Oxidative stress during insulin resistance in prediabetes: a review on role of antioxidants

Mohsina Hyder¹, Raja D¹, Visakh Varma², Ponnusankar S*¹

¹Department of Pharmacy Practice, JSS College of Pharmacy, JSS Academy of Higher Education and Research, Ooty – 643 001. The Nilgiris. India
²Department of Surgery, Aster Wayanad Specialty Hospital, Meppadi, Wayanad, Kerala, India

ABSTRACT

Oxidative stress is one of the major causal factors behind insulin resistance during prediabetes. It can impair insulin signalling by triggering stress activated signaling pathways and can also directly oxidize and damage the proteins of these pathways. Although cells have impressive stock of antioxidant enzymes and minor antioxidant moieties, these agents may not be adequate to maintain the redox balance during oxidative stress. The important functional antioxidant vitamins for tissue protection from excess free radicals comprises vitamin C, E and A. Vitamin C can improve insulin resistance by altering endothelial function and reducing oxidative stress. Vitamin E is an excellent trap for peroxyl radicals which suppresses ROS production in the pancreas, preserves pancreatic β cell function and maintains structural integrity of pancreatic islet cells. Vitamin A prevents tissue oxidative damage as well as exhibits a regenerative role in the pancreas. Like vitamins, minerals play a crucial role during oxidative stress and insulin resistance. Zinc is crucial for insulin actions and carbohydrate metabolism. Chromium activates insulin receptors through the oligopeptidochromudulin, which occurs in the insulin sensitive cells that binds to the insulin receptor, thereby increasing insulin signal transduction and sensitivity. Selenium up regulates glutathione peroxidase activity can inhibit NF-kappa B activation. The risk of diabetes and its complications will be more with elevating oxidative stress. Interventions with these antioxidants have proven beneficial role in reducing oxidative stress which can be utilized for reduction of insulin resistance in prediabetes.

INTRODUCTION

Insulin resistance is the stepping stone to the development of Type 2 Diabetes Mellitus and is prominent as well as at the starting stage in prediabetes stage. Several etiological factors have been put forward to describe the mechanisms leading to insulin resistance that includes obesity, inflammation, hyper-insulinemia, hyperlipidemia, genetic background, aging, oxidative stress, fatty liver, hypoxia, lipodystrophy and pregnancy. In obese prediabetes, oxidative stress occurs from oversupply of glucose and fatty acids into mitochondria. Generation of ROS occurs mainly in mitochondria during oxidation of fatty acid or glucose for ATP or energy production. ROS are required for body functions such as cellular growth, gene expression, infection defense and modulating endothelial function. It is also required for normal signal transduction in cells, but overproduction of ROS in obesity will induce oxidative stress.
stress. ROS are the oxygen metabolites that are created upon incomplete reduction of oxygen, which comprises hydroxyl radical, hydrogen peroxide and superoxide anion. Accumulation of intracellular triglycerides in obesity also plays a part in the elevation of oxidative stress since these triglyceride moieties elevates super oxide radical formation inside the electron transport chain by obstructing the mitochondrial adenosine nucleotide transporter. This obstruction decreases intra mitochondrial ADP production, which in turn decreases the proton flux through the ATP synthase reaction. Due to which electron build up occurs in the electron transport chain. Oxidative stress is one of the major pathways whereby obesity and insulin resistance leads to Type 2 Diabetes Mellitus in humans. Oxidative stress occurs due to the disproportionate state in which the production of free radicals is higher than the ability of the antioxidant defense system to detoxify these radicals. Chronic oxidative stress is markedly threatening for beta cells since pancreatic islets have the lowest levels of antioxidant enzyme expression and beta cells are having high oxidative energy requirements. Moreover, increased free radical production declines gene expression of key beta cell genes and can also weaken glucose stimulated insulin secretion. When oxidative stress was instigated in pancreatic beta cells in in vitro studies, the insulin gene promoter activity as well as mRNA levels were repressed, followed by the decreased activity of pancreatic and duodenal homeobox factor-1 (PDX-1), a major transcription factor for the insulin gene. In a study conducted in Indian population, the total antioxidant capacity was found to be lower in impaired glucose tolerant subjects than in subjects having normal glucose tolerance measured using levels of different antioxidant enzymes like superoxide dismutase and catalase (Vijayalingam et al., 1996).

