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Minireview

Molecules and Cells

Bioactive Eicosanoids: Role of Prostaglandin $F_{2\alpha}$ and F_2-Isoprostanes in Inflammation and Oxidative Stress Related Pathology

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Oxidative stress and inflammation are supposed to be the key players of several acute and chronic diseases, and also for progressive aging process. Eicosanoids, especially prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$) and F_2-isoprostanes are endogenous compounds that are involved both in physiology and the above mentioned pathologies. These compounds are biosynthesized mainly from esterified arachidonic acid through both enzymatic and non-enzymatic free radical-catalysed reactions *in vivo,* respectively. They have shown to possess potent biological activities in addition to their application as biomarkers of oxidative stress and inflammation. Recent advancement of methodologies has made it possible to quantify these compounds more reliably and apply them in various *in vivo* studies successfully. Today, experimental and clinical studies have revealed that both $PGF_{2\alpha}$ and F_2-isoprostanes are involved in severe acute or chronic inflammatory conditions such as rheumatic diseases, asthma, risk factors of atherosclerosis, diabetes, ischemia-reperfusion, septic shock and many others. These evidences promote that assessment of bioactive $PGF_{2\alpha}$ and F_2-isoprostanes simultaneously in body fluids offers unique non-invasive analytical opportunity to study the function of these eicosanoids in physiology, oxidative stress-related and inflammatory diseases, and also in the determination of potency of various radical scavengers, anti-inflammatory compounds, drugs, antioxidants and diet.

INTRODUCTION

Eicosanoids have been concerned in a vast number of inflammatory circumstances, including pain, arthritis, asthma, risk factors of atherosclerosis and cancer. Since the discovery in 1960s a huge number of different eicosanoids have been identified during the years, with several of them having potent bioactive signaling ability that are obligatory in both physiology and pathophysiology (Basu, 2007; Buczynski et al., 2010). Eicosanoid (*eicosa- means twenty in Greek)* is the mutual expression for oxygenated derivatives of three different 20-carbon essential polyunsaturated fatty acid namely, dihomo-gamma-linolenic acid, an omega-6 fatty acid with 3 double bonds, arachidonic acid, an omega-6 fatty acid with 4 double bonds and eico-sapentanoic acid, an omega-3 fatty acids with 5 double bonds. Many of the downstream products of these fatty acids are bioactive compounds, and control many of our physiological functions keeping our homeostasis, and in addition, several of them are also involved in inflammation and immunity, that relates to pathology of various diseases. They also act fundamentally as signaling molecules of variety of cellular biochemical cascades including free radicals. The classical eicosanoids are prosta-glandins, thromboxanes, prostacyclins and leukotrienes. Conversely, recent inclusion of several other classes of eicosanoids including those that are formed non-enzymatically are to be mentioned. These extended family of eicosanoids that are formed through various pathways are namely lipoxins, resolvins, epoxy eicosatrienoic acids, isoprostanes and isofurans etc. The conventional eicosanoids are released through phospholipases A_2 from membrane phospholipids in response to a variety of cellular stimuli whereas the some other eicosanoids that are formed through non-enzymatic reactions are generally formed from esterified arachidonic acid as esterified products, such as isoprostanes.

This review will specifically emphasize recent advancements of two key eicosanoids, e.g. the prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$) and F_2-isoprostanes that are biosynthesized by cyclooxygenases and through free radicals, the two classical pathways of biosynthesis, respectively. Their formation by catalysation through enzymatic and non-enzymatic pathways, the two unlike vital biochemical mechanisms and their well chemical stability *in vivo* composes these two eicosanoids are of immense interest in medical science for the last decades. Therefore, the following sections will exclusively highlight our current understanding on these two eicosanoids particularly in a few selected diseases.

Prostaglandin $F_{2\alpha}$

$PGF_{2\alpha}$ was chemically isolated and structurally characterized in 1963 by Samuelsson (Samuelsson et al., 1978) from human seminal fluid and evidently stimulated smooth muscles from rabbit duodenum. Prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$), a stable cyclooxy-

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genase-catalyzed major primary prostaglandin, regulates a number of important physiological functions, such as ovarian function, endometrial cyclic changes, tubal function, luteal maintenance of pregnancy, embryo development, induction of labor and parturition process (Basu, 1985; Basu and Kindahl, 1987; Basu et al., 1987; McCracken et al., 1999; Poyser, 1995). Current studies have shown that $PGF_{2\alpha}$, a potent smooth muscle stimulator, vaso- and broncho-constrictor, is also involved in acute, and chronic inflammatory diseases and sub-chronic inflammation in various cardiovascular dysfunction (Basu, 2007; Basu et al., 2001). In addition, analogues of $PGF_{2\alpha}$ have previously been developed for estrus-synchronization and abortion in domestic animals (Schultz, 1981; Seguin, 1981) and to regulate a number of major reproductive functions in humans (Cameron et al., 1986; Karim, 1969; 1970; Karim et al., 1978a; 1978b; Laurensen, 1979). Drugs with $PGF_{2\alpha}$ derivatives (Xalatan®, Pharmacia, Uppsala, Sweden, currently included in Pfizer) were successfully developed in the late 1990s, and are being widely used worldwide with high-success to reduce intraocular pressure in the treatment of glaucoma in humans (Bito et al., 1993; Stjernschantz, 2001). Recently, other analogues of $PGF_{2\alpha}$ are also developed for the treatment of ocular hypertension, open angel glaucoma and normal tension glaucoma (Faridi et al., 2010; Lee and McCluskey, 2010). Collectively, these multifaceted properties of $PGF_{2\alpha}$ implicate a specific but complex role of this luteolytic and bioactive compound in physiology and diseases, which opens for future advancement of this prostaglandin in diverse purposes. However, this chapter will specifically discuss the role of $PGF_{2\alpha}$ in inflammatory diseases.

