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Selenium: antioxidant support system in disease states

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Abstract: *Selenium, a chemical element which rarely occur in its elemental state or as pure compound in the earth's crust and also found in soils derived from seleniferous parent materials like sandstones, limestone, slate and coal series has been found to poses a wide variety of functions in the body which includes activity on the thyroid hormone metabolism, antioxidant defense system which involves the antioxidant enzymes such as glutathione peroxidase, thioredoxin reductase and iodothyronine deiodinases. Selenium has been shown to mop up the presence of reactive oxygen species known to cause damage to cellular lipids in the oxidation of low density lipoprotein. (LDL). The role of selenium in immune system is notable in Keshan disease, Kashin- Beck disease and Hashimoto's disease. Also on cancer and diabetes mellitus has it has been proven to significantly slow the progression of diabetes mellitus in some individuals.*

Keywords: *Diabetes mellitus, antioxidant defense system, reactive oxygen species, low density lipoprotein, Keshan disease.*

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I. Introduction

As an essential trace element, the importance of Selenium (Se) in humans is well established, and its deficiency has caused serious health effects in humans, such as cancer and heart disease (Campbell *et al.*, 2008). In recent years, selenium research has attracted tremendous interest because of its important role in antioxidant selenoproteins for protection against oxidative stress initiated by excess reactive oxygen species (ROS) and reactive nitrogen species (RNS) (Campbell *et al*., 2008). The synthesis of selenoproteins requires a unique incorporation of amino acid selenocysteine into proteins directed by the UGA codon, which is also a termination codon (Berry *et al.*, 2003). Interest in selenium research has led to the discovery of at least 30 Selenoproteins (Burk and Hill, 2003). However, the biochemical functional roles of some of these selenoproteins are still unknown (Bryns *et al.*, 2003). Besides, in the form of selenoproteins, Selenium can exist in many different chemical forms in biological materials either as organic Se compounds, such as Selenomethionine and dimethylselenide and inorganic selenites and selenates (Ahsan *et al.*, 2014). In foods, Se is predominantly present as selenomethionine, which is an important source of dietary Se in humans and also a chemical element form that is commonly used for Selenium supplements in clinical trials (Ahsan *et al.*, 2014). Concern for potential deficiency diseases associated with low Se status has led to the establishment of the recommended daily requirements for Se in many countries. However, excess Selenium intakes through supplementation and its potential misuse as health therapy could also pose a risk of adverse health effects if its use is not properly regulated (Esser *et al*., 2014). As an essential trace element, the importance of selenium in humans is well established, and its deficiency has caused serious health effects in humans, such as Keshan disease (Klein *et al*., 2011). Foods are major natural sources of selenium and its levels generally depend on soil selenium levels. Since its discovery as an important component of antioxidant enzymes, such as glutathione peroxidase (GPx), thioredoxin reductase (TrxR) and iodothyronine deiodinases (IDD), there has been an increased interest in the study of other selenium containing proteins or enzymes (Klein *et al*., 2011). There are at least 30 selenoproteins that have been identified in mammals and it has been estimated that humans have about 25 selenoproteins (Rayman, 2012). The functional roles of these selenoproteins are still not fully understood, even though they have been conserved throughout evolution because of their unique physio-chemical properties (Rayman, 2012). Because of their antioxidant activity, there has been a tremendous interest in the study of selenium and its compounds in cancer chemoprevention, heart disease and immunity.

Biological Role of Selenium in Type II Diabetes Mellitus

Although, it is toxic in large doses, selenium is an essential micronutrient for animals (Tanaka *et al*., 2002). In plants, it occurs as a bystander mineral, sometimes in toxic proportions in forage where some plants may accumulate selenium as a defense against being eaten by animals, but other plants, such as locoweed,

require selenium, and their growth indicates the presence of selenium in soil (Tanaka *et al.*, 2002). Selenium is a component of the unusual amino acids, selenocysteine and selenomethionine (Thompson, 2004). In humans, selenium is a trace element that functions as cofactor for reduction of antioxidant enzymes, such as glutathione peroxidases and certain forms of thioredoxin reductase found in animals and some plants as this enzyme occurs in all living organisms, but not all forms of it in plants require selenium (Thompson, 2004). The glutathione peroxidase family of enzymes (GSH-Px) catalyze certain reactions that remove reactive oxygen species such as hydrogen peroxide and organic hydroperoxides (Tobe *et al*., 2009).

$2\ GSH + H_2O_2$----GSH-Px $\rightarrow GSSG + 2\ H_2O$

The thyroid gland and every cell that uses thyroid hormone use selenium, which is a cofactor for the three of the four known types of deiodinases (thyroid hormone), which activate and then deactivate various thyroid hormones and their metabolites; the iodothyronine deiodinases are the subfamily of deiodinase enzymes that use selenium as the otherwise rare amino acid selenocysteine namely, the deiodinase and iodotyrosine deiodinase, which works on the last breakdown products of thyroid hormone, does not use selenium. Selenium may inhibit hashimoto thyroiditis, in which the bodies own thyroid cells are attacked as alien (Rayman, 2012). A reduction of 21% on antibodies is reported with the dietary intake of 0.2 mg of selenium (Rayman, 2012). Increased dietary selenium reduces the effects of mercury toxicity, although it is effective only at low to modest doses of mercury (Wang *et al.,* 2014). Evidence suggests that the molecular mechanisms of mercury toxicity include the irreversible inhibition of selenoenzymes that are required to prevent and reverse oxidative damage in brain and endocrine tissues (Wang *et al.,* 2008). An antioxidant, selenoneine, which is derived from selenium and has been found to be present in the blood of bluefin tuna, is the subject of scientific research regarding its possible roles in inflammatory and chronic diseases, methylmercury detoxification, and oxidative damages (Tujebajeva *et al*., 2000).

