**Aim:** Weill–Marchesani syndrome (WMS) is a rare systemic disorder with both autosomal recessive and dominant inheritances. Accumulation of reactive oxygen species such as \( \text{O}_2^\cdot \), \( \text{H}_2\text{O}_2 \) and \( \text{OH}^\cdot \) causes lipid peroxidation (LPO), whereas antioxidant enzymes (superoxide dismutase (SOD), glutathione peroxidase (GSHPx)) mediate defence against oxidative stress. Excess tumour necrosis factor (TNF)-\( \alpha \) and NO* react with \( \text{O}_2^\cdot \) and cause further antioxidant depletion with an increase in mutation frequency by \( \text{H}_2\text{O}_2 \). This study investigated the levels of SOD, GSHPx, catalase (CAT), TNF-\( \alpha \), NO* and LPO in patients with WMS.

**Methods:** A group of 10 WMS patients (four males, six females; age, 26.5 ± 19.0 years) and 10 age-matched and sex-matched controls (five males, five females; age, 27.3 ± 18.2 years) were included. Serum TNF-\( \alpha \) levels were determined by a spectrophotometer technique using immulite chemiluminescent immunometric assay. Malondialdehyde (MDA) was determined in plasma; CAT in red blood cells (RBCs), and SOD and GSHPx in both plasma and RBCs. Total serum NO* levels were evaluated by Griess reaction. **Results:** Mean levels of TNF-\( \alpha \) (8.3 ± 0.6 pg/ml) in WMS patients were significantly (p < 0.001) higher than controls (4.3 ± 0.2 pg/ml). Plasma MDA levels in patients and controls were 5.4 ± 0.8 and 1.8 ± 0.6 \( \mu \text{mol/l} \), respectively, and the difference was significant (p = 0.0002). SOD and GSHPx activities were significantly lower in both RBCs and plasma of WMS than in controls (RBC-SOD, 3981.9 ± 626.6 versus 5261.6 ± 523.0 U/g haemoglobin (Hb), p = 0.0005; plasma-SOD, 529.4 ± 49.3 versus 713.4 ± 55.7 U/g protein, p = 0.0002; RBC-GSHPx, 682.7 ± 42.0 versus 756.5 ± 47.6 U/g Hb, p = 0.0011; plasma-GSHPx, 107.3 ± 15.0 versus 131.4 ± 19.7 U/g protein, p = 0.0113). In addition, serum NO* (\( \text{NO}_2^\cdot + \text{NO}_3^\cdot \)) levels were also significantly (p = 0.0002) increased in WMS patients (54.4 ± 5.7 versus 20.9 ± 6.7 \( \mu \text{mol/l} \)), RBC-CAT levels were similar between groups (125.6 ± 21.3 versus 131.0 ± 21.5 k/g Hb, p = 0.8798). **Conclusions:** The elevated LPO, TNF-\( \alpha \) and NO* with decreased antioxidant enzyme activities indicated impaired antioxidative defence mechanisms with an oxidative injury and cell toxicity in WMS patients. The use of multiple antioxidants and free radical scavengers might be helpful in this genetic disorder.

**Key words:** Antioxidant enzymes, Lipid peroxidation, Nitric oxide, Tumour necrosis factor \( \alpha \), Weill–Marchesani syndrome

**Introduction**

In normal cells, a balance exists between oxidative damage and antioxidant defence. Although tumour necrosis factor (TNF)-\( \alpha \) and highly potent oxidant molecules such as superoxide anion (\( \text{O}_2^\cdot \) ), hydrogen peroxide (\( \text{H}_2\text{O}_2 \)) and hydroxyl radical (\( \text{OH}^\cdot \)) are produced by the immune system, excessive production of oxygen-derived free radical creates a condition known as oxidative stress, participating in various diseases and syndromes.1–7 Antioxidant defences in humans protect directly and indirectly the host against the damaging influence of such cytokines and oxidants stated earlier.3 These enzymes include superoxide dismutase (SOD, EC1.15.1.1), glutathione peroxidase (GSHPx, EC1.11.1.9) and catalase (CAT, EC1.11.1.6). First, SOD catalyses the dismutation of \( \text{O}_2^\cdot \) to \( \text{H}_2\text{O}_2 \).
GSHPx and CAT then independently convert H₂O₂ to H₂O.⁸ If H₂O₂ is produced in excess, it reacts with O₂⁻ and produces OH⁺, which is one of the most active reactive oxygen species (ROS). The ROS interacts with nucleic acids, proteins and lipids, thus enhancing TNF production, DNA mutations, cellular dysfunction and death.¹²