Prostaglandin synthase is the enzyme complex which metabolises unesterified arachidonic acid to $PGF_{2\alpha}$ and other prostaglandins, prostacyclin and thromboxanes (Fig. 1). Cyclooxygenases is the first of this enzyme system. There are primarily two isoforms of cyclooxygenases, namely cyclooxygenase-1 and cyclooxygenase-2. First, cyclooxygenases (COXs) also known as prostaglandin endoperoxide H synthases (PGHS) bioconvert arachidonic acid to highly reactive rather unstable endoperoxide PGG_2 by inserting two molecules of oxygen (Fig. 1). Then, 15-hydroperoxy group of PGG_2 bioconverts to 15-hydroxyl group by peroxidase and forms endoperoxide PGH_2. Prostaglandin $F_{2\alpha}$ is basically formed by the reduction of PGH_2 through PG endoperoxide synthase or reductase (Fig. 1). Nevertheless, PGF compounds can be formed in a minute quantity from other prostaglandins such as enzymatic reduction of 9-keto group of PGE compounds by 9-ketoreductases, which results in either 9α-hydroxyl, yielding PGFα compounds or more rarely, a 9β-hydroxyl, yielding PGFβ compounds (Samuelsson et al., 1975). PGF compounds may also be formed from PGD compounds by 11-keto reductases (Liston and Roberts, 1985a; 1985b; Liston et al., 1985; Roberts and Sweetman, 1985).

Following biosynthesis in the different parts of the body primary $PGF_{2\alpha}$ is quickly inactivated through metabolism principally through the lungs, liver, kidney by 15-prostaglandin dehydrogenase to 15-keto-$PGF_{2\alpha}$ and further by the Δ^{13}-reductase to 15-keto-13,14-dihydro-$PGF_{2\alpha}$ (15-keto-dihydro-$PGF_{2\alpha}$) in two steps of enzymatic degradation to deactivate its major biological potency (Basu et al., 1992; 1994)(Fig. 2).The half-life of $PGF_{2\alpha}$ is presumably less than 1 min in the circulation. Prior to excretion, $PGF_{2\alpha}$ is further degraded to yield dinor (C_{18}) or tetranor (C_{16}) metabolites by one or two steps of β-oxidation of the carboxyl side chain (Basu et al., 1987; Granstrom and Kindahl, 1982; Granstrom et al., 1982; Green, 1971a; 1971b; Hamberg and Samuelsson, 1971). These degraded shorter chain metabolites (C_{16}) called "11-keto-tetranor-PGF metabolites," remain in the peripheral circulation together with the parent 15-keto-dihydro-$PGF_{2\alpha}$ for an extended period, and thus, they are the major parameters to follow an endogenous biosynthesis and release of $PGF_{2\alpha}$.

