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Original Research Article

Evaluation of oxidative stress and cardiometabolic profile in hypothyroidism children

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Abstract

Background: Despite massive efforts, oxidative stress along with abnormality in cardiometabolic profile is a serious concern in children and adolescent. However, in this context, limited studies have been documented in hypothyroidism (HT) young patients.
Aim: The objective of present study was to determine the oxidative stress and metabolic profile (glycemic and lipid profile) in young hypothyroidism patients and to determine their role in disease complexity.
Material & Method: Fasting blood glucose, serum insulin, thyroid and lipid profile (serum total cholesterol, triglycerides, HDL, LDL and VLDL levels) along with marker of lipid peroxidation (malondialdehyde; MDA) were estimated by using standard methods in 25 patients of HT as Group II, and compared it with 25 age matched young healthy controls (Group I). The values were expressed as Mean ± SD and data from patients and controls were compared using students't' test.
Result: Fasting blood glucose, serum insulin, total cholesterol, triglycerides, LDL and VLDL levels along with MDA levels were significantly high ($p<0.001$) and serum HDL levels were significantly low ($p<0.001$) in patient group as compared to control group. These finding suggest that young HT patients are at enhanced risk to develop cardiovascular complication due to their altered lipid profile, insulin resistance and enhanced oxidative stress**.**
Conclusion: Therefore, regular screening of metabolic profiles, cardiac markers, control on oxidative stress and proper treatment of dyslipidemia along with maintenance of normal thyroid profile are necessary predictive and preventive measures which may help in reduction of CVD complications and its burden in the growing young population.
Keywords: Dyslipidemia, lipid peroxidation, hypothyroidism, cardiovascular disease.

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1. Introduction

Hypothyroidism (HT) is a most frequent hormone disorder in children and have found to be associated with metabolic alterations leading to serious complications such as cardiac complications, mental retardation, nephritic syndrome and delay in bone maturation etc.[1-3] In general, thyroid hormone is considered as a growth factor and its deficiency impairs child growth and development. Clinical conditions resulting from HT will depend on the degree and duration of the deficiency. In addition, HT has been associated not only with disorders of glucose and insulin metabolism but also with that of lipids too.[4] Therefore, alteration in thyroid levels in association with insulin resistance has a significant effect on lipid profile, and thereby associated with future risk of cardiac complications.

Despite intensive researches to unveil the etiology of hypothyroidism in children, it remains enigmatic. However, a growing body of evidence supports that oxidative stress can be associated with hormonal derangement and thyroid function abnormality.[5] Oxidative stress is potentially a key mechanism in precipitation of disease process that appears to act through

deterioration of biomolecules due to enhanced reactive oxygen species (ROS) production and reduction of antioxidant defense system.[6] Prime targets of ROS attack are the polyunsaturated fatty acid in the membrane lipids causing lipid peroxidation, have been found to be a major event in the abnormal thyroid hormone levels associated disorders in adult and pediatric group as well.[7,8]

Increased ROS accumulation and subsequent alterations in the levels of antioxidant defense components leads to the activation of stress-sensitive intracellular signaling pathways that, in turn, disrupt cellular homeostasis by promoting cellular damage and contribute to the development and progression of hypothyroidism associated secondary complications. [9]

Interestingly, aging and its related complications have been found to be associated with enhanced oxidative stress.[10] Contrary to aging process, recent study on Egyptian children with nephritic syndrome had demonstrated an association between thyroid profile and oxidative stress as measured by lipid peroxidation and antioxidant enzymes activities.[11] In addition, a plethora of studies have evidenced an array of complex intertwining between oxidative stress and altered metabolic profile in adult population.[12,13] Moreover, advancing of age with passage of time multifold enhances the cardiovascular disease (CVD) risk due to complex intertwining biochemical, genetic, and abnormal metabolic profile.[14] In general, presence of oxidative stress exerts their culprit effect in the favor of disease complexity irrespective of age.[15,16]

However, evidences related to assessment of oxidative stress in combination with altered metabolic profile in younger population to predict CVD risk are scanty. Interestingly, it is conceivable that young HT population may exert dyslipidemia in combination with hyperglycemia, insulin resistance and elevated lipid peroxidation, as important factors in future CVD risk development. Therefore, the present study was carried out to ascertain the extent of oxidative stress along with estimation blood glucose and serum lipid profile content in young patients of HT and to determine the relationship of altered metabolic profile with disease complexity along with lipid peroxidation, as an effective approach in the prediction of cardiovascular complication in young hypothyroidism patients.