Nitric oxide (NO⁺) is one of the most abundant free radicals in the body.⁵,⁵ Excess NO⁺ production causes respiratory enzyme inhibition of mitochondria, resulting in the cessation of DNA replication. The rapid reaction of NO⁺ with other radicals such as O₂⁻ to form the powerful oxidant is the general mechanism that greatly enhances the toxicity of NO⁺. Although O₂⁻ is scavenged by SOD, NO⁺ is the only known molecule that can be produced high enough to out-compete SOD for O₂⁻ ⁹

Weill–Marchesani syndrome (WMS) was first reported by Weill¹⁰ and Marchesani.¹¹ It is a congenital connective tissue disease characterised by short stature, brachyactly, microspherophakia, glaucoma, and ectopia lentis. Although we have previously reported a large family with autosomal dominant transmission,¹² recessive mode of inheritance has also been described.¹,² However, the exact aetiology of this unique disorder is unknown and the autosomal dominant form has been linked to mutation within the fibrillin-1 gene on chromosome 15q21.1, whereas autosomal recessive WMS mapped to chromosome 19p13.3-p13.2.¹³,¹⁴

In the present study, red blood cell (RBC) activities of SOD, GSHPx and CAT, and plasma activities of SOD and GSHPx were measured for the first time in 10 patients with autosomal dominant WMS and compared with age-matched and sex-matched healthy controls. Plasma TNF-α, malondialdehyde (MDA) and NO levels were also investigated.

**Patients and methods**

Ten patients with WMS (four males, six females) from two families showing dominant transmission and 10 age-matched and sex-matched healthy control subjects (five males, five females) were included in this study. Systemic and detailed ocular examinations were performed in all subjects in both groups. All patients with WMS had the classical systemic and ocular findings including brachymorphy (n = 10), all below or equal to the third percentile), brachyactly (n = 10), stubby fingers and/or clumsy feet), spherophakia or microspherophakia (n = 9), high refractive error (n = 6) and lens subluxation (n = 6) with iridophacodesis. Three patients demonstrated bilateral but asymmetric glaucomatous optic nerve damage with increased intraocular pressure. In addition, vitreous liquefaction (n = 9), strabismus (n = 2), microcornea (n = 1), scleral staphyloma (n = 1) and limited mobility of joints (n = 5) were also present. All control subjects had normal systemic and ocular findings.

**Blood collection**

The laboratory personnel were maintained masked to the clinical diagnosis and group of the subjects, matching each blood sample by letter coding, and so were the clinicians to subsequent levels until the end of the study. After informed consent was obtained from all patients and controls, antecubital whole-blood samples were drawn from a peripheral vein using a 25-gauge needle, avoiding haemolysis, into evacuated heparinised plain tubes in the morning hours (08:30–10:30) after an overnight fast and 15 min of supine rest. None of the patients and controls received any topical or systemic medication at least 4 weeks prior to blood collection. The samples were centrifuged at 3000 g for 10 min at 4°C, and the harvested plasma was collected and kept at −50°C until the time of analysis.

