



Arsenic and Oxidative Stress: An Overview

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Abstract

There are many people in the world that they are exposed to arsenic and in risk of related diseases such as diabetes, arteriosclerosis, neuropathy, infertility, and many types of cancer. Arsenic (As) is the most important toxic metalloid in the earth. Some causes of arsenic toxicity and the development of these disorders include: oxidative stress (OS), increased ROS (reactive oxygen species) production, alteration of some signaling pathway and gene expression, damages to structure and function of some proteins, especially SH-proteins, impairment of mitochondria, alteration of antioxidant defense system, changes in the secretion of some hormones such as FSH, LH, and testosterone (dysfunction of men and women reproductive system), disturbance in the structure of cellular components such as lipids, proteins, carbohydrates, and DNA. This section focused on the association of As with some diseases, e.g. diabetes, atherosclerosis, male and female infertility, and neurodegenerative disorders and sources of ROS production in these disease.

Keywords

Arsenic · Disease · Oxidative damage · Free radicals · Toxicity

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2.1 Generation of ROS in Oxidative Stress

Oxidative stress (OS) damages cell by disturbance of the balance between production of highly reactive molecules such as $\cdot\text{OH}$, $\text{O}_2^{\cdot-}$ (reactive oxygen species) and $\cdot\text{NO}$ or nitric oxide (reactive nitrogen species) and antioxidant defense system (Nordberg and Arnér 2001; Reuter et al. 2010; Valko et al. 2006; Ďuračková 2010). Free radicals are energetic molecules that have unpaired electrons in atomic orbits. The most important radicals in living system are ROS (Miller et al. 1990; Halliwell and Gutteridge 1999). ROS have a major role in stimulation of cell signaling pathway. However, overgeneration of ROS is deleterious (Thannickal and Fanburg 2000).

The overproduction of RNS (nitrosative stress) and ROS induces oxidative damage and damage to components of the cell such as DNA, lipid, protein, cell structure, and cell membranes (Valko et al. 2006; Noori 2012). ROS interact at the site of formation or far from their production site (Kohen and Nyska 2002). The toxic effects of arsenic are attributed to the generation of ROS and OS and the change of antioxidant enzymes activity (Heidari Shayesteh and Ranjbar 2013; Zargari et al. 2014). One of the mechanisms of arsenic toxicity is oxidative stress (Ercal et al. 2001).

The sources of ROS and RNS are exogenous and endogenous [*enzymatic* (produced under the physiological conditions, such as monoamine oxidase, NADPH oxidase, xanthine oxidase, cyclooxygenase, myeloperoxidase) and *non-enzymatic* (produced by Fenton's and Haber's reaction, such as H_2O_2 , $\cdot\text{OH}$, HOCl , ONOO)] (Noori 2012).

2.2 Arsenic and Oxidative Stress

Arsenic is the 33rd element of the periodic table and toxic metalloid in the form of inorganic (iAs) or organic compounds in the environment (Jomova et al. 2011). The most important forms in water are arsenite (As III: the most toxic and carcinogen form, reacting with enzymes and transcription factors) and arsenate (As 5^+). Arsenic levels of drinking water in some countries such as Mexico (García-Vargas et al. 1991), Tiwan (Yen et al. 2007), and Indo-Bangladesh are more than the amount recommended by WHO (10 $\mu\text{g}/\text{l}$) (Kinniburgh and Smedley 2001). Arsenic changes mitochondrial integrity and its membrane potential. Mitochondria is the most important organelle for the generation of ROS (by complex I and complex II of the electron transport chain). Arsenic acts directly or by the production and accumulation of ROS on the matrix of mitochondria (Pulido and Parrish 2003). The formation of superoxide anion radical and the decrease in cellular oxidant defense result in production of peroxy radicals ($\text{ROO}\cdot$), anionic form of O_2 ($\text{O}_2^{\cdot-}$), singlet oxygen or dioxygen ($^1\text{O}_2$), hydroxyl radical ($\cdot\text{OH}$), dihydrogen dioxide (H_2O_2), and dimethylarsine radical [$(\text{CH}_3)_2\text{As}\cdot$] (Flora et al. 2007). H_2O_2 is produced by the oxidation of arsenite to arsenate ($\text{H}_3\text{AsO}_3 + 2\text{H}_2\text{O} + \text{O}_2 \rightarrow \text{H}_3\text{AsO}_4 + \text{H}_2\text{O}_2$) (Valko et al. 2005). H_2O_2 with iron generates highly reactive hydroxyl radical (Fenton reaction) with

mutagenic effect (Hei et al. 1998). In addition, arsenic generates RNS during metabolism (Shi et al. 2004) (Fig. 2.1).

2.3 Arsenic Detoxification Mechanisms (Methylation of Arsenic)

The biotransformation of As or its detoxification and production of metabolites induces oxidative stress (Flora 2011). Arsenic detoxification mechanisms are as follows:

- Conversion of As^{+5} to As^{+3} by PNPase (purine nucleoside phosphorylase) in plasma (Radabaugh et al. 2002) [Tripeptide glutathione (GSH) and other thiol compounds are required for this conversion] (Scott et al. 1993; Flora et al. 2007).
- The methylation of As^{+3} via As^{+3} methyltransferase (As_3MT) (Hayakawa et al. 2005; Lin et al. 2002) in liver (Marafante et al. 1985) and the production of arsenic acid monomethyl (MMAA), and finally arsenic acid dimethyl (DMAA) [s_adenosyl_methionine (SAM) is involved in arsenic methylation) (Rossman 2003; Némethi and Gregus 2002). Like other toxic metals, it is converted to the less toxic form by methylation and other reductant factors, such as TR (thioredoxin reductase), TRX (thioredoxin), dihydrolipoic acid] (Waters et al. 2004). Arsenic can conjugate with GSH and produce arsenite triglutathione and then MMA (SG)₂(monomethylarsenic diglutathione and DMA (SG) (dimethylarsinic glutathione) (Kenyon et al. 2008).
- The reduction of methylation capacity increases the toxic effects of arsenic, e.g., hypo methylation of DNA leads to impaired gene expression, such as oncogenes or tumor—the suppressor genes (Roy and Saha 2002). In vitro studies indicated that MMAA inhibits glutathione reductase. MMAA is very toxic to human liver cells. The degree of cytotoxicity is: $\text{MMAA}^{+3} > \text{arsenite} > \text{arsenate} > \text{MMAA}^{+5} = \text{DMAA}^{+5}$ (Petrick et al. 2000).

