Diabetes & Metabolic Syndrome: Clinical Research & Reviews 13 (2019) 2286–2291

Contents lists available at ScienceDirect

Diabetes & Metabolic Syndrome: Clinical Research & Reviews

journal homepage: www.elsevier.com/locate/dsx

Original Article

"Sex hormone independent associations between insulin resistance and thyroid status –a gender based biochemical study on clinically euthyroid non-obese, overweight and obese type 2 diabetics"

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ARTICLE INFO

Article history:
Received 22 April 2019
Accepted 22 May 2019

Keywords:
Sex hormones
Anthropometry
Insulin resistance
Thyroid hormones
T2DM

ABSTRACT

Aim: Studies indicate that type 2 diabetes mellitus (T2DM) might contribute to the development of thyroid disorders (TD). However, few gender based reports are available describing therelationship between T2DM and TD in clinically euthyroid, anthropometry specified groups of type 2 diabetics. The aim of this study was to relategender based biochemical changes in anthropometry specified, clinically euthyroid type 2 diabetics.

Methodology: The study was carried out on clinically euthyroid type 2 diabetics (male n = 269; female n = 301) at a tertiary health care unit in Pondicherry, South India. Three groups were segregatedbased on Body mass Index: 153 non-obese type 2 diabetics (BMI = 18.5–24.99), 291 overweight type 2 diabetics (BMI = 25–29.99) and 126 obese type 2 diabetics (BMI ≥ 30). Biochemical parameters included glycated hemoglobin, insulin resistance, Cortisol and Thyroid profile.

Results: The study had included clinically euthyroid type 2 diabetics (52.8% females and 47.2% males). Statistically significant associationsweredifferently observed between insulin resistance (dependent variable) andother independent variables, irrespective of sex hormone status. Total protein was negatively related in non -obese male type 2 diabetics (R = 0.780); Triiodothyronine was inversely associated in overweight males, whereas cortisol and the divalent cations (Zinc and Magnesium) depicted positive association (R = 0.555) in the same group (overweight), butcortisol in non -obese female type 2 diabeticswas negative (R = 0.742); Glycated hemoglobin and calcium exhibited positive relationshipin obese type 2 female diabetics (R = 0.771)..

Conclusion: Our study has revealed distinctive relationship between T2DM and TD in the anthropometry specified, clinically euthyroid and gender based type 2 diabetics, independent of the sex hormones.

1. Introduction and scope of the present study

Diabetes mellitus is linked eitherto relative or absolute deficiency of insulin that eventually culminates in major aberrations in metabolism [1]. Insulin resistance is synonymous with an impaired ability of cells to respond to the action of insulin in facilitating the transport of glucose from the extracellular milieu into muscle and tissues. In humans, insulin resistance develops with obesityculminating inT2DM [2]. Generally, about 90–95% of cases of diabetes are of this type of diabetes [3]. Obesity *per se*enhances resistance to the cellular functions of insulin, synonymous with the decreased ability of insulin to inhibit glucose output from the liver and to promote glucose uptake in the insulin sensitive fat and muscle tissues [4]. Previous reports point to the fact that diabeticsare associated with a higher prevalence of thyroid disorders, with hypothyroidism being the most common disorder [5]. Prevalence of thyroid dysfunction varied from 2.2% to 17% in diabetics. Diabetic women are more frequently affected than men and hypothyroidism is more pronounced than thyrotoxicosis [6]. It must be said that thyroid hormones are basically insulin antagonists and an excess or deficit of any one can result in functional derangement of the other [7].

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https://doi.org/10.1016/j.dsx.2019.05.017
1871-4021/

The aim of our study was toprimarily compare and correlate Insulin resistance withthyroid hormone levels (T3 and T4, TSH), key biochemical parameters in gender based, anthropometry specified, clinically euthyroid type 2 diabetics, but independent of sex hormone status.

Pronouncedgender differences have been reported pointing to degrees of insulin resistance, body compositionand energy balance as such [8]. However, severalstudies have shown that total and free testosterone levels are reduced in proportion to the level of obesity [9]. Reports alsosuggest that obese males exhibit a decline in sperm quality withspecific changes in shape as well as the molecular structure of germ cells in the testis and mature sperms [10,11]. Male obesity usually expresses a unique endocrine profile that is typified by the nomenclature "hypogonadotropic hyperestrogenic hypogonadism". Both total and free testosterone levels are reduced in obese males. It is believed that central obesity appears to be associated with decline in the levels of circulating androgen [12]. Adiponectinelaborated by the adipose tissue isdecreased in states of insulin resistance and obesity [13,14]. Adiponectin lowers glucose production in the liver [15] and enhances insulin sensitivity in the muscle and liver by increasing free fatty acid oxidation [16]. Adiponectin levels have been reported to be significantly higher in women than in men [17]. A study undertaken onone thousand participants (Cross-sectional)had revealed that median adiponectin levels were significantly higher in women than in men even when the adjustment for differences in BMI was enabled [18]. However, it must be mentioned that very few studies are available globally, wherein the thyroid status has been documented in gender specific type 2 diabetic population segregated into non-obese, overweight and obese on the basis of Body Mass Index. Moreover, our study had duly taken into account clinically euthyroid type 2 diabetics, unlike several studies that point to frank hypo and hyperthyroidism in type 2 diabetics. In addition, we had embarked on creating evidences to suggest nexus between insulin resistance and thyroid independent of the measurement of androgens and estrogens.