Selenium is known for its cytoprotective properties, due to its ability to upregulate antioxidant selenoenzymes (Swanson *et al.,* 1991). Thus, it was believed that Selenium supplementation could prevent the onset of metabolic diseases, such as type II diabetes by counteracting oxidative stress (Swanson *et al.,* 1991). Indeed, Selenium in the form of selenate, was found to act as an insulin mimetic, displaying anti-diabetic effects (Van del *et al*., 2002). In support of this, two cross-sectional studies reported lower baseline Selenium levels to be associated with type II diabetes mellitus incidence among elderly French men, as well as in samples taken from a population in South Eastern Spain (Wastney *et al*., 2011). A more recent, longitudinal study conducted in the United States, reported high Selenium to be associated with lower type II diabetes risk (Wastney *et al.,* 2011). However, other cross-sectional studies, namely the National Health and Nutrition Examination Survey and NHANES 2003–2004, revealed an association between high Se intake and metabolic disease (Tobe *et al*., 2009). Moreover, increased type II diabetes risk was found to be a secondary outcome in the Nutritional Prevention of Cancer trial, a randomized, controlled trial assessing the efficacy of Se supplementation in the form of Selenium yeast (200 µg/day) in preventing skin cancer (Tobe *et al*., 2009). The Selenium and vitamin E cancer prevention trial, testing the effects of selenomethionine (SMet, 200 µg/day) and/or Vitamin E in preventing prostate cancer was curtailed as it became apparent Selenium supplementation did not appear beneficial in the prevention of prostate cancer, and a non significant trend towards type II diabetes mellitus in the experimental group was reported (Xu *et al*., 2010). Yet, other epidemiological studies and clinical trials failed to find a correlation between increased Selenium and type II diabetes mellitus susceptibility (Xu *et al*., 2010). One reason for the discrepancies in the human trials may be due to differences in baseline Selenium levels. For instance, the mean baseline Selenium levels in some subjects were already high (136 µg/L) whereas only the subjects in the upper third tertile of baseline Selenium (>122 µg/L) demonstrated higher incidence of type II diabetes (Xu *et al.,* 2010). Strengthening the idea of a narrow beneficial window of Selenium dose, it is likely that with regards to type II diabetes, Selenium supplementation may be advantageous in populations with low Selenium status, but detrimental in Selenium-replete populations. In fact, randomized, controlled trials of Se supplementation in elderly patients and pregnant women from the United Kingdom, who have lower baseline Selenium than United States subjects, did not result in increased type II diabetes risk, as determined by serum adiponectin concentration (Xu *et al*., 2010). Another source of the inconsistencies might be attributable to differences in Selenium source. As discussed in detail below, different Se forms vary in their bioavailability and biological effects. Thus, it is difficult to delineate a clear-cut relationship between Selenium status and type II diabetes mellitus based on evidence from the current human clinical trials and epidemiological studies (Xu *et al.,* 2010). To obtain a clearer picture of the role of Selenium in metabolic disease, this review will focus on the current understanding of the connections between dietary Selenium, selenoproteins, and energy metabolism, with an emphasis on animal models. Particularly interesting is that the relationship between Selenium metabolism and glucose homeostasis appears to be sexually dimorphic (Xu *et al*., 2010).

Forms of Selenium

Selenium occurs ubiquitously in the environment, but its biological activity is determined by the form that reaches an organism and how this form is metabolized (Akbaraly *et al.,* 2010). In general, the Selenium content of plants reflects the Selenium content of the surrounding soil and its bioavailability, and crop and livestock Selenium content will also reflect the Selenium content of the soil and the forage items they ingest (Akbaraly *et al.,* 2010). Besides the dependence on the soil content, plant Selenium content may also vary according to pH and the presence of soil ions that can form complexes with Selenium, enhancing or decreasing its bioavailability, according to the bacterial species present in the roots, and according to the ability of plants to uptake, accumulate and metabolize Selenium in its various forms (Bifano *et al.,* 2013). During amino acid synthesis, plants generally employ Selenium and sulfur nonspecifically in their metabolic processes (Bifano *et al*., 2013). Thus, most plants form methionine (Met) and SeMet in amounts that reflect the relative sulfur and Selenium concentrations of the soils in which they are grown (Bifano *et al*., 2013). The metabolic processes of SeMet and its downstream metabolites are generally analogous to those of methionine in both plants and animals. Nevertheless, once incorporated in animal proteins in place of Methionine, the Selenium of SeleniumMet can become part of an unregulated pool of Selenium, or be released when the amino acid is metabolized via methionine cycle or transulfuration pathways, becoming part of the highly regulated selenocysteine pool (Bifano *et al*., 2013). Efficient uptake and metabolism of dietary Selenium in animals will depend on which chemical form was ingested. Predominant forms of inorganic Selenium are selenite and selenate, both water-soluble (Carlson *et al*., 2004). Organic forms of Selenium mostly include the amino acids SeMet and Selenocysteine, and rare organic forms such as selenoneine, Se-methylselenocysteine, and selenoglutathione may have important biological roles that are currently unknown (Carlson *et al*., 2004). Inorganic selenite is absorbed by the enterocytes at rates that vary from 50% to 90% depending on age, sex, and dietary constituents (Combs, 2001). However, the molecular mechanism responsible for Selenium absorption is poorly understood (Combs, 2001). Gastrointestinal selenate absorption is conducted transcellularly, possibly by the multifunctional anion exchanger family, and paracellularly through the intestinal tract with virtually 100% efficiency (Combs, 2001). Nevertheless, it is necessary for selenate to be reduced to selenite prior to being metabolized, and thus these inorganic forms possess lower retention rates when compared to organic forms. In the case of organic Selenomethionine, more than 90% is uptaken transcellularly by enterocytes (Combs, 2001)**.** Although the available data for Selenium absorption is limited, the European Safety Food Authority (ESFA) recently stated the Selenium absorption efficiency on a normal diet to be less than 70%. However, the United States National Institutes of Health (USNIH) guidelines does not state an overall absorption value for Selenium, due to the discrepancies in absorption rates of different Selenium forms (Combs, 2001). Physiological to low-toxic doses of Selenium are known to be excreted as methylated sugar metabolites, specifically 1β-methylseleno-*N*-acetyl-D-galactosamine in the urine, while toxic levels of Selenium lead to the excretion of trimethylselenonium ion and dimethylselenide in the urine and breath (Copeland *et al*., 2001) .