The erythrocytes were subsequently washed twice with two volumes of 0.9% sodium chloride solution to remove the plasma remnants. Following this, the erythrocytes were haemolysed with two-fold volumes of ice-cold distilled water. After centrifugation (5000 g, 10 min, 4°C) the supernatant was subdivided and transferred into polyethylene tubes and frozen at −70°C to be used in the assay of FRSEs in erythrocytes (SOD, GSHPx and catalase). The plasma was used to measure the end product of lipid peroxidation (LPO) (MDA), TNF-α, total nitrite/nitrate levels (NO₂⁻ + NO₃⁻) as an indicator of NO levels, and antioxidant enzymes (SOD, GSHPx, CAT). The haemoglobin (Hb) content of whole blood was also measured, and enzyme activity was determined per mg Hb.

**Cytokine analysis**

Cytokine analysis was performed according to the Immulite® (Diagnostic Products Corporation, Los Angeles, CA, USA) chemiluminescent enzyme immunoassay. The technique is based on a solid-phase (bead) two-site assay. The solid phase, a polystyrene bead, is coated with a monoclonal specific antibody. After the incubation for 30–60 min at 37°C, unbound conjugate is then removed by a centrifugal wash (three times), after which a chemiluminescent substrate (a phosphate ester of adamantyl dioxetane) is added, and the test unit is incubated for a further 10 min. The Immulite® system automatically handles sample and reagent additions, the incubation and separation step, and measurement of the photon output via the temperature-controlled luminometer. It calculates test results for control and
patient samples from the observed signal, using a stored master curve, and generates a printed report. The values of inter-assay imprecision were similar to those from the intra-assay study with coefficient of variation (CV) ranging from 2% to 11.5%. The CV for the measured cytokine was around 5%. The linearity is satisfactory, with a regression coefficient higher than 0.99 ($r^2$).

There is an excellent practicality of the system and good stability of the calibration curve (15 days). It is a good reliable method yielding a good precision along with a satisfactory detection limit. The antibody used in the Immulite® for TNF-α is highly specific for each cytokine and chemokine, with no cross-reactivity to other cytokines that may be present in the serum samples.

A master curve is constructed by the manufacturer using a material calibrated against the National Institute for Biological Standards and Control. An adjustment of the calibration slope is made by the user by measuring two-serum matrix vials (low and high) designated as ‘adjusters’. It should be mentioned that between-run and within-run imprecision data were similar, which is very important for a stat measurement.**

**Plasma MDA analysis**

LPO is frequently investigated in biomedical research and the assays for thiobarbituric acid-reactive substances (TBARS) are much more widely used than any other index of LPO in biological samples. Thiobarbituric acid (TBA) reacts with LPO aldehydes, such as MDA. Therefore, assessment of TBARS is a useful index of oxidative deterioration and LPO determination in body fluids.

Plasma MDA level was measured according to the method described by Wasowicz et al.19 The principal of the method is based on the coupling of TBARS with TBA. All measurements (standards and samples) were performed at the upper $n$-butanol phase of the reaction mixture. In brief, 50 μl of plasma or an adequate volume of MDA working standard solution was introduced into 10 ml glass tubes containing 1 ml of distilled water. After addition of 1 ml of the solution containing 29 mmol/l TBARS in acetic acid and mixing, the samples were placed in a water bath and heated for 1 h at 95–100°C. After the samples were cooled, 25 μl of 5 mol/l HCl was added, and the reaction mixture was extracted by agitation for 5 min with 3.5 ml of $n$-butanol. Butanol phase was separated by centrifugation at 1500 g for 10 min. The butanol extract was measured with a spectrofluorometer (F-4010 fluorescence spectrophotometer; Hitachi, Tokyo, Japan) at wavelengths of 525 nm for excitation. The calibration curve was prepared with MDA standards of 0–10 μmol/l. Intra-assay and inter-assay CVs were 3.5% and 6%, respectively. Results were expressed as nanomoles per millilitre.

