MEDICAL SCIENCE MONITOR

CLINICAL RESEARCH

e-ISSN 1643-3750
© Med Sci Monit, 2017; 23: 2519-2526
DOI: 10.12659/MSM.905190

Received: 2017.05.06
Accepted: 2017.05.16
Published: 2017.05.25

Myocardial Performance Index for Patients with Overt and Subclinical Hypothyroidism

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Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
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Source of support: Departmental sources

Background: Hypothyroid has several effects on the cardiovascular system. Global myocardial performance index (MPI) is used in assessment of both left ventricular (LV) systolic and diastolic function. We compared MPI in hypothyroidism patients *vs.* normal control subjects.

Material/Methods: Eighty-two hypothyroid patients were divided into 2 groups: a subclinical hypothyroid (SH) group (n=50), and an overt hypothyroid (OH) group (n=32). The healthy control group (CG) constituted of 37 patients. TSH, FT3, and FT4, anti-TPO, anti-TG, insulin, lipid values, and fasting glucose levels were studied. All patients underwent an echocardiographic examination. Myocardial performance indexes were assessed and standard echocardiographic examinations were investigated.

Results: MPI averages in OH, SH, and control groups were 0.53±0.06, 0.51±0.05, and 0.44±0.75 mm, respectively. MPI was increased in the OH and SH groups in comparison to CG (p<0.001, p<0.001, respectively).

Conclusions: MPI value was significantly higher in hypothyroid patients in comparison to the control group, showing that regression in global left ventricular functions is an important echocardiographic finding. Future studies are required to determine the effects of this finding on long-term cardiovascular outcomes.

MeSH Keywords: Cardiovascular Abnormalities • Echocardiography • Hypothyroidism

Full-text PDF: http://www.medscimonit.com/abstract/index/idArt/905190

2490 4 1 20

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Background

Hypothyroidism is a clinical manifestation that results in insufficiency or lack of thyroid hormone in tissues. Frequently observed symptoms include weakness, fatigue, poor concentration, drying of skin, hair loss, constipation, rough voice, infertility, muscle pain, depression, bradycardia, and relaxation of reflexes [1]. If this clinical manifestation is due to thyroid gland insufficiency, it is classified as primary hyperthyroid; if it is due to thyroid stimulating hormone (TSH) insufficiency, it is classified as secondary hypothyroidism; and if it is due to thyroid releasing hormone (TRH) insufficiency, it is classified as tertiary hyperthyroidism. The most common cause of primary hypothyroidism is Hashimoto thyroiditis, which is referred to as overt and subclinical according to serum TSH level. If TSH level is high but T3 and/or T4 level is low and there are no overt clinical hypothyroidism symptoms, it is assessed as subclinical hypothyroidism. When TSH is 4–10 mIU/L, it is assessed as mild, but when TSH >10 mIU/L, it is referred to as severe subclinical hypothyroidism [2,3]. The prevalence of subclinical hypothyroidism varies in the general population from 4% to 10%, and it is seen more frequently in women around the age of 60 years [4]. Clinicians commonly encounter subclinical hypothyroidism due to its high prevalence. The main question is whether these patients should be treated or monitored without any treatment [5]. Many studies have found that subclinical hypothyroid (SH) is associated with hypertension, hyperlipidemia, and increased cardiovascular diseases (CVD), and some studies reported that SH is an independent risk factor for CVD [6]. The global myocardial performance index (MPI) (Tei index) is used as an echocardiographic parameter in the assessment of left ventricular (LV) systolic and diastolic function. Global MPI was first defined by Tei Chuwa et al. [7,8]. This index can easily be measured in Doppler traces obtained from mitral and aortic flows, which are not affected by heart rate, ventricular structure, and preload. This index is calculated by the ratio of total isovolumetric contraction time (ICT) and isovolumetric relaxation time (IRT) to ejection time. This parameter is a commonly acceptable one since it is easy to obtain it through echocardiographic examination and the interobserver variability is rather low. It has earlier been revealed that MPI predicts morbidity and mortality due to idiopathic dilated cardiomyopathy, cardiac amyloidosis, and primary pulmonary hypertension [9,10]. A recent study performed on patients with heart failure (HF) found that this index is a powerful predictor of cardiovascular mortality in patients with systolic HF [11]. There are also studies suggesting that it is a cardiovascular mortality predictor independent of conventional cardiovascular risk factors in elderly males and other cardiac measurements [12]. MPI may be helpful in patient follow-up and determination of prognosis in cases where an angioplasty procedure is performed after AMI [13]. MPI is a useful clinical measurement of total LV function and can be a valuable tool for assessment of any potential cardiac insufficiency that may develop. Increased CVD risk in subclinical hypothyroidism was also indicated in studies performed earlier. After calculating MPI, which is an echocardiographic parameter for hypothyroid patients with high TSH, we planned to compare it with that of healthy volunteers. Thus, we aimed to provide a significant resource for prospective studies that may determine whether or not MPI could be a predictive parameter in research for cardiovascular disease development in hypothyroid patients.