2.4 Arsenic and Signaling Pathways

Arsenic altered some signaling pathways, such as:

- Tyrosine phosphorylation pathway including receptor tyrosine kinase (RTKs), such as growth factor receptors and nonreceptor tyrosine kinase (NTKs), such as Src family (Blume-Jensen and Hunter 2001). Arsenic induces the phosphorylation of epidermal growth factor receptor (EGFR) in the cell. It interacts with the SH-group of EGFR (Wu et al. 1999)
- The mitogen-activated protein (MAP) kinase (Kumagai and Sumi 2007)
- Alteration of the major transcription factors, such as NF-Kappa B and activated protein-1 (AP-1) (stress-induced transcription factors), regulating proinflammatory genes in defense of cell (Chen and Shi 2002)

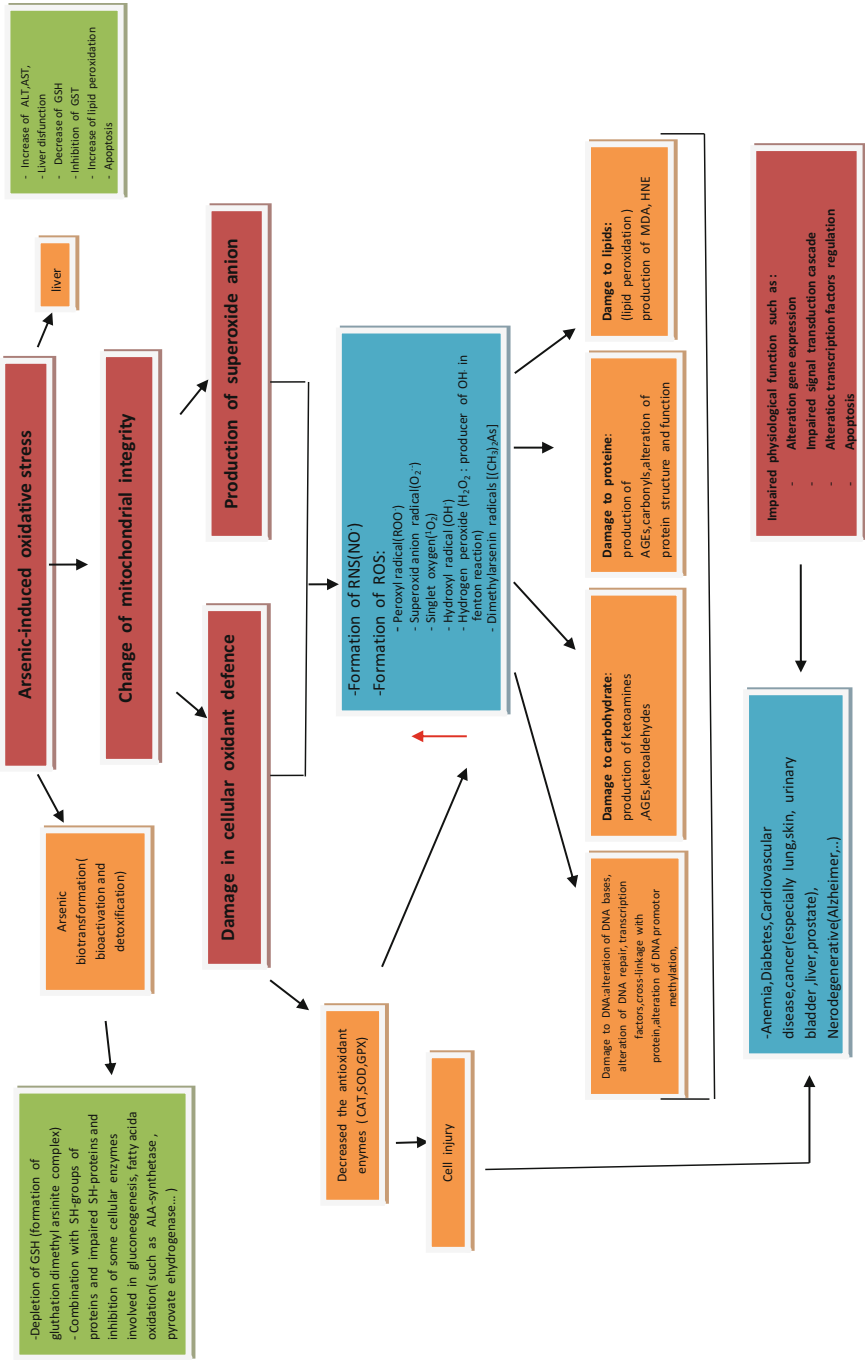


Fig. 2.1 Mechanism of arsenic-induced oxidative stress

- The activation of p53 and the induction of apoptosis (Filippova and Duerksen-Hughes 2003). Arsenic-induced apoptosis, due to the increase in cytochrome c, imbalance of Ca^{++} , increased Bax expression, and the downregulation of Bcl-2 (Das et al. 2009)

2.5 Arsenic and Antioxidant Enzymes Activity

The activity of antioxidant enzymes (SOD, CAT, GPx, GST, GR) increases with short term and low levels of arsenic exposure. The chronic exposure of arsenic decreases their activity (Shi et al. 2004; Zargari et al. 2015).

2.6 The Effect of Arsenic-Induced Oxidative Stress on Proteins

Some ROS such as $\cdot\text{OH}$ and $\text{O}_2^{\cdot-}$ damage proteins (Stadtman 2004; Samuel et al. 2005; Valko et al. 2006; Kaneto et al. 2005). Arsenic has different effects on proteins that some of them are as follows:

- The production of aldehydes, keto compounds, and carbonyls [3-nitrotyrosine as protein oxidative marker] (Kaur et al. 2011; Stadtman and Oliver 1991; Blokhina et al. 2003)
- Damage to the specific amino acid residues [in particular oxidation of cysteine and methionine residue, which may cause the formation of disulfides between (-SH) group of proteins or the formation of glutamyl semialdehyde and impaired SH-proteins] (Dalle-Donne et al. 2003)
- A change in protein structure, degradation, unfolding, fragmentation, inactivation of enzymes (Kaneto et al. 2005; Kelly and Mudway 2003; Dean et al. 1985)
- Altered cellular function (e.g., changing the energy production, due to the inhibition of pyruvate dehydrogenase by especially MMAIII) (Reichl et al. 1988; Hughes 2002)
- The change in the type and level of cellular proteins (the reduction of antioxidant enzymes) (Flora 1999)
- Production of AGEs or advanced glycated proteins. They are produced by the reaction between carbohydrates and the free amino group of proteins, e.g. pentosidine and carboxymethyl lysine (CML) as the most important of AGEs (Dalle-Donne et al. 2005)
- Increased proteolysis due to production of reactive carbonyl groups (RCGs) (Mahata et al. 2007; Kelly and Mudway 2003)

2.7 Arsenic-Induced Oxidative Stress and DNA

DNA is sensitive to the free radicals, due to the unsaturated bounds in purine and pyrimidine rings. Arsenic damages DNA by ROS production and alteration of the enzymes that are needed to repair DNA (Bartsch and Nair 2004; De Vizcaya-Ruiz et al. 2009). The important damages of arsenic on DNA are as follows:

- The alteration of DNA bases: 8-hydroxydeoxyguanosine: 8-OHdG as the marker of oxidative damage to DNA or 8-oxoadenine [detected in urine of animal exposed arsenic] thymine glycols, 5-hydroxymethyl-uracil are produced in oxidation of DNA (Bartsch and Nair 2004; De Vizcaya-Ruiz et al. 2009; Cooke et al. 2003). Binding of altered bases to transcription factors alters the expression of some dependent genes (Ghosh and Mitchell 1999)
- DNA strand break (single and double) (Ying et al. 2009; Mourón et al. 2006; Dong and Luo 1993)
- The loss of purines (the formation of apurinic sites) (Yamanaka et al. 1995)
- The cross-linkage of DNA–protein (Huang et al. 2004)
- Altered gene expression as a result of damage to the transcription factors (Huang et al. 2004; Lantz and Hays 2006; Díaz-Villaseñor et al. 2007). However, based on an in vitro study, As does not effect on the transcriptional regulator of DNA (Lantz and Hays 2006)