2. Subjects and methods

The study was carried out on patients with T2DM (both genders) who were apparently euthyroid. These subjects were drawn from the clinicsat a tertiary health care unit in Pondicherry, South India. Following the enrolment into the study, three groups were segregated, based on Body Mass Index: 153 non-obese type 2 diabetics (BMI = 18.5–24.99), 291 overweight type 2 diabetics (BMI = 25–29.99) and 126 obese type 2 diabetics (BMI $\geq$ 30).

2.1. Inclusion criteria

Clinically euthyroid type 2 diabetics n = 570 (both genders in the age group 35–70 years). One proportion test (Male n = 269; Female n = 301).

2.2. Exclusion criteria

Patients with a previous history of thyroid diseases were excluded. Patients with a documentedhistory of cardiac, liver and muscle diseases were also excluded from the study, besides patients with other endocrine and chronic diseases.

The study was approved by the duly constituted Research Advisory committee (vide minutes of the Research Advisory Committee, dated 26.12.2014) and Institutional Human Ethics Committee (vide certificate of approval, duly signed by the Secretary, IHEC dated 5.6.2015)

2.3. Biochemical measurements

All the quantitative determinations were enabled by established methods/procedures approved by the International Federation of Clinical Chemistry (IFCC). Stringent Quality Control was promulgated. The Internal quality Control was enabled through samples provided by M/S Biorad USA. External Quality Assessment, under the aegis of ACBI was facilitated through the Clinical Biochemistry laboratory of Christian Medical College (CMC), Vellorewhich has beenaccredited by NABL under ISO/IEC 15189).

Fasting and postprandial glucosewere estimated, based on glucose oxidase-peroxidase method.

Fasting insulin (venous plasma) levels were determined by automated electro chemiluminiscence. The insulin resistance index was assessed by the homeostatic model assessment of Insulin resistance and computed using the formula: HOMA-IR = (concentration of glucose in venous plasma (mmol/l) $\times$ concentration of insulin in venous plasma (mU/L)/22.5 [19]. Glycated hemoglobin was estimated by HPLC. Triacylglycerols (TAG) in serum was measured by glycerol kinase method. Total cholesterol was quantitated by the enzymatic method. HDL cholesterol was measured bypolyanion precipitation. LDL cholesterol was computed using Friedwald equation i.e., LDL cholesterol = total cholesterol-(HDL cholesterol + VLDL) where VLDL = TAG/5.

Small dense LDL particles were quantitated using the surrogate marker (TAG/HDL). FreeTriiodothyronine, Free Thyroxine, Thyrotropin and Cortisol in serum were quantitated based on automated electro chemiluminiscence method. Total and Direct bilirubin were estimated by the method ofJendrassik–Grof.Total protein in serum was detected by Biuret method. The transaminases (aminotransferases), namely Aspartate aminotransferase (AST) and Alanine aminotransferase (ALT), as well as alkaline phosphatase (ALP) were quantitated spectrophotometrically by UV Kinetic methods.

2.4. Reference ranges for biochemical parameters

Fasting plasma glucose 70–100 mg/dL; Fasting plasma insulin 0.7–9 μIU/ml. HOMA-IR 1.7–2. Others: 15–40 mg/dl for urea; 0.2–1.4 mg/dl for creatinine; 150–200 mg/dl for Total Cholesterol 75–150 mg/dl for Triacylglycerols; 30–60 mg/dl for HDL. TSH: 0.27–4.2 μu/mL; 2–4.4 pg/ml for Free T3 and 0.93–1.7 ng/dl for Free T4; 5–40 IU/L for ALT & AST; 40–125 IU/L for ALP; 6–8 g/dl for Total protein; 3.5–5 g/dl for Albumin; 2.5–3.5 g/dl for Globulin, 0.2–1 mg/dl for Bilirubin(T); <0.4 mg/dl for Bilirubin(D).

3. Statistical analysis

Pearson correlation coefficient was calculated with reference to the study parameters. P value < 0.05 was considered statistically significant. As statistically significant correlation was observedamong the anthropometry specified groups (non-obese, overweight and obese) in males and females (clinically euthyroid type 2 diabetics), we had promulgated multiple regression and these results form the crux of the results of the present study.

