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THYROID HORMONE PROFILING AND ENZYMATIC ANTIOXIDANT STATUS IN DIAGNOSIS AND MANAGEMENT OF TYPE-II-DIABETES MELLITUS: A REVIEW OF LITERATURE

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ABSTRACT
Diabetes mellitus (DM) is a chronic metabolic disease resulting from diminished or absent secretion of insulin or due to reduced tissue sensitivity to insulin and has a global health burden especially in developing countries like Nigeria. The present review focuses on the role of thyroid hormone profiling and enzymatic antioxidant status in diagnosis and management of type-II-diabetes mellitus. Diabetes Mellitus and thyroid disorders are the two most common endocrine disorders encountered in clinical practice and this is as a result of interaction between thyroid hormones and insulin. The clinical relationship between diabetes mellitus and thyroid function is becoming more widely recognized with hypothyroidism among diabetes mellitus patient. Type 2 diabetes is accompanied with increased formation of free radicals otherwise called reactive oxygen species (ROS) leading to oxidative damage of cell components. ROS production in diabetes plays a key role in the pathogenesis of diabetic complications by accelerating important molecular mechanisms involved in hyperglycaemia induced oxidative damage. Thus, increased ROS and impaired antioxidant defense contribute to the initiation and progression of micro- and macrovascular complications experienced in diabetics. Hyperinsulinamia initiates a negative feedback mechanism leading to hypothyroidism in Type 2 Diabetes Mellitus. Also, a decrease in enzymatic antioxidants increases the risk of Type 2 Diabetes mellitus. Therefore, thyroid hormone function profiling and antioxidant assays may be incorporated as part of routine tests for Type 2 Diabetes Mellitus.

KEY WORDS: Diabetes Mellitus, Thyroid Hormone, Oxidative Stress, Free Radicals, Enzymatic Antioxidants.

INTRODUCTION

Diabetes mellitus (DM) is a chronic metabolic disease which results from diminished or absent secretion of insulin or even by reduced tissue sensitivity to insulin (International Diabetes Federation, 2015; American Diabetes Association, 2016). It is a diverse group of diseases with different group of etiology such as social, environmental and genetic factors which acts concurrently or mutually. Diabetes is a global endemic with rapidly increasing prevalence in developing countries such as Nigeria and Type 2 diabetes mellitus is one of the leading causes of preventable death in the world, with stroke, myocardial infarction and other cardiovascular diseases being the most common causes of death for adults with diabetes, with its main pathophysiological features been impaired insulin secretion and increased insulin resistance (Kaku, 2010). A number of factors including less glycemic control, smoking, high blood pressure, elevated cholesterol levels, obesity, and lack of regular exercise are considered to be risk factors that accelerate the deleterious effects of diabetes (Elfaki *et al*., 2014).

Interestingly, thyroid disorders have been implicated in Type-2-Diabetes Mellitus. Diabetes Mellitus and thyroid disorders are an endocrine disorder that are interrelated to each other (Rahman *et al*., 2007) and have a propensity to appear together and this is as a result of interaction between thyroid hormones and insulin (Feely and Isles, 1979). Thyroid diseases and diabetes mellitus are the two most common endocrine disorders encountered in clinical practice. They have been shown to mutually influence each other and associations between both conditions have been reported previously (Tiwari and Rao, 2002). The clinical relationship between diabetes mellitus and thyroid function is becoming more widely recognized with hypothyroidism among diabetes mellitus patient (Ghazali and Abbiyesuku, 2010; Singh *et al*., 2011; Demitrost and Ranabir, 2012; Yadav *et al*., 2012; Valerie *et al*., 2014; Datchinamoorthi *et al*., 2016; Afrin *et al*., 2017). Thyroid disease is common in the general population and the prevalence increases with age (Wu, 2000). However, there is reported higher prevalence of thyroid dysfunction in type 2 diabetics than in the general population (Vondra *et al*., 2005).

Type 2 diabetes is accompanied with increased formation of free radicals otherwise called reactive oxygen species (ROS) leading to oxidative damage of cell components (Bashan *et al*., 2009; Noori, 2012). ROS production in diabetes plays a key role in the pathogenesis of diabetic complications (Van Campenhout *et al*., 2006). ROS accelerates important molecular mechanisms involved in hyperglycaemia induced oxidative damage; it increases the stress signalling pathways that lead to beta-cell apoptosis (Rhodes, 2005). Different studies have provided evidences of increased oxidative stress with depleted antioxidant enzymes in type 2 diabetes (Likidlilid *et al*., 2010; Al-Rawi, 2011; Bigagli *et al*., 2012). Hyperglycemia, a hallmark of diabetic condition, depletes natural antioxidants and facilitates the production of ROS, which has the ability to react with all biological molecules like lipids, proteins, carbohydrates, DNA and exert cytotoxic effects on cellular components (Dincer *et al*., 2002). Thus, increased ROS and impaired antioxidant defense contribute for initiation and progression of micro- and macrovascular complications in diabetics (Ceriello and Motz, 2004).

Antioxidant enzymes are endogenous proteins that work in combination to protect cells from reactive oxygen species (ROS) damage. Antioxidants are instrumental in repairing damages caused by free radicals and the resulting oxidation; these enzymes action occurs by triggering chemical reactions that rid the body of free radicals and ROS (Kulbacka *et al*., 2012). Of all the enzymes, Superoxide Dismutase (SOD), Glutathione Peroxidase (GPx) and Catalase (CAT) are the ones with the most antioxidant activity and thus considered the main antioxidant enzymes that regulate free radical activity (Giacco and Brownlee, 2010). They constitute a mutually supportive team of defense against ROS (Krishnamurthy and Wadhwani, 2012). SOD is considered a first-line defense against ROS and is present in nearly all cells. It converts superoxide ion (O_2-) to hydrogen peroxide (H_2O_2). H_2O_2 may still react with other free radicals; it is thus degraded by either one of the other two antioxidant enzymes, GPx or CAT. GPx removes H_2O_2 by coupling its reduction with the oxidation of glutathione (GSH). GPx can also reduce other peroxides, such as fatty acid hydroperoxides. CAT which is localized primarily in peroxisomes, detoxifies the H_2O_2 converting it into water and molecular oxygen (Krishnamurthy and Wadhwani, 2012). However, several studies have shown decreased enzymatic antioxidants (SOD, GPX and CAT) activities in type 2 diabetes mellitus than in the non diabetic population (Djordjević *et al*., 2011; Rains and Jain, 2011; Bigagli *et al*., 2012; Hisalkar *et al*., 2012; Brown and Briggs, 2016; Ngaski, 2018). Therefore, the present review seeks to evaluate the Thyroid hormone profiling and enzymatic antioxidant status in diagnosis and management of type-2-diabetes mellitus.

Type 2 diabetes mellitus

Classification is based on the production of insulin by the pancreas or the cells of the body response properly towards the insulin production. The relative importance of defects in insulin secretion or in the peripheral action of the hormone in the occurrence of type 2 diabetes mellitus has been and will continue to be cause for discussion. In type 2 diabetes, the body does not create enough insulin to address its own particular issues or cell does not respond properly against the insulin. This is known as insulin resistance (Arthur, 2016; Zain, 2016). Insulin resistance, which is the inability of cells to respond adequately to normal levels of insulin, occurs primarily within the muscles, liver, and fat tissue (Lippincott and Wilkins, 2007). In the liver, insulin normally suppresses glucose release. However, in the setting of insulin resistance, the liver inappropriately releases glucose into the blood (Melmed *et al*., 2011). The proportion of insulin resistance versus beta cell dysfunction differs among individuals, with some having primarily insulin resistance and only a minor defect in insulin secretion and others with slight insulin resistance and primarily a lack of insulin secretion (Gardner *et al*., 2011).