2.8 The Effect of Arsenic-Induced Oxidative Stress on Lipid

Many clinical studies indicated that arsenic causes lipid peroxidation (Wirtitsch et al. 2009; De Vizcaya-Ruiz et al. 2009). Some important damages of arsenic on lipids include:

- Production of cyclic endoperoxide, isoprotans, and hydrocarbons
- Peroxidation of cell membrane lipids. The high concentration of unsaturated fatty acids in the cell membrane leads to oxidative damage and inactivation of membrane-bound receptors.
- The formation of fatty acid radical (ROO[·]).
- The formation of lipid hydroperoxide, leading to a chain reaction and the oxidation of fatty acids in the membrane of the cells (Halliwell and Gutteridge 2015)
- Peroxidation of membrane lipids and generation of two important markers of lipid peroxidation called malondialdehyde (MDA) and 4-hydroxy-2-nonenal (HNE) (Wirtitsch et al. 2009)

2.9 The Effect of Arsenic-Induced Oxidative Stress on Carbohydrates

- Producing ketoamines and ketoaldehydes and changing carbohydrate metabolism (the inhibition of pyruvate dehydrogenase complex, hyperglycemia, and glucose intolerance) (Ghafghazi et al. 1980)
- Producing AGEs.

2.10 Arsenic-Induced Oxidative Stress and Some Disorders

Some disorders linked to arsenic-induced oxidative stress are diabetes, cardiovascular disease, neurodegenerative disease, and infertility, which are discussed in the following.

2.10.1 Oxidative Stress and Diabetes

Some studies have demonstrated the relationship between the oxidative stress, diabetes and its complications, as micro- and macro-vascular dysfunction such as retinopathy, neuropathy, stroke, heart disease, and atherosclerosis (Phillips et al. 2004; Asfandiyarova et al. 2006). Diabetes mellitus (DM) refers to the metabolic disorder, which is characterized by the elevated levels of blood glucose caused by the lack or insufficient insulin secretion or defects in insulin action (Maritim et al. 2003). Insulin is a hormone secreted by β -cells of pancreatic islets, which has an important role in glucose, lipids, and proteins metabolism. Some mechanisms of oxidative stress-induced diabetes are as follows:

- The auto-oxidation of glucose and hyperglycemia increases the OS (Rains and Jain 2011; Maritim et al. 2003) [NADPH oxidase, an important producer of ROS in various cells, has a major role in hyperglycemia-induced oxidative stress] (Jain 1989; Wolff and Dean 1987; Jiang et al. 1990). Reactive compounds such as ketoaldehydes, superoxide anion radicals, peroxynitrite, and toxic hydroxyl radicals are produced in the presence of oxidized glucose, transition metals, and nitric oxide (Hogg et al. 1993; Halliwell and Gutteridge 1990)
- A change in the redox balance status [reduced glutathione (GSH), vit E, impaired antioxidant defense]. Glutathione is a tripeptide consisting of three amino acids cysteine, glycine, glutamate and has an important role in antioxidant defense, transference of amino acids, redox balances, scavenging of free radicals, and enzymatic reaction (Tsai et al. 2012; Gregus et al. 1996). Some studies showed that the level of GSH reduces in diabetes. The decreased GSH results in β -cells dysfunction and other complications in diabetes, such as hyperlipidemia, inflammation, and DNA damage. Keeping the GSH redox state may be useful for diabetic patients (Dinçer et al. 2002; Das et al. 2012; Livingstone and Davis 2007; Tan et al. 2012).

- The damage to β -cells and the reduction of insulin secretion as a result of the low levels of antioxidant enzymes (Ceriello and Motz 2004; Lipinski 2001) and the production of mitochondrial superoxide activating UCP-2 [uncoupling protein-2, a mitochondrial inner membrane protein], reduction of ATP/ADP and increase of the superoxide formation (Brownlee 2003).
- The increased protein cyclin-dependent kinase inhibitor 1 and decreased insulin mRNA (Maechler et al. 1999).
- The disturbances of lipid profile, such as the production of ox LDL, and lipid oxidation (the formation of highly reactive compounds such as MDA and HNE). A change in the cellular structure and its function, especially alteration of membrane-bound receptors and membrane proteins with thiol groups. Ox LDL is associated with the risk for atherosclerosis (Tsai et al. 1994; Kawamura et al. 1994; Rabini et al. 1994; Guo et al. 2012; Cai and Harrison 2000; Goldstein et al. 1979).
- The disturbance of insulin signaling cascade that leads to the insulin resistance (Rains and Jain 2011; Ogihara et al. 2004).
- The increased stress signaling pathway, such as NF-kappaB and apoptosis of B cells by glycated proteins, reduction of insulin expression due to alteration of JNK pathway (Rhodes 2005; Kaneto et al. 2005; Mohamed et al. 1999).
- The damage to the proteins [the production of modified, nonfunctional, denatured, and glycated proteins (AGEs) such as glycated hemoglobin, glycation of lens proteins, and cataract formation (Ramalho et al. 1996; Yano et al. 1989)]. The protein oxidation is in side chain of cysteine, methionine, and tyrosine. The products of protein oxidation in oxidative stress are carbonyls [the marker of protein oxidation], advanced oxidation protein products [AOPPs], known as proinflammatory and prooxidant compounds (Suzuki and Miyata 1999; Pandey and Rizvi 2010; Witko-Sarsat et al. 1996).
- The damage to the mitochondria function, which increases the free radicals production, due to impaired electron transfer chain (Turrens et al. 1985; Liu et al. 2002).
- Alteration of antioxidant enzymes activity such as CAT, SOD, GPx (Goth and Eaton 2000; Giugliano et al. 1995; Shukla et al. 2012; Maritim et al. 2003). CAT is present in all living organisms and regulator of hydrogen peroxide metabolism. Catalase plays a major role in oxidative stress. The deficiency of CAT leads to the damage of β -cells, containing a large amount of mitochondria and H_2O_2 producer (increasing ROS and fibronectin expression) (Hwang et al. 2012). Patel et al. (2013) showed that high blood glucose leads to increased H_2O_2 production and downregulation of expression of CAT gene. Some studies indicated the decreased SOD level in diabetic blood and tissues (He et al. 2011; Shukla et al. 2012; Giugliano et al. 1995). SOD is an enzyme found in mammalian tissues and converts superoxide anion to molecular oxygen and hydrogen peroxide. Three forms of SOD include: cytosolic Cu-Zn superoxide dismutase (SOD1), mitochondrial Mn-SOD (SOD2), and extracellular SOD(SOD3 or EC-SOD). SOD1 and SOD2 have an important role in diabetic nephropathy and SOD3 or EC-SOD

involves in scavenging of superoxide radicals in extracellular (Oury et al. 1996; Zelko et al. 2002) (Fig. 2.2).