**Oxidative stress sensitive signaling pathways**

Prolonged vulnerability to oxidative stress triggers a chain of stress sensitive signaling pathways namely Nuclear Factor-κB (NF-κB), NH$_2$- terminal Jun kinases/ stress activated protein kinases (JNK/SAPK), and p38 MAPK (Rains and Jain, 2011) Figure 1. These stress activated signaling pathway negatively effects insulin signaling which modulates the glucose and lipid homeostasis in the body. Numerous studies which already been conducted points out that in oxidative stress which impairs insulin signaling would ultimately result in insulin resistance to the target cells (Eriksson, 2007). ROS dysregulated insulin signaling is due to the altered mitochondrial activity; decreased GLUT 4 gene transcription, disturbed cellular reallocation of insulin signaling constituents or inducing IRS serine/threonine phosphorylation. Mitochondria generated ROS activated by TNF-α can arouse apoptosis signal regulating kinase-1 (ASK-1) that triggers JNK, also increases Ser-307 phosphorylation of IRS-1 and decreases insulin triggered tyrosine phosphorylation. One vital intracellular site of oxidative stress is the transcription factor NF-κB. NF-κB can be triggered by numerous exogenous and endogenous impel, inclusive of obesity triggered higher FFA, ROS, TNF-α, IL-1β and other proinflammatory cytokines. NF-κB activation prompts insulin resistance through impaired nitric oxide synthase regulation, higher concentrations of asymmetric dimethylarginine as well as endothelial dysfunction that emerge from varied fatty acid flow. The NH$_2$- terminal Jun kinases/ stress activated protein kinases and P38 MAPKs are constituents of the complicated super family of MAP serine/threonine protein kinases. The important role assigned to the JNK/SAPK pathway is as an intermediary of apoptosis. Once initiated; these protein kinases are capable to phosphorylate numerous targets, like the Insulin Receptor (IR) and Insulin Receptor Substrate proteins (including IRS-1 and IRS-2). Elevated phosphorylation of IR or IRS Proteins upon serine threonine sites declines the insulin triggered tyrosine phosphorylation followed by activities of downstream signaling molecules get decreased which results in reduced insulin action and resistance. Moreover, chronic awakening of the P38 MAPK pathway is frequently correlated with inflammation and ischemia as it plays a vital role in the generation of pro inflammatory cytokines like TNF-α, IL-6 and IL-1.

**Role Of Antioxidants**

Antioxidants are enzymatic and non-enzymatic molecules that safeguard cells from the after effects produced by unstable molecules like free radicals. An antioxidant is a molecule which has the ability to slow or arrest the oxidation of other molecules. Antioxidants functions in coordination in the normal cells to block tissue damage as well as to maintain the pro-oxidant-antioxidant balance. The body contains a large number of enzymatic [superoxide dismutase (SOD), glutathione peroxidase (Gpx) and catalase (CAT)] and non-enzymatic antioxidants [Eg: glutathione (GSH), Vitamin C and E, albumin and bilirubin] that prevent formation and scavenging of ROS to prevent oxidative damage. Higher ROS formation without an associated elevation in antioxidant defense mechanisms can change the redox balance inside the cell, causing oxidative destruction to proteins, lipids and nucleic acids. Previous studies show that dietary antioxidants have been

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Figure 1: Involvement of antioxidants in oxidative stress and insulin activity

Figure 2: Structure of Vitamin C
seen to protect against the occurrence of diabetes by blocking peroxidation chain reactions (Halliwell and Gutteridge, 1989). The important functional antioxidant vitamins for tissue protection from free radical over production comprises vitamin C, E and A. Vitamin like molecule alpha lipoic acid acts via Nrf-2-mediated antioxidant gene expression and by alteration of PPAR regulated genes. It also blocks NF-κB while stimulates 5'AMP-activated protein kinase (AMPK) pathway in skeletal muscles which enhances the insulin sensitivity (Biewenga et al., 1997). Several endocrine societies suggest that five servings per day of vegetables as well as fruits can lower insulin levels in insulin resistance conditions.