**Plasma total nitrite/nitrate (NO$_2^-$ + NO$_3^-$) analysis**

Because total nitrite is the stable end product of NO$^*$ metabolism, NO$^*$ synthesis was determined as total nitrite using a spectrophotometric assay based on the Griess reaction as described previously. In short, samples (250 μl) were incubated at room temperature with 250 μl of substrate buffer (0.1 mol/l of imidazole, 210 μmol/l of NADPH, 3.8 μmol/l of flavine adenine dinucleotide; pH 7.6) in the presence of nitrate reductase (Aspergillus niger; Sigma, St. Louis, MO, USA) for 45 min to convert nitrate (NO$_3^-$) to nitrite (NO$_2^-$). Excess reduced NADPH, which interferes with the chemical detection of nitrite, was oxidised by continuation of the incubation of 5 μg (1 μl) of LDH (Sigma), 0.2 mmol/l (120 μl) of pyruvate (Sigma) and 79 μl of water. Total nitrite was then analysed by reacting the samples with Griess reagent (1% sulfanilamide, 0.1% naphthalene–ethylene diamine dihydrochloride in 5% H$_2$PO$_4$). Activity was assessed in the ethanol phase of the lysate after 1.0 ml of ethanol/chloroform mixture (5/3, v/v) was added to the same volume of the hemolysate and centrifuged. One unit of SOD is defined as the amount of protein or Hb that inhibits the rate of NBT reduction by 50%. Results were defined as units per gram of protein or haemoglobin (U/g protein or U/g Hb).

**RBCs and plasma-SOD analysis**

SOD activity in plasma and supernatant was measured according to the method of Sun et al.25 by determining the inhibition of nitroblue tetrazolium (NBT) reduction with xanthine–xanthine oxidase as an O$_2^-$ generator. Activity was assessed in the ethanol phase of the lysate after 1.0 ml of ethanol/chloroform mixture (5/3, v/v) was added to the same volume of the hemolysate and centrifuged. One unit of SOD is defined as the amount of protein or Hb that inhibits the rate of NBT reduction by 50%. Results were defined as units per gram of protein or haemoglobin (U/g protein or U/g Hb).

**RBCs and plasma GSHPx analysis**

GSHPx activity in plasma and supernatant was measured according to the method of Paglia and Valentine.20 Enzyme activity was determined from the oxidation of reduced NADPH in the presence of H$_2$O$_2$ used as substrate. The decrease in concentration of NADPH was monitored and recorded at 340 nm in a mixture containing reduced glutathione and glutathione reductase (pH 7.8, 25°C). Enzyme units were defined as the number of micromoles of NADPH oxidised per minute. Results were defined as...
as international units per gram of protein or of Hb (U/g protein or U/g Hb).

RBC-CAT analysis

CAT activity in supernatant was determined according to the method of Aebi27 by monitoring the initial rate of disappearance of H2O2 (initial concentration, 10 mM) at 240 nm (ε = 0.041/mmol x 1/cm) in a cuvette containing 10.5 mM H2O2 in 1 ml of 50 mM phosphate buffer (pH 7, 25°C), in a spectrophotometer. Results were reported as the constant rate per second per gram of Hb (K/g Hb). Protein concentrations in plasma samples were measured according to Lowry et al.28

Statistical analysis

The Mann–Whitney U-test was used for the statistics, and the results expressed as mean ± standard deviation. The two-tailed statistical significance between two means was considered p < 0.05. Statistical analysis was performed with Statistical Package for the Social Sciences for Windows (release 7.5; SPSS/PC+ Inc., Chicago, IL, USA).