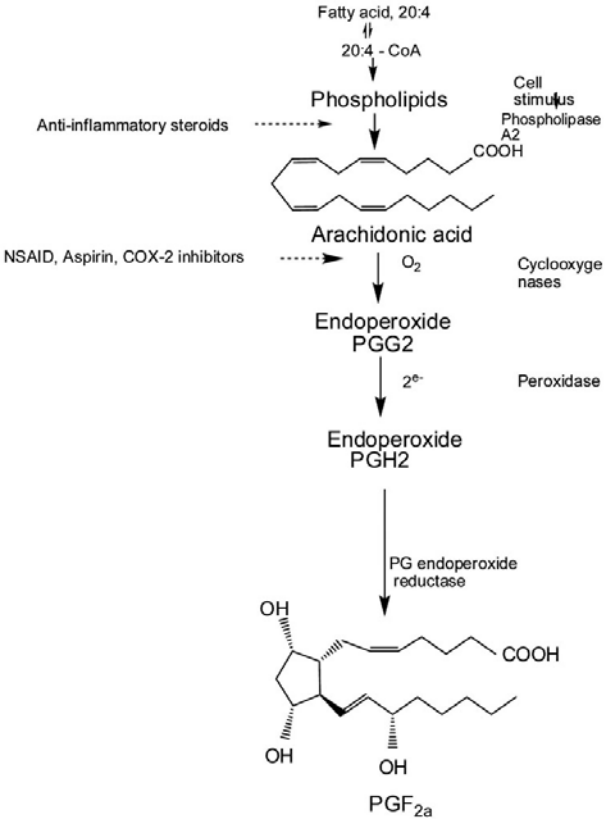

Fig. 1. Biosynthesis of $PGF_{2\alpha}$ from arachidonic acid

F_2-Isoprostanes

Isoprostanes, a group of prostaglandin-like compounds are biosynthesized primarily from esterified arachidonic acid by a non-enzymatic free radical-catalysed reaction *in vivo* that has unfolded a novel aspect of detection of free radical species involvement in biology (Basu, 2008; Montuschi et al., 2007; Morrow and Roberts, 1996; Morrow et al., 1990). Several of these short half-lived isoprostanes have shown to possess significant biological potencies mainly through pulmonary and renal vasoconstriction by activating thromboxane receptors. Following biosynthesis, rapid hydrolysis of the esterified isoprostanes and further metabolism the primary isoprostanes and their β-oxidised products are secreted in the plasma, and later excrete efficiently into the urine. Both clinical and experimental studies have evidenced the association of isoprostanes with severe acute or chronic inflammatory conditions such as asthma, atherosclerosis, chronic obstructive pulmonary diseases (COPD), diabetes, ischemia-reperfusion, rheumatic diseases, septic shock etc. There are plentiful studies that have shown that F_2-isoprostanes are reliable biomarkers of lipid peroxidation, and could thus be used as potential *in vivo* indicator of oxidant stress of miscellaneous characters, and on the evaluation of various antioxidants, diet or drugs. Since bioactive F_2-isoprostanes (mainly 8-iso-$PGF_{2\alpha}$) are regularly formed in various tissues and rather small amount of these potent compounds are found unmetabolised form in plasma. This review will offer

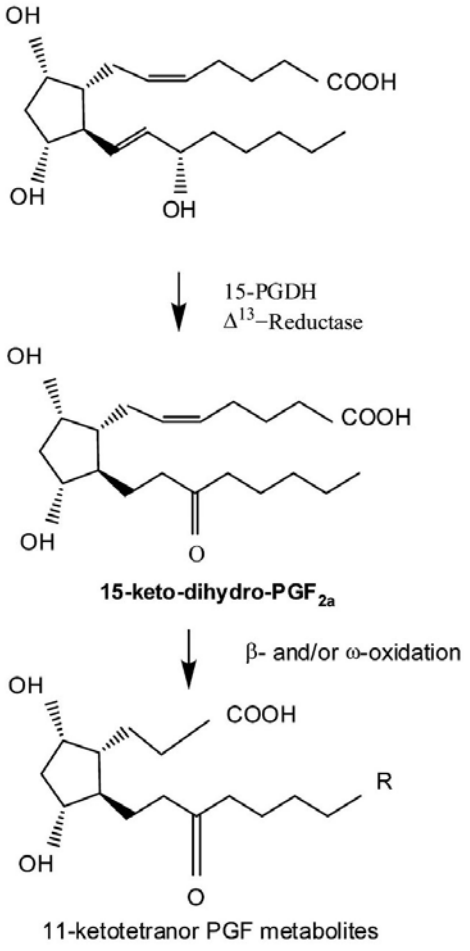

Fig. 2. Metabolism of $PGF_{2\alpha}$ to15-keto-dihydro-$PGF_{2\alpha}$ and to more polar β- and ω-oxidized shorter C-16 metabolites. 15 PGDH = 15-prostaglandin dehydrogenase.

an overall up-to-date picture of isoprostanes as biomarkers of oxidative stress and their impact in diseases in concert with their relationship with cyclooxygenase-catalysed $PGF_{2\alpha}$ as described above.

A simplified mechanism of formation of isoprostanes from arachidonic acid precursor is shown in Fig. 3. Metabolism of isoprostanes has shown to occur basically through the same metabolic pathway as enzymatically-formed primary prostaglandins. Studies *in vitro* and *in vivo* demonstrated that oxidation of the 15-hydroxy group at C-15 by 15-prostaglandin dehydrogenase (15-PGDH) is the early step of 8-iso-$PGF_{2\alpha}$ metabolism (Basu, 1998; Roberts et al., 1996). A reduction of C-13,14-double bond by Δ^{13}-reductase and formation of 15-keto-13,14-dihydro-8-iso-$PGF_{2\alpha}$ occurred in the subsequent step of metabolism (Fig. 4). Therefore, 15-PGDH and Δ^{13}-reductase are the central enzymes involved in the degradation of 8-iso-$PGF_{2\alpha}$. Both β- and ω-oxidation are very common reactions in later steps of isoprostanes metabolism. It has been revealed in the rabbits that 15-keto-13,14-dihydro-8-iso-$PGF_{2\alpha}$ quickly degrades through two steps of β-oxidation largely to α-tetranor-15-keto-13,14-dihydro-8-iso-$PGF_{2\alpha}$ and also to numerous other β-oxidised metabolites. In humans, the main metabolite is 2,3-dinor-5,6-dihydro metabolite of 8-iso-$PGF_{2\alpha}$. There are several other isoprostanes of series D_2 and E_2, thromboxane A_2,

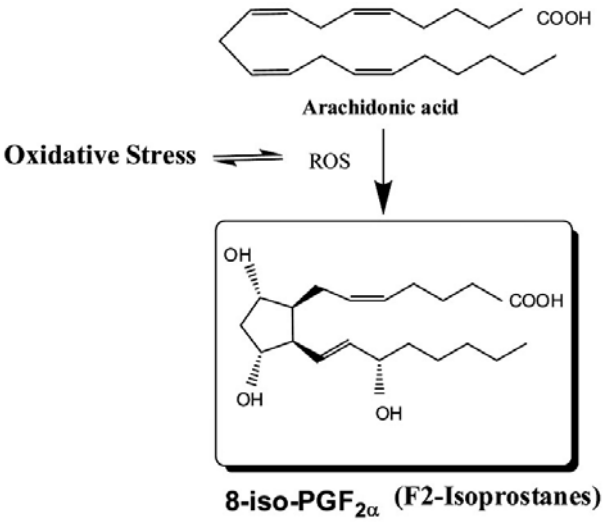

Fig. 3. A simplified scheme of biosynthesis of 8-iso-$PGF_{2\alpha}$ (F_2-isoprostanes) from arachidonic acid. ROS = Reactive oxygen species; PGF = prostaglandin F.