**Vitamins**

**Vitamin C**

Vitamin C Figure 2 is a vital water soluble antioxidant as well as enzyme cofactor seen in plants and animals. Humans do not have the capability to produce this antioxidant within the body so must obtain through diet. The absence of the enzyme L-Gulonolactone oxidase which is the catalyst in the final step in the formation of ascorbic acid is the reason why it cannot be synthesized in the human body. Vitamin C and glucose have similarity in chemical structure which makes the two compounds compete with each other. Vitamin C can scavenge oxygen derived free radicals which makes them inevitable. This vitamin has recently been revealed to reduce protein glycosylation in vitro and in vivo. Longer exposition to the high glucose levels is the cause for non enzymaticglycation of proteins and the production of Advanced Glycation End products (AGEs). AGEs can not only act as intermediary for the development of diabetic complications, but also in conditions like ageing, erectile dysfunction and Alzheimers disease. Vitamin C can improve insulin resistance by altering endothelial function and reducing oxidative stress. Vitamin C can avoid harm to biomembranes from lipid peroxidation by preventing peroxyl radicals in the aqueous phase. As vitamin C is present in the aqueous phase of cells, it donates to radical scavenging. It has been proved that vitamin C can regenerate vitamin E directly so, the concurrent use of vitamin C can augment the effect of vitamin E in the treatment of different cardiovascular and neurological diseases. Vitamin C elevates intracellular glutathione levels, playing a prime role in protein thiol group protection against oxidation. Vitamin C has the characteristic of easily giving up electrons to render stability to ROS. It is a powerful reducing agent therefore readily takes part in redox reactions. The 2 chemical forms of vitamin C where the reduced form is ascorbic acid; AA and the oxidized form is dihydro ascorbic acid: DHA. The reduced form is more dominant chemical structure in the humans, appearing as a prime micronutrient participating in several chemical and biological functions. Ascorbic acid can be oxidized to dihydro ascorbic acid and vice versa in the body and both these forms are essential in oxidation as well as reduction reac-
tions. Vitamin C is capable of shifting between its oxidized and reduced forms by electron donors and that protects at the intracellular level DNA, proteins and lipids against oxidative stress. This vitamin is also essential for carbohydrate metabolism, synthesis of lipids and proteins and cellular respiration. Vitamin C supplementation in healthy humans causes a major cutback in oxidative stress and inflammation by decreasing the concentration of F2\textsubscript{\beta}-Isoprostanes, prostaglandin E\textsubscript{2}, and monocyte chemotactic protein -1 in the body (Dhingra and Bansal, 2006). Three month supplementation of vitamin C and E decreased hypertension, blood glucose while increasing superoxide dismutase and glutathione levels (Rafighi et al., 2013). H\textsubscript{2}O\textsubscript{2} generation, JNK/SAPK (Stress Activated Protein Kinases) activity and resultant apoptosis caused by diabetes could also be oppressed by vitamin C. A low vitamin C level which is an indicator of unhealthy life style increases the chance for future development of type 2 diabetes. Vitamin C arrest endothelial dysfunction by scavenging free radicals and elevating the availability of nitric oxide in the body. Since vitamin C is required for regeneration of alpha tocopherol it can probably help prevent LDL from the oxidative attack. Vitamin C supplementation has shown to potentiate insulin action and improves glucose uptake in humans (Paolisso et al., 1994). A major reduction in serum HbA1c and LDL levels was noted in subjects provided with 1000 mg/day of vitamin C for 6 weeks period (Forghani et al., 2001). Combination of vitamin C with flavonoids like grape seed extract can improve the benefits of vitamin C in preventing insulin resistance and can be highly useful in prediabetes and oxidative stress conditions. Obese adults with prediabetes have higher vitamin C requirements, which raises the need for future research on whether taking more vitamin C foods or vitamin C supplements could reduce the risk of progression to type 2 diabetes.