4. Results

Gender specific comparison of biochemical parameters in clinically euthyroid non-obese, overweight and obese type 2 diabetics (To determine the relationship between insulin resistance and Thyroid status irrespective of sex hormone status)

A comparison of biochemical parameters between males and

females was enabled, based on anthropometric segregation into non-obese, overweight and obese groups. All the type 2 diabetics were found to be clinically euthyroid, as mentioned before.

Various parameters were measured for promulgating statistically significant comparison. These included glycemic control, insulin resistance, lipid profile, mono-and di-valent cations, small density lipoprotein(enabled through the surrogate marker, viz. TAG/HDL), cortisol and organ function tests with particular reference to thyroidstatus and hepatic profile.

All the parameters under consideration were common to males and females as well as the three anthropometric groups (non-obese, overweight and obese). However, for the sake of brevity and clarity, only the statistically significant parameters have been included in the results and duly taken up for discussion. Fig. 1 shows Gender wise distribution of T2DM patients in number of subjects.

Table 1 summarizes the linear regression model for non-obese T2DM males by effecting HOMA-IR as the dependent variable,-with reference to independent variables. The duration of T2DM, albumin and globulinexhibited positive associations, whereas uric acid, total protein depicted negative influence with reference to Insulin resistance, as enabled through HOMA-IR (R value = 0.780).

Table 2 summarizes the linear regression model for overweight T2DM males by effecting HOMA-IR as the dependent variable. Negative influence with Triiodothyroninewas depicted, whereas zinc, cortisol, magnesium and uricacidexerted positive influence with reference to each other(R value = 0.555). However, in obese T2DM males, no significant association was observed (Results not shown here).

Table 3 depicts the results of linear regression model for non-obese T2DM females with HOMA-IR as the dependent variable. Zinc and Cortisol exhibited positive and negative influence with respect to Insulin resistance(R value = 0.742).

Table 4 shows the results of linear regression model for Obese T2DM females by including HOMA-IR as the dependent variable. Glycated hemoglobin (HbA1c), calcium and albumin globulin ratio(R value = 0.771) depicted positive influence, when considered in the light of insulin resistance.

5. Discussion

Men and women differ with reference to several facets includingbody composition, insulin resistance, adiposity and energy balance. For a given BMI, men possess a higher lean mass and more visceral and hepatic adipose tissue, whereas women show elevated general adiposity. These differences in adipose tissue distribution may largely be related to gender based differences perceived in insulin sensitivity and resistance, thereby pointing to a greater insulin-sensitive environment in women.

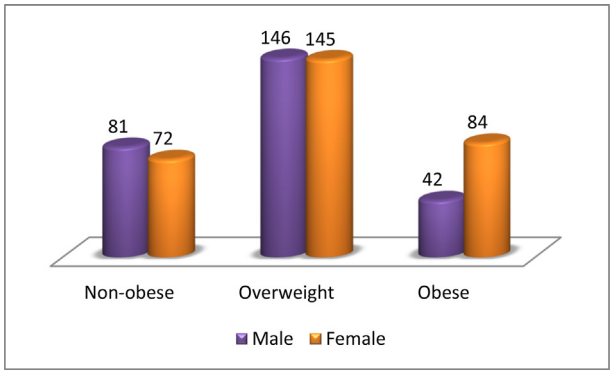

Fig. 1. Gender wise distribution of T2DM patients (number of subjects).

Table 1
Results of linear regression model for non-obese T2DM males (Dependent Variable −HOMA-IR).

Model	Unstandardized Coefficients		Standardized Coefficients	T	Sig.
	B	Std. Error	Beta		
DURATION	.640	.128	.532	5.010	.000#
UA	−1.098	.557	-.218	−1.973	.054
TP	−135.518	60.045	−12.923	−2.257	.028*
ALB	129.047	58.933	7.791	2.190	.033*
GlOB	139.269	60.961	12.464	2.285	.026*

P < 0.05 * significant and p < 0.01# highlysignificant.
UA- Uric acid; TP- Total protein; ALB- Albumin; GLOB- Globulin.

Table 2
Results of linear regression model for Overweight T2DM males (Dependent Variable −HOMA-IR).

Model	Unstandardized Coefficients		Standardized Coefficients	t	Sig.
	B	Std. Error	Beta		
T3	−3.674	1.839	-.198	−1.998	.048*
Zn	.145	.052	.232	2.759	.007#
Cortisol	.389	.184	.233	2.118	.036*
Mg	5.327	2.404	.195	2.216	.029*
UA	2.729	.970	.264	2.815	.006#

P < 0.05 * significant and p < 0.01# highly significant.
T3- Triiodothyronine; Zn- Zinc;Mg- Magnesium;**UA- Uric acid**.