cyclopentanone -A_2 and -J_2 are also formed *in vivo* by rearrangement of PGH_2-like isoprostane intermediate (Roberts and Milne, 2009).

PROSTAGLANDIN $F_{2\alpha}$ AND F_2-ISOPROSTANES IN DISEASES

Inflammation and oxidative stress are thought to be concurrently involved in various diseases. But hardly few studies have studied the role of both oxidative stress and inflammation concomitantly. In this concern, the two eicosanoids formed from the same parent compound, arachidonic acid through distinctly unlike biosynthetic pathways namely, $PGF_{2\alpha}$ and F_2-isoprostanes could be suitable parameters to investigate simultaneously in diverse diseases as described below where both oxidative stress and inflammation are supposed to be involved.

Ischemia and reperfusion injury

Inflammatory tachycardia is caused by a direct action on the heart of $PGF_{2\alpha}$ formed under systemic inflammatory conditions (Takayama et al., 2005). A cardiopulmonary bypass (CPB) operation has an immediate impact on the initiation of the oxidative stress and following inflammatory response, and was studied in patients with coronary artery disease who took low-dose aspirin (ASA) treatment regularly until 1 week before CPB (Ulus et al., 2003). No significant increase of plasma $PGF_{2\alpha}$ metabolite was found during and up to 24 h post-operatively in these earlier ASA-treated patients. A large inter-individual difference on the $PGF_{2\alpha}$ synthesis was seen in these patients. When oxidative stress was evaluated in these patients by measuring 8-iso-$PGF_{2\alpha}$ in plasma, a significant increase of this parameter was observed within 3 min after the start of CPB and continued until 50 min. This indicates that free radical-catalysed F_2-isoprostane formation takes place rapidly as a consequence of ischemia at an early stage of CPB, possibly due to the disrupted vasculature and the limitation of molecular oxygen in the circulation. Thus, oxidative stress seems to be a major pathology in this state.

In an additional study, in acute myocardial infarction (AMI) patients treated with PCI, no increase of $PGF_{2\alpha}$ metabolite was

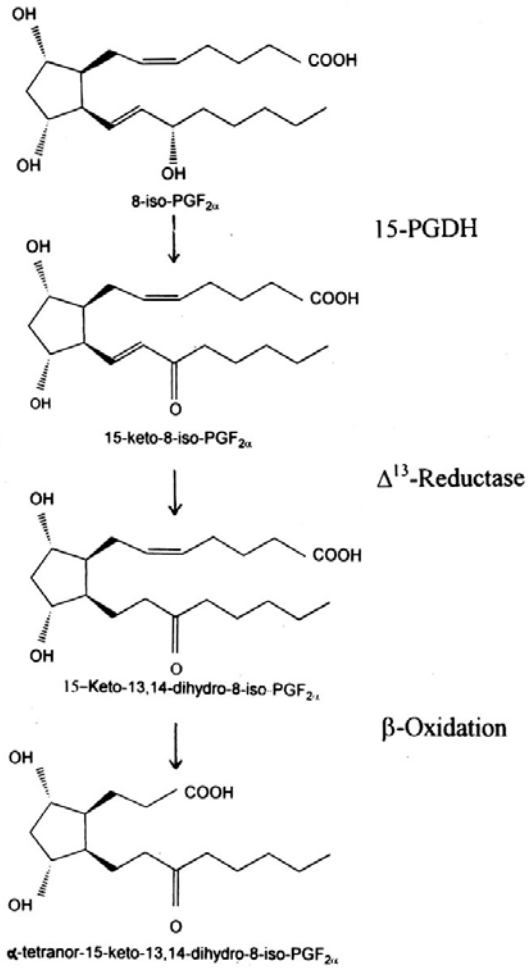

Fig. 4. Metabolism of 8-iso-$PGF_{2\alpha}$ to 15-keto-dihydro-8-iso-$PGF_{2\alpha}$ and to more polar shorter C-16 metabolites. 15 PGDH = 15-prostaglandin dehydrogenase.