2.10.1.1 Arsenic Toxicity and Diabetes Mellitus (DM)

In Taiwan Lai et al. (1994) reported for the first time that there is a relationship between the prevalence of diabetes and chronic exposure to the arsenic. Other researches in Bangladesh, Swedish, and Mexico confirmed the high prevalence in the postmenopausal women (>50 years) (Rahman and Axelson 1995; Rahman et al. 1998; Coronado-González et al. 2007). Other studies indicated the relationship between diabetes and iAs (inorganic arsenic) (Tsai et al. 1999; Navas-Acien et al. 2006). Some mechanisms of diabetes are induced by inorganic arsenic (Fig. 2.3) and its methylated metabolites, especially trivalent arsenicals and they are as follows:

- The phosphorus substitution, increasing ROS and altering some genes expression, such as increasing renal hexokinase II: HK-II expression in mice, which causes pathological changes in kidney (Tseng 2004; Pysker et al. 2007).
- The insulin resistance and alteration of glucose homeostasis [by inhibiting the AKT signaling pathway and inhibiting glucose transporter 4 transposition to plasma membrane (Rudich et al. 1998; Paul et al. 2007; Hamann et al. 2014).
- The reduction of the expression of many genes, such as GLUT4, AKT (Walton et al. 2004; Paul et al. 2007; Hamann et al. 2014).
- The upregulation of Nr-f2 signaling pathway in mice increased the expression of antioxidant enzymes and the inhibition of glucose uptake (Xue et al. 2011; Duan et al. 2015).
- The inhibition of adipogenesis and decreased lipid storage capacity by inhibiting the adipocyte differentiation [the alteration of the expression of PPAR- γ and CEBP- α]. PPAR- γ is a nuclear receptor that regulates the storage of fatty acids and glucose metabolism. CEBP- α is a transcription factor and the inducer of adipogenesis (Hou et al. 2013; Hamann et al. 2014; Wauson et al. 2002).
- The damage to β -cells. One of the most important causes of β -cells dysfunction is oxidative stress. β -cells damage occurs due to low antioxidant defense, mitochondrial damage, and generation of superoxide (Kaneto et al. 2007; Tiedge et al. 1997). Arsenic is involved in the development of diabetes through damage to function of β -cells, secretion and synthesis of insulin (Zhu et al. 2014; Lu et al. 2011).
- The programmed cell death or apoptosis of β -cells, due to the production of arsenic-induced ROS and production of the activated caspase 3 and increased NF-kappaB activity (Rhodes 2005).
- The upregulation of some essential transcription factors such as Nr-f2. It is the regulator of expression of the cellular antioxidant proteins. Inhibition of TXNRD1 protein (thioredoxin reductase 1), imbalance of intracellular redox status, and inhibition of insulin secretion (Xue et al. 2011).