Table 3
Results of linear regression model for non-obese T2DM females (Dependent Variable: HOMA-IR).

Model	Unstandardized Coefficients		Standardized Coefficients	t	Sig.
	B	Std. Error	Beta		
Zn	.246	.098	.365	2.512	.016*
Cortisol	-.787	.365	-.339	−2.154	.036*

P < 0.05 * significant.Zn- Zinc.

Table 4
Results of linear regression model for Obese T2DM females (Dependent Variable: HOMA-IR).

Model	Unstandardized Coefficients		Standardized Coefficients	t	Sig.
	B	Std. Error	Beta		
HbA1C	.831	.353	.364	2.353	.022*
Ca	2.770	.864	.424	3.204	.002#
A/G	5.955	2.963	.456	2.010	.049*

P < 0.05 * significantand p < 0.01# highly significant.
HbA1c- Glycated hemoglobin; Ca- Calcium; A/G- Albumin globulin ratio.

Estrogens have a favourable effect on insulin and glucose homeostasis, adipose tissue distribution, and several proinflammatory markers. Adiponectin, an insulin-sensitizing hormoneis also significantly higher in women as compared to men, and whether this is attributed to differences in sex hormones or variations in adipose tissue distribution remains to be clearly delineated. The differences observed in resting energy expenditure(basal metabolism) between men and women might be explained in the light of lean body mass, particularly the high metabolic-rate organ masses. On the other hand, physical energy expenditure might have a nexus with percent body fat in men.

Hence, it is in the fitness of things to state that gender-specific avenues of research into insulin resistance should duly take cognizance of these differences in adipose distribution and adipokine secretion. In addition, gender-tailored treatment of insulin resistance may benefit from focusing on visceral and hepatic adiposity, besides hypoadiponectinemia, which are more pronounced in men than in women. As an extension of these considerations, correcting the thyroid condition is related to sex hormone status.

However, we specifically took up this study to determine the associations between insulin resistance and thyroid status in clinically euthyroid non-obese, overweight and obese type 2 diabetics, but most importantly independent of sex hormone status.

It is believed that unidentified thyroid dysfunction (latent dysfunction) couldexert an influence oninsulin resistance associated with T2DM and its complications [20,21]. Reciprocal influences citing sex hormones and thyroid status have been observed. With advancing age and steady decline in sex hormones and that in conjunction with the nutritional state of the thyroid and accompanying factors, it is possible to visualize altered thyroid status [22]. In women, thyroid dysfunction becomes conspicuous at menopause. Estrogen directly stimulates the thyroid gland to produce more of thyroid hormones, which will be synonymous with lowered TSH levels [23].

Cross-sectional studies have reported that serum free thyroxine was negatively related to insulin resistance, whereas a positive relationship was found between TSH and insulin resistance [24–27]. As per a study from Pondicherry (South Indian) population undertaken on clinically euthyroid T2DM patients, Free Triiodothyronine and Free Thyroxine were more significant in obese group, as compared against insulin resistance (cut off value for HOMA-IR 2.69) [20]. Studies have illustrated the relationship among Thyroid hormones, TSH, and T2DM in the general population [28], but fewer studies are availableon gender based population, to the best of our knowledge. Furthermore,more detailed studies are deemed necessary in order to explore as to whether these results could be applied to other adult populations, especially in the light of gender based differences.

The results of our present study depict a similar relationship for insulin resistance in both males and females, but the gender differencesas well as anthropometric variations were observed in delineating the relationship of insulin resistance among independent variables such as Zinc, Cortisol, Mg, uricacid and T3. We took care to determine the possible biochemical relationship, irrespective of androgen and estrogen status.

Cortisol, a counter regulatory hormone with respect to Insulin is produced by the Adrenal cortex. Cortisol is a glucocorticoid that is directly involved in altering the gene expression of the key enzymes of gluconeogenesis. Cortisol in additionmodulates sex hormones at the level of intracellularreceptors. This essentially means that stress could envisage changes in theproduction of sex hormones. Furthermore, Cortisol and Epinephrine (produced from the adrenal medulla) increase the production ofreverse T3 (rT3). Thus, when under stressT4 gets converted into reverse T3(inactive T3). Sincethyroid hormone normally help insulin to shuttle glucose, the condition of insulin resistance develops a nexus with hormones of stress (Cortisol, Epinephrine)

Excess insulin blocks the conversion of T4 to T3. In our study, this is depicted by the results seen with reference to the overweight males wherein insulin resistance and T3 levels elicit negative influence. Surprisingly such a relationship was not perceived in our study either in overweight females or in the non-obese and obese groups (males, females).

Our results thus point to two important factors.

