greater postoperative mortality and morbidity in women compared with men undergoing CA bypass surgery [69–72]. In addition to MMP, variants of mPGES-1 gene and their association with disease severity demonstrated sexual difference [73].

In conclusion, our previous and present study show that the induction of mPGES-1 enzyme and consequently elevated PGE2 release under inflammation lead to increased MMP activity in human bypass grafts (IMA, SV) and CA. This positive association between PGE2 and MMP-1 is confirmed by their correlation determined in plasma of obese women probably through the regulatory role of estrogen. In addition, we have compared MMP levels between bypass grafts and CA. The greater MMP activity observed in SV may contribute to the increased prevalence of graft failure in SV vs. IMA following bypass surgery. Finally, our results suggest that mPGES-1 inhibitor could be a promising drug for prevention of graft failure and obesity-related vascular remodeling by decreasing inflammation-induced MMPs releases mostly in women.

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Compliance with ethical standards

Conflict of interest PJJ is a member of the board of Gensynta Pharma AB. All other authors declare that they have no conflicts of interest.

Table 1 The correlations between prostaglandin E2 (PGE2) and matrix metalloproteinases (MMP) or tissue inhibitors of matrix metalloproteinase (TIMP) in human plasma

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<th>Men</th>
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<td>$r^2$</td>
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<td>$r^2$</td>
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<tr>
<td>MMP-1</td>
<td>$&lt;10^{-2}$</td>
<td>0.95</td>
<td>0.55</td>
<td>$&lt;10^{-3}$*</td>
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<tr>
<td>MMP-2</td>
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<td>0.11</td>
<td>0.12</td>
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<tr>
<td>MMP-3</td>
<td>0.06</td>
<td>0.17</td>
<td>0.04</td>
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<tr>
<td>MMP-9</td>
<td>0.09</td>
<td>0.08</td>
<td>0.01</td>
<td>0.69</td>
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<tr>
<td>TIMP-1</td>
<td>0.02</td>
<td>0.42</td>
<td>0.36</td>
<td>0.002*</td>
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<tr>
<td>TIMP-2</td>
<td>0.01</td>
<td>0.66</td>
<td>0.04</td>
<td>0.36</td>
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* $p<0.05$, significantly different; Spearman’s or Pearson’s analysis. Data are derived from $n=31–34$ for men, $n=23–24$ for women.

Table 2 The correlations between prostaglandin E2 (PGE2) and anthropometric parameters in human plasma

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<tr>
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<td>WC</td>
<td>0.23</td>
<td>0.006*</td>
<td>0.14</td>
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BMI body mass index, WC waist circumference, WHR waist-to-hip ratio, WHtR waist-to-height ratio *$p<0.05$, significantly different; Spearman’s or Pearson’s analysis. Data are derived from $n=30–34$ for men, $n=21–24$ for women.
Inflammation increases MMP levels via PGE2 in human vascular wall and plasma of...
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