Material and Methods

We included patients diagnosed with hypothyroidism upon application to the Department of Endocrinology and Metabolism Diseases, Medical Faculty, Dicle University, or those who were diagnosed with hypothyroidism and under follow-up. It was stipulated that thyroid hormone test results of the patients diagnosed with hypothyroidism and followed up should be consistent with those of hypothyroidism when they first applied.

A total of 82 patients diagnosed with hypothyroidism and 37 healthy control group (CG) subjects were included into the study. Patients with hypothyroidism diagnosis were divided into 2 sub-groups as overt hypothyroidism (OH) and subclinical hypothyroidism (SH) according to their TSH and free T4 (FT4) levels. The total number of patients was 82: 8 males and 42 females in the SH group, and 4 males and 28 females in the OH group. The SH group consisted of newly diagnosed patients and the AH group was constituted of new patients or those patients under follow-up whose TFT (thyroid function tests) values varied in favor of hypothyroid following their application. The patients with increased TSH (>4.20 mIU/mL), decreased ST4 (<12 mIU/mL) and positive anti-thyroid peroxidase (anti-TPO) (>35 mIU/mL) were assigned to the OH group, and the patients with increased TSH, normal ST4, and positive anti-TPO were assigned to the SH group. The mean age and sex ratio in the control group were similar to those in the hypothyroid patient groups, and these cases were selected from among volunteers who did not have any known chronic diseases and who had normal TFT and anti-TPO levels. All patients and healthy controls were told why they were included in this study by the researcher, and their written consent was obtained. After receiving Ethics Committee approval, we started to conduct the study (Project Number: 223, Approval date 15.04.2015).

No patients with known systemic diseases such as heart disease, diabetes mellitus, and hypertension (TA >140/90) were included in the study.

The weight, height, and body mass index (BMI) of the patients and controls were measured and recorded to exclude

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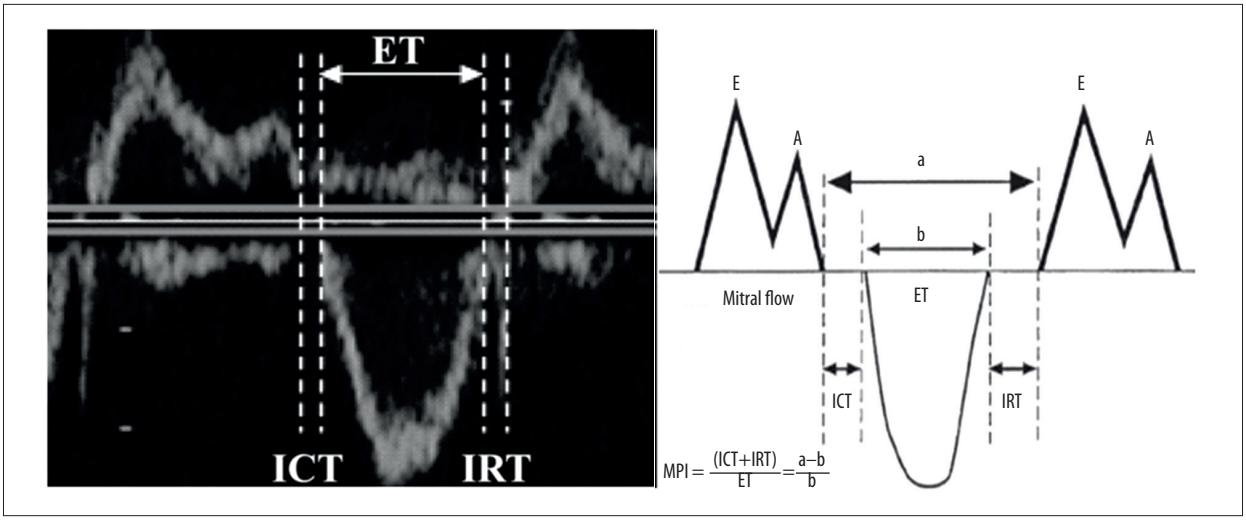