1). Hormonal influence (sex hormones) is considered significant with reference to insulin resistance linked alterations in thyroid status. But, our study has determined relationship between insulin resistance and thyroid status, irrespective of the sex hormones
2). Similar changes may not be directly linked to insulin receptors, since we would have perceived differences especially in the obese group, where down regulation of insulin receptors are a certainty. Thus, it remains to be clearly delineated as to what other factors are deemed cardinal in explaining alterations in thyroid status in the anthropometric specific groups.

Molecular mechanisms remain unclear, though sex hormonesregulate thyroid function [29], andestrogenslevelinfluencethedevelopmentofT2DM [30]. As per a previous report published from our laboratory pre- and post-menopausal women, irrespective of estrogens, depicted differential thyroid status as reflected by insulin resistance in T2DM patients [31].

Sex differences in body composition and/or insulin sensitivity are evident in humans throughout the lifespan. Similarly, estrogens and progestins used for contraception and hormone replacement therapy affect glucoregulation. The influences of endogenous and exogenous gonadal steroids are emphasized [32]. In one study, estradiol and progesterone were positively associated with insulin resistance and should be considered in studies of insulin resistance among premenopausal women [33]. For instance, administration of exogenous androgens [34,35] and oral contraceptives [36] have been reported to cause glucose intolerance and hyperinsulinemia. Moreover, increased concentrations of free testosterone and decreased concentrations of sex hormone-binding globulin (SHBG)- an indirect index of androgenicity [37] have been deemed to be associated with glucose intolerance and hyperinsulinemia in both pre- [38] and postmenopausal women [39]. Low levels of SHBG also have been observed to predict the development of T2DM in women [40,41]. SHBG has been proposed as a marker for insulin resistance [42]. In another study, they have reported that sex hormones were not associated with glucose oxidation. These associations are difficult to be explained by the associations with obesity or body fat distribution. However, upper-body adiposity remains to be the strongest predictor of insulin concentrations and total nonoxidative whole-body glucose disposal [43]. Recent studies have clearly demonstrated that an androgen profile is better than testosterone in evaluating androgen balance in pre- and postmenopausal women, provided that androgens are measured by appropriate new methodologies such as liquid chromatography-tandem mass spectrometry (LC-MS/MS), which affords the mandated high sensitivity and specificity [44]. The most important finding of the study by Muka et al. is that estradiol blood levels and the risk for T2DM were positively associated, regardless of BMI or years since menopause [45]. Another reason for the findings may be as a culmination of high oxidative stress generated in diabetic patients who could affect the normal functioning of the pituitary gland and hypothalamus [46]. More studies are deemed appropriate to comprehensively delineate the biochemical and physiological mechanisms underlying reduced testosterone synthesis in diabetes [47].

Several studies have depicted an association of thyroid function with body mass index (BMI) and insulin resistance based on the homeostatic model assessment of insulin resistance (HOMA-IR) [48–51]. HOMA-IR and BMI are important for the assessment of DM and cardiovascular risk. We found out the relationship with insulin resistance, in the light of thyroid status, with Low density Lipoprotein particle size, T3, T4, TSH, Insulin, divalent cations and Adiponectin gene polymorphism. Gene polymorphism of

adiponectin has been studied by researchers using insulin resistance as the pivot. One such polymorphism is SNP+45 of Adiponectin. We extended the study on adiponectin gene polymorphism as linked to insulin resistance, but with reference to thyroid status. Our study showed that even the wild type SNP+45 in exon 2, namely TT could itself be used as a molecular indicator of altered thyroid status in Insulin resistant type 2 diabetics, as studied in overweight and obese. Our study further depicted differential effects of gene polymorphism with reference to SNP +45 in obese, non-obese and overweight type 2 diabetics. The same study of ours indicated LDL to be statistically significant while comparing non-obese and overweight T2DM. An interesting observation that had emerged from our data is that there was a perfect association between Triacylglycerol/High Density Lipoprotein ratio (a surrogate marker of Low Density lipoprotein) and Low Density lipoprotein signifying that the Low Density Lipoprotein particle size is a crucial entity that needs due consideration, while evaluating thyroid status in typ2 diabetics, as observed in the non-obese, overweight and obese groups. Hence, we had pronounced that both wild and heterozygous SNP +45 should necessarily be studied alongside the anthropometric parameter, namely BMI in order to delineate the thyroid status in insulin resistant overweight type 2 diabetics, in addition to the other two groups namely non-obese and obese that have been frequently reported in the literature [52]. This was a recent finding of ours that could attract attention from the perspective of weight management as well as planning therapeutic modalities for alleviating insulin resistance and restoring euthyroid status. Markers of ER stress were upregulated in both insulin-sensitive tissues in models of type 2 diabetes and in atherosclerotic plaques [53].