**Vitamin E**

Vitamin E Figure 3 includes tocotrienols and tocopherol compounds among which alpha tocopherol is plentiful and biologically active form. This is a vital essential fat soluble antioxidant that reduces oxidative stress. Administration of vitamin E improved the sensitivity to insulin and elevates the potency of drugs which proceed through this pathway. Vitamin E acts its function as an antioxidant in the glutathione peroxidase pathway. Vitamin E is an excellent trap for peroxyl radicals, a chain interrupting antioxidant that blocks the free radicals generation in membranes as well as in plasma lipoproteins. Vitamin E has the ability to cease the process of lipid peroxidation and transforms free radicals to less reactive forms. During antioxidant reactions, alpha tocopherol is turned to an alpha tocopherol radical by the donation of labile hydrogen to a lipid or lipid peroxyl radical. Alpha tocopherol radical can thus be reduced to the original alpha tocopherol form by ascorbic acid. Beta cell apoptosis as a result of oxidative stress can be partially reversed by vitamin E. Vitamin E not only saves the integrity of plasma membranes by arresting lipid peroxidation but also lipoproteins especially LDL from the damage due to the cellular oxidative stress. Vitamin E, with Omega 3 fatty acids and alpha lipoic acid exhibited major improvements in oxidative stress as well as insulin resistance as compared to placebo group and among that vitamin E produced maximum changes in parameters of lipid metabolism (Udupa et al., 2012). This proves that vitamin E has a protective mechanism against oxidative stress. Increased occurrence of diabetes was found with reduced levels of vitamin E. It plays a crucial role in preventing complications of diabetes by inhibiting platelet aggregation and adhesion, decreasing lipid oxidation and protein glycation. Vitamin E has been comparatively a non toxic compound since long term clinical trials shown no harmful side effects with its supplementation. Vitamin E, C and \(\beta\) carotene improves insulin sensitivity and preserves the insulin receptor structure and function probably through the inhibition of free radical production and restoration of cell redox status (Mazière et al., 2004). Vitamin E also protects some proteins like insulin kinases and glucose transporters, which mediate the insulin metabolism from the oxidative alterations. Vitamin E suppresses ROS production in the pancreas, preserves pancreatic \(\beta\) cell function and maintains structural integrity of pancreatic islet cells in diabetes. In some clinical trials the dose of vitamin E used with 500 mg/day for 6 weeks in type 2 diabetics decreased the urinary F2 Isoprostanes which is a standard marker of lipid peroxidation (Wu et al., 2007), and as high dose vitamin E or placebo supplementation to obese subjects for 6 months (3 months 800 IU vitamin E/day, 3 months 1200 IU vitamin E/ day) lowered plasma lipid hydro peroxide concentrations in the vitamin E group (Manning et al., 2004). Vitamin E has the ability to alter the expression of the IL-2 and IL-4 genes as well as its post-transcriptional inhibitory action on 5-lipoxygenase which gives them anti-inflammatory actions as well. Vitamin E can down regulate NF-\(\kappa\)B and can exert lipophilic antioxidant effect on LDL moieties. This vital micro nutrient can be explored more in prediabetic subjects since it have anti inflammatory, antioxidant as well as insulin sensitizing properties in previously proven
clinical studies.