Type 2 diabetes is also known as Non-Insulin-Dependent Diabetes Mellitus (NIDDM) or "adult-onset diabetes (Batra and Singh, 2016) and has a prevalence of 75 to 90% occurring in all instances of diabetes globally. Type 2 diabetes as a rule grows steadily after some time. Most people with the condition might be ignorant of their ailment particularly at early stages as there might be no particular side effects (Nishimura, 2016). Most individuals with Type 2 diabetes exhibit intra-abdominal (visceral) obesity, which is closely related to the presence of insulin resistance. In addition, hypertension and dyslipidemia (high triglyceride and low HDL-cholesterol levels; postprandial hyperlipidemia) often are

present in these individuals. This is the most common form of diabetes mellitus and is highly associated with a family history of diabetes, alcoholism, older age, obesity and lack of exercise.

PATHOPHYSIOLOGY OF DIABETES MELLITUS

An understanding of the pathophysiology of diabetes rests upon knowledge of the basics of carbohydrate metabolism and insulin action. Following the consumption of food, carbohydrates are broken down into glucose molecules in the gut. Glucose is absorbed into the bloodstream elevating blood glucose levels. This rise in glycemia stimulates the secretion of insulin from the beta cells of the pancreas. Insulin is needed by most cells to allow glucose entry. Insulin binds to specific cellular receptors and facilitates entry of glucose into the cell, which uses the glucose for energy. The increased insulin secretion from the pancreas and the subsequent cellular utilization of glucose results in lowering of blood glucose levels. Lower glucose levels then result in decreased insulin secretion. If insulin production and secretion are altered by disease, blood glucose dynamics will also change. If insulin production is decreased, glucose entry into cells will be inhibited, resulting in hyperglycaemia. The same effect will be seen if insulin is secreted from the pancreas but is not used properly by target cells. If insulin secretion is increased, blood glucose levels may become very low (hypoglycemia) as large amounts of glucose enter tissue cells and little remains in the bloodstream. Multiple hormones may affect glycemia. Insulin is the only hormone that lowers blood glucose levels. The counter-regulatory hormones such as glucagon, catecholamines, growth hormone, thyroid hormone, and glucocorticoids all act to increase blood glucose levels, in addition to their other effects (Meley *et al.*, 2006).

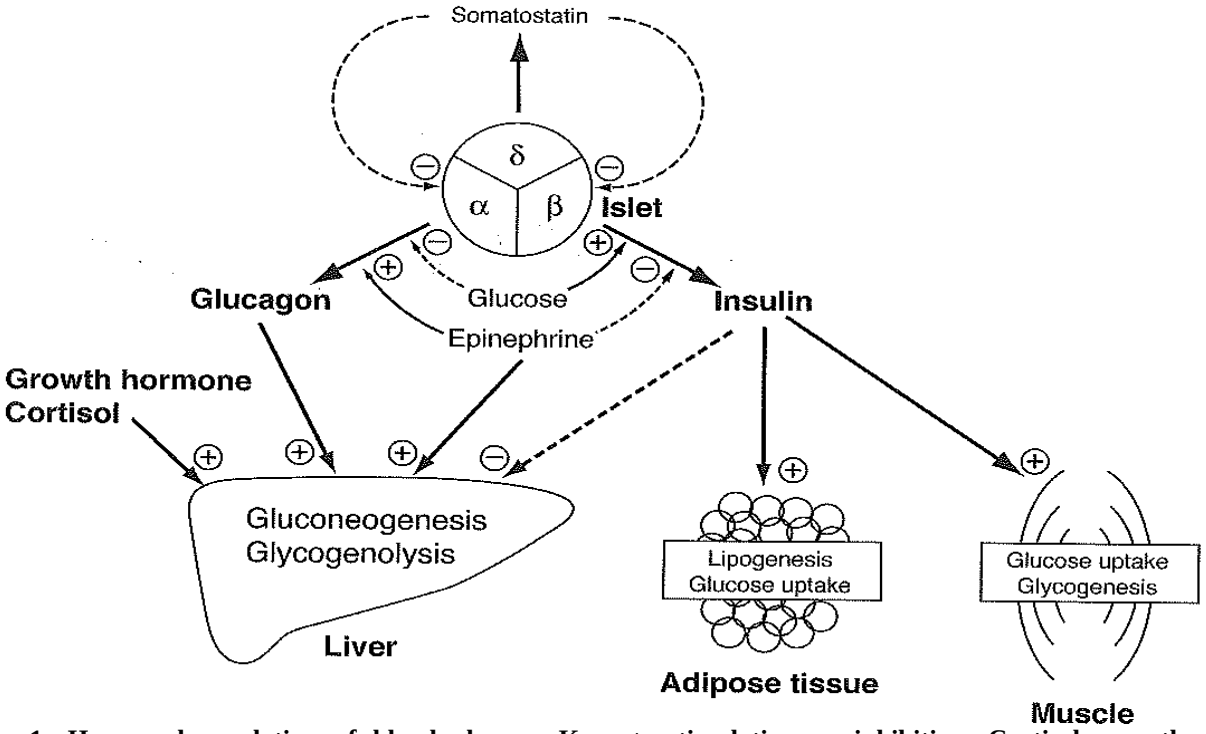

Fig. 1: Hormonal regulation of blood glucose. Key: +, stimulation; -, inhibition. Cortisol, growth, and epinephrine also antagonize the effect of insulin (Burtis and Bruns, 2015).

Pathogenesis and Pathophysiology of type 2 Diabetes Mellitus

In type 2 diabetes these mechanisms break down, with the consequence that the two main pathological defects in type 2diabetes are impaired insulin secretion through a dysfunction of the pancreatic β-cell, and impaired insulin action through insulin resistance (American Diabetes Association, 2010). In situations where resistance to insulin predominates, the mass of β-cells undergoes a transformation capable of increasing the insulin supply and compensating for the excessive and anomalous demand. In absolute terms, the plasma insulin concentration (both fasting and meal stimulated) usually is increased, although "relative" to the severity of insulin resistance, the plasma insulin concentration could be insufficient to maintain normal glucose homeostasis. Keeping in mind the intimate relationship between the secretion of insulin and the sensitivity of hormone action in the complicated control of glucose homeostasis, it is practically impossible to separate the contribution of each to the etiopathogenesis of DM2 (Kumar and Clark, 2002). Insulin resistance and hyperinsulinemia eventually lead to impaired glucose tolerance (Mahler and Adler, 1999).

Aetiology of type 2 diabetes

Type 2 diabetes results from an imbalance between insulin sensitivity and insulin secretion. Both

longitudinal and cross-sectional studies have demonstrated that the earliest detectable abnormality in type 2 diabetes is an impairment of the body's ability to respond to insulin.

Impaired insulin action is observed in several tissues e.g., skeletal muscle, adipose tissue and the liver. It leads to increased insulin secretion from the pancreas to overcome impaired insulin action. Compensatory hyperinsulinemia maintains glucose level within normal range, but in individual at high risk of developing diabetes, beta cells function eventually declines and leads to the development of impaired glucose tolerance and eventually overt diabetes mellitus (Bloomgarden, 1998; Stumvoll *et al*., 2005). A number of factors including less glycemic control, family history of diabetes, alcoholism, older age, smoking, high blood pressure, elevated cholesterol levels, obesity, and lack of regular exercise are considered to be risk factors that accelerate the deleterious effects of diabetes.

Signs and symptoms of diabetes

- Excessive thirst (polydipsia) - Excessive urination (polyuria) and dehydration
- Excessive hunger or appetite (polyphagia)
- Unexplained weight loss
- Blurred vision, nearsightedness or other vision problems
- Frequent infections, including skin infections, thrush, gingivitis, urinary tract infections and yeast infections
- Slow healing of sores
- Skin problems, such as itchiness
- Fatigue, lethargy or drowsiness
- Shakiness or trembling
- Mood swings or irritability
- Dizziness or fainting
- Numbness, tingling or pain in the feet, legs or hands (American Diabetes Association; 2005; Rother, 2007).

Epidemiology of type 2 diabetes mellitus

According to International Diabetes Federation (IDF), in 2017, approximately 425 million adults were living with diabetes and it is estimated to affect up to 629 million people by the year 2045 (IDF, 2017). Diabetes Mellitus has become a major public health problem in Nigeria accounting for a prevalence of 2.4% with total number of mortality amounting to 3028 deaths in 2017 (IDF, 2017).In the world, WHO estimates that, globally, 422 million adults aged over 18 years were living with diabetes in 2014 accounting for a prevalence of 8.5% among the adult population, of which 90% have type 2 diabetes mellitus (T_2DM), largely the result of physical inactivity and excess body weight (WHO, 2016). T_2DM accounts for well over 90% of diabetes mellitus in Sub-Saharan Africa, and population prevalence proportions ranged from 1% in rural areas to 12% in urban (Hall *et al*., 2011).

THYROID HORMONES

All cells in the body are targets for thyroid hormones. While not strictly necessary for life, thyroid hormones have profound effects on big time physiologic processes, such as development, growth and metabolism, and deficiency in the thyroid hormones is not compatible with normal health. Additionally, many of the effects of thyroid hormones have been delineated by study of deficiency and excess states. The primary function of the thyroid is the production of the iodine-containing thyroid hormones, triiodothyronine (T_3) and thyroxine (T_4) and the peptide hormone calcitonin. T_3 is so named because it contains three atoms of iodine per molecule and T_4 contains four atoms of iodine per molecule (Guyton and Hall, 2011). The major form of thyroid hormone in the blood is thyroxine (T_4), which has a longer half-life than T_3 (Irizarry *et al.*, 2014). In humans, the ratio of T_4 to T_3 released into the blood is approximately 14:1. T_4 is converted to the active T_3 (3-4 times more potent than T4) within the cell by deiodinases. Thyroxine is believed to be a prohormone and a reservoir for the most active and main thyroid hormone T_3 (Irizarry *et al.*, 2014). The hormonal output from the thyroid is regulated by the thyroid-stimulating hormone (TSH) secreted from the anterior pituitary gland, which itself is regulated by thyrotropin–releasing hormone (TRH) produced by the hypothalamus (Boron and Boulapep, 2012).

BIOSYNTHESIS OF THYROID HORMONES

Iodide is actively taken up by thyroid gland under the control of thyroid-stimulating hormone (TSH) via a sodium iodide (Na/I-) symporter. The concentration of I^- in the gland is at least 20 times that in plasma. Iodide is rapidly converted to iodine within the thyroid gland, catalyzed by thyroid peroxidase (TPO). Iodination of tyroxine residue in thyroglobulin takes place to form mono-iodotyroxine (MIT) and di-iodotyroxine (DIT) mediated by the enzyme TPO (Crook, 2012). Iodo-tyroxines are coupled to T_4 (DIT and DIT) and T_3 (DIT and MIT) which are stored in the lumen of the follicular cells. Normally, much more T4 than T3 is synthesized, but if there is an inadequate supply of iodide, the ratio of T_3 to T_4 increases. The thyroid hormones still incorporated in thyroglobulin are stored in collid of the thyroid follicule. Prior to the secretion thyroid hormones, thyroglobulin is taken up by the follicular cells, by a process involving endocytosis and phagocytosis, and T_4 and T_3 are released by proteolytic enzymes into the blood stream. This process is stimulated by TSH and inhibited by iodide. The thyroid hormones are immediately bound to plasma proteins. MIT and DIT, released at the same time are de-iodinated and the iodine is reused. Each step is controlled by specific enzymes and congenital deficiency of any of these enzymes can lead to goiter and, if severe, hypothyroidism. The uptake of iodide, as well as synthesis and secretion of thyroid hormones, is regulated by TSH, secreted from the anterior pituitary gland. About 10 times more T_4 than T_3 is formed, with most of the latter being formed by de-iodination in the liver, kidney and muscle (Crook, 2012).

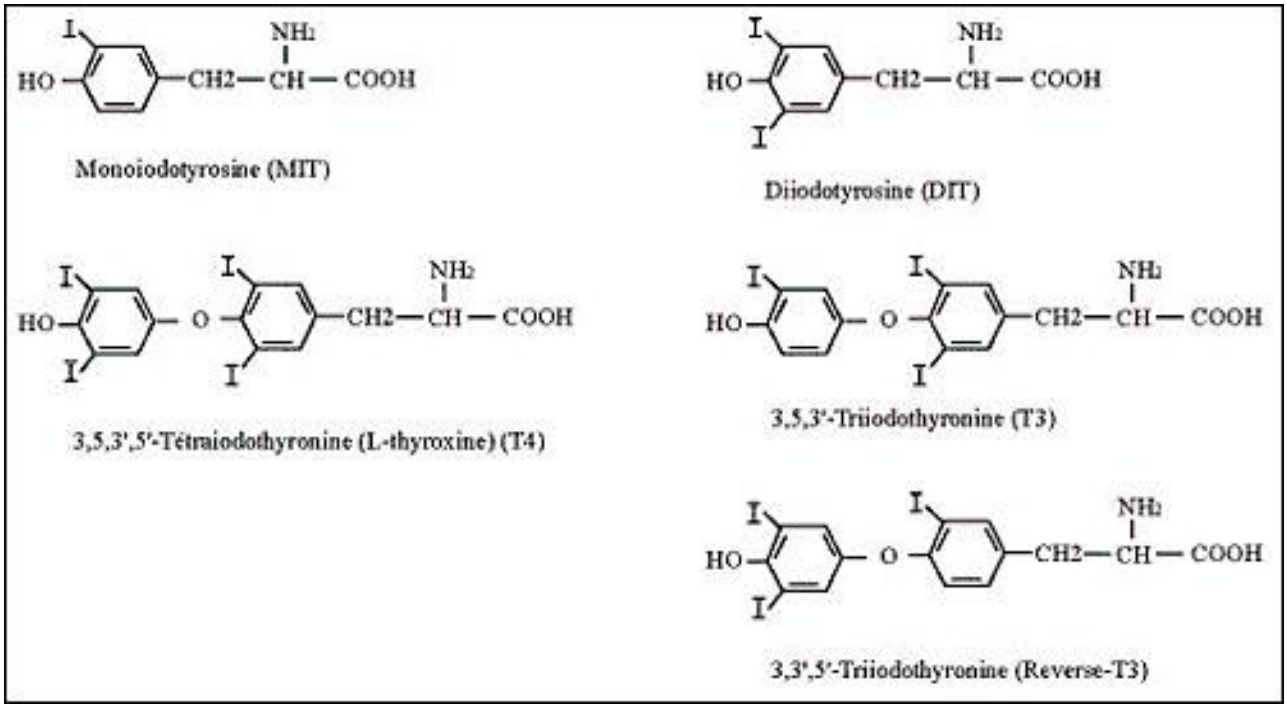

Fig. 2: structure of thyroid hormones.

GENERAL FUNCTIONS OF THYROID HORMONES

METABOLISM: thyroid hormones stimulate diverse metabolic activities in most tissues, leading to an increase in basal metabolic rate. One consequence of this activity is to increase body heat production, which seems to result, at least in part, increased oxygen consumption and rates of ATP hydrolysis.

Some of the metabolic effects of thyroid hormone include

1. **Lipid metabolism**: Increased thyroid hormone levels stimulate fat mobilization, leading to increased concentrations of fatty acids in many tissues. Despite increasing free fatty acids, thyroid hormones decreases cholesterol levels, perhaps by increasing the rate of secretion of cholesterol in bile. Plasma concentration of cholesterol and triglycerides are inversely correlated with thyroid hormone levels (Guyton and Hall, 2011)
2. **Carbohydrate metabolism**: Thyroid hormones stimulate almost all aspects of carbohydrate metabolism, including enhancement of insulin-dependent entry of glucose into cells and increased gluconeogenesis and glycogenolysis to generate free glucose.
3. **Growth:** Thyroid hormones are clearly necessary for normal growth in children and young animals, as evidenced by growth-retardation observed in thyroid deficiency. Not surprisingly, the growth promoting effects of thyroid hormones is intimately intertwined with that of growth hormone; a clear indication that complex physiologic processes like growth depends upon multiple endocrine controls.
4. **Development**: Normal levels of thyroid hormone are essential for development. They increase the growth rate of young people, and cells of the developing brain are a major target for the thyroid hormones. Thyroid hormone plays a crucial role in brain maturation during fetal development and few years of postnatal life (Guyton and Hall,2011).

Mechanism of Action of Thyroid Hormones

T_3 and T_4 bind to nuclear receptors (thyroid hormone receptors) (Lazar and Chin, 1990). T_3 and T_4, although being lipophilic, are not able to passively diffuse through the phospholipid bilayers of target cells (Dietrich *et al.*, 2008), instead relying on transmembrane iodothyronine transporters. The lipophilicity of T_3 and T_4 requires their binding to the protein carrier thyroid-binding protein (TBG) (thyroxine-binding globulins, thyroxine binding prealbumins, and albumins) for transport in the blood. The thyroid receptors bind to response elements in gene promoters, thus enabling them to activate or inhibit transcription. The sensitivity of a tissue to T_3 is modulated through the thyroid receptors. When triiodothyronine (T3) binds a receptor, it induces a conformational change in the receptor, displacing the corepressor from the complex. This leads to recruitment of coactivator proteins and RNA polymerase, activating transcription of the gene (Wu and Koenig, 2000). Although this general functional model has considerable experimental support, there remain many open questions (Ayers and Stephen, 2014).

Regulation of Thyroid Hormones (Hypothalamic–Pituitary–Thyroid Axis)

The hypothalamic pituitary thyroid axis (HPT axis) also known as thyroid homeostasis or thyrotropic feedback

control is part of the neuroendocrine system responsible for the regulation of metabolism. As its name suggests, it depends upon the hypothalamus, the pituitary gland, and the thyroid gland. The hypothalamus senses low circulating levels of thyroid hormone (Triiodothyronine (T_3) and Thyroxine (T_4)) and responds by releasing thyrotropin releasing hormone (TRH). The TRH stimulates the pituitary to produce thyroid-stimulating hormone (TSH). The TSH, in turn, stimulates the thyroid to produce thyroid hormone until levels in the blood return to normal. Thyroid hormone exerts negative feedback control over the hypothalamus as well as anterior pituitary, thus controlling the release of both TRH from hypothalamus and TSH from anterior pituitary gland (Dietrich *et al.*, 2012). Thyroid homeostasis results from a multi-loop feedback system that is found in virtually all higher vertebrates. Proper function of thyrotropic feedback control is indispensable for growth, differentiation, reproduction and intelligence. The pituitary gland secretes thyrotropin (TSH; Thyroid Stimulating Hormone) that stimulates the thyroid to secrete thyroxine (T_4) and, to a lesser degree, triiodothyronine(T_3). The major portion of T3, however, is produced in peripheral organs, e.g. liver, adipose tissue, glia and skeletal muscle by deiodination from circulating T_4. Deiodination is controlled by numerous hormones and nerve signals including TSH, vasopressin and catecholamines. Both peripheral thyroid hormones (iodothyronines) inhibit thyrotropin secretion from the pituitary (negative feedback). Consequently, equilibrium concentrations for all hormones are attained. TSH secretion is also controlled by thyrotropin releasing hormone (thyroliberin, TRH), whose secretion itself is again suppressed by plasma T_4 and T_3. Recent research suggested the existence of an additional feed forward motif linking TSH release to deiodinase activity in human (Hoermann *et al.*, 2014; Dietrich *et al.*, 2015; Hoermann *et al.*, 2015).The existence of this TSH-T_3 shunt could explain why deiodinase activity is higher in hypothyroid patients and why a minor fraction of affected individuals may benefit from substitution therapy with T_3 (Hoerman *et al.*, 2015).

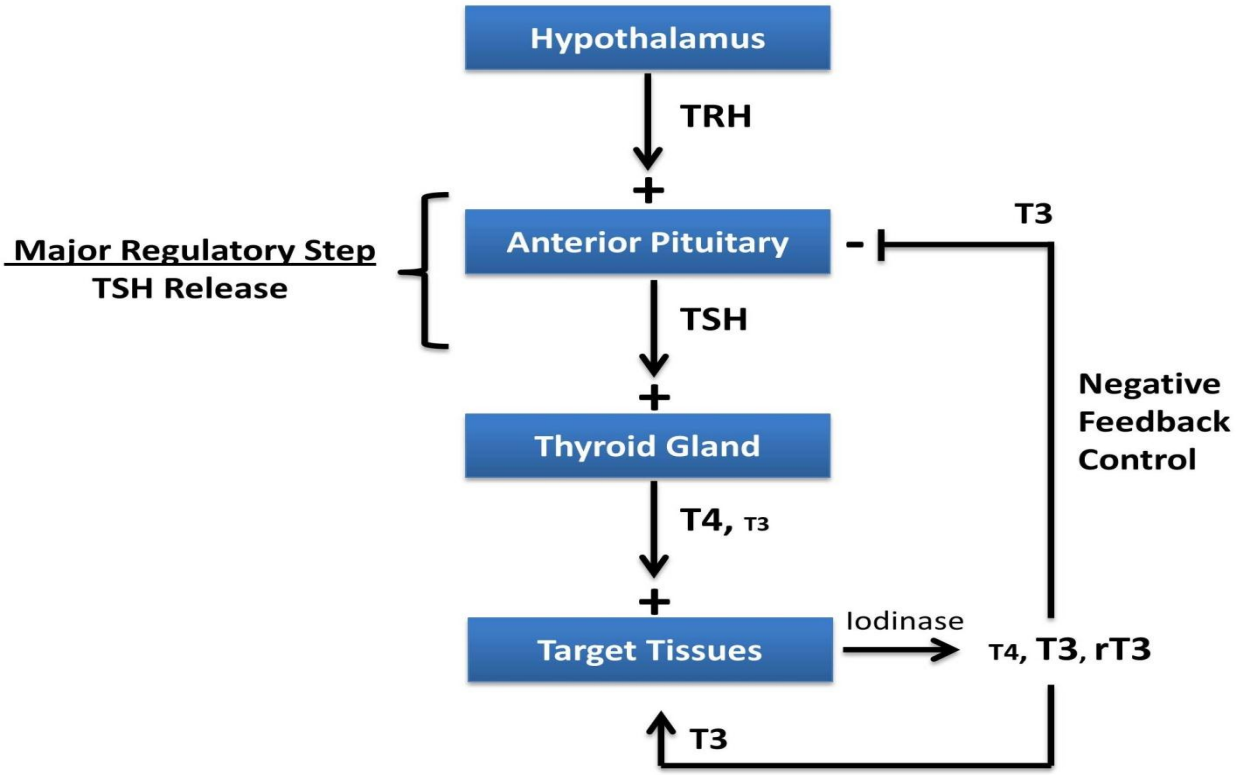

Fig. 3: regulation of thyroid hormone synthesis and secretion (hypothalamic–pituitary–thyroid axis). Retrieved from: http://www.pathwaymedicine.org/thyroid-hormone-regulation.

Oxidative stress

The shift in the balance between oxidants and antioxidants in favor of oxidants is termed "oxidative stress." As remarkable as our antioxidant defense system is, it may not always be adequate. The term "oxidative stress" has been coined to represent a shift towards the pro-oxidants in the pro-oxidant/antioxidant balance that can occur as a result of an increase in oxidative metabolism. Increased oxidative stress at the cellular level can come about as a consequence of many factors, including exposure to alcohol, cigarette smoke, medications, trauma, cold, infections, poor diet, toxins, radiation, or strenuous physical activity. Protection against all of these processes is dependent upon the adequacy of various antioxidant substances that are derived either directly or indirectly from the diet.

Consequently, an inadequate intake of antioxidant nutrients may compromise antioxidant potential, thus compounding overall oxidative stress. Oxidative damage to DNA, proteins, and other macromolecules has been implicated in the pathogenesis of a wide variety of diseases, most notably heart disease and cancer (Halliwell, 1994) . Oxidative stress causes damage to proteins, nucleic acids and lipids due to lipid peroxidation, which in turn leads to changes in the cellular structure and function, and ultimately cell death via apoptosis or necrosis (Jancsó, 2015). The term "oxidative stress" is used to describe the condition of oxidative damage resulting when the critical balance between free radical generation and antioxidant defenses is unfavorable (Rock *et al*., 1996). Oxidative stress, arising as a result of an imbalance between free radical production and antioxidant defenses, is associated with damage to a wide range of molecular species including lipids, proteins, and nucleic acids (McCord, 2000). Excessive free radical formation and/or a reduction in the antioxidant capacity may upset the balance between prooxidants and antioxidants, leading to oxidative stress.

The mitochondria are the energy power houses of the cell. It has been suggested that certain chronic illnesses related to muscle pain and chronic fatigue, e.g., myofascial pain syndrome (MPS), fibromyalgia syndrome, and chronic fatigue immunodeficiency syndrome (CFIDS), are disorders in which there is an aberration or dysfunction of mitochondrial energy production. It has been suggested that mitochondrial dysfunction is related to damage caused by ROS produced as a consequence of increased oxidative stress and insufficient antioxidant defenses. Levels of ROS produced within the mitochondria are reported to increase with age. Consequently, oxidative damage to mitochondria would also appear to increase with age. This damage results in a decrease in energy production by some of the cell's mitochondria. Mitochondrial function is supported by a broad spectrum of nutritional modulators including antioxidants and antioxidant support systems.

ANTIOXIDANTS

Antioxidants are the substance that when present in low concentration compared to those of the oxidisable substrates significantly delay or inhibit the oxidation of that substance. Antioxidants defense, both enzymatic and non enzymatic reactions protect the body against oxidative damage. The term "antioxidant" refers to any molecule capable of stabilizing or deactivating free radicals before they attack cells. Humans have evolved highly complex antioxidant systems (enzymic and nonenzymic), which work synergistically, and in combination with each other to protect the cells and organ systems of the body against free radical damage (Lobo *et al*., 2010). Therefore, it is imperative to X-ray the underlying events "free radicals" and "oxidative stress" which antioxidants seeks to ameliorate its deleterious effects.

TYPES OF ENZYMATIC ANTIOXIDANTS

1. Superoxide Dismutase

Superoxide dismutase (SOD) is the antioxidant enzyme that catalyses the dismutation of superoxide anion (O_2^-) into hydrogen peroxide and molecular oxygen (Wang *et al*., 2012). SOD plays important protective roles against cellular and histological damages that are produced by ROS. It facilitates the conversion of superoxide radicals into hydrogen peroxide, and in the presence of other enzymes it converted into oxygen and water (Davari *et al*., 2013). All mammalian tissues contain three forms of SOD: Cu-Zn-SOD, Mn-SOD, and extracellular EC-SOD, and each of them is a product of a distinct gene (Li *et al*., 2012). Cu-Zn-SOD or SOD 1 (EC 1.15.1.1) is localized in cytosol, Mn-SOD or SOD 2 (EC 1.15.1.1) in mitochondria, and EC-SOD or SOD 3 (EC 1.15.1.1) in extracellular space (Zelko *et al*., 2002). Superoxide reacts rapidly with nitric oxide (NO), reducing NO bioactivity and producing the oxidative peroxynitrite radical (Guzik *et al*., 2002). SOD, a major defender against superoxide, in the kidneys during the development of murine diabetic nephropathy and down regulation of renal SOD (SOD 1 and SOD 3) may play a key role in the pathogenesis of diabetic nephropathy (Fujita *et al*., 2009). Over expression of SOD or the supplements of antioxidants including SOD mimetics, targeted to overcome oxidative stress, reduce ROS, and increase antioxidant enzymes, has been shown to prevent diabetes mellitus (Wang *et al*., 2012). EC-SOD is found in the extracellular matrix of various tissues including pancreas, skeletal muscle, and blood vessels, and is themajor extracellular scavenger of superoxide radicals (Fattman *et al*., 2003). The higher level of EC-SOD resulted in a 6-fold increase in the total superoxide dismutase activity of the islets; therefore, superoxide radicals secreted to the extracellular space does not contribute to the β-cell destruction (Sandstr¨om *et al*., 2002). The elevated level of SOD is shown to reduce oxidative stress; decrease mitochondrial release of cytochrome C and apoptosis in neurons; and, in mice, prevent diabetes-induced glomerular injury, thus suggesting a major role of SOD in the regulation of apoptosis (Kowluru *et al*., 2006). Decline in the level of SOD in diabetic tissue and blood has been reported in many studies (He *et al*., 2011; Shukla *et al*., 2012).
Recently Kim (2013) reported that diabetic skin tissues express a relatively small amount of extracellular protein and concluded that extracellular SOD is related to the altered metabolic state in diabetic skin, which elevates ROS production (Kim, 2013). Study performed by Lucchesi and colleagues (Lucchesi *et al*., 2013) to observe the oxidative balance of diabetic rats reported diminished activity of SOD and other antioxidative enzymes in in the liver tissue.

2. Glutathione

Glutathione (GSH), a tripeptide, γ-Lglutamyl-L-cysteinylglycine, is present in all mammalian tissues at 1–10mM concentrations (highest concentration in liver) as the most abundant nonprotein thiol that defends

against oxidative stress (Lu, 2013). GSH can maintain SH groups of proteins in a reduced state, participate in amino acid transport, detoxify foreign radicals, act as coenzyme in several enzymatic reactions, and also prevent tissue damage (Tsai *et al*., 2012). It is an efficient antioxidant present in almost all living cells and is also considered as a biomarker of redox imbalance at cellular level (Rizvi and Chakravarty, 2011). There are several reports that claim reduced level of GSH in diabetes (Rahigude *et al*., 2012; Calabrese *et al*., 2012). Decreased GSH level may be one of the factors in the oxidative DNA damage in type 2 diabetics (Dinc *et al*., 2002). As a consequence of increased oxidative status, GSH showed the frequent alteration in its concentration. Plasma GSH/GSSG showed a significant decrease in type 2 diabetes as compared to normal (Calabrese *et al*., 2012). Hyperlipidemia, inflammation, and altered antioxidant profiles are the usual complications in diabetes mellitus as results decreased GSH/GSSG ratio (Das *et al*., 2012). Abnormal GSH status is involved in *β*-cell dysfunction and in the pathogenesis of long-term complications of diabetes. The dysregulation is widely implicated in disease states (Livingstone and Davis, 2007). Glutathione reductase (GSR) plays an important role through the reduction of GSSG to GSH and oxidation of NADPH to NAD+. GSSG is unable to perform antioxidant functions; however, GSH can be reclaimed from GSSG through the use of glutathione reductase (GSR) by the use of NADPH as a cofactor. Unfortunately, this GSH system can be overwhelmed if ROS are produced in excess (Morris *et al*., 2013). Uncontrolled type 2 diabetes has severely deficient synthesis of GSH attributed to limited precursor availability. Dietary supplementation with GSH precursor amino acids can restore GSH synthesis and lower oxidative stress and oxidant damage in the face of persistent hyperglycemia (Sekhar *et al*., 2011). It has been observed that GSH deficiency in diabetics increased their susceptibility to melioidosis. It is hypothesized that maintenance of GSH redox state may be a new therapeutic avenue to protect diabetic patients against some intracellular bacterial pathogens (Tan *et al*., 2012).

3. Catalase

Catalase is an antioxidative enzyme present nearly in all living organisms. It plays an important role against oxidative stress-generated complications such as diabetes and cardiovascular diseases (Chelikani, 2004). Catalase acts as main regulator of hydrogen peroxide metabolism. Hydrogen peroxide is a highly reactive small molecule formed as natural by-product of energy metabolism. Excessive concentration of hydrogen peroxide may cause significant damages to proteins, DNA, RNA, and lipids (Takemoto *et al*., 2009). Catalase enzymatically processes hydrogen peroxide into oxygen and water and thus neutralizes it. Increased risk of diabetes has been documented in patients with catalase deficiency. The deficiency of this enzyme leads, in the *β*-cell, to an increase in oxidative stress and ultimately to a failure of this cell type. *β*-cells are rich in mitochondria, and thus this organelle might be a source of ROS (G´oth and Eaton, 2000).

Catalase protects pancreatic *β*-cells from damage by hydrogen peroxide (Tiedge *et al*., 1998). Low catalase activities, which have been reported in patients with schizophrenia and atherosclerosis (G´oth and Vitai, 1996), are consistent with the hypothesis that long-term oxidative stress may contribute to the development of a variety of late-onset disorders, such as type 2 diabetes (G´oth, 2000). Deficiency of catalase increases mitochondrial ROS and fibronectin expression in response to free fatty acids, which were effectively restored by catalase over expression or N-acetyl cysteine (Hwang *et al*., 2012). Low catalase activities can cause methemoglobinaemia and hemolytic anemia which may be attributed either to deficiency of glucose-6-phosphate dehydrogenase or to other unknown circumstances and also may damage heme proteins, cause cell death, and, together with redox active metal ions, produce highly toxic hydroxyl radicals (G´oth and Bigler, 2007). Patel and coworkers (Patel *et al*., 2013), during investigation of hyperglycemia- induced functional changes: superoxide, hydrogen peroxide production, mitochondrial membrane polarization, and gene expression fingerprints of related enzymes in endothelial cells, have reported that hyperglycemia increased hydrogen peroxide production, hyperpolarized mitochondrial membrane, and down regulated CAT gene expression.

PATHOPHYSIOLOGY OF THYROID HORMONE PROFILE IN T_2DM

The thyrotrophin-releasing hormorne (TRH) released from the hypothalamus signals the pituitary gland to produce and release Thyroid Stimulating Hormone (TSH). TSH stimulates the synthesis and release of thyroid hormones from the thyroid gland (Crook, 2012). The physiological function of thyroid hormones requires the interaction of THs and their nuclear receptors (TRs). There are two major TR isoforms, encoded on separate genes (Sap *et al*., 1986; Weinberger *et al*., 1986): TR*α* and TR*β*. The TR*β* gene encodes three TR*β* isoforms: TR*β*1, TR*β*2, and TR*β*3. All TR*β* isoforms bind to their cognate ligand T3 with high affinity to mediate target gene expression. In contrast, among the three TR*α* isoforms, only TR*α*1 is able to bind to T_3 in order to activate or repress target genes, whereas TR*α*2 and TR*α*3 do not bind T_3, antagonizing T_3 action. The musculoaponeurotic fibrosarcoma oncogene family A (MaFA) is present in the human pancreas and promotes *β* cell maturation and proliferation through its target genes after birth (Eto *et al*., 2014). In pancreas, there are receptors of TH which are important for a normal development of the islets. *MAF* gene encode transcription factors, and the expression of *MafA* isotype has as its main objective to regulate the growth, proliferation and development of β pancreatic cells (Aramata *et al*., 2007) which in turn results in the secretion of insulin. Hyperinsulinemia triggers the

negative feedback mechanism which down regulates the synthesis and secretion of TSH that results in subsequent decrease in the synthesis and secretion of thyroid hormones (T_3 and T_4) leading to hypothyroidism. In hypothyroidism, there is an increase of insulin secretion stimulated by glucose in the β cells, and the opposite occurs in hyperthyroidism, reducing the secretion of insulin stimulated by glucose (Stanick *et al.*, 2005; Mitrou *et al.*, 2010). This is in consonance with several studies (Udiong *et al*., 2007; *Yadav et al., 2012;* Datchinamoorthi *et al*., 2016; Afrin *et al*., 2017).

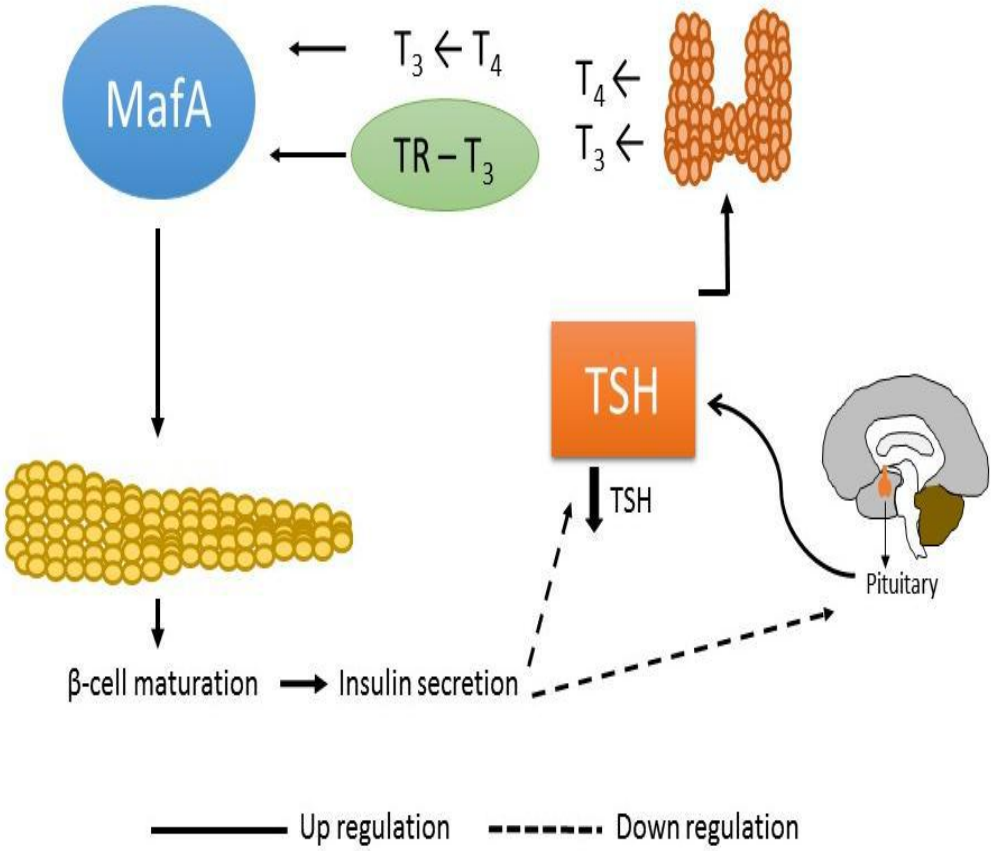

Fig. 5: Role of insulin in control of thyroid hormones through hypothalamic-pituitary axis (da Silva *et al*., 2017).

OXIDATIVE STRESS AND EZYMATIC ANTIOXIDANT ROLE IN T2DM

Oxidative stress is defined in general as excess formation and/or insufficient removal of highly reactive molecules such as reactive oxygen species (ROS) and reactive nitrogen species (RNS) (Maritim *et al*., 2003). ROS include free radicals such as superoxide ($^{\bullet}O_2^-$), hydroxyl ($^{\bullet}OH$), peroxyl ($^{\bullet}RO_2$), hydroperoxyl ($^{\bullet}HRO_2^-$) as well as nonradical species such as hydrogen peroxide (H_2O_2) and hydrochlorous acid (HOCl) (Evans *et al*., 2002).

RNS include free radicals like nitric oxide ($^{\bullet}NO$) and nitrogen dioxide ($^{\bullet}NO_2^-$), as well as nonradicals such as peroxynitrite ($ONOO^-$), nitrous oxide (HNO_2) and alkyl peroxynitrates (RONOO) (Evans *et al*., 2002). Of these reactive molecules, $^{\bullet}O_2^-$, $^{\bullet}NO$ and $ONOO^-$ are the most widely studied species and play important roles in the diabetic cardiovascular complications. $^{\bullet}NO$ is normally produced from L-arginine by endothelial nitric oxide synthase (eNOS) in the vasculature (Turko *et al*., 2001). $^{\bullet}NO$ mediates endothelium-dependent vasorelaxation by its action on guanylate cyclase in vascular smooth muscle cells (VSMC), initiating a cascade that leads to vasorelaxation. $^{\bullet}NO$ also displays antiproliferative properties and inhibits platelet and leukocyte adhesion to vascular endothelium (Turko *et al*., 2001). Therefore, $^{\bullet}NO$ is considered a vasculoprotective molecule. However, $^{\bullet}NO$ easily reacts with superoxide, generating the highly reactive molecule $ONOO^-$, and triggering a cascade of harmful events as discussed below (Vega-Lopez *et al*., 2004). Therefore its chemical environment, i.e. presence of $^{\bullet}O_2^-$, determines whether $^{\bullet}NO$ exerts protective or harmful effects. Production of one ROS or RNS may lead to the production of others through radical chain reactions. As summarized in Fig. 6: $^{\bullet}O_2^-$ is produced by one electron reduction of oxygen by several different oxidases including NAD(P)H oxidase, xanthine oxidase, cyclooxygenase and even eNOS under certain conditions as well as by the mitochondrial electron transport chain during the course of normal oxidative

phosphorylation, which is essential for generating ATP (Evans *et al*., 2003). Under normal conditions, $^{\bullet}O_2^-$ is quickly eliminated by antioxidant defense mechanisms. $^{\bullet}O_2^-$ is dismutated to H_2O_2 by manganese superoxide dismutase (Mn-SOD) in the mitochondria and by copper (Cu)-SOD in the cytosol (Evans *et al*., 2003). H_2O_2 is converted to H_20 and O_2 by glutathione peroxidase (GSH-Px) or catalase in the mitochondria and lysosomes, respectively. H_2O_2 can also be converted to the highly reactive $^{\bullet}OH$ radical in the presence of transition elements like iron and copper. A previous study demonstrated that hyperglycemia-induced generation of $\bullet O_2^-$ at the mitochondrial level is the initial trigger of vicious cycle of oxidative stress in diabetes (Brownlee, 2001). Previously, a number of studies have shown depleted antioxidant status (SOD, GPX and CAT) in type 2 diabetic patients (Verma *et al*., 2013; Briggs *et al*., 2016; Medhini *et al*., 2016; Brown and Briggs, 2016; Kayalvizhi, 2017; Ngaski, 2018).