Direct associations of trace macro elements with diabetes mellitus have been observed in many research studies [54]. Insulin action on reducing blood glucose was reported to be potentiated by some trace elements such as chromium, magnesium, vanadium, zinc, manganese, molybdenum and selenium [55]. In one study they have found that higher serum uric acid levels are inversely associated with diabetes mellitus in both men and women [56]. However, unlike the results shown in this study of ours, thyroid status has not been taken up comprehensively by other workers and more so when the type 2 diabetic subjects of our study were clinically euthyroid.

6. Conclusion

Insulin resistance is a progressive condition and differentially perceived in male and female type 2 diabetics who were clinically euthyroid. This is in turn might be linked to anthropometry specified groups, namely non-obese, overweight and obese. Anthropometry specification could be considered cardinal, because the status of thyroid with reference to Insulin resistance is dependent on the former (anthropometry), as exemplified by our results.

Our study points to an important facet, namely physiological adaptation in the overweight group pertaining to insulin resistance (HOMA-IR), wherein the status of T3, the biologically significant and active form of thyroid hormone could belinked to flux in free radical/oxidative stress. This is in view of the fact that both Zinc (divalent) and the endogenously formed antioxidant, viz., uric acid (antioxidants) were associated with the thyroid status (as exemplified by T3 status) in overweight, gender specified (male) type 2 diabetics who were clinically euthyroid. Though our study revealed gender based biochemical considerations, the fact remains that these were enabled, irrespective of sex hormonal status.

Such a mechanism as explained above has not been perceived in the other study groups, possibly attributed to: Endocrine influence mediated through androgens and estrogens may be exerting an additional influence. In obesity, insulin receptor availability will ever be in question and is largely attributed to down regulation. This could mean that there is/are mechanism(s) dependent on insulin receptor that could modulate thyroid status in the anthropometric, gender specified groups.

The counter regulatory hormone, viz., Cortisol might be an additional player in the molecular cross-talk that also needs to be taken cognizance of, while discussing and interpreting the thyroid status in type 2 diabetics who were otherwise clinically euthyroid.

Funding

No funding from external agencies.

Conflicts of interest

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

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Acknowledgement

The authors wish to thank Prof. M. Ravishankar, Dean- Mahatma Gandhi Medical College and Research Institute, Prof. C. Adithan, Dean-Research, Sri Balaji Vidyapeeth and Prof. S.C.Parija, Hon'ble Vice-Chancellor, Sri Balaji Vidyapeeth for their interest in facilitating this study.

References

[1] Tiwari AK, Roa JM. Diabetes mellitus and multiple therapeutic approaches of phytochemicals: present status and future prospectus. Curr Sci 2002;83:30–8.
[2] Shepherd PR, Kahn BB. Glucose transporters and insulin action: implications for insulin resistance and diabetes mellitus. N Engl J Med 1999;341:248–57.
[3] Zimmet P, Alberti KG, Shaw J. Global and societal implications of the diabetes epidemic. Nature (London) 2001;414:782–7.
[4] Saltiel AR, Kahn CR. Insulin signalling and the regulation of glucose and lipid metabolism. Nature 2001;414:799–806.
[5] Wu P. Thyroid disease and diabetes. Clin Diabetes 2000;18:1–10.
[6] Papazafiropoulou A, Sotiropoulos A, Kokolaki A, Kardara M, Stamataki P. Prevalence of thyroid dysfunction among Greek type 2 diabetic patients attending an outpatient clinic. J Clin Med Research 2010;2:75–8.
[7] Singh G, Gupta V, Sharma AK, Gupta N. Frequency of thyroid dysfunction among diabetes in Punjabi population. Adv Biores 2011;2:3–9.
[8] Isidori AM, Caprio M, Strollo F, Moretti C, Frajese G, Isidori A, Fabbri A. Leptin and androgens in male obesity: evidence for leptin contribution to reduced androgen levels. J ClinEndocrinolMetab 1999;84:3673–80.
[9] Moller DE, Flier JS. Insulin resistance—mechanisms, syndromes, and implications. N Engl J Med 1991;325:938–48 [PubMed: 1881419].
[10] Teerds KJ, de Rooij DG, Keijer J. Functional relationship between obesity and male reproduction: from humans to animal models. Hum Reprod Update 2011;17:667–83.
[11] Tsai EC, Matsumoto AM, Fujimoto WY, Boyko EJ. Association of bioavailable, free, and total testosterone with insulin resistance: influence of sex hormone-binding globulin and body fat. Diabetes Care 2004;27:861–8.
[12] Giagulli VA, Kaufman JM, Vermeulen A. Pathogenesis of the decreased androgen levels in obese men. J ClinEndocrinolMetab 1994;79:997–1000.
[13] Diez JJ, Iglesias P. The role of the novel adipocyte-derived hormone adiponectin in human disease. Eur J Endocrinol 2003;148:293–300 [PubMed: 12611609].
[14] Motoshima H, Wu X, Sinha MK. Differential regulation of adiponectin secretion from cultured human omental and subcutaneous adipocytes: effects of insulin and rosiglitazone. J ClinEndocrinolMetab 2002;87:5662–7 [PubMed: 12466369].
[15] Batterham RL, Cowley MA, Small CJ. Gut hormone PYY(3-36) physiologically inhibits food intake. Nature 2002;418:650–4 [PubMed: 12167864].
[16] Yamauchi T, Kamon J, Waki H. The fat-derived hormone adiponectin reverses insulin resistance associated with both lipoatrophy and obesity. Nat Med 2001;7:941–6 [PubMed: 11479627].
[17] Cnop M, Havel PJ, Utzschneider KM. Relationship of adiponectin to body fat