Selenoproteins in Type II Diabetes Mellitus

Selenoproteins are important metabolites of dietary Selenium (Fagegaltier *et al*., 2000). Fulfilling the catalytic effects of Selenium, thus, in order to clarify the discrepancies in the association between Selenium supplementation and metabolic disease, it is necessary to understand the role of each selenoprotein in maintaining glucose homeostasis (Fagegaltier *et al*., 2000).

Glutathione Peroxidase 1 (GPx1) is the primary cytosolic peroxide scavenger, reducing peroxides to water, and protecting the cell from free radical damage considered to be a stress responsive selenoprotein, GPx1 expression is sensitive to Selenium intake (USA Institute of Medicine, 2000). Overexpression of GPx1 in mice yielded surprising results, leading to reduced glucose clearance, hyperinsulinemia, hyperglycemia, and diminished insulin signalling (USA Institute of Medicine, 2000). Diet restriction alleviated all metabolic symptoms except hyperinsulinemia, suggesting the functional role of GPx1 lies in regulating insulin production (Hintze *et al.,* 2002). Indeed, it was found that the H3 and H4 histones in the proximal promoter region of the insulin gene transcription factor, pancreatic duodenal homeobox-1 (PDX1), were hyperacetylated, ultimately leading to hyperinsulinemia (Hintze *et al.,* 2002). Although not shown directly, the hyperacetylation was speculated to be due to enhanced H_2O_2 scavenging (Hintze *et al*., 2002). The importance of H_2O_2 in cellular signalling was established further when it was demonstrated that GPx1 null mice have increased insulin sensitivity in the muscle, resulting in a high fat diet-resistant phenotype (Hintze *et al*., 2002). The absence of GPx1 allowed for the oxidation of phosphatase and tensin homolog (PTEN). Oxidation of PTEN inhibits its activity, sensitizing insulin signalling (Kryukov *et al.,* 2003). In contrast, several studies suggest that GPx1 might play a protective role against type II diabetes (Kryukov *et al.,* 2003). GPx1 overexpression in some cells protects against β-cell dysfunction induced by ribose treatment (Kryukov *et al*., 2003). As ribose was found to induce oxidative stress in human islets, it is possible that GPx1 promotes β-cell survival through its ability to

scavenge peroxides (Kurokawa *et al.,* 2011). Although constitutive GPx1-/- mice appear to preserve insulin signaling in response to an obesogenic diet, in the context of insulin secretion, GPx1 deficiency can be detrimental in the absence of GPx1. In hepatocytes isolated from GPx1-/- mice, the presence of excess ROS inactivates PTPN2, which negatively regulates STAT5-induced lipid synthesis (Kurokawa *et al*., 2011).

Selenoprotein P in humans has a positive correlation with type II diabetes as reported (Howard *et al.,* 2013). In this same study, increased hepatic Selenoprotein P and mRNA expression was also associated with reduced glucose tolerance and higher fasting glucose levels, which are indicative of insulin resistance (Howard *et al*., 2013). However, it is important to note that serum Selenoprotein levels become saturated at high Selenium intake (Howard *et al.,* 2013). One limitation of this study is that the patient's Selenium intake levels were not reported (Howard *et al.,* 2013). Likely, the usefulness of Selenoprotein as a biomarker is limited to subjects who do not receive an optimal Selenium intake (Howard *et al*., 2013). Additionally, since Selenium deficiency has been reported in type II diabetes patients, it is possible that Selenoprotein 1 mRNA expression is elevated in the diseased state, as Selenium transport will be in higher demand (Labunsky *et al*., 2011). Thus, the elevation of Selenoprotein1 may be a secondary effect of type II diabetes, rather than a cause (Labunsky *et al,* 2011). Nevertheless, adiponectin, an adipokine with anti-diabetic effects, was found to be inversely correlated with serum Selenoprotein levels in type II diabetes patients (Labunsky *et al*., 2011). Moreover, elevated serum Selenoprotein levels were positively correlated with carotid intima-media thickness and C-reactive protein, both of which are predictors for cardio metabolic disease (Labunsky *et al*., 2011). Studies of Selenoprotein I genetic variants reveal selenoprotein polymorphisms to be associated with fasting insulin and the acute insulin response. Taken together, Selenoprotein1 appears to be involved in glucose homeostasis, although direct conclusions cannot be made due to the correlative nature of these studies (Lee *et al*., 1989). Mouse models and cell lines have been used to delineate the mechanistic relationship between Selenoprotein1 and carbohydrate metabolism. For example, studies in Hepatic G2 cells revealed that hepatic Selenoprotein1 mRNA and promoter activity are under the control of insulin and a supramolecular complex, which also regulates gluconeogenic enzymes Phospho enol pyruvate carboxykinase and Glucose -6 – phosphatase (Lee *et al.,* 1989). Additionally, Selenoprotein1 was found to negatively regulate insulin signaling in the liver, through AMPK inactivation in female mice (Lippman *et al*., 2009). Selenoprotein1 also down regulates insulin signaling in the muscle, although the mechanism remains unclear (Lippman *et al.,* 2009). Mice with Selenoprotein1 deletion were found to be protected from diet induced obesity and insulin resistance (Lippman *et al*., 2009). In a follow-up study, Selenoprotein 1 deletion in mice were found to be protected from the drop in serum adiponectin levels in response to a high-sucrose, high-fat diet, although adiponectin levels were not completely restored to wild-type (Lippman *et al.,* 2009). This implicates a partial, but direct role for Selenoprotein1 in regulating adiponectin, because Selenoprotein1 is associated with gluconeogenic enzymes and downregulation of the insulin signaling pathway was proposed as a potential drug target (Lipmann *et al,* 2009). In fact, the commonly prescribed glucose lowering drug, metformin, suppresses Selenoprotein1 expression and further investigation demonstrated that metformin-induced inhibition of Selenoprotein1 expression occurs in an AMPK dependent pathway (Lipmann *et al*., 2009).