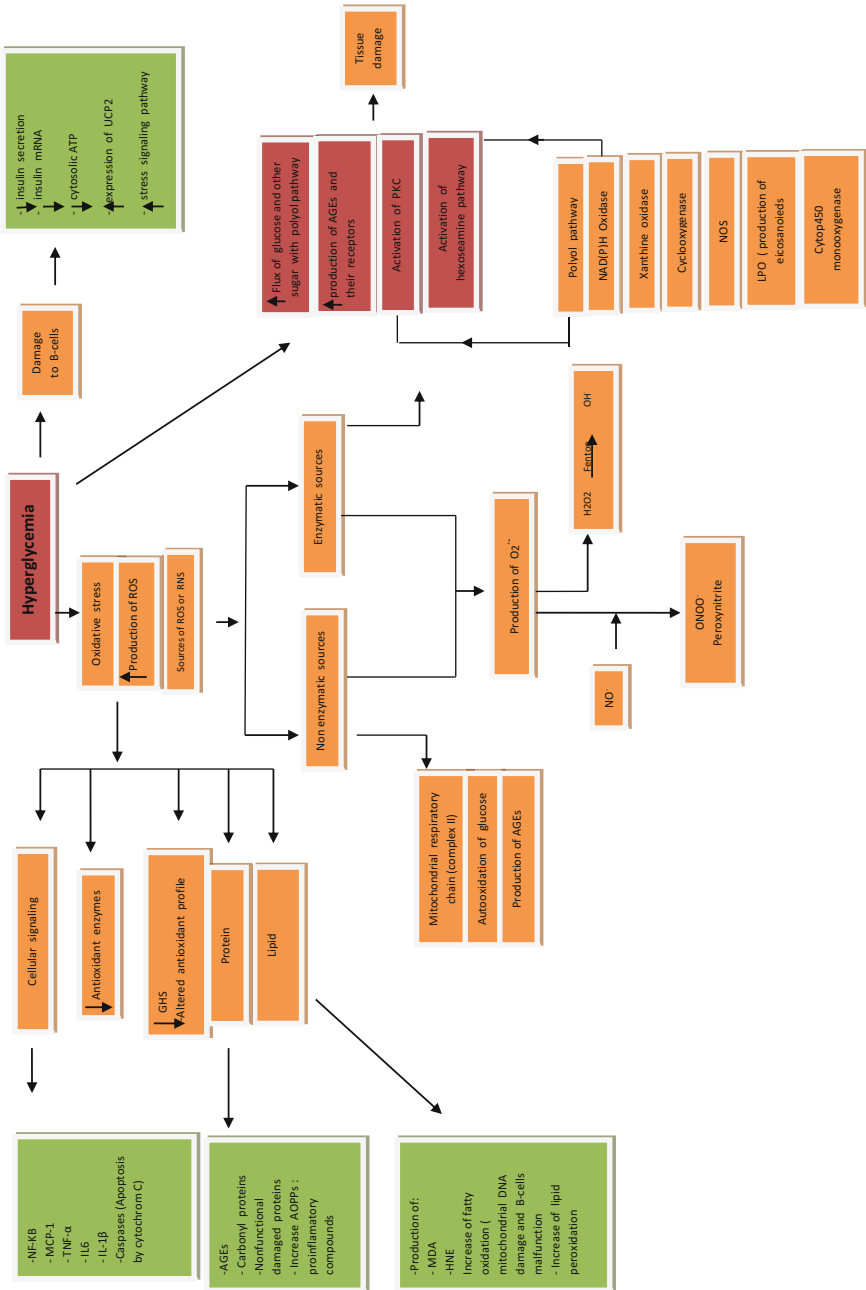


Fig. 2.2 Hyperglycemia induced oxidative stress

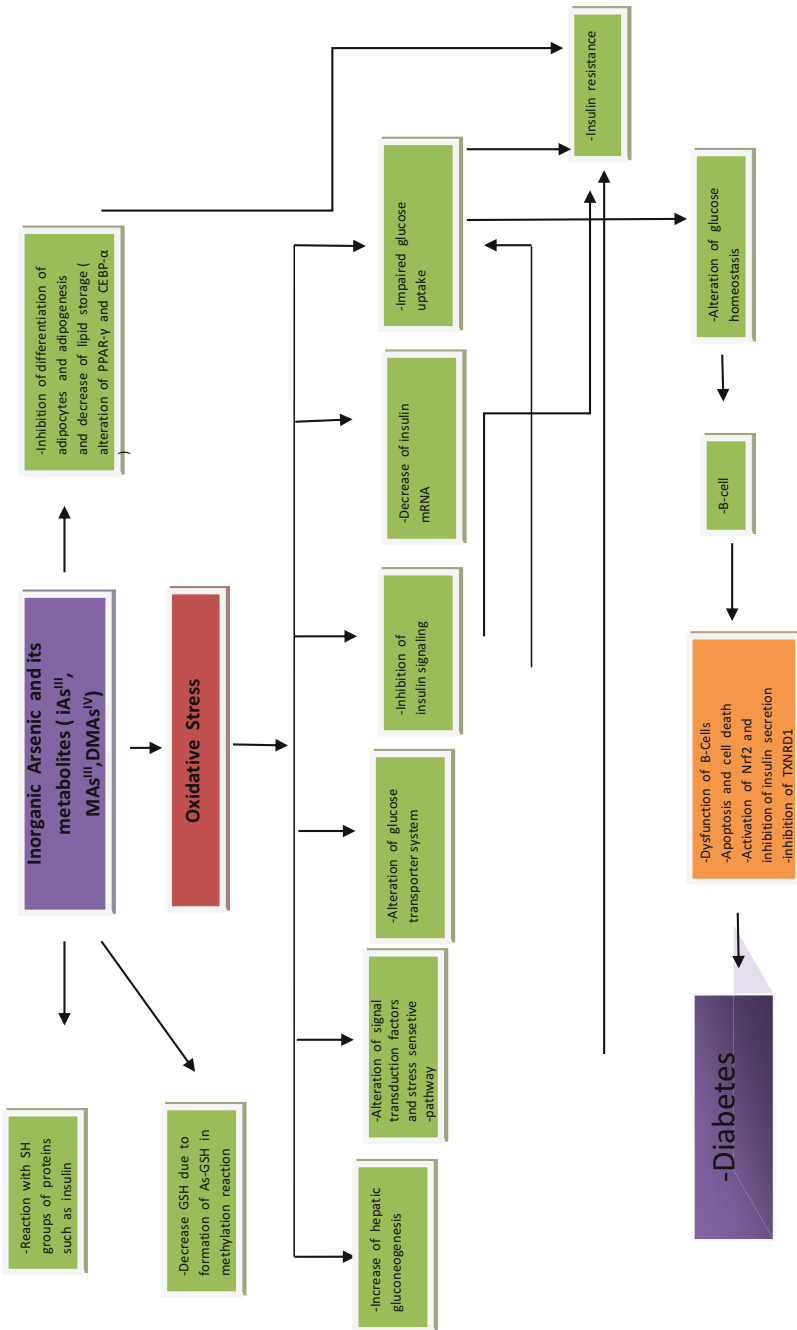


Fig. 2.3 Mechanism of arsenic-induced diabetes

- Decreased production of insulin-related mRNA due to overproduction of ROS (Díaz-Villaseñor et al. 2006).
- The stimulation of hepatic gluconeogenesis. The induction of expression of PEPC [an enzyme in the metabolic pathway of gluconeogenesis] results in fasting hyperglycemia (Díaz-Villaseñor et al. 2007).

2.10.2 Oxidative Stress and Arteriosclerosis

Arteriosclerosis is a disease characterized by hardening and thickening of the arterial wall due to the accumulation of serum lipoprotein LDL (low density lipoprotein) and endothelial damage. The oxLDL (oxidized form of LDL) plays an important role in the formation of foam cells and atherosclerosis plaque in the arterial wall (Lusis 2000). The oxLDL increases the expression of intracellular adhesion molecule-1 (ICAM-1), platelet, and selectins that facilitate the leukocytes binding and plaque formation. Plaques contain a central lipid core with crystals of cholesterol plaques, resulting in the myocardial infarction or stroke (Hennig et al. 2001; Inoue and Node 2006; Stocker and Keaney 2004; Madamanchi et al. 2005; Devasagayam et al. 2004; Lum and Roebuck 2001).

Some studies demonstrated that OS has an effective role in the development of disease and various cardiovascular disorders (Dhalla et al. 2000; Kukreja and Hess 1992).

The main and important ROS sources in atherosclerosis include:

- Smooth muscle cells (SMCs) and immune cells (macrophages) in blood vessel arteries (Antoniades et al. 2007).
- Hypercholesterolemia. It stimulates the production of superoxide anion ($O_2^{\cdot-}$) from the smooth muscle cells (Vepa et al. 1999).
- Mitochondria. One of the major sources of superoxide anion ($O_2^{\cdot-}$) production is electron transport chain in mitochondria. Mitochondrial dysfunction is associated with the atherosclerosis (Singh and Jialal 2006; Madamanchi et al. 2005).
- Enzymatic sources:
 - Nicotinamide adenine dinucleotide phosphate oxidase (NAD(P) H oxidase), in the vascular cells, leads to production of ROS. Some stimulators such as Ang II (angiotensin II), PDGF (platelet derived growth factor), TNF- α (tumor necrosis factor α) regulate its production (Griendling et al. 2000; Harrison et al. 2003; Droge 2002).
 - XO (xanthine oxidase) is a flavoprotein found in serum and endothelial cells. It is not present in smooth muscle cells. Two forms of XO exist, including xanthine dehydrogenase (XD) and XO and XD is transformed into oxidase. During the conversion of hypoxanthine and xanthine to uric acid by the XO superoxide anion is produced. The enzyme level is increased in the coronary

patients and in asymptomatic young individuals with familial hypercholesterolemia (Spiekermann et al. 2003; Droge 2002; Harrison et al. 2003).

- Myeloperoxidase (MPO) produces hypochlorous acid, as more potent oxidant, from H_2O_2 and expressed in neutrophil granulocytes. Increased MPO level is shown in patients with coronary disease, due to the oxidation or modification of lipo-proteins, such as LDL by MPO and the production of modified apolipoproteins. Serum level of MPO can be utilized to prediction of cardiovascular disease (Daugherty et al. 1994; Heinecke 2003; Zouaoui Boudjeltia et al. 2004; Baldus et al. 2003; Brennan et al. 2003; Bergt et al. 2004; Pennathur et al. 2004).
- NOS (nitric oxide synthase) produces potent vasodilator nitric oxide (NO) from L-arginine under normal condition. NO production is required for the endothelial function. Endothelial NOS (eNOS) produces O_2^- , H_2O_2 , and peroxynitrite in absence of L-arginine and increases OS. eNOS plays an essential role in protecting the wall of blood cells from atherosclerosis. Some experimental studies indicate that the activity of eNOS in atherosclerosis is decreased (Schächinger and Zeiher 2002; Singh and Jialal 2006; Cai and Harrison 2000)
- LPO, lipoxygenase(s), catalyze the dioxygenation of polyunsaturated fatty acids (arachidonic acid) and produce biologically active lipids such as prostanoids (prostaglandins, thromboxanes, and prostacyclin), lipoxin, and leukotrienes. They are involved in inflammatory reaction and increased vascular permeability and atherogenesis (Stocker and Keaney 2004). Some experimental studies indicated some lipoxygenases oxidized LDL (Folcik et al. 1995)

2.10.2.1 ROS-Induced Damage to Vascular Function

- The damage to the cell membrane, nuclei, especially hydroxyl radicals, and dysfunction of endothelial (Suwaidi et al. 2000; Antoniades et al. 2003; Schächinger et al. 2000)
- The interaction with the vasoactive mediators in cells of endothelium (Antoniades et al. 2003).
- The formation of oxLDL. oxLDL activates monocytes and inhibits migration of macrophage and releases proinflammatory cytokines (Antoniades et al. 2007; Hennig et al. 2001).
- The production of NF-kappaB and activator protein-1 (AP-1) in oxidative stress. They increase the expression of vascular cell adhesion molecule-1 (VCAM-1), ICAM-1, E-selectin, and other cytokines. Accumulation of these molecules on the endothelial wall causes change in vascular permeability and endothelial wall dysfunction (Hennig et al. 2001; Bourcier et al. 1997; Tousoulis et al. 2007).