**Vitamin A**

This fat soluble vitamin are of two specific types that are found in animal and plant based products Figure 4. Preformed vitamin A present in animal products like meat, fish, poultry and dairy foods while pro-vitamin A seen in fruits and vegetables. Among which common type of pro-vitamin A was found to be beta carotene. Vitamin A can be obtained through dietary supplement usually it is found as retinyl acetate or retinypalmitate (preformed vitamin A), beta-carotene (pro-vitamin A) or a combination of preformed and pro-vitamin A. Vitamin A prevents tissue oxidative damage as well as exhibits a regenerative role in the pancreas. Retinoids as antioxidant helps to maintain the organism’s homeostasis when subjected to various forms of stress. Retinoids are also involved in hepatic lipid metabolism, adipogenesis as well as pancreatic beta cell function. Retinoids mainly helps in glucose transporter 4 (GLUT4) expression and beta cell regeneration. Retinol secreted into circulation will be bound to serum retinol-binding protein (RBP), it is deposited in liver while taken up by small intestine. Retinol binding protein (RBP) is the protein that transports retinoids, has an important effect on insulin sensitivity, acting as adipokines. Circulating retinol will be utilized by extra hepatic tissues or turned back to liver several times before it is completely metabolized. Retinol binding protein (RBP) particularly RBP4, together with transtyrethin (TTR) transports retinol from the liver to peripheral tissues by binding to specific cell receptors and has been linked to lipid metabolism and insulin sensitivity. Carotenoids are converted into retinal and then retinol in hepatocytes and enterocytes. Carotenoids carry conjugated double bonds while its antioxidant activity is because of its capability to delocalize unpaired electrons. Carotenoids can also scavenge peroxyl radical which arrests the destruction in lipophilic compartments. \( \beta \) carotene protects cell against DNA oxidation as well as both lipid peroxidation and it exhibits antioxidant activity at lesser oxygen partial pressure where as it become pro-oxidants at high pressure of oxygen. Combination of carotenoids or relating with other antioxidants like vitamin E can improve their antioxidant activity. Supplementation with vitamins C, E, and A can lower conditions like oxidative stress, insulin resistance and improve glucose disposal (Paiva and Russell, 1999). Another trial exhibited an inverse relationship between serum levels of carotenoids and marker of oxidative stress (circulating extracellular superoxide dismutase (SOD) inflammation (total leukocyte count (TLC), CRP and endothelial dysfunction (soluble P-selectin, soluble intracellular adhesion molecule -1(ICAM-1) (Facchini et al., 1996). Beta carotene is an efficient quencher of singlet oxygen and comprises several isomers able to inhibit the oxidative modification of LDL-Cholesterol. The antioxidant activity of beta carotene and Lycopene could improve inflammation and oxidative stress as well as higher vascular nitric oxide bioavailability gives protection against cardio vascular disease. Carotenoids are efficient deactivators of electronically excited sensitizer molecules and give protection to cellular membranes and lipoproteins against oxidative destruction as a result of lipophilicity along with special property to scavenge peroxyl radicals. Vitamin A is also capable to alter gene expression, regulates insulin release and energy homeostasis. Supplementation of 100,000 IU of vitamin A on alternate days 5 times in rats resulted in a marked decrease in lipid peroxidation of the tissue homogenates (Iqbal and Naseem, 2015). Chronic intake of vitamin A rich food was found to improve insulin sensitivity in obese rats via increased insulin receptor phosphorylation by mechanism of protein tyrosine phosphatase 1 B regulation (Jeyakumar et al., 2011). However, role of vitamin A in glucose metabolism is still not well understood. From the conflicting findings from previous clinical studies, the role of retinol and carotenoids in insulin resistance is still indecisive and more studies should be carried out as it could be beneficial in prediabetes too. Since in prediabetes insulin resistance is the primary etiological factor and insulin deficiency is just at its starting phase.