Selenoprotein M (SelM) is localized in the endoplasmic reticulum (ER) and is thought to participate in thiol-disulfide exchange through its thioredoxin-like domain (Loh *et al*., 2009). *In vitro*, Selenoprotein M has been shown to regulate calcium signalling and protect against oxidative stress. Because of its high expression levels in the brain, it was initially hypothesized that Selenoprotein M offered neuroprotective properties (Loh *et al*., 2009). However, no deficits in learning and memory were observed in Selenoprotein M knockout deletion in mice under a Selenium adequate diet (Loh *et al*., 2009). Interestingly, Selenoprotein M deletion in mice results in adult-onset body weight gain and increased adiposity, suggesting Selenoprotein M may play a role in obesity (Mao *et al*., 2016). Immuno-histochemistry further supported this hypothesis, as Selenoprotein M was revealed to be highly expressed in the paraventricular nucleus and the arcuate nucleus of the hypothalamus, regions that are implicated in energy homeostasis (Mao *et al*., 2016). The arcuate nucleus contains neurons expressing the leptin receptor, which is activated by the adipocyte-derived peptide, leptin (Mao *et al*., 2016). Leptin resistance in the hypothalamus leads to metabolic disease, although a direct mechanistic relationship remains to be tested, Selenoprotein M may play a role in energy metabolism through regulating leptin signalling (Mcclung *et al.,* 2004). Whole body Selenoprotein M deletion in mice results in elevated circulating leptin levels and diminished phosphorylated levels in the hypothalamus, which are indicative of leptin resistance (Mao *et al*., 2016). Furthermore, endoplasmic reticulum stress has been implicated in hypothalamic leptin resistance. As Selenoprotein M is an endoplasmic reticulum-resident protein, there is a possibility Selenoprotein M to promote leptin signalling by protecting against endoplasmic reticulum stress (Mcclung *et al*., 2004). Currently, it is unknown whether Selenoprotein M contributes to human obesity (Merry *et al*., 2014). Given the possibility, that Selenoprotein M may promote leptin signalling by mitigating endoplasmic reticulum stress (Merry *et al.,* 2014).

In **Iodothyronine Deiodinase 2** Low Selenium levels have been associated with thyroid disorders such as goiter (Laclaustra *et al*., 2009). Moreover, thyroid hormones exert strong effects on obesity (Laclaustra *et al*., 2009). The primary thyroid hormone in the bloodstream is -3, 3′, 5, 5′ tetraiodothyronine or thyroxine (T4), a pro-hormone with four iodine's and a long half-life (Lippman *et al.,* 2009). To become biologically active, one iodine is removed from T4, producing L-3, 5, 3′ triiodothyronine (T3) (Laclaustra *et al.,* 2009). Thyroid hormone deiodination is catalyzed by a selenoprotein family, the iodothyronine deiodinases (Dio). Dio1 and Dio2 mostly convert T4 into active T3, and Dio3 converts T4 into inactive reverse T3 (rT3), or T3 into T2, leading to either inactivation or degradation of thyroid hormone. Local deiodination via Dio enzymes allow tight, controlled regulation of thyroid hormone levels (Laclaustra *et al*., 2009). Thyroid hormones are known for the regulation of metabolism and basal metabolic rate via regulation of energy expenditure, thus, tight control of thyroid hormone levels can dictate effects on energy balance (Merry *et al*., 2014). Diet-induced obesity in male mice has also been demonstrated to depend on Dio2 activity in the anterior pituitary activated by the c-Jun N-terminal kinase (JNK) pathway, controlling TSH levels and consequent thyroid hormone-dependent energy expenditure (Merry *et al*., 2014) . Moreover, mice with targeted deletion of Dio2 in the pituitary have less body fat, despite maintaining their oxygen consumption normally (Merry *et al*., 2014). Specifically, Dio2 controls adaptive thermogenesis induced by cold and by diet in the brown adipose tissue (Laclaustra *et al*., 2009). Mice with targeted disruption of Dio2 lack proper adaptive thermoregulation and are more prone to high fat diet-induced obesity. Male and female mice are insulin resistant even on a normal chow diet, with increased gluconeogenesis, and accumulate triglycerides in the liver, despite not yet displaying significant weight gain (Merry *et al*., 2014). Dio2 activity also controls feeding at the arcuate nucleus of the hypothalamus via local control of T3 levels, which contributes further to energy balance. Inability to properly activate thyroid hormone via Dio2 was linked to glucose intolerance through hepatic insulin resistance (Lippman *et al.,* 2009). Intriguingly, human Dio2 gene expression is inhibited by the heterodimerization of liver X-receptor (LXR) with the retinoid X-receptor (RXR). Dio2 regulation by a classic lipogenic transcription factor was observed in LXRα and LXRβ double KO mice, which ectopically express Dio2 in the liver, suggesting a role for Dio2 inhibition in hepatic lipid deposition and obesity (Merry *et al*., 2014).