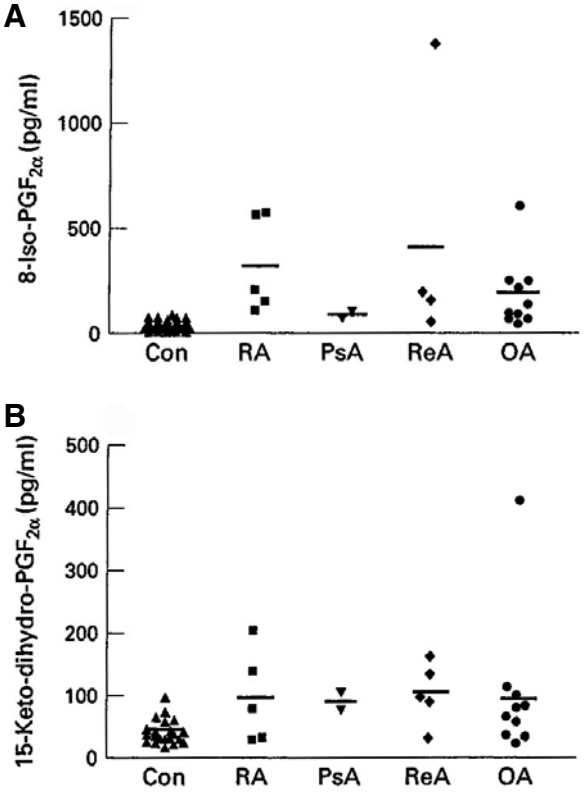

Fig. 5. The mean and individual serum levels of 8-iso-$PGF_{2\alpha}$ (upper panel) and 15-keto-dihydro-$PGF_{2\alpha}$ (lower panel) in various types of rheumatoid arthritis. The bars indicate the mean levels and the dots indicate the individual values of 8-iso-$PGF_{2\alpha}$ and 15-keto-dihydro-$PGF_{2\alpha}$ (adapted from Basu et al., 2001).

observed during reduction of blood flow and hypoxia. A post-surgical (at 24 h) rise in $PGF_{2\alpha}$ metabolite and HsCRP was also observed in these patients (Berg et al., 2004). Thus, a significant augment in $PGF_{2\alpha}$ metabolite and HsCRP in plasma was seen at 24 h post-surgery among elective percutaneous coronary interventions (PCI) who took low-dose ASA drug. Hence, inflammatory mechanisms are associated in the post-surgery related complications and may be related to commonly faced future neurological deficits in such patients. The levels of $PGF_{2\alpha}$ metabolite in the AMI patients were lower than those undergone elective PCI and was possibly due to a large dose of ASA (300 mg) prior to the CPB operation. When oxidative stress was evaluated, 8-iso-$PGF_{2\alpha}$ levels in plasma increased transiently by 87% in the PCI treated patients (Berg et al., 2004). The levels of 8-iso-$PGF_{2\alpha}$ in plasma returned back to the baseline 24 h after surgery. Thus, a moderate increase of oxidative stress but no such increase of inflammation observed in the PCI-treated patients in the early phase of surgery whereas inflammatory activity was evident but not oxidative stress at 24 h after surgery compared to baseline values.

Rheumatic diseases

Rheumatoid arthritis is a systemic autoimmune chronic inflammatory disease characterized by inflammation of synovial joints and variable degrees of bone and cartilage erosion that affects roughly 1% of the population worldwide. An elevated oxidative stress may lead to connective tissue degradation leading to joint and periarticular deformities in rheumatoid arthritis. It had shown that both PGE_2 and PGI_2 levels were increased in the synovial fluid collected from knee joints of arthritic patients (Bombardieri et al., 1981; Brodie et al., 1980). Further, local (knee joints) and systemic measurements of inflammatory response parameter in conjunction with oxidative stress were determined in the synovial fluid and plasma, respectively. High levels of serum $PGF_{2\alpha}$ metabolite were found among the patients suffering from rheumatoid arthritis, psoriatic arthritis, reactive arthritis and osteoarthritis (Fig. 5, lower panel) (Basu et al., 2001). Besides, higher levels of $PGF_{2\alpha}$ metabolite were also noticed in the synovial fluid collected from these patient groups (Fig. 6, lower panel). An earlier study with rheumatoid arthritis also detected high levels of $PGF_{2\alpha}$ metabolite in both plasma and urine (Trang et al., 1977). Treatment with NSAID effectively lowered the $PGF_{2\alpha}$, PGE_2 and TXB2 levels in joint fluid. Synovial cells from rheumatoid arthritic patients are also capable of producing $PGF_{2\alpha}$ (Seppala, 1987; Seppala et al., 1987) that suggests that $PGF_{2\alpha}$ is intimately associated with various types of rheumatic diseases, and thus $PGF_{2\alpha}$ has a recognized role in chronic inflammatory diseases.

High levels of systemic 8-iso-$PGF_{2\alpha}$ were found among rheumatoid arthritis, psoriatic arthritis, reactive arthritis and osteoarthritis patients (Fig. 5, upper panel) (Basu et al., 2001).