2.10.2.2 Arsenic Toxicity and Atherosclerosis

The association between cardiovascular disease (CVD) and arsenic exposure has not been established and evidences are limited and mechanisms are unclear (Navas-Acien et al. 2005; Wang et al. 2007a, b). Lemaire et al. (2011) demonstrated that arsenic may have proatherogenic effects on mice. Some epidemiological studies in Taiwan and Bangladesh indicated a positive association between the arsenic and

heart disease and high pulse pressure, which may be related to the arsenic detoxification and the increase of homocysteine and cardiovascular disease (Hsueh et al. 1998; Chen et al. 2007; Gamble et al. 2005; Zakharyan and Aposhian 1999; Araki et al. 1989; Lim and Cassano 2002). Based on the results of some studies, there is a relationship between arsenic and some genes expression, such as NOS3 (Balakumar and Kaur 2009; Desjardins and Balligand 2006), SOD2, monocyte chemoattractant protein-1 (MCP-1), interleukin 6 (IL-6) and ET-1 (endothelin-1) mRNA in mice (Sun et al. 2009; Lee et al. 2005; Soucy et al. 2005). They are involved in endogenous defenses against ROS and other risk factors for vascular dysfunction and maintaining vascular tone. Overproduction of ROS leads to loss of mitochondrial function, oxidative stress, alterations in the mitochondrial structure and cellular damage, endothelial cells death (Wang et al. 2002; Andreyev et al. 2005; Packer 1961). Endothelial vascular damage occurs as a result of reduced synthesis of NO and inactivation of eNOS and overgeneration of ROS. Dysfunction of vascular endothelial is a risk marker of atherosclerosis (Kumagai and Pi 2004; Lee et al. 2003; Cai and Harrison 2000; Balakumar and Kaur 2009; Davignon and Ganz 2004).

Based on the animal experimental studies, MDA and HNE accumulate in advanced lesions. They play an important role in the constitution of atherosclerotic lesion. Due to the production of proinflammatory factors such as MCP-1, IL-6, and TNF-alpha in exposure to arsenic it is an important risk factor for atherosclerosis (Tsou et al. 2005).

As induces hypertension. Many studies are needed due to increased sensitivity to calcium in blood vessels, phosphorylation of myosin and disruption of the antioxidant defense (Yang et al. 2007) (Fig. 2.4).

2.10.3 Oxidative Stress and Neurodegenerative Disease

Oxidative stress leads to neurotoxicity, mitochondrial dysfunction, severe disorders of neuronal cells and cell death (Caito and Aschner 2015; Cicero et al. 2017; Hsieh and Yang 2013).

Free radicals damage brain and neuronal cells (Chance et al. 1979; Floyd and Carney 1992; Marklund et al. 1982; Zaleska et al. 1989; Pamplona 2008; Halliwell et al. 1992). Brain and neuronal cells are prone to oxidative damage due to their high concentration of polyunsaturated fatty acids, high oxygen and glucose consumption, presence of some metals, such as Cu, Fe, vitamin C, and low levels of antioxidant enzymes.

Oxidative damage to neuronal cells leads to neurodegenerative diseases such as Alzheimer's and Parkinson's disease (Perry et al. 2002). In Alzheimer's disease (AD) there is an accumulation of misfolded protein called beta-amyloid ($A\beta$) plaque in the brain (Opazo et al. 2002). Parkinson's disease (PD) is associated with the accumulation of abnormal α -synuclein protein, degradation of dopaminergic neurons, in the brain due to oxidative stress (Segura-Aguilar et al. 2014; Gasser 2001; Dalfó et al. 2005). These misfolded proteins inhibit mitochondrial function

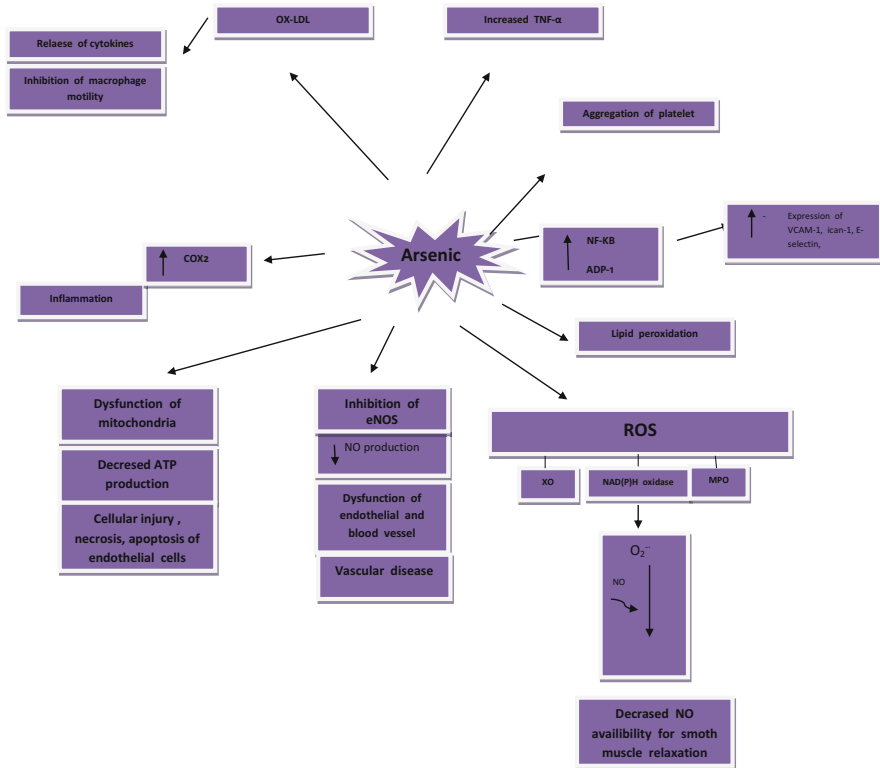


Fig. 2.4 Mechanism of arsenic-induced atherosclerosis

and induce more OS (Abramov et al. 2017; Caspersen et al. 2005). The dysfunction of mitochondria is important in both AD and PD process (Angelova and Abramov 2017; Schapira 2008; Andersen 2004). The etiology and mechanisms of damage to the neuron cells in neurodegenerative disease are unclear but the important sources of oxidative stress are related to AD and PD, which are discussed in the following.

2.10.3.1 Oxidative Damage in Alzheimer's Disease

- Decreasing the complex IV activity in the mitochondria and generation of ROS (Sheehan et al. 1997; Du et al. 2010).
- Increasing the H_2O_2 production, due to $A\beta$ peptide accumulation and cytochrome C release (Lloret et al. 2008).
- Increasing the protein carbonyl (Bogdanovic et al. 2001; Sultana et al. 2010).
- Increasing the AGEs production and their receptors (Takeuchi et al. 2007).
- Increasing the mitochondrial VDAC1 (voltage-dependent anion channel 1) as a regulator of important metabolic function of the cell, such as homeostasis of calcium, OS, and apoptosis (Shoshan-Barmatz et al. 2018).

- Increasing the intracellular free ca^{++} that results in the reduction of GSH and accumulation of ROS (Ferreiro et al. 2008).