distribution, insulin sensitivity and plasma lipoproteins: evidence for independent roles of age and sex. Diabetologia 2003;46:459–69 [PubMed: 12687327].
[18] Salas-Salvado J, Granada M, Bullo M. Plasma adiponectin distribution in a Mediterranean population and its association with cardiovascular risk factors and metabolic syndrome. Metabolism 2007;56:1486–92 [PubMed: 17950098].
[19] Matthews DR, Hosker JP, Rudenski AS. Homeostasis model assessment insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. Diabetologia 1985;28:412–9.
[20] Jayanthi R, Srinivasan AR, Hanifah M, Maran AL. Association among Insulin Resistance, Triacylglycerol/High Density Lipoprotein [TAG/HDL ratio] and Thyroid hormone levels – a study on Type 2 diabetes mellitus in obese and overweight subjects. Diabetes Metabolic Syndrome: Clin Res Rev 2017;11S: 121–6.
[21] Jayanthi R, Srinivasan AR, Gopal Niranjan, Ramaswamy Ramesh. Association of divalent cations and insulin resistance with thyroid hormones in patients with type 2 diabetes mellitus. Diabetes Metabolic Syndrome: Clin Res Rev 2017;11S:885–90.
[22] Krassas GE, Poppe K, Glinoer D. Thyroid function and human reproductive health. Endocr Rev 2010;31:702–55.
[23] Santin AP, Furlanetto TW. Role of estrogen in thyroid function and growth regulation. J Thyroid Res 2011;2011:875125.
[24] Park SB, Choi HC, Joo NS. The relation of thyroid function to components of the metabolic syndrome in Korean men and women. J Korean Med Sci 2011;26: 540–5.
[25] Mehran L, Amouzegar A, Tohidi M, Moayedi M, Azizi F. Serum free thyroxine concentration is associated with metabolic syndrome in euthyroid subjects. Thyroid 2014;24:1566–74.
[26] Garduno-Garcia JdeJ, Alvirde-Garcia U, Opez-Carrasco G, PadillaMendoza ME, Mehta R, Arellano-Campos O, et al. TSH and free thyroxine concentrations are associated with differing metabolic markers in euthyroid subjects. Eur J Endocrinol 2010;163:273–8.
[27] Roos A, Bakker SJ, Links TP, Gans RO, Wolffenbuttel BH. Thyroid function is associated with components of the metabolic syndrome in euthyroidsubjects. JClinEndocrinolMetab 2007;92:491–6.
[28] Yeqing Gu, Huihui Li, Xue Bao, Zhang Qing, Liu Li, Ge Meng, et al. The relationship between thyroid function and the prevalence of type 2 diabetes mellitus in euthyroid subjects. J ClinEndocrinolMetab, February 2017;102: 434–42.
[29] Boucai L, Hollowell JG, Surks MI. Anapproachfordevelopmentof age-, gender-, and ethnicity-specific thyrotropin reference limits. Thyroid 2011;21:5–11.
[30] Mauvais-Jarvis F, Clegg DJ, Hevener AL. The role of estrogens in control of energy balance and glucose homeostasis. Endocr Rev 2013;34:309–38.
[31] Jayanthi Rajendran, Srinivasan Abu Raghavan, Gopal Niranjan. Thyroid status in premenopausal and postmenopausal women – a biochemical study on insulin resistance in non obese, overweight And obese type 2 diabetics. Diabetes Metabolic Syndrome: Clin Res Rev 2018;12:859–62.
[32] Bruns CM, Kemnitz JW. Sex hormones, insulin sensitivity,and diabetes mellitus. ILAR J 2004;45:160–9.
[33] Yeung Edwina H, Zhang Cuilin, Mumford Sunni L, Aijun Ye, Trevisan Maurizio, Chen Liwei, et al. longitudinal study of insulin resistance and sex hormones over the menstrual cycle:The BioCycle Study. J. Clin Endocrinol. Metab 2010;95(12):5435–42.
[34] Shoupe D, Lobo RA. The influence of androgens on insulin resistance. Fertil Steril 1984;41:385–9.
[35] Woodard TL, Burghen GA, Kitabchi AE, Wilmas JA. Glucose intolerance and insulin resistance in aplastic anemia treated with oxymethalone. J ClinEndocrinolMetab 1981;53:905–8.
[36] Beck P. Contraceptive steroids: modification of carbohydrate and lipid metabolism. Metabolism 1973;22:841–55.