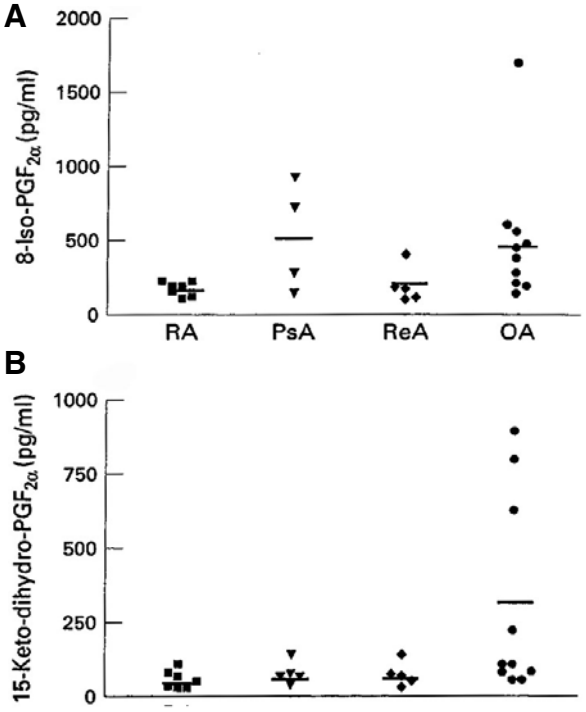

Fig. 6. The mean and individual synovial fluid levels of 8-iso-$PGF_{2\alpha}$ (upper panel) and 15-keto-dihydro-$PGF_{2\alpha}$ (lower panel) in various types of rheumatoid arthritis. The bars indicate the mean levels and the dots indicate the individual values of 8-iso-$PGF_{2\alpha}$ and 15-keto-dihydro-$PGF_{2\alpha}$ (adapted from Basu et al., 2001).

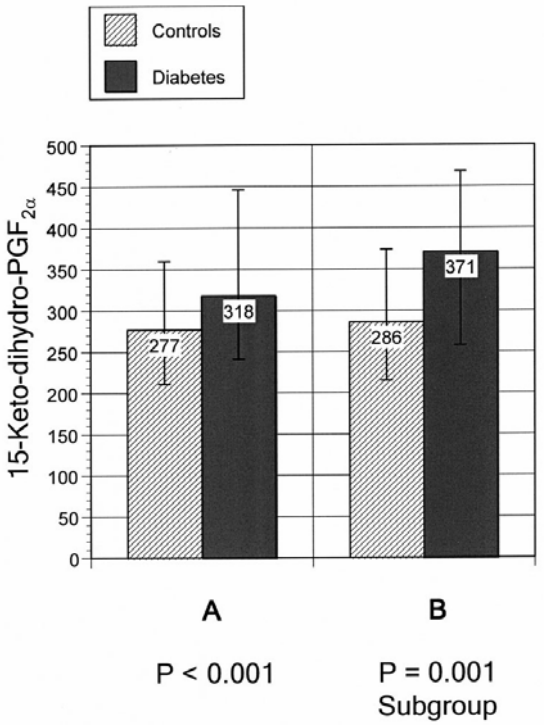

Fig. 7. Urinary 15-keto-dihydro-$PGF_{2\alpha}$ levels (pmol/mmol creatinine) in control subjects and diabetic patients in median (interquartile range). (A) All participants (controls, n = 585; diabetes, n = 101). (B) Subgroup without both CVD and low-dose aspirin treatment (controls, n = 349; diabetes, n = 50) (adapted from Basu et al., 2001).

In addition, elevated levels of 8-iso-$PGF_{2\alpha}$ were also seen in the synovial fluid collected from these patients (Fig. 6, upper panel). Urinary levels of a tetranor-dicarboxylic acid metabolite of F_2-isoprostanes concentrations were significantly higher in patients with scleroderma than in healthy controls (Stein et al., 1996). Urinary levels of 8-iso-$PGF_{2\alpha}$ in systemic sclerosis patients were higher compared to sex-matched healthy controls (Volpe et al., 2006). Similarly, urinary levels of iPF2alpha-III was approximately twice as high in patients as in control subjects (Cracowski et al., 2001). Urinary levels of 15-isoprostane F2t were higher in the rheumatoid arthritis patients (Kageyama et al., 2008). These suggest that both $PGF_{2\alpha}$ and F_2-isoprostane are involved in the rheumatic diseases as a signature of oxidative stress and inflammation mutually.

Asthma

Asthma is a common chronic inflammatory disease of the airway characterized by irreversible airflow obstraction, hypersensativeness to bronchoconstriction and also remodeling of the airways (Whitehead et al., 2003). When prostaglandin formation was evaluated in asthma, 2,3 dinor-9 alpha-11beta-PGF(2) in urine was found to be higher in aspirin-intolerant bronchoconstriction (Higashi et al., 2010). In an experimental model of asthma in mice that had challenged with ovalbumin (OVA) to induce airway inflammation, 8-iso-$PGF_{2\alpha}$ levels in bronchoalveolar lavage (BAL) were increased compared to the control mice. In addition in a immunohistochemistry study, OVA treated mice had more intense staining of 8-iso-$PGF_{2\alpha}$ in lung tissue than the control mice lung (Jonasson and Basu, 1986). Other studies with allergen challenge in human and murine have also shown an increase levels of 8-iso-$PGF_{2\alpha}$ *in vivo* (Dworski et al., 1999; 2001; Talati et al., 2006; Xie et al., 2009). Exercise-induced bronchoconstriction (EIB) in the asthmatic child is associated with persistent airway inflammation and increase of F_2-isopro-stane (Barreto et al., 2009). Thus, both *in vivo* and *in situ* localization of 8-iso-$PGF_{2\alpha}$ in lung tissue was feasible in the experimental models of asthma. Togetherly, PGF metabolite and F_2-isoprostane are involved in the asthmatic diseases, and suggest a role for oxidative stress and inflammation in bronchial hyperreactivity.