**Minerals**

**Zinc**

Zinc is one among the important trace elements and a vital constituent of hundreds of enzymes and plays a major part during the synthesis, storage as well as liberation of insulin. Zinc performs several functions in the pancreatic cells which evolves synthesis, delivery and signaling of insulin, glucagon liberation, and pancreatic digestive enzyme formation as well as its activity. Zinc is available numerously in the granules of acinar cells of pancreas over to which digestive proenzymes are deposited and delivered via exocytosis. Zinc deficiency leads to oxidative DNA damage. It is one of the constituents of several proteins in the mitochondrial electron transport chain and its insufficiency may lead to the liberation of oxidants. Thus, mitochondrial disturbance could be the source of high oxidative stress with zinc loss. A reduction in zinc availability is related to an elevation in cellular oxidants which causes
modulations in the antioxidant defense mechanisms and more tissue oxidation parameters. Chronic zinc deprivation usually leads to increased sensitivity to some oxidative stress. In zinc deficiency, pathways like JNK, MAPKs and p38 are activated and cause increase in p38 and JNK phosphorylation. Zinc has a regulatory role in Nrf2 as it upregulates its activity. Irregular Nrf2 activation as a result of reduced zinc availability can raise the vulnerability of neurons and such cells to oxidant stressors. While increased serum zinc availability results in improvement in insulin sensitivity. The anti-oxidant activities of zinc can delay the progress of insulin resistance and diabetes. Zinc brings about the activities of metal binding protein metallothionein, which is prosperous in cysteine and is a super scavenger of OH ions. Supplementation of 30 mg of zinc sulphate daily for a period of 6 months improved a variety of parameters like fasting glucose, lipids, CRP as well as HOMA scale among the prediabetic population of Bangladesh (Wiernsperger and Rapin, 2010). The blockade of ROS by zinc, decreases glucose toxicity and activates metallothionein transcription, which possesses antioxidant effects. Zinc raises the activation of antioxidant enzymes like glutathione, catalase and SOD while it also inhibits the functions of oxidant promoting enzymes like NAPDH oxidase and nitric acid synthase. Zinc boosts phosphorylation of insulin receptors by increasing the transfer of glucose over to cells. Zinc facilitates reduction reactions as well as neutralization of free radicals. Zinc act as a cofactor of the superoxide dismutase enzyme (SOD), by modifying the glutathione (GSH) metabolism and metallothionein expression. The iron and copper ions can catalyze the synthesis of lipid peroxides and if it is replaced with zinc in the plasma membrane could cease lipid peroxidation in diabetes. Zinc modulates the expression of glutamate –cysteine ligase enzyme present in the synthesis of glutathione, which works on the neutralization of free radicals directly and as a cofactor of glutathione peroxidase indirectly. Zinc is structurally related to antioxidant enzyme superoxide dismutase and its deficiency inhibits their synthesis resulting in increased oxidative stress. Zinc is essential in insulin action as well as carbohydrate metabolism. Previous clinical studies have proven that diabetes coexists with hypozincemia (Chaussier, 1998). Zinc administration in diabetes subjects improved insulin secretion while suppressed glucagon and glucose 6 phosphatase levels. Clinical trials have also shown that zinc improves peripheral insulin sensitivity, as it can boost up insulin stimulated glucose transport. Zinc also has crucial role in the beta cell physiology. Zinc exhibits a vital role in insulin homeostasis. Zinc gives protection from immune-mediated free radical attack by safe guarding sulphydryl (SH) groups from oxidation and involving in the inhibition of the free radical production in the Haber Weiss cycle by fighting with transition metals. Supplementation of 45 mg elemental zinc gluconate in 20 elderly for 6 months in a double blind placebo controlled trial, in which zinc group plasma antioxidant power was increased and plasma oxidative stress markers were decreased (Prasad, 2014). Thus the potential benefits of zinc should be utilized in the prediabetes stage for effective diabetes prevention.

**Selenium**

Selenium is one of the vital dietary micro nutrients of human health. Selenium is predominantly obtained from sea foods, grains, cereals, and organ meat. Selenium works as a cofactor and as an active center in redox reactions of selenium dependent glutathione peroxidase, converting hydrogen peroxide, destructive lipids and phospholipid hydrogen peroxide into less toxic products in the body. Selenium deficiency down regulates the LDL-receptor which can alter the cholesterol levels in plasma. Since selenium helps to decrease the formation of oxidized LDL, it would decrease the risk of heart diseases as well. Selenium supplementation also increases the activities of the selenoproteins, GSH-Px and TR (Thioredoxin Reductase) which serves as cellular antioxidants (Dhingra and Bansal, 2006). Selenoproteins carries a vital role in redox homeostasis as well as thyroid hormone metabolism. These proteins could also give protection from oxidative stress and inflammation. A major portion of the mineral selenium which circulates in human blood plasma occurs as selenoprotein P. It performs a crucial role in antioxidant defense system in defending the attacks from destructive ROS and RNS. The seleno enzymes include six groups of the GPx- GPx1, GPx2, GPx3, GPx4, GPx5, and GPx6 all are found to have potent antioxidant activity. These GPx can protect the cells against oxidative damage from ROS and RNS like superoxide, hydrogen peroxide, hydroxyl radicals, nitric oxide and peroxynitrite. Selenium exerts similar effects in insulin in glucose metabolism due to stimulation of tyrosine kinases present in the insulin signaling cascade. Selenium by up regulating glutathione peroxidase activity can inhibit NF-kappa B activation, which is the underlying mechanism of its anti inflammatory activity. In inflammatory conditions, selenium supplementation gains back the
depleted hepatic and serum selenium levels by elevating selenoprotein production leading to lesser CRP production. Dietary selenium, as it is involved in the biosynthesis of glutathione peroxidase, acts in a secondary antioxidant role as a hydro peroxide reducer. Selenium have potent insulin mimic actions like stimulating glucose uptake and regulating metabolic pathways like gluconeogenesis, glycolysis, pentose phosphate pathway, fatty acid synthesis as well as activates key proteins of insulin signaling cascade. Supplementation with 960 microgram selenium for 3 months in 56 type 2 diabetic patients with similar glycemic control, NF-κB activity was significantly reduced in the selenium group compared to placebo, reaching the same level as the non-diabetic control group (Tappel, 1980). A Study conducted among Indian prediabetics showed a considerable deficiency of serum zinc selenium and magnesium (Yadav et al., 2017) suggests its supplementation would be beneficial.