Results

The mean age between patients (26.5 ± 19.0 years; range, 6–68 years) and controls (27.3 ± 18.2 years; range, 8–65 years) was comparable (p > 0.05). The mean value of TNF-α (8.5 ± 0.6 pg/ml) was significantly (p < 0.001) higher in WMS than control subjects (4.3 ± 0.2 pg/ml). RBC activities of SOD (3981.9 ± 626.6 U/g Hb) and GSHPx (682.7 ± 42.0 U/g Hb) were significantly lower in WMS patients when compared with controls (5261.6 ± 523.0 U/g Hb), p = 0.0005 and 756.5 ± 47.6 U/g Hb, p = 0.0011, respectively) (Table 1). The RBC-CAT activity of patients with WMS (125.6 ± 21.3 k/g Hb) was comparable with controls (131.0 ± 21.5 k/g Hb, p = 0.8798). The plasma levels of SOD (529.4 ± 49.3 U/g protein) and GSHPx (107.3 ± 15.0 U/g protein) were also significantly lower in WMS patients than those in controls (713.4 ± 55.7 U/g protein, p = 0.0002 and 131.4 ± 19.7 U/g protein, p = 0.0113, respectively). Plasma MDA levels in WMS patients and controls were 5.4 ± 0.8 μmol/l and 1.8 ± 0.6 μmol/l, respectively, and the difference was significant (p = 0.0002). Plasma NO concentrations in WMS patients (54.4 ± 5.7 μmol/l) were also significantly (p = 0.0002) higher than in healthy control subjects (26.9 ± 6.7 μmol/l).

Discussion

WMS is a very rare systemic connective tissue disorder with systemic and ocular findings.12 Brachymorphy, brachydactyly and, significantly, myopia were noted among parents and other relatives, suggesting that the gene might be dominant with a severely reduced penetrance or a wide range of expressivity.13,29 Alternatively, the syndrome may be considered incompletely recessive with partial expression in the heterozygote.30 Although GEMSS syndrome (glaucoma–ectopia–microspherophakia–stiff joints–short stature) has been suggested as an acceptable name for the autosomal dominant form,31 the relationship between the dominant and recessive WMS is not known. Therefore, early differential diagnosis is mandatory, especially in subtle cases, for prognostic, therapeutic and genetic reasons (genetic counselling) in order to make a nosologic diagnosis and to prevent potentially life-threatening systemic complications.

Increased oxidative damage with decreased SOD activity has been suggested in the pathogenesis of Down syndrome as well as in the ageing process.32 Electron microscopic study of the microspherophakic lens obtained from a patient with WMS clearly demonstrated epithelial cell degeneration, marked liquefaction and destruction of the subcapsular cortical fibres.33 Such degeneration and necrosis of the cells are caused by various factors including

| Table 1. Plasma LPO, NO* and antioxidant enzyme activities in plasma and erythrocytes of patients with WMS and controls |
|---------------------------------------------------------------|---------------------------------------------------------------|---------------------------------------------------------------|---------------|
| Weill - Marchesani syndrome (n = 10; four male, six female) | Healthy controls (n = 10; five male, five female) |               |
| Age (years) | 26.5 ± 19.0 | 27.3 ± 18.2 | 0.8205 |
| Plasma-MDA (μmol/l) | 5.4 ± 0.8 | 1.8 ± 0.6 | 0.0002 |
| RBCs-SOD (U/g Hb) | 3981.9 ± 626.6 | 5261.6 ± 523.0 | 0.0005 |
| Plasma-SOD (U/g protein) | 529.4 ± 49.3 | 713.4 ± 55.7 | 0.0002 |
| RBC-GSHPx (U/g Hb) | 682.7 ± 42.0 | 756.5 ± 47.6 | 0.0011 |
| Plasma-GSHPx (U/g protein) | 107.3 ± 15.0 | 131.4 ± 19.7 | 0.0113 |
| RBC-CAT (k/g Hb) | 125.6 ± 21.3 | 131.0 ± 21.5 | 0.0798 |
| TNF-α (pg/ml) | 8.3 ± 0.6 | 4.3 ± 0.2 | <0.001 |
| Plasma NO (μmol/l) | 54.4 ± 5.7 | 26.9 ± 6.7 | 0.0002 |

Data presented as mean ± standard deviation.

* Mann–Whitney U-test.
ageing, inflammation and trauma. Destruction of the cortical fibres is a common histological change seen in lenses with senile cortical cataracts. Therefore, premature ageing process may participate in WMS.