Atherosclerosis and its risk factors

Atherosclerosis is a complicated vascular disease that relates to thinning of the carotid and coronary arteries by the formation of stable and unstable plaques depending upon the degree of lipid accumulation and the grade of chronic inflammation. Although the underlying mechanism(s) causing carotid atherosclerotic plaque to become symptomatic are still unclear, evidences suggest that mediators of inflammation are not only the leading cause of the formation of plaque but may also be involved in rapid progression of atheromatous lesions and intraluminal thrombosis (DeGraba, 1997). The vascular cells secrete various prostaglandins related to inflammation including PGE_2, $PGF_{2\alpha}$ and PGI_2 (Papp et al., 1986). Several of the risk factors such as diabetes, smoking habits, obesity and thickening of intima-media of the carotid artery are associated with the increase of low-grade inflammation as evidenced by a reasonable but significant increase of $PGF_{2\alpha}$ metabolite equally with cytokines (IL-6) and acute phase proteins (HsCRP) *in vivo* (Basu et al., 2005a; 2005b; Helmersson et al., 2004; 2005; Talati et al., 2006; Wohlin et al., 2007).

Carotid intima media thickening is an early signal of devel-

opment of atherosclerosis. Cross-sectional relations between CCA-IMT (carotid intima media thickness) were measured by B-mode ultrasound technique and cyclooxygenase-mediated inflammation as measured by 15-keto-dihydro-$PGF_{2\alpha}$, IL-6, HsCRP and serum amyloid A protein in a population-based sample of elderly men (n = 234) free from anti-inflammatory medications (Wohlin et al., 2007). In a backwards stepwise regression analysis of correlates of 15-keto-dihydro-$PGF_{2\alpha}$, CRP, interleukin-6 (IL-6), serum amyloid A (SAA), 8-iso-$PGF_{2\alpha}$, tocopherols, β-blocker treatment, diabetes, body mass index (BMI), statin treatment, smoking, hypertension and cholesterol, only 15-keto-dihydro-$PGF_{2\alpha}$, CRP, β-blocker treatment, diabetes and BMI were independent predictors of CCA-IMT. However, no correlation between urinary 8-iso-$PGF_{2\alpha}$ and intima media thickening has been observed in this well-known Swedish cohort in elderly men of age 77. This study showed that both cyclooxygenase- and cytokine-mediated inflammation are independently associated with common carotid artery intima media thickness, suggesting an involvement of $PGF_{2\alpha}$ in atherogenesis.

Type 1 diabetes

Diabetes consists of progressive hyperglycemia, insulin resistance and pancreatic β-cell failure that relates to the development of atherosclerosis. Type 1 diabetes, type 2 diabetes and atherosclerosis might share the common inflammatory components. Type 1 diabetes is coupled to an increased risk of microvascular complications and premature atherosclerosis. Urinary $PGF_{2\alpha}$ metabolite levels together with plasma interleukin-6 (IL-6) were increased in subjects with type 1 diabetes compared to a matched control population. In this study, urinary levels correlated with the degree of glycemic control, hemoglobolin A_{1c} (HbA_{1c}) (Basu et al., 2005a; 2005b).

Concerning type 1 diabetes, elevated levels of 8-iso-$PGF_{2\alpha}$ in urine from patients with type 1 diabetes patients was evidenced (Davi et al., 1999). Nonetheless, a number of other reports showed no such discrepancies in isoprostane levels in patients with type 1 diabetes compared to controls (Davi et al., 2003; Gleisner et al., 2006; Hoeldtke et al., 2003; O'Byrne et al., 2000; Vessby et al., 2002). Metabolically well-controlled young Swedish type 1 diabetic patients had no increase in 8-iso-$PGF_{2\alpha}$ concentrations compared to those of matched controls (Vessby et al., 2002). Likewise, no increase in the urinary 2,3-dinor-5,6-dihydro metabolite of 8-iso-$PGF_{2\alpha}$ was established in type 1 diabetes (O'Byrne et al., 2000). Thus, both COX- and cytokine-mediated inflammatory pathways are notably involved in type 1 diabetes that might contribute to the common inflammatory hypothesis in this disease. The role of F_2-isoprostanes and thereby oxidative stress in type 1 diabetes still under controversy as discussed above.

Type 2 diabetes

In a study of elderly male type 2 diabetes patients, it showed significantly elevated levels of $PGF_{2\alpha}$ metabolite compared to the control subjects, and also in a subgroup of patients without both cardiovascular diseases (CVD) and low-dose aspirin treatment compared to the control subjects (Fig. 7) (Helmersson et al., 2004). Elevated levels of 8-iso-$PGF_{2\alpha}$ have been found in plasma or urinary samples from type 2 diabetic patients, compared to the non-diabetic controls (Davi et al., 1999; Gopaul et al., 1995; 2001; Murai et al., 2000). In a large cross-sectional study in elderly men (77 years), it was also shown that the 24-h urinary level of 8-iso-$PGF_{2\alpha}$ was significantly higher in men with type 2 diabetes (n = 101) than in the control men (n = 585) of the similar ages (Helmersson et al., 2004). Though, in a subgroup of these patients with disease duration < 7 years since disease diagnosis did not demonstrate any difference between the type 2 diabetes patients and control subjects. Consequently, type 2 diabetes seems to be associated with a higher isoprostane level only in patients with disease duration > 7 years in this population. However, this study only limits elderly patients of age 77. Induced hyperglycemia in patients with type 2 diabetes undergoing a glucose tolarence test has also been reported to cause an acute increase of isoprostane levels (Sampson et al., 2002). A positive relation has also been observed between glucose and F_2-isoprostanes in some studies (Davi et al., 1999; Gopaul et al., 2001), but not in the others (Gopaul et al., 1995; Helmersson et al., 2004). These suggest that chronic inflammation is involved in elderly type 2 diabetic patients as manifested by an increase of cyclooxygenase-catalyzed $PGF_{2\alpha}$ formation whereas oxidative stress measured as F_2-isoprostanes perhaps appear at a later stage of the disease.