2. Material and Methods

In the present study, 25 healthy children and 25 young patients with hypothyroidism (15 males and 10 females) of either sex belonging to age group 07 to 16 years were taken in study group as Group I and Group II respectively. A general information or pre-experimental questionnaire regarding demographic information, family history and limited physical examination was completed from all the subjects after taking informed consent from their parents, approval of protocol by ethics committee of college and checking their fulfillment with inclusion criteria.

2.1 Inclusion criteria

The inclusion criteria adopted were children and adolescents belonged to 07 to 16 years of age, newly diagnosed and untreated cases for hypothyroidism.

2.2 Exclusion criteria

Patients suffering from diabetes, cardiovascular disease, hepatic disease, tuberculosis, renal disease, hematuria, hypertension and taking drugs like steroid, lithium, antioxidant vitamin supplement or non-steroidal anti-inflammatory drugs, antihypertensive drugs and other medications that alter thyroid functions and lipid levels led to exclusion from the study.

Fasting blood sample (5 ml) was collected from the anticubital vein of the study group subjects and kept in a syringe for half an hour for proper coagulation followed by serum separation at 2000 rpm to estimate serum MDA, thyroid and lipid profile.

Fasting blood glucose levels were measured by using enzymatic kit based on glucose oxidase method. Glucose, in presence of glucose oxidase, converted into gluconic acid along with production of Hydrogen peroxide, which later oxidatively coupled with 4-aminoantipyrine /phenol (in presence of peroxidase) and red quinoneimine dye was produced. The intensity of the color complex was directly proportional to the glucose in specimen and showed absorption maxima at 505 nm.[17] Estimation of serum thyroid profile (T3, T4 and TSH) was done in VITROS EciQ immunodiagnostic system using an immunometric assay technique.

Serum insulin levels were measured by radioimmunoassay (Diagnostic System Laboratories, Texas, USA). Insulin resistance was estimated using homeostasis model assessment (HOMA-$_{IR}$) from fasting serum glucose and insulin level by using the following formula: [18,19]

$$\text{HOMA-}_{IR} = \frac{\text{(Fasting plasma glucose (mmol/l)X fasting insulin (µU/ml)}}{22.5}$$

Serum MDA levels were estimated by thiobarbituric acid (TBA) reaction. Serum lipid peroxide was measured by precipitating lipoproteins with trichloroacetic acid (pH 2-3) and boiled with thiobarbituric acid which reacts with Malondialdehye, forming a MDA-TBA to get pink color. The pink colored complex that occurred was refrigerated to room temperature and measured by using a spectrophotometer at 530 nm [20]. Serum total cholesterol was estimated by enzymatic kit method which involves the conversion of cholesterol ester into free cholesterol and fatty acid by cholesterol esterase. In the second reaction, cholesterol oxidase acts on cholesterol and produce cholest-4-ene3-one and hydrogen

peroxide. H_2O_2 oxidatively couples with 4-aminoantipyrine and phenol to produce red quinoneimine dye. This dye had absorbance maximum at 510 nm. [21]

Enzymatic kit method was also used in the estimation of serum triglyceride. Triglyceride was hydrolysed by lipoprotein lipase to release glycerol which was converted into glycerol 3 phosphate by glycerol kinase. In addition, glycerol phosphate oxidase converts glycerol 3 phosphate into dihydroxy aceteone phosphate and hydrogen peroxide. In presence of peroxidase, hydrogen peroxide oxidizes phenol chromogen to red color compound. The intensity of color was directly proportional to concentration of triglyceride and measured at 510 nm.[22]

Serum high density lipoprotein (HDL) was estimated by using phosphotungstic acid/Mg^{2+} which precipitates chylomicrons, VLDL and LDL fraction whereas HDL fraction remains unaffected in supernatant. Cholesterol content of HDL fraction was assayed using Autozyme cholesterol.[23]

Serum LDL-cholesterol and VLDL-cholesterol levels were calculated by Friedwald's formula.[24]

LDL-C = TC - [(TG/5)+HDL-C]

VLDL cholesterol = Total cholesterol – (HDL + LDL)

2.3 Statistical analysis

The data collected from patients and control were entered separately in Microsoft Excel sheet of windows 2007 and values were expressed as Mean ± SD. The significance of mean difference between groups was compared by using Student's t-test and distribution of probability (P).

3. Result

Demographic indices of younger HT subjects and healthy controls which includes general information pertaining to age, height, weight and BMI of the study group subjects, are represented in Table 1. Patients with HT have insignificant variation ($p<0.1$) with respect to age as compared to healthy controls. Healthy younger subjects and HT patients were belonged to age group 07- 16 years i.e. 11.4 ± 2.3 and 14.5 ± 2.7 years in Group I and Group II respectively, as represented in Table 1. The recruited younger population with hypothyroidism had positive family history of HT i.e. in 72%. Group II subjects were overweight as they had significantly high ($p<0.05$) BMI with respect to healthy controls which reflect the role of increased body weight in enhancing future risk of CVD development as one of the important risk factor. However, incidence of HT in male are more than female HT subjects as 17 males and 08 females were recruited as younger HT patients. However, waist hip ratio in the patients group subjects was insignificantly increased ($p<0.1$) of as compared to healthy controls.