**Chromium**

Chromium is widely available as chromium dinitocinate (CDN) or chromium picolinate (CP) which is highly used by the diabetes subjects. Chromium acts by potentiating insulin action, the mechanisms include elevation in the number of insulin receptors, higher activation of insulin receptor in the presence of insulin and more binding of insulin to the insulin receptor. It also increases insulin receptor phosphorylation causing increased glucose transfer into muscle, liver and adipose tissue. Chromium treatment inhibits the release of pro-inflamatory cytokines like TNF-α, IL-6, CRP and it also inhibit protein glycosylation and lipid peroxidation in erythrocytes which helps in reduction of oxidative stress. Chromium decreases oxidative stress in cultured monocytes and isolated human mononuclear cells exposed to the high glucose environment (Jain et al., 2006). Since chromium is essential for the process of glucose and lipid metabolism; its deficiency can negatively affect blood glucose, insulin, total cholesterol, triglycerides and HDL. Addition of chromium to the diet increases lean muscle mass reduces body fat, increase sensitivity to insulin and maintains glucose tolerance. Chromium is beneficial in reducing carbohydrate cravings and appetite, which helps in preventing insulin resistance. Chromium activates insulin receptors through the oligopeptidechromudulin, which occurs in the insulin sensitive cells that binds to the insulin receptor, thereby increasing insulin signal transduction and sensitivity. Chromium augments insulin dependent GLUT4 membrane translocation, increases insulin-stimulated tyrosine kinase activity and IRS-1 phosphorylation under insulin resistant conditions. Chromium inhibits lipid peroxidation and hydrogen peroxide mediated oxidation of thiols. Some clinical trials shows chromium deficiency is related to higher blood glucose, insulin, and lipid levels that interrupts with the management of diabetes. One hundred and eighty men and woman with type 2 diabetes were randomly assigned to groups either receiving placebo, 100 mcg chromium picolinate twice daily or 500 mcg chromium picolinate twice daily for 4 months significantly reduced glucose and insulin levels, suggestive of an decrease in insulin resistance (Guallar et al., 2005). The exact mechanism of chromium is still under research, but it's proven that deficiency of chromium can interfere with normal glucose metabolism.

**CONCLUSIONS**

Previous trials have proven the fact that obesity induced oxidative stress can progress to insulin resistance which also puts at risk to Type 2 Diabetes Mellitus. Antioxidant vitamins like vitamin C, E and A as free radical scavengers improve insulin resistance probably by improving endothelial function and protecting biomembranes against lipid peroxidation. Trace elements like zinc, chromium, and selenium is working as a key part of the oxidative enzymes and it also controls the insulin homeostasis. Further research can also confirm the hidden causal relationships between obesity and oxidative stress in the birth and maturation of insulin resistance by measuring various oxidative stress biomarkers and insulin resistance scales in a larger diverse population. This review suggests the hypothesis that the oxidative stress is deeply related to insulin resistance and antioxidants could be a target for insulin sensitization to further prevent progression to T2DM. Large scale clinical trials with antioxidants showed varied results both positive and negative in obese diabetics but this could show a better profile in prediabetes which is the starting stage with insulin resistance and lower beta cell damage. In future clinical trials, more works can be conducted with newer and classic antioxidants either through planning in diet or supplements to control the oxidative stress there by insulin resistance for decreasing the incident rates of diabetes. Exercise induced oxidative stress during Prediabetes could also be counteracted by effective use of antioxidants.

**Abbreviations**

TNF-α Tumor Necrosis Factor alpha
IL-6 Interleukin 6
PPAR Peroxisome Proliferator Activated Receptor
HDL High Density Lipoprotein
ROS Reactive Oxygen Species
GLUT 4 Glucose Transporter type 4
FFA Free Fatty Acids
IR Insulin Receptor
IRS Insulin Receptor substrates
CRP C-Reactive Protein
RNS Reactive Nitrogen Species
LDL Low Density Lipoprotein

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Conflict Of Interest
None

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