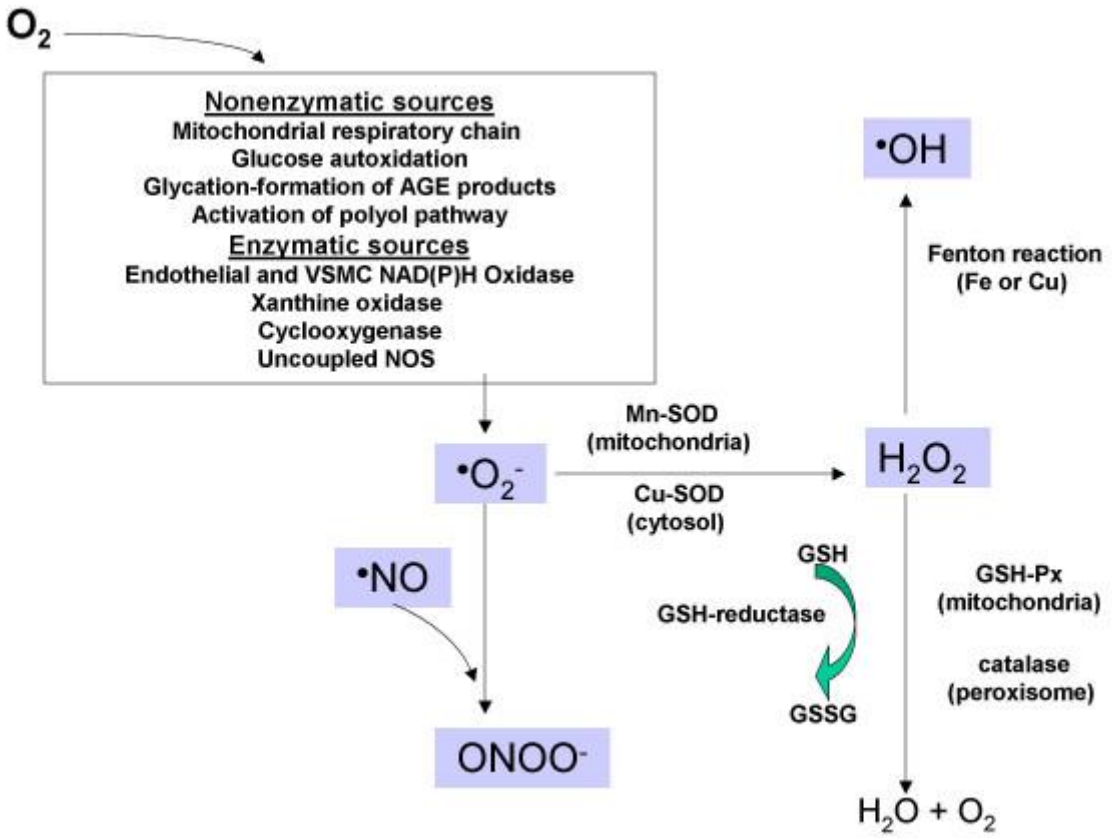

Fig. 6: Generation of reactive species in type 2 diabetes mellitus (Jeanette *et al*., 2005). .

Highlighted in gray are some of the most important ROS and RNS in vascular cells. Oxygen is converted to $^{\bullet}O_2^-$ via the activation of enzymatic and nonenzymatic pathways, which is then dismutated to H_2O_2 by SOD. H_2O_2 can be converted to H_2O by catalase or glutathione peroxidase (GSH-Px) or to $^{\bullet}OH$ after reaction with Cu or Fe. Glutathione reductase regenerates glutathione (GSH). In addition, $^{\bullet}O_2^-$ reacts rapidly with $^{\bullet}NO$ to form $ONOO^-$.

LABORATORY DIAGNOSIS OF TYPE 2 DIABETES MELLITUS

In individuals diagnosed of diabetes mellitus, glucose monitoring is essential for glycemic control (Yoon *et al*., 2015). Currently, the laboratory tests used to diagnose Diabetes Mellitus are glycated hemoglobin ($HbA1_C$), fasting plasma glucose (FG) and two-hour plasma glucose (2HPPG) after a 75g oral glucose tolerance test (OGTT) (Sacks *et al*., 2011; ADA, 2016). Of the glycemic indices, the American Diabetes Association recommends glycated hemoglobin (HbA1c) testing in all diabetic patients as an initial assessment and then as a part of continuing care (ADA, 2014). This recommendation is derived from clinical data that shows that HbA1c reflects average glycemic status over 2-3 months and predicts diabetic complications (Lee *et al*., 2013). Currently, glycated albumin is been used along side with glycated hemoglobin. Albumin is one of the most abundant plasma proteins (Tiwari *et al*., 2015).The glycation of albumin to form glycated albumin (GA) is ten times more than the glycation of hemoglobin in type 2 DM (Tahara *et al*., 1995). GA is a marker which reflects a short-term glycemic control (Yoon *et al*., 2015). One advantage of utilizing serum albumin as a measure of glycemic control is its shorter half-life of 21 days, which renders its serum concentration more sensitive to recent change in average blood glucose level

than HbA1C (Guerin-Dubourg *et al*., 2012). Studies have shown decreased albumin levels associated with increased HbA1c and total protein (Malawadi and Adiga, 2016; Nazki *et al*., 2017). The following laboratory tests is thus pivotal in the diagnosis of type 2 diabetes mellitus and they include: Urinalysis, blood glucose estimation (FBS, 2HPP, OGTT), HBA_1c, glycated albumin estimation.

Importantly, the use of thyroid function testing to assay the levels of TSH, T3 and T4, fT_3 and fT_4 index as well as T_3/T_4 ratio which are not used routinely by many laboratories may be included.

I. **Thyroid-stimulating hormone assay (TSH):** TSH produced by the pituitary is decreased in hyperthyroidism. Thus, the diagnosis of hyperthyroidism is nearly always associated with a low (suppressed) TSH level. If the TSH levels are not low, then other tests must be run.

II. **Triiodothyronine (T_3) Estimation**
Thyroid hormones themselves (T3, T4) are increased. For a patient to have hyperthyroidism, they must have high thyroid hormone levels. Sometimes all of the different thyroid hormones are not high and only one or two of the different thyroid hormone measurements are high. This is not too common, as most people with hyperthyroidism will have all of their thyroid hormone measurements high (except TSH).

III. **Free Triiodothyronine (Ft_3) Estimation:** Triiodothyronine, a thyroid hormone, circulates in blood almost completely bound (>99.5%) to carrier proteins (Wild, 1994). The main transport protein is thyroxine-binding globulin (TBG). However, only the free (unbound) portion of triiodothyronine is believed to be responsible for the biological action. Further, the concentrations of the carrier proteins are altered in many clinical conditions, such as pregnancy. In normal thyroid function as the concentrations of the carrier proteins alters, the total triiodothyronine level changes so that the free triiodothyronine concentration remains constant. Thus, measurements of free triiodothyronine concentrations correlate more reliably with clinical status than total triiodothyronine levels.

CONCLUSION

An important progress occurred in the comprehension of TH roles mediating metabolic actions related to DM, acting in several glands and energetic substrates regulator tissues. Some theme, such as the action of TH over the ionic regulation in the cells altering their activity in different paths; as well as, over a negative feedback by down regulation on insulin action, increasing pancreatic β cells, indicate important directions to research. The action mechanisms related to thyroid hormones and insulinotropic action form a counterbalance, in which occurring an imbalance (hyper or hypothyroidism) it may be observed the presence of DM or IR. Type 2diabetes is associated with decreased anti-oxidative status as the levels of the antioxidant enzymes SOD and GPx are usually significantly reduced in the diabetic subjects. Hyperglycaemia, an inevitable consequence of Type 2 diabetes and increased generation of ROS depresses the endogenous antioxidant defence system, exposing cells to damage from oxidative stress which could lead to the development of diabetic complications. Hyperinsulinamia initiates a negative feedback mechanism leading to hypothyroidism in Type 2 Diabetes Mellitus. Also, a decrease in enzymatic antioxidants increases the risk of Type 2 Diabetes mellitus.

RECOMMENDATION

1. Balanced diet, healthy life style and regular medical check are encouraged.
2. Awareness creation by medical personnel is essential in the prevention and management of Type 2 Diabetes Mellitus.
3. Thyroid hormone function profiling and antioxidant assays should be incorporated as part of routine tests for Type 2 Diabetes Mellitus.

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