Figure 1. Doppler Echocardiographic and schematic display of MPI calculation.

any situations that may have adverse effects on left ventricular functions. Patients with metabolic syndrome and obesity (BMI >30) were not included into the study. Systolic and diastolic blood pressures of the patients were measured with a mercury sphygmomanometer in a silent environment when patients were seated. Lipid profile, insulin, glucose, urine, creatine, and complete blood cell count tests were performed.

MPI measurement

Transthoracic echocardiography and systolic and diastolic functions of left ventricle and MPI measurements were performed. Bi-dimensional, pulsed Doppler, M-mod, and color flow Doppler echocardiographic examinations were performed. Echocardiographic images from parasternal and apical windows were taken when the patients lay down on their left side. LV and valve functions were assessed, and parasternal long and short axes, apical 4- and apical 2-cavity images were used.

Mitral inflow velocity pattern was recorded by inserting pulsed wave Doppler sample volume between the edges of mitral leaflets. LV outflow pattern was measured from the apical 5-cavity window by placing pulsed wave Doppler sample volume just right under the aorta valve. Doppler measurements were performed using 3 sequential heart cycles. Doppler time intervals were measured from time intervals of mitral inflow and LV outflow velocities, as shown in the Figure 1. Interval 'a" is the period starting from the end of mitral inflow until its start. Interval 'a' is equal to the total of isovolumetric contraction time (ICT), ejection time (ET), and isovolumetric relaxation time (IRT). LV ejection time 'b' is the period for LV outflow velocity profile (Figure 1). Thus, isovolumetric contraction time and isovolumetric relaxation time is obtained by extracting 'b' from 'a'. Compound index of LV systolic and diastolic functions (MPI) (dividing total of isovolumetric contraction time and isovolumetric relaxation time into ejection time) is calculated as 'a-b/b'.

Left ventricular strain parameters, epicardial fat thickness, and carotis-intima media thickness measurements were also measured during echocardiographic examinations.

Hormone and biochemical measurements

In our Endocrinology Polyclinic, hypothyroid patients attended control examinations every 1–3 months, and their treatments are planned. During these examinations, each patient underwent routine complete blood cell count tests, liver function tests, kidney function tests, fasting plasma glucose, and thyroid function tests. Other biochemical indicators and radiologic examinations are also requested, if required. During our study, we obtained the values of complete blood cell count tests, liver function tests, kidney function tests, fasting plasma glucose, and thyroid function tests performed in the last 1 month for the cases entered into the database of our hospital. These examinations were performed for the patients who did not have any records in the database. Additionally, TFT, anti-TPO, and anti-thyroglobulin (anti-TG) antibody titers, 12-h fasting insulin level, low-density lipoprotein cholesterol (LDL-Chol), high-density lipoprotein cholesterol (HDL-Chol), triglyceride (TG), total cholesterol (T-Chol), and very low-density lipoprotein cholesterol (VLDL) values of the cases were examined. In our hospital, hemography is performed by flow cytometry method; ALT and AST are assessed by spectrophotometry method; and thyroid stimulating hormone (TSH), free thyroxin (FT4), free triiodotironin (FT3), anti-Tg, and anti-TPO are assessed by electrochemiluminescence immunoassay (ECLIA) method. According to the kits used in our hospital, the ranges of 0.270–4.20 mlU/mL, 12–22 pmol/L, and 0–35 lU/mL were accepted as normal values in terms of TSH, ST4, and anti-TPO,

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Table 1. