Divalent cations- The magic ions at the confluence of Insulin sensitivity and Insulin resistance- perspectives with reference to Thyroid status

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Abstract

The effect of Euthyroid Type 2 diabetic patients on divalent cations has not been well established and the underlying mechanisms are not well understood. Only few data on the association between thyroid function and T2DM on divalent cations exists. The use of mineral and other complementary nutrition-based therapies has increased dramatically in the United States. Many health care providers are also beginning to explore the use of these therapies in their practices. For those of us who work in conventional health care settings, this is a new venture. But for many of our patients who have been self-medicating with supplements, it is not. This article reviews how micronutrient requirements are determined and summarizes current recommendations for supplementation and the most pertinent research on the use of key vitamins and minerals in diabetes management. This review explores the role of various mineral elements in management of euthyroid type 2 diabetic patients. The literature regarding their modes of action in lowering blood glucose levels is also discussed in the review.

Key words: Divalent cations, Insulin sensitivity, Insulin resistance, clinically euthyroid.

Introduction

Role of ions in physiological and biochemical processes

Nutrition is often said to be the cornerstone of diabetes care [1]. The nutritional management of diabetes can affect long term health and quality of life. The goal for nutritional management is optimal metabolic control through a balance between food intake, physical activity, and if necessary, medication to avoid complications. In type 2 diabetes, nutritional goals aim for improved glycemic and lipid levels and weight loss when required [2]. Deficiencies of certain minerals, such as potassium, magnesium, zinc and chromium aggravate carbohydrate intolerance. Micronutrients are essential nutrients that are required by the body in trace amounts or tiny quantities on a day to-day basis in order to function properly. Minerals are involved in a variety of chemical reactions in metabolism, regulating electrolyte balance in maintaining bone, in the process of blood clotting and the transmission of nerve impulses. Their role as enzyme cofactors is a key in various physiological processes. Glucose homeostasis involves a fine coordination of events where hormonal control by insulin plays a key role [3]. However, the role of minerals such as magnesium, zinc, chromium, iron and selenium in diabetes is less obvious and, in some cases, may be controversial. This review offers information for these five elements and their correlation with diabetes. This includes four major classes: macro elements, trace elements, vitamins, and organic acids. Macro elements include chloride, calcium, phosphorous, magnesium, sodium, potassium, and iron. The trace elements include cobalt, boron, chromium, copper, sulfur, iodine, fluoride, selenium, manganese, zinc, and molybdenum.

Divalent cations in metabolism associated with the role of Insulin

Magnesium (Mg) is the fourth most abundant cation in the body and the second most common intracellular cation as a cofactor of many enzymes involved in glucose metabolism. Magnesium has an important role in insulin action, and insulin stimulates magnesium uptake in insulin-sensitive tissues. An impaired biological response to insulin is referred to as insulin resistance. Intracellular magnesium concentration is low in type 2 diabetes mellitus and in hypertensive patients. Reduced intracellular Mg concentrations result in a defective tyrosine-kinase activity, postreceptorial impairment in insulin action and worsening of insulin resistance in diabetic patients[4]**.** In patients with type 2 diabetes an inverse association exists between the plasma magnesium and insulin resistance due to intracellular changes. The suppressed intracellular magnesium concentration may result in defective tyrosine kinase activity and modify insulin sensitivity by influencing receptor activity after binding or by influencing intracellular signaling and processing. Intracellular magnesium deficiency may affect the development of insulin resistance and alter the glucose entry into the cell. Magnesium is required for both proper glucose utilization and insulin signaling. Metabolic alterations in cellular magnesium, which may play the role of a second messenger for insulin action, contribute to insulin resistance [5].

Hypertriacylglycerolemia was pronounced in type 2 diabetes mellitus patients with accompanying hypomagnesemia. This compared well with that of the glycemic control. Low Mg levels, high TG levels in association with enhanced HbA1c levels could thus serve as a reliable biochemical indicator of insulin status and action without resorting to the usage of criteria for insulin sensitivity and resistance [6].

Minerals	**Functions**
Magnesium	The magnesium is an essential ion involved in multiple levels in insulin's secretion and its

	binding and its activity; and it is also a critical cofactor of many enzymes in carbohydrate metabolism. The magnesium plays an important role to improve insulin resistance [7].
Zinc	The zinc plays an important role in glucose metabolism. It helps in the utilization of glucose by muscle and fat cells. It is required as a cofactor for the function of intracellular enzymes that may be involved in protein, lipid, and glucose metabolism. The zinc may be involved in the regulation of insulin receptor-initiated signal transudation mechanism and insulin receptor synthesis [8].
TSH, T3 and T4	A thyrotropic hormone stimulates the thyroid gland to produce thyroxine and triiodothyronine which stimulates the metabolism of almost every tissue in the body. Together these hormones regulate our body's temperature, metabolism and heart rate [9].
Insulin	An important part of metabolism and necessary for turning glucose into energy and distributing it to cells. Also helps the liver, muscle and fat cells to store the glucose [10].
Adiponectin	A protein hormone that modulates number of metabolic process, including glucose regulation and fatty acid oxidation [11].
Liver functions	An insulin-resistant liver ignores the hormone's signal to stop sending glucose to the blood that raises blood glucose levels and increases the risk of type2 diabetes. Diabetes also may be a cause of fatty liver and liver disease [12].

People with uncontrolled hyperglycemia, especially those on chronic diuretic therapy, are prone to develop deficiencies in some minerals, notably potassium, magnesium, and zinc [13,14]. Deficiencies of certain minerals such as potassium, magnesium, and possibly zinc and chromium may predispose one to carbohydrate intolerance. People with uncontrolled diabetes have increased zinc losses in the urine. Ordinarily, these losses are counterbalanced by enhanced zinc

absorption in the gut [13,15]. However, it is conceivable that the latter compensatory mechanism may not be sufficient to prevent zinc deficiency in some people. Some studies have shown that calcium and vitamin D are not only required for skeletal health but also may have a role in immune modulation and pancreatic insulin secretion and action. [16,17]

Normal thyroid function plays an important role in regulation of cellular activity, and influences basal metabolic rate and general body metabolism Thus, thyroid dysfunction is often associated with dyslipidemia and disturbed mineral metabolism [18].

Micronutrients are vitamins and minerals that our bodies require in small quantities for specific functions, as well as it can regulate metabolism and gene expression which influence the development and progression of many chronic diseases. [16]. Magnesium functions as an essential cofactor for more than 300 enzymes. It is essential for all energy-dependent transport systems, glycolysis, oxidative energy metabolism, biosynthetic reactions, normal bone metabolism, neuromuscular activity, electrolyte balance, and cell membrane stabilization [17]. The kidney primarily regulates magnesium homeostasis.

Magnesium deficiency has been associated with hypertension, insulin resistance, glucose intolerance, dyslipidemia, increased platelet aggregation, cardiovascular disease, complications of diabetes, and complications of pregnancy [18]. Decreased magnesium levels and increased urinary magnesium losses have been documented in both type 1 and type 2 diabetic patients [19] Low dietary magnesium intake has been associated with increased incidence of type 2 diabetes in some, [20] but not all, studies. [21]

The mechanisms by which magnesium affects insulin resistance, hypertension, and cardiovascular disease are unknown. However, the widespread use of magnesium in normal

metabolism of macronutrients, cellular transport systems, intracellular signaling systems, platelet aggregation, vascular smooth muscle tone and contractility, electrolyte homeostasis, and phosphorylation and dephosphorylation reactions [15] suggests that these effects are multifactorial.

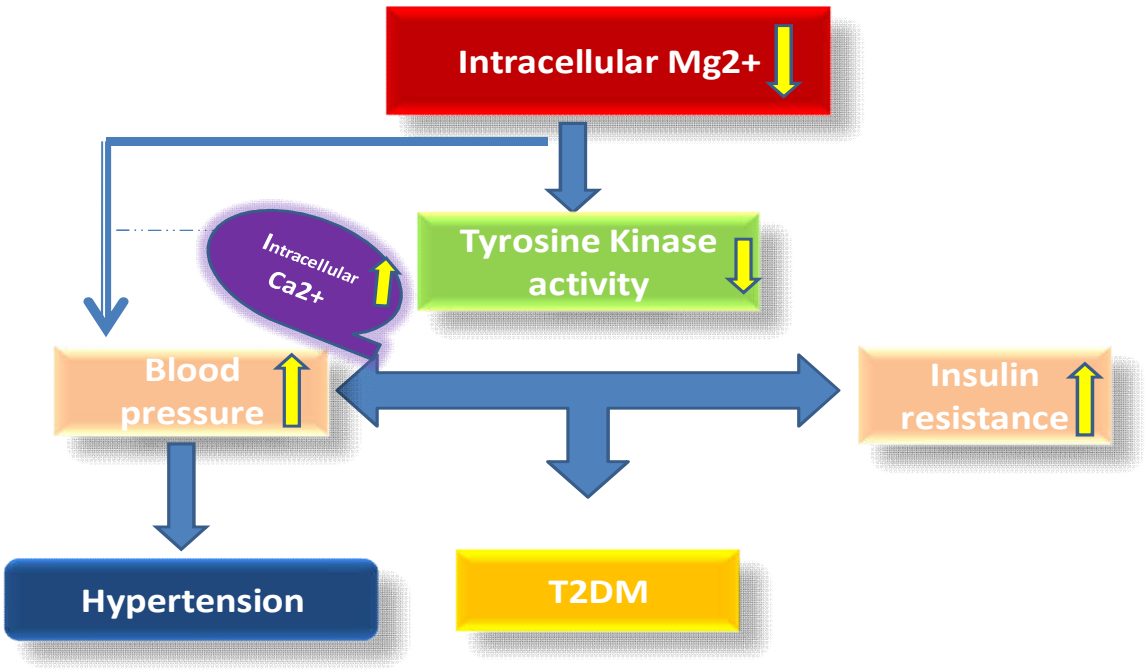
Extracellular cations Vs Intracellular cations- a status check frequently encountered facet

The body contains a large variety of ions, or electrolytes, which perform a variety of functions. Some ions assist in the transmission of electrical impulses along cell membranes in neurons and muscles. Other ions help to stabilize protein structures in enzymes. Still others aid in releasing hormones from endocrine glands. Electrolytes in living systems include sodium, potassium, chloride, bicarbonate, calcium, phosphate, magnesium, copper, zinc, iron, manganese, molybdenum, copper, and chromium.

Type 2 diabetes is frequently associated with both extracellular and intracellular magnesium (Mg) deficits. A chronic latent Mg deficit or an overt clinical hypomagnesemia is common in patients with type 2 diabetes, especially in those with poorly controlled glycemic profiles. Insulin and glucose are important regulators of Mg metabolism. Intracellular Mg plays a key role in regulating insulin action, insulin-mediated-glucose-uptake and vascular tone [22]. Reduced intracellular Mg concentrations result in a defective tyrosine-kinase activity, postreceptorial impairment in insulin action and worsening of insulin resistance in diabetic patients. Low dietary Mg intake has been related to the development of type 2 diabetes and metabolic syndrome [23]. Benefits of Mg supplementation on metabolic profiles in diabetic patients have been found in most, but not all clinical studies and larger prospective studies are needed to support the potential role of dietary Mg supplementation as a possible public health strategy in diabetes risk.

Biochemical functions of divalent cations- center stage in Insulin sensitivity and Insulin resistance

Magnesium (Mg2+) is an essential mineral for human health and plays an important role in the regulation of glucose homeostasis and insulin actions [25]. Despite the widespread clinical evidences for the association of Mg2+ deficiency (MgD) and type 2 diabetes mellitus (T2D), molecular mechanisms by which Mg2+ contributes to insulin resistance (IR) are still under discussion. Mg2+ regulates electrical activity and insulin secretion in pancreatic beta-cells. Intracellular Mg2+ concentrations are critical for the phosphorylation of the insulin receptor and other downstream signal kinases of the target cells. Low Mg2+ levels result in a defective tyrosine kinase activity, post-receptor impairment in insulin action, altered cellular glucose transport, and decreased cellular glucose utilization, which promotes peripheral IR in T2D [26]. Mg depletion triggers chronic systemic inflammation that also potentiates IR. People with T2D may end up in a vicious circle in which Mg depletion increases IR and IR causes Mg depletion, which requires periodic monitoring of serum Mg2+ levels [27].



Implications of Divalent cations in thyroid status- a succinct update

Thyroid hormone is a central regulator of body haemodynamic, thermoregulation and metabolism. Thyroid hormones perform a wide array of metabolic functions including regulation of lipid, carbohydrate, protein and electrolyte and mineral metabolisms. While the effect of thyroid hormones on lipid metabolism is well known, the effect on electrolytes and minerals has not been well established and also the underlying mechanisms are not well understood [28].

In many literatures different electrolyte disorders are associated with thyroid dysfunction. In severe hypothyroidism and myxoedema hyponatraemia is described to be a consequence of enhanced renal water retention mediated by vasopressin. On the other hand, hypokalaemia, hypomagnesaemia and hypercalcaemia were mentioned in patients with thyrotoxicosis [29]. Recently, the disorders of thyroid function particularly hypothyroidism is receiving greater

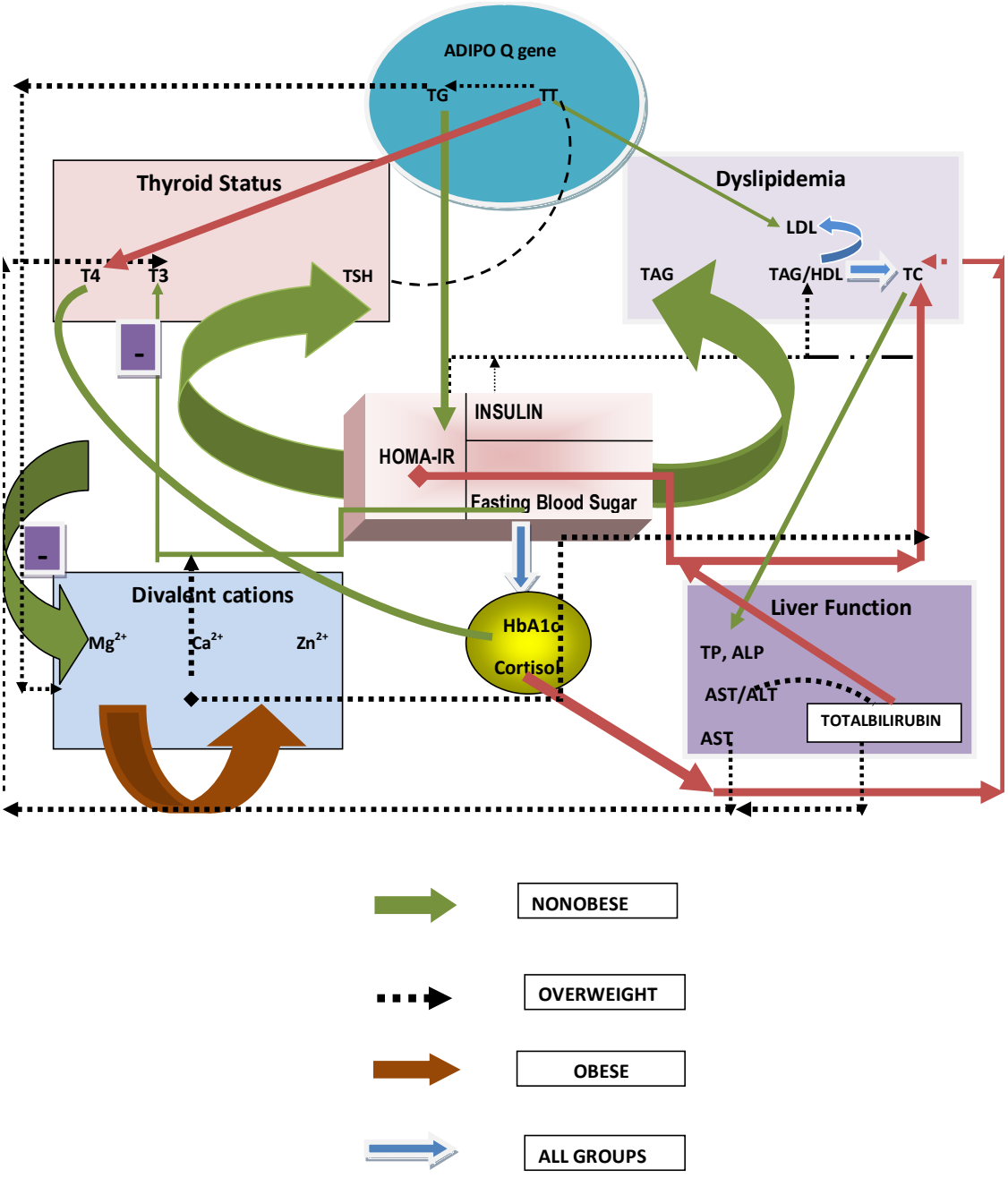
attention as an important cause of disturbance in mineral metabolism by their direct action on bone turnover [30], and also as one of the causes for secondary osteoporosis. Calcium (Ca^{2+}), phosphorus (PO_4^{2-}), and magnesium (Mg^{2+}) are all divalent metal ions, which are necessary for metalloenzymes and various crucial metabolic pathways directly or indirectly regulated by thyroid hormones [31].

The thyroid gland plays a role in calcium metabolism and regulation, by secreting when needed and the thyroid stimulating hormones (TSHs) are key to regulate the metabolism of thyroid gland to produce both T4 (thyroxine) and T3 (tri-iodothyronine). T4 is the main product and is converted in the periphery via de iodination to T3 which is the main biological active of thyroid hormones. [32] The production of TSHs is regulated by thyrotrophic; therefore, thyroid stimulating hormone in response is regulated by a negative feedback mechanism related to serum level of free T3 and T4. The liver enzyme has an important role in amino acid metabolism. Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) are enzymes found mainly in the liver. They are also found in red blood cells, heart muscle tissues and other organs such as the pancreas and kidney. [32]. AST or ALT levels are valuable aid primarily in the diagnosis of liver diseases but not specific for diagnosis of liver disease [33].

Divalent cations and their purported role in latent thyroid comorbidity – our original contribution with reference to Insulin resistance as a function of body mass index.

A study investigated the association of Magnesium and Zinc levels in the serum of adult Non-obese and Obese type 2 diabetic patients, with particular reference to thyroid comorbidity. Correlation among Glycemic control, Insulin resistance, Thyroid hormones, divalent cations and

dyslipidemia depict differential characteristics in obese and non-obese type2 diabetes with Thyroid comorbidity [34].



The proposed model for associating divalent cations and Thyroid status with special reference to insulin resistance, as applied to anthropometric, biochemical and Molecular biology parameters

(Adiponectin gene polymorphism with reference to SNP+45 in exon 2) has been depicted distinctly for non- obese, overweight and obese type 2 diabetics.

In overweight, clinically euthyroid type 2 diabetics, HOMA-IR, a measure of insulin resistance correlated well with TAG/HDL ratio, a surrogate marker of small dense LDL. In obese, clinically euthyroid type 2 diabetics, HOMA-IR correlated with both free triiodothyronine and free thyroxine. In the overweight group, TAG/HDL ratio could be used as a reliable marker for insulin resistance with associated thyroid comorbidity (latent). Until now, studies have shown the relevance of TAG/HDL ratio as a surrogate marker of small dense LDL; however, our study has indicated the additional value of TAG/HDL ratio in highlighting insulin resistance with associated thyroid status in the overweight group. Moreover, intervention is possible at this stage, as weight reduction and delay of entry from being overweight into obesity would alleviate insulin resistance, besides removing the latent thyroid comorbidity.

In the obese group of clinically euthyroid type 2 diabetics, insulin resistance correlated very well with both free triiodothyronine and free thyroxine. This essentially means that insulin resistance is an objective biochemical marker (predictor) of actual thyroid status in the obese group, wherein objective thinking is possible, since free T4 and its peripherally converted product and more active form, namely free T3 are both related to insulin resistance. This would facilitate newer pharmacologic modalities based on drugs that could modulate thyroid receptors in T2DM, thereby alleviating insulin resistance, besides conferring near euthyroid status in obese type 2 diabetics.

In the non-obese group of clinically euthyroid type 2 diabetics, glycemic status correlated well with free T4; TSH depicted a positive association with insulin resistance. Free T3 and insulin

had negative correlation with magnesium. In the obese group of clinically euthyroid type 2 diabetics, the divalent cations magnesium and zinc exhibited pronounced association. In both the groups, TAG/HDL ratio, a surrogate marker of SD-LDL associated itself pronouncedly with LDL. Glycemic control assumes great relevance in non-obese diabetics, since this group is quite exclusive, wherein we do not envisage insulin resistance, as much pronounced as that which is observed in obese diabetics. Hence, Free T4 estimation could be considered as a significant and reliable biochemical marker in bringing out the latent thyroid comorbidity in non-obese type 2 diabetics.

In the non-obese type 2 diabetics, TSH depicted an association with insulin resistance. Hence, we opine that the hypothalamus-anterior pituitary axis is directly implicated in insulin resistance.

Hypomagnesemia has already been implicated in hyperinsulinism and insulin resistance by earlier groups of workers [6]. Our study has portrayed a negative association of magnesium with insulin and furthermore magnesium had negative association with FT3 in non-obese type 2 diabetics. This is a paradox because normally magnesium is indicated in the conversion of T4 to T3 which means that as per our study, low magnesium levels should have been associated with T3, but on the contrary, magnesium was inversely associated with T3 showed that the inverse correlation observed in type 2 diabetics exposed to stress**.** This opens up an interesting proposition that the counter regulatory hormones to insulin, especially cortisol might have an effect on peripheral deiodinase activity and another missing link could be reverse T3 which we have not estimated that would have enabled us to study T3/rT3 ratio. It is also opined that the apparent shift from T3 to rT3 may reflect more severely depressed tissue T3 levels, but we have

estimated only blood FT3 levels. Hence, the conventional association between magnesium and FT3 is not perceived in our study, despite the factor of insulin resistance.

In obese type 2 diabetics who are clinically euthyroid, it is possible that hypothalamus -anterior pituitary- thyroid axis could afford scope leading to therapeutic interventions, especially aimed at alleviating Insulin resistance. This we feel could exclude the significance of insulin receptor in all probability, from the discussion, in view of the fact that the down regulation of receptors (for insulin) will not be intense, unlike that which would occur in obese type 2 diabetics. However, insulin post receptor effects may occur that needs to be looked into in greater detail.

All of the above considerations will be perceptible in non- obese, where hypomagnesaemia would be linked to positive associations with thyroxine and insulin. However, Insulin resistance encompasses both hyperinsulinism, as well as depletion depending upon the phase in which insulin resistance resides. This study hence corroborates the fact that the levels of divalent magnesium and thyroxine levels will be inversely related in clinically euthyroid non- obese type 2 diabetics during hyperinsulinemic phase of insulin resistance. This means that regulation of thyroxine levels with analogs would prove to be beneficial in removing the latent thyroid comorbidity, besides delaying the progression of insulin resistance from the hyperinsulinemic phase to beta cell failure- the culminating point of IR.

Furthermore, nutritional supplementation of magnesium in association with the estimation of thyroxine levels in non -obese type 2 diabetics inherent with latent /subclinical thyroid comorbidity will be taking care in monitoring the hyperinsulinism associated phase of insulin resistance. In obese type 2 diabetics, the divalent cations, namely magnesium and Zinc associated positively which could be explained by citing the fact that the event is mediated by the

objective and apparent availability of the insulin receptors, since the down regulation of receptors is a prominent feature in obese individuals and also in other clinical conditions such as metabolic syndrome.

In recent times, the value of the endogenous antioxidant bilirubin is being increasingly recognized to have implications in metabolic syndrome/ insulin resistance. However, our study has added a new dimension, namely thyroid status. In the overweight group, the predictive role of post prandial blood sugar and FT3 has been confirmed. It is possible that in the living system the total bilirubin would increase with increasing thyroid hormone. Liver is the site of thyroid hormone conjugation and secretion, besides its (liver) role in producing thyroid binding globulin.

1. *De ritis* ratio correlated well with total bilirubin, in terms of the fact that transaminases would rise with a greater increment in Aspartate amino transferase in obese type 2 diabetics who are clinically euthyroid. It is also quite possible that in overweight type 2 diabetics, oxidative stress induced lowering of the active form, namely FT3 will be initially present that would eventually be overcome by the antioxidant nature of total bilirubin.
2. *De ritis* ratio *hitherto* has been globally used to signify alcoholic liver diseases (alcoholic steatohepatitis). However, a revelation that has emerged from our study is that the ratio can predict imminent thyroid disorders in clinically euthyroid, type 2 diabetics, but with latent thyroid comorbidity which could worsen if dietary intervention and insulin resistance are not promulgated in overweight type 2 diabetics.
3. T3, the biochemically active form of thyroid hormone is formed peripherally in the cells of the body by the action of type 1 deiodinase on T4. Whereas, we feel that type 2 deiodinase present in the anterior pituitary gets stimulated in the overweight type 2 diabetics leading to

the formation of T3 locally (in the pituitary). This in turn will lead to decreased release of TSH, thereby leading to either normal or low TSH levels systemically. This could explain why we did not envisage any pronounced change in TSH levels, as reflected in our results.

4. A revelation that has emerged from our study is that bilirubin (total) could act as a predictor of insulin and insulin resistance in obese type 2 diabetics, especially in the light of the fact that oxidative stress has been described by many workers to correlate well with hyperinsulinism and moreover, the predictor nature of total bilirubin could be used to assess the hyperinsulinemic phase of insulin resistance that precedes total beta cell depletion or beta cell failure, the eventual event in type 2 DM .

A positive association was found between SNP +45 T > G in exon 2 and T2DM (T>G vs IR) in the study population. Data on genotyping among non-obese vs. overweight depicts association with LDL in TT (Homozygous), while in TG (Heterozygous) phenotype, a strong association was perceived with Insulin resistance. Associations concerning TSH in TT; Mg in both TT & TG in obese vs. overweight and T4 in TT were observed in non-obese vs. obese T2DM.

This also could open newer vistas in pharmacogenomics and personalized medicine, wherein the judicious use of thyroid hormone analogues, in combination with hypoglycemic drugs could serve as the panacea to alleviate insulin resistance with associated thyroid comorbidity in type 2 diabetics, independent of body mass index- a new finding that has emerged from our study. Magnesium levels, VLDL- a lipoprotein fraction that transports endogenous TAGs, serum TAGs are all considered significant in obese type 2 diabetics where hyperinsulinism and insulin resistance are considered inseparable and more so in view of the limited availability of insulin receptors that would have undergone down regulation.