Selenoprotein T (SelT) was first identified *in silico*, using an algorithm to identify insertion sequence elements in the human containing a thioredoxin-like fold. Selenoprotein T was proposed to possess redox activity, but its precise function remains unknown (Wilber, 2010). Bioinformatics analysis revealed Selenoprotein T to be localized to the endoplasmic reticulum, possibly being trafficked to the plasma membrane. Selenoprotein T expression in mice appears to be highest during development, with Selenoprotein T mRNA expression in most tissues decreasing in adulthood, except in endocrine tissues such as the thyroid, pituitary, testis, and thymus (Wilber, 2010). The pituitary adenylate cyclase activating polypeptide is a neuropeptide which increases cAMP through adenylate cyclase stimulation, having implications in a variety of cellular processes, including cell survival and secretory function (Wilber, 2010). Selenoprotein T was recently identified as a target of pituitary adenylate cyclise activating polypeptide and in differentiated cells, Selenoprotein T is necessary for PACAP-dependent neuroendocrine secretion by regulating intracellular Ca^{2+} levels (Wolffram *et al*., 2010). Many neuropeptides regulate energy homeostasis, such as NPY (neuropeptide Y), Agrp (agouti-related peptide), α-MSH (α-melanocyte stimulating hormone), among others, identifying the neuropeptides under Selenoprotein T regulation could provide greater understanding of the connection between dietary Selenium and energy metabolism (Wolffram *et al.,* 2010). Immunofluorescence demonstrated Selenenoprotein T to be highly expressed in the adult pancreatic β and δ-cells, the latter of which secretes somatostatin, indicating Selenoprotein T may be involved in glucose homeostasis and conditional knockout of Selenoprotein T in the β-cell resulted in defective insulin secretion, suggesting Selenoprotein T is critical to β-cell function. Studies in the glucose responsive murine β-cell line, MIN6, determined that PACAP-induced insulin secretion depends on Selenoprotein T expression (Wolffram *et al*., 2010). This indicates that Selenoprotein T may regulate blood glucose at multiple levels. Although Selenoprotein T is expressed in other metabolic tissues such as the pituitary and thyroid, the function of Selenoprotein T in these tissues is still unknown (Wolffram *et al.,* 2010).

Selenoprotein T, just like Selenoprotein S (SelS) was first identified *in silico*, and was shown to localize to the plasma membrane (Xu *et al.,* 2007). Functionally, Selenoprotein S has implications in endoplasmic reticulum-associated degradation (ERAD), inflammation, and the transport of multi-protein complexes (Xu *et al.,* 2007). In 2003, a novel protein, Tanis, was characterized as a glucose-regulated protein in *Psammomys obesus*, an animal model for type II diabetes. Tanis was found to be expressed in insulin-sensitive tissues such as adipose tissue, liver, and skeletal muscle. Through yeast two-hybrid screening, Tanis was found to interact with serum amyloid A, a family of proteins associated with the acute-phase inflammatory response, which is typically elevated in type II diabetes patients (Xu *et al.,* 2007). Potentially, Tanis acts as a receptor for serum amyloid A. Tanis was later identified to be a Selenoprotein S homolog leading to the hypothesis that Selenoprotein S links inflammation to type II diabetes (Xu *et al.,* 2007). In support of this, a positive correlation between serum

amyloid A levels and Selenoprotein S expression in the skeletal muscle and adipose tissue of type II diabetes patients was reported. Selenoprotein S appears to be dysregulated in the disease state, as insulin stimulation increases Selenoprotein S mRNA expression in the adipocytes of type II diabetes subjects but not healthy subjects (Xu *et al*., 2007). Conversely, a different study found subcutaneous adipocyte Selenoprotein S mRNA expression to increase in response to insulin in both obese and lean subjects. This study also failed to find a correlation between serum amyloid A and Selenoprotein S expression. However, Selenoprotein S expression was found to be higher in obese subjects, with increased subcutaneous Selenoprotein S expression in obese subjects associated with body mass index, sagittal diameter, serum HDL, triglycerides, insulin, and insulin resistance (Xu *et al.,* 2007). Additionally, Selenoprotein S polymorphisms were correlated with higher diastolic blood pressure and circulating insulin. These individuals were also at a higher risk for cardiovascular disease. Taken together, these studies support the role of Sel S in metabolic disease while Selenoprotein S (SelS) has been associated with type II diabetes, while its role in metabolic disease remains unknown (Zhang *et al.,* 2014). One possibility is that Sel S plays a protective role for instance; Sel S has been shown to be upregulated in the hepatoma-derived HepG2 cells in response to glucose deprivation, albeit the physiological relevance is debated, as the low glucose concentration tested was 2 mM, well below the range of normal blood glucose levels in humans. However, Sel S was also found to increase in response to ER stress, while overexpression of Sel S conferred protection against oxidative stress MIN6 cells. Thus Sel S may play a protective role, counteracting oxidative stress in type II diabetes (T2D) development (Zhang *et al.,* 2014).