The observation made reveal significant changes in thyroid profile (including T3, T4 and TSH levels) in both the young patients group as compare to healthy controls. Alteration in serum thyroid and glycemic profile was represented in Table 2. Serum T3 level was significantly low ($P< 0.05$, 17.41% low) in Group II subjects as compared to control. Similarly, serum T4 level was significantly low ($P< 0.05$, 21.67% low) in both Group II subjects as compared to control. Serum TSH level was significantly high ($P< 0.001$, 286.4% high) in Group II subjects as compared to control.

Fasting plasma glucose level was increased significantly (28.73 % high; $P< 0.05$) in Group II subjects with respect to healthy controls. HOMA $_{IR}$ index was increased significantly ($P< 0.05$) in Group II subjects as it was greater than 2.5 (the cut off for normal and impaired insulin sensitivity) with respect to Group I subjects. Increased HOMA index i.e. enhanced insulin resistance was observed in HT subjects due to abnormality in serum insulin levels. Fasting insulin levels were significantly high ($p< 0.001$; 86.67 % high) in the patients group (Group II) as compared to healthy control group subjects (Group I).

Marker of lipid peroxidation (MDA) and metabolic profile are presented in Table 3. Serum MDA levels were found to be significantly high ($p<0.001$; 71.95% high) in patient group as compared to healthy controls which reflect the role of oxidative stress in association with hypothroidism in etiopathology of future CVD risk in young HT patients. As compared to normal healthy controls, abnormalities in lipid profile were observed in study group subjects with HT, as represented in Table 3. In the Group II subjects, dyslipidemia was highly prevalent and believed to be significantly associated with future CVD complication in HT children and adolescents. Patients with HT showed significantly increased level of total cholesterol ($P< 0.05$; 17.69% high), triglycerides ($P< 0.05$; 19.37% high), LDL-cholesterol ($P< 0.001$; 21.54% high) and VLDL ($P< 0.001$; 24.47% high) whereas HDL-cholesterol levels were significantly reduced in Group II ($P< 0.05$; 8.60% low) subjects as compared to healthy younger controls.

Table 1: **Clinical characteristics and demographic profile of the study group subjects (Mean ± SD)**

S. No.	Parameters	Group I (n=25)	Group II (n=25)
1	Age (years)	11.4±2.3	14.5±2.7
2	Males/Females	15/10	17/08
3	Family history	-	72 %
4	Height (meter)	152.40±8.3	149.52±7.9
5	Weight (Kg)	40.8±3.4	47.5±4.2
6	BMI (Kg/m^2)	17.83±1.20	23.39±1.31**
7	Waist: Hip ratio	0.78±0.04	0.94±0.05*

Where, * $p<0.1$: Non-significant; ** $p<0.05$: Significant; *** $p<0.001$: Highly Significant

Table 2: **Thyroid and glycemic profile of study group subjects (Mean ± SD)**

S. No.	Parameters	Group I (n=25)	Group II (n=25)
1	Fasting Blood Glucose (mg/dl)	76.50±4.30	98.48±3.15***
2	Serum insulin (nmol/l)	0.15±0.03	0.28±0.04***
3	$HOMA_{IR}$	2.95±0.42	8.07±1.85***
4	Tri-iodo thyronin (T3) (ng/dl)	106.5±20.18	87.95±17.05**
5	Thyroxin (T4) (µg/dl)	8.4±1.20	6.58±1.15**
6	Thyroid stimulating hormone (TSH) (uIU/ml)	2.65±0.82	10.24±2.48***

Where, *p<0.1: Non significant; **p<0.05: Significant; ***p<0.001: Highly significant

Table 3: Marker of oxidative stress and metabolic profile in the study group subjects (Mean ± SD)

S. No.	Parameters	Group I (n=25)	Group II (n=25)
1	MDA (nm/ml)	1.64 ± 0.50	2.82 ± 0.46***
2	Total cholesterol (mg/dl)	140.38 ± 8.26	165.22 ± 7.50**
3	Triglyceride (mg/dl)	92.5 ± 8.15	110.42 ± 9.32**
4	HDL-cholesterol (mg/dl)	40.21 ± 2.35	36.75 ± 2.53**
5	LDL-cholesterol (mg/dl)	82.48 ± 9.51	100.25 ± 8.40***
6	VLDL-cholesterol (mg/dl)	26.27 ± 2.06	32.70 ± 2.17***