Obesity

Obesity is significantly associated with the metabolic syndrome and low-grade inflammation. Inflammatory factors initiating from obesity-induced visceral fat may cause oxidative stress that has been coupled with insulin resistance and cardiovascular risk factors. 15-Keto-dihydro-$PGF_{2\alpha}$, a major metabolite of $PGF_{2\alpha}$, was measured in 274 adolescents aged between 13-17 years (M = 153; F = 121) as an indicator cyclooxygenase-mediated inflammatory response in concurrence with the isoprostane measurement. Oxidative stress was related with obesity (Sinaiko et al., 2005). In addition, $PGF_{2\alpha}$ metabolite levels were significantly correlated with BMI, waist circumference and fasting insulin (Basu et al., 2005b). Among the males, $PGF_{2\alpha}$ metabolite levels were correlated with waist and insulin levels. These associations were not significant after adjustment for BMI. Children in the highest quartile of BMI and waist circumference had the highest levels $PGF_{2\alpha}$ metabolite. A significant relation between obesity and prostaglandin-mediated inflammation and oxidative stress is already present in metabolically-dysfunctional adolescents.

In a recent cross-sectional study from the Framingham Heart Study reports that abdominal visceral and subcutaneous adipose tissue volumes are correlated to F_2-isoprostanes (Pou et al., 2007). Women with BMI of > 28 have shown to have higher formation of 8-iso-$PGF_{2\alpha}$ despite of distribution of fat (Davi et al., 2002). Patients with cardiovascular risk factors except obesity is linked with enhanced oxidative stress. Further, loss of weight has been linked to lower 8-iso-$PGF_{2\alpha}$ levels (Davi et al., 2002). Nonetheless, conflicting reports have been reported in epidemiological studies. A positive correlation between BMI and 8-iso-$PGF_{2\alpha}$ levels is claimed in some studies (Block et al., 2002; Dietrich et al., 2002; Keaney et al., 2003) but not corroborated in a recent study of elderly men (Helmersson et al., 2004). Obese men had significantly higher plasma concentrations of 8-epi-$PGF_{2\alpha}$ than non-obese men, and plasma levels of 8-epi-$PGF_{2\alpha}$ were significantly correlated with body mass index (BMI) (Urakawa et al., 2003). Collectively, these studies support that obesity is closely related to oxidative stress and successive higher *in vivo* isoprostane formation.

Smoking

Cigarette smoking is associated with the accumulation of polycyclic aromatic hydrocarbons in respiratory tissues that may direct to miscellaneous pathologies including accelerating atherosclerosis and respiratory disease and potential development of cardiovascular diseases. $PGF_{2\alpha}$ metabolite, isoprostanes and serum interleukin-6 (IL-6) were quantified in a popula-

tion-based cohort (n = 642) of 77-year old men without diabetes (Helmersson et al., 2005). Fifty-five men were current smokers and 391 were former smokers. $PGF_{2\alpha}$ metabolite levels were significantly increased in current smokers ($PGF_{2\alpha}$ metabolite $p < 0.001$; IL-6, $p = 0.01$) than non-smokers. Additionally, former smokers had higher levels of $PGF_{2\alpha}$, IL-6 than did non-smokers. This study showed that smokers have elevated formation of $PGF_{2\alpha}$, consequently enhanced COX-mediated inflammatory response, in addition to increased levels of cytokines and isoprostanes. Subclinical COX- and cytokine-mediated inflammation and oxidative stress are constant processes not only in active smokers but also in former smokers, which may add to the accelerated atherosclerosis associated with smoking. Other studies with cigarette smoking has enhanced COX-2 expression (Martey et al., 2004). Early confirmation of the association of isoprostanes has shown among the smokers (Morrow et al., 1995). This has further been corroborated later in several other studies (Ahmadzadehfar et al., 2006; Helmersson et al., 2005; Montuschi et al., 2000). It has also been evidenced an increased levels of F_2-isoprostanes among former smokers but the levels are lesser than the current smokers (Helmersson et al., 2005). Thus, cigarette smoking is linked to both oxidative stress and inflammation equally.

CONCLUSION

Eicosanoids, specifically prostaglandin $F_{2\alpha}$ and F_2-isoprostanes are endogenous bioactive comounds that are involved both in physiology and pathophysiology. The importance of these two particular stable compounds seems to be of great significance in medical science since these compounds are formed both enzymatic and non-enzymatic reactions *in vivo* from the same essential fatty acid in the body, namely arachidonic acid. These compounds have not only specific biological effects but also could be used as novel *in vivo* biomarkers of inflammation and oxidative stress, respectively. Their application both as biomarker and controlling their *in vivo* formation have evidenced great importance in biology and medicine.

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