Selenium Biochemistry and Metabolism

Selenocysteine is recognized as the 21st amino acid and it forms a predominant residue of selenoproteins and selenoenzymes in biological tissues (Chavatee *et al*., 2005). During protein synthesis, the selenocysteine residue is co-translationally inserted and encoded by the UGA codon, which is normally associated with a termination codon. The molecular structure of selenocysteine is an analogue of cysteine where a sulphur atom is replaced by selenium. Even though selenium and sulphur share some similar chemical properties, there are also some differences (Chavatee *et al*., 2005). For instance, in the form of a selenoate anion, as a conjugated base of selenocysteine, Selenium is more stable than cysteine thiolate. Furthermore, selenium as selenol (R-seH) is more acidic than thiol (R-SH) and readily dissociated at physiological pH, which may contribute to its biological reactivity. In the body as both organic Selenocysteine , Selenomethionine and inorganic selenite and selenate (Chavatte *et al*., 2005). Selenium compounds are readily metabolized to various forms of selenium metabolites of particular importance, during this metabolic process is the formation of hydrogen selenide (H_2Se) from selenite after the action of glutathione- coupled reactions via selenodiglutathione and glutathione selenopersulfide (Chavatte *et al*., 2005). H_2Se is further metabolized and involved in the formation of methylselenol and dimethyselenide, which are exhaled or secreted via the skin. Selenium is also excreted in urine as trimethyselenonium ion and selenosugar compounds (Chavatte *et al*., 2005). Hydrogen selenide can also be used as a substrate for selenocysteine biosynthesis, directed by specific codon in proteins; however, this is not the case with selenomethionine where it's incorporation into proteins is non specific and random in place of methionine (Finley *et al*., 1999). The selenoenzymes that are found to have strong antioxidant activity include six groups of the GPx-GPx1, GPX3, GPX4, GPX5 and GPX 6. These GPX play a significant role in protecting cells against oxidative damage from reactive oxygen species (ROS) and reactive nitrogen species (RNS), which includes Superoxide, hydrogen peroxide, hydroxyl radicals, nitric oxide and peroxynitrite. The other essential antioxidant selenoenzymes are the thioredoxin where they use thioredoxin as a substrate to maintain a thioredoxin/ thioredoxin reductase system in a reduced state for removal of harmful hydrogen peroxide (Finley *et al.,* 1999). There are three types of thioredoxin reductases that have been identified, and these include cytosolic thioredoxin1, mitochondria thioredoxin 2 and spermatozoa specific thioredoxin. Increasing evidence suggest that Selenoprotein P may also play a significant role in antioxidant defense system in preventing attack from harmful reactive oxygen species (ROS) and reactive nitrogen species (RNS) (Finley *et al.,* 1999).

Inorganic Selenium

There is very little doubt concerning the ability of animal tissues to convert inorganic selenium to organic forms. This is demonstrated by the incorporation of selenium from selenite to dimethyl selenide, GSH-Px and into selenoamino acids (Zeng *et al.,* 2009). Although the pathways for reduction of selenite to selenide have been fairly well established, the pathways for conversion of selenide to selenoamino acids have not been fully delineated (Zeng *et al.,* 2009). Since selenocysteine is one of the forms of selenium identified in animal tissues, most of the work has been done on its incorporation into proteins. Evidence has been presented for a specific transfer RNA in rat liver for selenocysteine (Zeng *et al.,* 2009). By this mechanism, the selenocysyeine could be incorporated during translation via the action of this tRNA and its charging enzymes. An alternative mechanism is that the selenocysteine is formed *in situ* from some previously incorporated amino acid such as cysteine or serine, which would be susceptible to a posttranslational modification (Zeng *et al.,* 2009). This type

of reaction could occur similarly to the cysteine synthase reaction, which can produce cysteine from serine and sulfide, if selenide or its equivalent is substituted for the sulfide (Zeng *et al.,* 2009)

Organic Selenium

In contrast to sulfur, selenium compounds tend to undergo reductive pathways in tissues. However, reduced selenium compounds can be metabolized by animal tissues. Here, some evidence has been presented for formation of selenocystathione, selenoglutathione, selenotaurine and selenocysteic acid in tissue homogenates of chicks and mice injected with 75se- selenomethionine (Sors and Ellis, 2005). However, differences in either the metabolism of various selenium compounds or their bipotency have been observed (Sors and Ellis, 2005)).

Nutritional sources

The richest sources of Selenium are cereals, grains and Brazil nuts (Navarro-Alarcon *et al.,* 1999). Vegetables and fruits also provide small amounts of selenium. The amount of selenium consumed by an individual is almost entirely dependent on levels of selenium in the soil where crops are grown. The amount of selenium needed for normal body function is about 40 micrograms per day with the recommended dietary allowance being 55 micrograms (Navarro-Alarcon *et al*., 1999). Dietary selenium comes from nuts, cereals and mushrooms. Brazil nuts are the richest dietary source (though this is soil-dependent, since the Brazil nut does not require high levels of the element for its own needs). The U.S. Recommended Dietary Allowance (RDA) for teenagers and adults is 55 µg/day (Navarro-Alarcon *et al.,* 1999). Selenium as a dietary supplement is available in many forms, including multi-vitamins and mineral supplements, which typically contain 55 or 70 µg/serving and Selenium-specific supplements typically, contain either 100 or 200 µg/serving (Navarro-Alarcon *et al.,* 1999). In June 2015, the U.S. Food and Drug Administration (FDA) published its final rule establishing the requirement of minimum and maximum levels of selenium in infant formula. The selenium content in the human body is believed to be in the 13–20 milligram range (Navarro-Alarcon *et al.,* 1999).

Toxicity

Although Selenium is an essential micro element, it is toxic if taken in excess, exceeding the tolerable maximal consumption of 400 micrograms per day can lead to selenosis (Moreno-Reyes *et al.,* 2001). This 400 tolerable upper intake level is based primarily on a 1986 study of five Chinese patients who exhibited overt signs of selenosis and a follow up study on the same five people in 1992 (Moreno-Reyes *et al*., 2001). The 1992 study actually found the maximum safe dietary Se intake to be approximately 800 micrograms per day (15 micrograms per kilogram body weight), but suggested 400 micrograms per day to avoid creating an imbalance of nutrients in the diet and to accord with data from other countries. In China, people who ingested corn grown in extremely selenium-rich stony coal (carbonaceous shale) have suffered from selenium toxicity. This coal was shown to have selenium content as high as 9.1%, the highest concentration in coal ever recorded (Moreno-Reyes *et al.,* 2001). Signs and symptoms of selenosis include a garlic odor on the breath, gastrointestinal disorders, hair loss, sloughing of nails, fatigue, irritability, and neurological damage while extreme cases of selenosis can exhibit cirrhosis of the liver and pulmonary oedema or death (Moreno-Reyes *et al*., 2001). Elemental selenium and most metallic selenides have relatively low toxicities because of low bioavailability. By contrast, selenates and selenites have an oxidant mode of action similar to that of arsenic trioxide and are very toxic. The chronic toxic dose of selenite for humans is about 2400 to 3000 micrograms of selenium per day. Hydrogen selenide is an extremely toxic, corrosive gas (Moreno-Reyes *et al*., 2001). Selenium also occurs in organic compounds, such as dimethyl selenide, selenomethionine, selenocysteine and methylselenocysteine, all of which have high bioavailability and are toxic in large doses. Selenium poisoning of water systems may result whenever new agricultural runoff courses through normally dry, undeveloped lands. This process leaches natural soluble selenium compounds (such as selenates) into the water, which may then be concentrated in new "wetlands" as the water evaporates. Selenium pollution of waterways also occurs when selenium is leached from coal flue ash, mining and metal smelting, crude oil processing, and landfill (Moreno-Reyes *et al.,* 2001).