[37] Anderson DC. Sex hormone-binding globulin. ClinEndocrinol 1974;3:69–96.
[38] Evans DJ, Hoffman RG, Kalkhoff RK, Kissebah A. Relationship ofandrogenic activity to body fat topography, fat cell morphology, and metabolic abnormalities in premenopausal women. J ClinEndocrinolMetab 1983;57:304–10.
[39] Haffner SM, Dunn JF, Katz MS. Relationship of sex hormonebinding globulin to lipid, lipoprotein, glucose, and insulin concentrations in postmenopausal women. Metabolism 1992;41:278–84.
[40] Lindstedt G, Lundberg PA, Lapidus L, Lundgren H, Bengtsson C, Bjorntorp P. Low sex hormone-binding globulin as independent risk factor for development of NIDDM: 12-year follow-up of population study in Gothenburg, Sweden. Diabetes 1991;40:123–8.
[41] Haffner SM, Valdez RA, Morales PA, Hazuda HP, Stern MP. Decreased sex hormone-binding globulin predicts non-insulin-dependent diabetes mellitus. J ClinEndocrinolMetab 1993;77:56–60.
[42] Nestler JE. Sex hormone-binding globulin: a marker for hyperinsulinemia and/or insulin resistance (Editorial). J ClinEndocrinolMetab 1993;76:273–4.
[43] Haffner Steven M, Karhapaa Pauli, Mykkanen Leena, Laakso Markku. Insulin resistance, body fat distribution, and sex hormones in men. Diabetes February 1994;43:212–9.
[44] Fanelli F, Belluomo I, Di Lallo VD, et al. Serum steroid profiling by isotopic dilution-liquid chromatographymass spectrometry: comparison with current immunoassas and reference intervals in healthy subjects. Steroids 2011;76: 244–53.
[45] Muka T, Nano J, Jaspers L. Associations of steroid sex hormones and sex hormone-binding globulin with the risk of type 2 diabetes in women: a population based cohort study and meta-analysis. Diabetes 2017;66:577–86.
[46] Onah CE, Meludu SC, Dioka CE, Onuegbu JA, Amah UK, Olisekodiaka MJ, Okwara JE, Onah CF, Ezeugwunne IP. Pattern of male sex horones in type 2 diabetic patient in Nnewi. South East. Niger. 2013;10:65–70.
[47] Verma S, Saxena S, Kushwaha JS, Giri R, Priyadarshi BP, Singh P. Serum testosterone levels in type 2 diabetes mellitus. JIACM 2013;14:115–8.
[48] Maratou E, Hadjidakis DJ, Kollias A, Tsegka K, Peppa M, Alevizaki M, et al. Studies of insulinresistance in patients with clinical and subclinical hypothyroidism. Eur J Endocrinol 2009;160(5):785–90. https://doi.org/10.1530/EJE-08-0797.
[49] Singh BM, Goswani B, Mallika V. Association between insulin resistance and hypothyroidism in females attending a tertiary care hospital. Indian J Clin Biochem 2010;25(2):141145.
[50] Al Sayed A, Al Ali N, Bo Abbas Y, Al Fadhli E. Subclinical hypothyroidism is associated with early insulin resistance in Kuwaiti women. Endocr J 2006: 653–7.
[51] Ren R, Jiang X, Zhang X, Guan Q, Yu C, Li Y, et al. Association between thyroid hormones and body fat in euthyroid subjects. ClinEndocrinol 2014;80: 585–90.
[52] Jayanthi Rajendran, Srinivasan Abu Raghavan, Niranjan Gopal. Gene polymorphism of adiponectin SNP + 45 with reference to thyroid status - a comparative study among non-obese, overweight and obese type 2 diabetics. J Obese Weight-Loss Medic 2018;4:020.
[53] Ozcan L, Tabas I. Calcium signalling and ER stress in insulin resistance and atherosclerosis. J Intern Med 2016;280:457–64.
[54] Nourmohammadi I, Shalmani IK, Shaabani M, Gohari L. Zinc, copper, chromium, manganese and magnesium levels in serum and hair of insulin-dependent diabetics. Arch Iran Med 2000;2:88–100.
[55] Candilish DJ. Minerals. J Am Coll Nutr 2000;17:286–310.
[56] Bandaru Pavani, Shankar Anoop. Association between serum uric acid levels and diabetes mellitus. Int. J. Endocrinol. 2011 Article ID 604715, 6 pages, 2011, https://doi.org/10.1155/2011/604715.