2.10.3.2 Parkinson's Disease and Oxidative Stress

- Dopamine (DA) metabolism. Dopamine quinone [6-hydroxydopamine as a neurotoxin (Graham 1978; Tse et al. 1976)] is produced from oxidation of dopamine. That leads to production of misfolded proteins, such as α -synuclein, Parkin protein, DJ-1, and inactivation of DA transporter, tyrosine hydroxylase, damage to mitochondria and decreased complex I in mitochondria (Betarbet et al. 2002; Schapira et al. 1989; Parker et al. 2008; Kuhn et al. 1999; Sulzer and Zecca 2000; Gluck and Zeevalk 2004; Jana et al. 2007; Van Laar et al. 2009; Whitehead et al. 2001; Andersen 2004; Betarbet et al. 2002; Parker et al. 1989).

- Mitochondrial dysfunction

The peroxidation of cardiolipin leads to apoptosis due to release of cytochrome C (Betarbet et al. 2002; Parker et al. 1989).

The damage to the complex I transporter chain and decreased ATP production (Mizuno et al. 1987).

The dysfunction of some proteins, such as DJ-1, as a recognizer of OS, redox-chaperone protein, and related genes to PD, leads to more damage of mitochondria (Van Laar et al. 2009; Conway et al. 2001; LaVoie et al. 2005).

The alteration of related genes in the regulation of mitochondrial homeostasis in PD (PINK 1- PARK-2) that inhibits the complex I activity (Valente et al. 2004; Gilks et al. 2005).

- The inflammation of neurons.

The production of ROS and inflammatory cytokines, due to the production of neuromelanin from DA oxidation, which can interact with iron and leads to overgeneration of ROS (Garrido-Gil et al. 2013)

2.10.3.3 Arsenic Toxicity and Neurodegenerative Disease

Less investigation has been done on the association between exposure to As and neurodegenerative disease. Arsenic is one of the most important environmental risk factors for these disorders (Chin-Chan et al. 2015; Engström et al. 2010; Butterfield et al. 2002; Loh et al. 2006; Cheung et al. 2007). Recent studies indicated that As damages the mitochondria and function of neurological cells. The highest accumulation of As and its methylated components are in the hypophysis (Sanchez-Pena et al. 2010). Positive association between soil arsenic and mortality from Alzheimer's disease was reported by Li et al. in Mainland China (2020).

Some mechanisms of arsenic toxicity in the brain (Fig. 2.5) are as follows:

- The alteration of some signaling pathway, e.g., glucocorticoid signaling (interaction with glucocorticoid receptors and the inhibition of some transcription factors and alteration of nuclear function), cholinergic and monoaminergic signaling (Kaltreider et al. 2001; Kobayashi et al. 1987; Chandravanshi et al. 2019).
- Decreased activity of choline acetyltransferase (CHAT) and acetylcholinesterase (ACHE) (Baldissarelli et al. 2012; Nagaraja and Desiraju 1994).

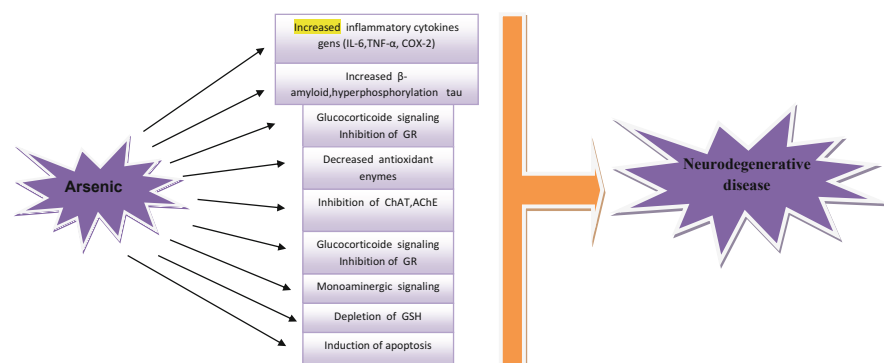


Fig. 2.5 Mechanism of arsenic-induced neurodegenerative disease

- Increased the β -amyloid protein, tau protein hyperphosphorylation, endothelial cell dysfunction, and inflammation in cell culture studies (Vahidnia et al. 2007; Giasson et al. 2002; Fry et al. 2007; Hardy and Higgins 1992; Zarazúa et al. 2011).
- The depletion of GSH and the induction of OS (Chang et al. 1991; Huang et al. 1993; Bermejo et al. 2008; Jomova and Valko 2011).
- The alteration of some transporter systems, such as brain monoamines especially dopamine, serotonin (5-HT), and noradrenaline (NA) (Martinez et al. 2008).
- Change of gene expression of some antioxidant (SOD, Trx-1) (Rodríguez et al. 2010; Lau et al. 2008; Zhang 2006).
- Activation of p38, MAPK and JNK3 signaling pathway and induction of apoptosis, oxidative damage which leads to Alzheimer's disease (Chandravanshi et al. 2018; Namgung and Xia 2001; Lu et al. 2011; Yen et al. 2012).
- The adjustment of the expression of inflammatory cytokine genes (Sun et al. 2017; Praticò and Trojanowski 2000; McGeer et al. 2006).
- The enhancement of Bcl2/Bax ratio and change in the potential of the mitochondrial membrane in brain, stimulation of apoptotic signaling, especially caspases-3, decrease in the level of Nr-f2 and Tex (Lu et al. 2014; Pradelli et al. 2010; Friedlander 2003; Shacka and Roth 2005; Srivastava et al. 2014).
- The storage of α -synuclein protein (SYN) and the oligomerization of SYN and synucleinopathies (Cholanians et al. 2016)
- Arsenic has a synergistic effect on the toxicity of dopaminergic cells in PD, as As and DA can increase toxicity in the neuronal cells, leading to the development of PD, probably with the production of DA quinone as a highly toxic free radical (Shavali and Sens 2008; Sulzer and Zecca 2000).

2.10.4 Infertility and Oxidative Stress

Infertility is considered as a serious health problem over the last decades. Recently, studies demonstrated that the oxidative stress and the overproduction of ROS (such as, OH, H₂O₂, O₂^{·-}) damage the normal function of sperm and cause male or female infertility. One of these ROS is the H₂O₂ with the beneficial and damaging effect on sperm. The low level of H₂O₂ increases sperm–oocyte fusion (phosphorylation of tyrosine leads to the binding of sperm membrane to zona pellucida ZP3 protein) (de Lamirande and Gagnon 1995; Sharma and Agarwal 1996; Agarwal and Saleh 2002; Saleh and HCLD 2002; Twigg et al. 1998; Aitken and Clarkson 1987; Aitken et al. 1995, 1998).

There is no sufficient information about the ROS or OS and function of reproductive system. Some mechanisms of the effect of OS on the reproduction (Cicinelli et al. 1996; Halliwell and Gutteridge 1984; Penniston 1983) are as follows:

- Lipid damage, the production of lipid hydroperoxides, as cytotoxic, leads to the inactivation of enzymes, damage to DNA, cell leakage, membrane disruption (permeability to electrolytes).
- The modification of some transcriptional factors and gene expression (Paszkowski and Clarke 1996)
- The depletion of ATP, produced in the mitochondria during oxidative phosphorylation, for example, gametes use the produced ATP for mobility (Liu and Keefe 2000; Liu et al. 2000; Valko et al. 2007).