Selenium and Heart Disease

The increased production of reactive oxygen species can exert oxidative stress in the physiological system, and if excess reactive oxygen species are not properly regulated, they can cause damage to cellular lipids, proteins and DNA (Mizutani *et al.,* 1999). The damage caused by reactive oxygen species has been linked to various human diseases, including heart diseases. The presence of reactive oxygen species can also cause the oxidation of low density lipoprotein (LDL) and it has been reported to be associated with initiation of atherogenesis in heart diseases (Mizutani *et al*., 1999). One hypothesis is that the presence of high Selenium as antioxidant selenoenzymes and seelenoproteins may help to reduce the incidence of heart diseases (Mizutani *et al*., 1999). In animal studies, selenium deficiency has been shown to down regulate the LDL- receptor which is important in regulating the cholesterol level in plasma. The presence of selenoprotein P, which is found mainly in plasma, may play a significant role in regulating the plasma cholesterol level by protecting the LDL oxidation

from reactive oxygen species (Mizuatani *et al*., 1999). This study provides further evidence that selenoprotein P plays an important antioxidative role in protecting LDL from oxidation and the prevention of artherosclerosis (Mizuatani *et al*., 1999). It has also been reported that thioredoxin reductase plays a significant role in preventing the development of artherosclerosis by reducing oxidative stress and increasing nitric oxide bioavailability. In epidemiological studies, however, the associations of low Selenium status in humans with increased risk of heart diseases and mortality are still uncertain and controversial (Okuno *et al.,* 2005). Early supportive evidence from epidemiological studies in the United States of America suggested that a higher mortality of heart diseases was linked to selenium deficient areas. However, subsequent epidemiological studies from other countries gave inconclusive results (Okuno *et al*., 2005).

Selenium and Cancer

Selenium is a powerful mineral needed only in very small amounts and it plays a crucial role in cells defenses against cancer (Okuno *et al*., 2005). It is a central part of the enzymes that knock out free radicals and the unstable molecules that can attack the cells and ultimately lead to cancer. It also plays a role in recycling antioxidants through the body. These antioxidants, such as vitamin E, then lower the risk of cancer by preventing free radicals from damaging cells (Okuno *et al*., 2005). Selenium may also protect the body against contaminants such as mercury, cadmium and silver as they help speed the elimination of cancer cells and slow tumour growth (Okuno *et al*., 2005). A selenium deficiency is very serious and can cause nerve and heart dysfunction. Fortunately, most people in the world get plenty of Selenium, except, perhaps in unusual areas where soil Selenium is low and food fortification is inadequate (Okuno *et al.,* 2005). Studies have shown that selenium intake above the recommended dietary allowance (RDA), while not necessary for normal body function, may protect against certain cancers (Pillai *et al*., 2012). In one region of China, where epidemic rates of esophageal and gastric cancers occurred, the risk was cut in half after large dose of Selenium were given. In populations at higher risk for prostate cancer, Selenium supplements decreased risk and growth rate of tumours (Pillai *et al.,* 2012). Selenium supplements may also be able to halt the growth of polyps in the colon and reduce the risk of lung and liver cancers. There are a multitude of studies investigating the effect of Selenium on cancer and several recent reviews focus on the potential mechanisms of action using evidence from *in vitro* cell culture studies and *in vivo*, mainly animal model (Pillai *et al.,* 2012). Studies proposed mechanisms of the effects of Selenium on cancer include regulation of cell cycle and apoptosis, antioxidant effect through the action of selenoproteins in particular glutathione peroxidases and thioredoxins, modulation of angiogenesis and the extracellular matrix, histone deacetylase inhibition, carcinogen detoxification, induction of GSTs, alteration of DNA damage and repair mechanisms and also immune system modulation (Pillai *et al*., 2012). However the effect of Selenium on cancer are species specific , dose specific and cancer type specific and may also be affected by genotype and the bioavailability of selenium (Pillai *et al*., 2012).

Mechanism of action of cancer

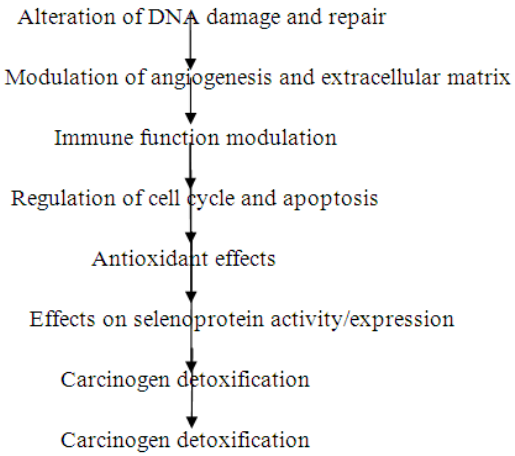

Fig. 1 Stepwise illustration of cancer proliferation in cells. The effects of selenium on cancer are dependent on cancer location, type, cancer stage and tissue metabolism. Adapted from Pillai *et al*., 2012.