The model has been built on insulin resistance as a nuclear point which essentially comprises of blood sugar and insulin both pertaining to the venous plasma in the fasting state. In other words, insulin resistance as indicated by HOMA-IR has been used as the central biochemical feature or pillar upon which the following considerations have been duly taken into account. Firstly, anthropometric measure namely BMI, WC and WHR, However in order to include the frequently neglected group, namely overweight, BMI was considered superior as far as our study is concerned. Secondly, lipid profile is considered cardinal owing to the fact that dyslipidemia endears itself with IR. Furthermore, as a unique, sensitive and economical (also reliable) indicator of small dense LDL, we had included TAG/HDL ratio as a surrogate marker to facilitate easy access in even small and medium size clinical laboratories. Another purpose for choosing small dense LDL is its implications with reference to not only IR but also thyroid status which has not been addressed by many scientific workers *hitherto*. Thirdly, divalent cations namely Mg^{+2} and Zn^{+2} assume great relevance with reference to insulin sensitivity, carbohydrate metabolism and thyroid status also. Moreover, Magnesium and Zinc levels are considered important in the light of their antioxidant role. Extending this statement it has to be mentioned that free radicals and oxidative damage are involved in both IR as well as thyroid comorbidity. This is appropriate for our study and designated specific roles of these cations. Fourthly, liver plays a crucial role in handling glucose as well as modulating the half life of insulin. Moreover, liver is the house of important transminases that have been intrinsically linked to insulin sensitivity and steatohepatitis, an accompanying feature of IR. In recent years, bilirubin has been viewed through a different perspective in metabolic syndrome associated with obesity, in hyperinsulinism, hypertension and dyslipidemia. However, very few studies have been focussed on the role of bilirubin as a natural antioxidant in alleviating IR and also influencing thyroid

status. Furthermore, India being a third world country, our model will assume significance in advocating cost effective, sensitive and reliable biomarkers of IR in type 2 diabetes mellitus in general and with reference to thyroid status in type 2 diabetes, in particular. Last, but not the least the thyroid status has been addressed in type 2 diabetes frequently as isolated entities either with dyslipidemia or with liver function. We specifically included clinically euthyroid cases of adult T2DM. Unlike the work done by other researchers where frank comorbidity (T2DM and Thyroid disorder) was obvious, we had taken up the study on type 2 diabetics in clinically euthyroid scenario. This model, we believe would serve as an integrated feature that encompasses anthropometry, routine biochemistry, organ function test and also state –of- the- art gene polymorphism studies, with reference to adiponectin SNP +45 in exon 2 which has till now not been attempted in clinically euthyroid non obese, overweight type 2 diabetics.

Conclusion

Insulin resistance can be depicted through HOMA-IR in the presence of divalent cations, namely Mg^{2+} and Zn^{2+} to differentially assess the thyroid status as related to Insulin resistance in the anthropometry specified groups. As health care providers interested in promoting the optimal health of people with diabetes, we need to act as an unbiased resource on the numerous treatments available to our patients. Above all, we need to encourage our patients' involvement in and ownership of their diabetes, and help them to focus their efforts where they are likely to receive the greatest benefits. In the future, this will likely include nutritional supplements for people whom research has identified as having the genetic or clinical potential to benefit from them.

Conflict of Interest: The authors declare that there is no conflict of interest in this study.

The authors thank Prof. Seethesh Ghosh, Dean, Mahathma Gandhi Medical College and Research Institute, a constituent teaching unit of Sri Balaji Vidhyapeeth, Dr. S.R. Rao, Vice-President (Research, innovation & Development), Sri Balaji Vidypeeth and Prof.(Dr) Nihar Ranjan Biswas Vice-Chancellor, Sri Balaji Vidyapeeth for enabling this communication

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