Where, *p<0.1: Non significant; **p<0.05: Significant; ***p<0.001: Highly significant

4. Discussion

Contrary to common belief hypothyroidism (HT) is not a trivial illness but a most common hormone disease that affects the quality of human life of not only middle aged and older population but also of younger population as well [1,4]. The incidence of thyroid abnormality and its complications are increasing at alarming pace with advancing of medical science. However, HT is frequently asymptomatic and may go undiagnosed in children. Disorders of glucose and insulin metabolism involving defective insulin secretion in response to glucose, hyperinsulinemia, altered peripheral glucose disposal and insulin resistance have been found to be associated with HT.[25] In the present study, fasting blood glucose was significantly increased in hypothyroidism patients which could be explained on the basis of impaired glucose utilization in muscles, overproduction of hepatic glucose and enhanced absorption of splanchnic glucose.[26]

In addition, alteration of thyroid hormone levels and its association with insulin resistance has received much attention in pediatric group. The present study illustrates the complex interplay between the depletion of thyroid hormone and elevation of serum insulin levels in the pathogenesis of insulin resistance. The possible pathogenic mechanism involved in insulin resistance includes the decreased blood flow in the peripheral tissues and reduced sensitivity of tissues to insulin due to low thyroid hormone levels in HT children.[25]

Alteration in thyroid levels along with insulin resistance, as characterized by increased HOMA index in the present HT children group, has a significant effect on lipid profile. It has been reported that insulin resistance augments the deleterious effect of hypothyroidism on the lipid profile.[27] Moreover, abnormal lipid profile or dyslipidemia in HT patients is an alarming condition of future health complications predominantly cardiovascular diseases (CVD) such as myocardial infarction, atherosclerosis etc.[1] In this context, the present study revealed a significant increase in the serum total cholesterol LDL-c, VLDL and triglyceride levels along with reduced HDL levels in the younger HT subjects as compared to healthy controls. Thus, the findings of present study authenticates the fact that children and adolescents with HT are at enhanced risk of future cardiovascular complications due to elevated levels of serum total cholesterol along with LDL and depleted levels of HDL. Similarly, Nandkeoliar *et al* observed a characteristic altered serum lipid profile in children and adolescent of diabetic patients. [28]

Interestingly, increased oxidative stress mediated lipid peroxidation has been implicated in enhancing the risk of future CVD complication in patients with thyroid abnormalities.[8] It generates a variety of hydroperoxide and aldehyde products that are highly reactive with cellular components and extracellular matrix. Malondialdehyde (MDA) is a well known toxic aldehydic end product of lipid peroxidation. It has been reported that excess endogenous aldehyde production (lipid peroxides) plays a significantly role in CVD risk elevation by binding sulphydryl groups of membrane proteins, altering Ca^{2+} channels and increasing cytosolic free Ca^{2+} that cause further extensive membrane damage leading to peripheral vascular resistance and hypertension.[10] The present study also showed significant increase in the serum MDA levels along with dyslipidemia and hyperglycemia in the younger HT subjects as compared to healthy controls. High MDA levels could be explained on the basis of ROS mediated attack on PUFA of the cell membranes associated with enhanced TSH levels. Similarly, Dardano *et al* reported that excess TSH leads to enhanced oxidative stress.[29] Our findings were in congruence with the findings of previous investigators where association of HT with increased oxidative stress, characterized by elevated MDA levels, are well documented.[8,11] Enhanced oxidative stress in combination with insulin resistance and altered metabolic profile such as dyslipidemia and hyperglycemia may be implicated as the main patho-physiological basis attributed to future CVD risk in younger HT population. The present study had certain limitations which include relatively small sample size due to inclusion of pediatric group only. Therefore, a large-scale study is required to validate our findings and to get more authenticated outputs.

5. Conclusion

Thus, on the basis of present observations and findings, it is obvious that the incidence of HT is not related to aging factor and it affects not only in middle age and elderly but also in the children and adolescents. The early recognition of clinical features of HT in children and adolescents in combination with screening of cardiomatabolic profile plays a crucial role in order to reduce the morbidity and mortality caused by HT and its related future cardiovascular disease. In addition to maintaining the normal body weight and inclusion of light exercises as life style modification, incorporation of food stuff containing iodine, regular monitoring of glycemic and lipid profile along with marker of oxidative stress, are required to prevent the development of childhood hypothyroidism population in general, and in children with positive family history of altered thyroid profile. Moreover, the study group parameters are reliable and affordable diagnostic markers for children; even they do not reveal clinical symptoms in early stage of life.

Furthermore, antioxidant therapy along with thyroid hormone supplement may reduce the burden of future cardiac complication in HT children. ,

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