In the present study, we have studied plasma LPO and TNF-α levels with the antioxidant system SOD, CAT and GSHPx in both RBCs and plasma of patients with WMS. Both plasma and RBCs activities of SOD and GSHPx were found to be decreased whereas RBC-CAT activities did not changed. In addition, plasma MDA, TNF-α and NO* levels were also significantly increased when compared with controls. Because free radicals play a significant role in the multifactorial syndrome, which constitutes systemic and ocular manifestations, our results suggest that both RBCs and serum of WMS patients have an unbalanced antioxidant system with increased LPO and TNF-α, thus participating in the manifestations of this unique disease.

Free radicals are mainly derived from a univalent sequential reduction of molecular oxygen. Mitochondria are the main location of intracellular production, which may also result from auto-oxidation of small molecules or function of some enzymes. The free-radical theory of cell dysfunction is basically found on three main observations: (1) free radicals are extremely reactive species; (2) the production of oxy free radicals, mainly O2−, is a constant phenomenon in the organism with beneficial (defence against microbial aggression by phagocytes) and damaging effects at the cellular and molecular levels; and (3) natural defence or control mechanisms occur by enzymatic antioxidants. Therefore, an imbalance between production and control mechanisms is supposed to result in the continuous or progressive accumulation of deleterious changes throughout the cells and tissues, thus generating intense functional disorder at each level of organisation of ultrastructures, cells and organs.

The cell defence system against free-radical-induced toxic LPO (MDA), referred to TBARS, consist of antioxidative free-radical scavenging molecules such as SOD, GSHPx and CAT. These enzymes block the initiation of free-radical chain reactions. Many syndromes such as Hutchinson–Gilford, Werner’s and Down’s syndromes are genetically controlled. Because genetic mutations result in distributed activities of the antioxidative enzymes such as SOD, GSHPx and CAT, the genomic and free-radical theories are closely linked as the altered SOD/ (GSHPx plus CAT) ratio may affect gene expression by altering the binding and/or availability of transcription factors to DNA. Indeed, this study demonstrated that there was a significant increase in LPO characterised by elevated plasma MDA levels in patients with WMS when compared with healthy controls. It is well known that increased production of free radicals as a result of decreased antioxidant enzymes SOD and GSHPx can lead to the formation of LPO. In addition, both erythrocyte and plasma SOD levels as well as GSHPx activities were significantly decreased when compared with controls. If SOD levels decrease concomitantly with GSHPx, then the first (O2−) and second step (H2O2) intermediate radicals accumulate. These oxygen free radicals could undergo the Fenton’s reaction, generating hydroxyl radicals, which may lead to LPO in cells. Therefore, the increased plasma LPO levels in this syndrome may affect the susceptible target tissues more seriously.

It should be noted that the interaction between NO* and O2−, producing a cytotoxic oxidant, peroxynitrite, has recently received a great deal of attention. Indeed, decreased SOD and GSHPx activities paired with increased NO* react with O2− and cause further antioxidant depletion and, therefore, oxidative damage.

There is a debate whether a relation exists between the activation of the inflammatory mediator cascade and changes of the organism’s antioxidative system. Because free radicals are among the key mediators of a TNF-α-induced killing event, TNF-α-induced apoptosis may be mediated by free radicals and LPO in WMS.

In conclusion, although much more is known about the systemic and ocular manifestations of WMS with attempts to define still the gene, the exact aetiology is still unclear and, to our knowledge, there is no molecular study performed on WMS patients. Many other biochemical changes within the body, especially in molecular basis, cannot be ruled out. Increased LPO and NO* levels with decreased antioxidant enzyme activities found in the present study may suggest that NO*, O2− and H2O2 are generated in excess resulting in oxidative stress in WMS. These changes may affect cellular macromolecules as well as nucleic acids, leading to DNA mutation and the cessation of DNA replication. Our results are consistent with the notion that ROS may contribute to the process of cellular dysfunction in mammalians. Therefore, further studies in a larger group of patients are needed in this respect to confirm this interpretation and hypothesis.

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