In the normal condition, low levels of ROS are essential for spermatocytes function, motility, hyperactivation, acrosome reaction, the interaction of sperm with oocyte, due to peroxidation of plasma membrane lipids and adhesion of sperm–oocyte (Agarwal et al. 2004; Griveau and Lannou 1997; Kodama et al. 1996) However, an unbalance between the production of ROS and their removing causes the development of oxidative stress in the seminal (Sikka et al. 1995; Sikka 2001; Sharma and Agarwal 1996). Spermatozoa (immature sperms) and white blood cells (leukocytes) in human semen are the most important sources of ROS. ROS are produced in spermatozoa by the NADPH oxidase in the membrane of plasma and NAD(P)H-dependent oxidoreductase in the mitochondria. High pressure of oxygen leads to the loss of sperm motility, flexibility, less or lack of interaction with oocyte for fertilization (Aitken et al. 1992, 1994; Gavella and Lipovac 1992; Aitken and Baker 1995; MacLeod 1943; Whittington et al. 1999; Kao et al. 2008).

Oxidative stress impairs to spermatocytes (Alvarez and Storey 1995; Jones et al. 1979; Aitken and Fisher 1994; De Lamirande and Gagnon 1995; Sharma and Agarwal 1996; Penniston 1983; Holland and Storey 1981; Holland et al. 1982) for:

- Low levels of scavenging enzymes [lack of integral catalase or glutathione]
- High levels of PUFA in their plasma membrane [rich in unsaturated lipids]
- High levels of mitochondria [for supply of energy]

The overproduction of ROS and defects of oxidative phosphorylation are the most important molecular mechanisms in men infertility (Cummins et al. 1994).

Excessive production of ROS damages mitochondrial function and stimulates high ROS production. Disturbance of mitochondrial membrane induces apoptosis and DNA fragmentation (by activating of caspase cascade). The different forms of damage to DNA include: DNA cross-links, the modification or deletion of bases, chromosomal rearrangement (Duru et al. 2000; Plante et al. 1994; Appasamy et al. 2007; Vermes et al. 1995; Wang et al. 2003). Some reports indicated excessive production of ROS (high levels of ROS) in the semen of infertile men. The mitochondrial system has the major role in production of ROS in infertile men [impaired and immature sperms in the semen are considered] (De Lamirande and Gagnon 1995; Padron et al. 1997; Plante et al. 1994; Huszar et al. 1997; Aitken 1999). OS has an important role in the function of ovary. Endothelial cells, phagocytic macrophages, and parenchymal steroidogenic cells are the most main sources of ROS in the ovaries. Under normal condition, ROS are involved in the maturation of follicle, ovulation, and folliculogenesis (Halliwell and Gutteridge 1988; Tamate et al. 1995; Sugino et al. 1996; Jozwik et al. 1999; Sabatini et al. 1999). The activity of some antioxidative enzymes, such as Cu-Zn SOD, Mn-SOD, GPx in human ovary is needed for normal reproduction (Suzuki et al. 1999; El Moutassim et al. 1999; Paszkowski et al. 1995). The low expression of GPx in follicular fluid is associated with infertility. Increased nitric oxide (NO) is shown in the infertility (NO may lead to the apoptosis and fragmentation of embryo) (Bedaiwy et al. 2004). Peroxidation of lipids (increased MDA) and decreased antioxidant enzymes have reported in the infertile women (Polak et al. 2001; Shanti et al. 1999; Murphy et al. 1998).

2.10.4.1 Arsenic Toxicity and Infertility

Some human (occupational) and animal researches reported the effects of small amounts of some toxic metals, such as arsenic (As) on male reproduction. As directly affects the testicular tissue. Exposure to As in animal models leads to the reduction of testicular weight, production of sperm, number of spermatids, and decreased sperm mobility (Pant et al. 2004; Sarkar et al. 2003; Centeno et al. 2002; ATSDR 2007, 2012, 2019). As activates some signaling pathway such as ERK/AKT/NF-KB and leads to spermatogenesis disorders and reproductive toxicity (Huang et al. 2016). As exposure damages to the sperm DNA and leads to male infertility. Arsenic influences the steroid receptors activity, such as glucocorticoid and mineralocorticoid receptors. It may cause infertility by the inhibition of activity of androgen receptor (AR) (Kaltreider et al. 2001; Bodwell et al. 2006; Rosenblatt and Burnstein 2009). Some environmental pollutants such as heavy metals (lead, arsenic, cadmium), may lead to the reproductive disease by altering hormone levels. Arsenic increases ovarian tumors. Studies showed that serum As was high in infertile women (Lei et al. 2015; Mendola et al. 2008; Bloom et al. 2011; Gallagher et al. 2010; Guo et al. 2011; Tokar et al. 2011). Arsenic exposure leads to the inhibition of ovarian steroidogenesis, secretion of gonadotropins, and reduction of plasma testosterone (Chattopadhyay et al. 1999; Vreeburg et al. 1988; Hardy et al. 2005; Jana et al.

2006). The several possible mechanisms of As toxicity (Uckun et al. 2002; Jana et al. 2006; Sarkar et al. 2008) are as follows:

The direct action on testis: ROS affect the testicular function. Based on the results of the researches, exposure to the arsenic causes OS and reduction of some semen parameters, such as the reduction of number of sperm, motility of sperm, plasma levels of testosterone, FSH, LH hormones in the testis of rabbits (Manna et al. 2008; Zubair et al. 2014). The experimental studies indicated that As has toxic effects on the testis and damages the structure of testes and reduces the sex hormones (LH, FSH, testosterone) (Soleymani and Hemadi 2007; Pires Das Neves et al. 2004; Jana et al. 2006). Many researches reported the accumulation of arsenic in the testes, prostate glands. As toxicity alters the activity of mitochondrial enzymes, mitochondrial membrane potential, impairs DNA sperm and reduces testosterone. Inhibition and reduction of enzymes 3β -hydroxysteroid dehydrogenase (3β -HSD) and 17β -HSD, and wasting of Leydig cells, and reduction of testosterone occur in the presence of arsenic. Arsenic influences the hypothalamic-pituitary axis, impairs Leydig cells function, and binds directly to sperm. The thiol containing proteins have main role in the motility of sperm. High levels of SH-proteins are in sperm (sperm chromatin and flagellum contain plenty of sulfhydryl) and As has high affinity to binding to these proteins. Arsenic induces cell death or apoptosis and ROS production [the peroxidation of PUFA of spermatozoa] (Das et al. 2009; Danielsson et al. 1984; Pant et al. 2001; De Vizcaya-Ruiz et al. 2009; Morakinyo et al. 2010; Sudha 2012; Kumar et al. 2002; Jana et al. 2006; Sarkar et al. 2003).

Shortly, *arsenic in male reproductive system* causes a reduction in the number of sperm, high productions of ROS in testes, abnormal secretion of hormone, a decrease in the testicular weight, abnormality of enzymes, such as LDH, sorbitol dehydrogenase, acid phosphatase, γ -glutamyl transpeptidase, a decrease in FSH, LH, resulting in low sperm count and male infertility, a decrease in the sperm mobility and viability, depletion of GSH, increases of MDA, and protein carbonyl in testes and effects on 3β -HSD and 17β -HSD, which are important for biosynthesis of testosterone.

Arsenic in female reproductive system results in the suppression in the ovarian steroidogenesis, the degeneration of ovarian cells, follicular cells and uterine cells, alteration of neurotransmitter secretion like norepinephrine, dopamine, and serotonin, leading to reduction of gonadotropin secretion, FSH, LH, and estradiol, and alteration of Δ^5 - 3β -HSD and 17β -HSD, as the regulator enzymes of steroidogenesis.

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