Hashimoto Thyroiditis

Hashimoto thyroiditis, also known as chronic lymphocytic thyroiditis and Hashimoto's disease. This is caused as a result of an autoimmune destruction where the thyroid gland is gradually destroyed (Seyedali and Berry, 2014). Early on, there may be no symptoms but over time, the thyroid may enlarge erupting a painless goiter (Seyedali and Berry, 2014). Hypothyroidism is eventually developed by some people accompanied by

weight gain, tiredness, constipation, depression and general body pains. After many years, the thyroid typically shrinks in size and potential complications such as thyroid lymphoma may be experienced (Seyedali and Berry, 2014). Hashimoto's thyroiditis is thought to be due to a combination of hereditary and environmental lifestyle conditions. Risk factors include a family history of the condition and having another autoimmune mutilation or destruction. Diagnosis is confirmed with blood tests for thyroid stimulating hormone (TSH), tetraiodothyronine (T4) and antibodies having anti thyroid metabolites (Seyedali and Berry, 2014). Grave's disease and non toxic modular goiter has been categorized as one of those conditions that could produce similar symptoms and Hashimoto's thyroiditis is typically treated with levothyroxine. If hypothyroidism is not present some may recommend no treatment while others may treat to try to reduce the size of the goiter. Those affected should avoid eating significant amounts of iodine. However, sufficient iodine is required especially during pregnancy (Singh and Banerjee, 2011). Surgery is rarely required to treat the goiter. Hashimoto's thyroiditis affects about 5% of the population at some point in their life. It typically begins between the ages of 30 and 50 and is much more common in women than men. Rates of disease appear to be increasing. It was first described by a researcher in Japan namely, Hashimoto Hakaru in 1912. In 1957 it was recognized as an autoimmune disorder (Seyedali and Berry, 2014).

Keshan disease

Keshan disease is a congestive cardiomyopathy caused by a conglomerate of low intake of selenium in the diet and the presence of a mutated strain of Coxsackievirus, named in respect to a country, Keshan located in the Heilongjiang province, Northeast China, where symptoms were first noted (Stranges *et al.*, 2007). These symptoms were later found prevalent in a wide belt extending from Northeast to Southwest China, all due to low selenium rich soils (Stranges *et al.*, 2007). The disease peaked in 1960–1970, claiming thousands of lives. Often fatal, the disease afflicts children and women of child bearing age, characterized by arrhythmic heart rate and excessive fluid accumulation in the body. Over decades, supplementation with selenium reduced this affliction and thus, it had been linked to the coxsackie virus (Stranges *et al.*, 2007). Current research suggests that the lack of selenium results in a more virulent strain of the coxsackievirus becoming the dominant specie from virus origin present in the population of virus, but the mechanism of this selection event is unclear (Stranges *et al.*, 2007). The disease got its name from the province in which it was discovered: Keshan, China and since its discovery, it can also be found in New Zealand and Finland (Stranges *et al.*, 2007). Keshan disease results from a selenium deficiency which is a nutrient we receive in our diet from eating foods that were grown in selenium enriched soils. Because of that factor, Keshan deficiency can be found anywhere that the level of selenium present in the soil is low (Steinbrenner *et al.*, 2013). An individual with Keshan disease will have an abnormally large heart. Keshan disease can also lead to higher rates of cancer, cardiovascular disease, hypertension, and strokes. In addition, an individual can experience eczema, psoriasis, arthritis, cataracts, alcoholism, and infections (Streinbrenner *et al*., 2013).

Kashin- Beck disease

Kashin–Beck disease (KBD) has been revealed to be chronic in manifestation and it's a localized type of disease that affects the bone often leading to osteochondropathy (disease of the bone) that is mainly distributed from Northeastern to Southwest of China (Pinto *et al*., 2012). KBD usually involves children ages 5–15. To date, more than a million individuals have suffered from KBD (Pinto *et al*., 2012). The symptoms of KBD include joint pain, morning stiffness in the joints, disturbances of flexion and extension in the elbows, enlarged inter-phalangeal joints, and limited motion in many joints of the body (Pinto *et al*., 2012). Death of cartilage cells in the growth plate and articular surface is the basic pathologic feature. This can result in growth retardation and secondary osteoarthrosis. Histological diagnosis of KBD is particularly difficult. Here, clinical and radiological examinations have proven to be the best means for identifying KBD (Burk and Hill, 2015). Little is known about the early stages of KBD before the visible appearance of the disease becomes evident in the destruction of the joints. This disease has been recognized for over 150 years but its cause has not yet been completely defined (Burk and Hill, 2015). Currently, the accepted potential causes of KBD has been found in mycotoxins present in grain, trace amount of minerals as well as fulvic acid in drinking water in high levels (Burk and Hill, 2015). Selenium and iodine have been considered the major deficiencies associated with KBD. Mycotoxins from fungi can contaminate grain, which may cause KBD because mycotoxins cause the production of reactive free radicals. T2 is the mycotoxin implicated with KBD, produced by members of several fungal genera and T2 toxin can cause lesions in blood, lymph nodes, intestines and cartilage tissues, especially in physeal cartilage (Pinto *et al*., 2012). Fulvic acid present in drinking water damages cartilage cells. Selenium supplementation in selenium deficient areas has been shown to prevent this disease. However, selenium supplementation in some areas showed no significant effect, meaning that deficiency of selenium may not be the dominant cause in KBD (Burk and Hill, 2015). Recently a significant association between SNP rs6910140 of

COL9A1 and Kashin–Beck disease was discovered genetically, suggesting a role of COL9A1 in the development of Kashin–Beck disease (Burk and Hill, 2015).

II. Conclusion

Selenium dietary supplement if taken within the acceptable dose has shown to posses various beneficial properties some of which includes its role on the thyroid hormone, antioxidant defense, immune system, fertility, cancer, cardiovascular diseases and diabetes. However, the antioxidant properties of selenium are a veritable tool in mediating possible reactive oxygen species that could arise in any diseased state.

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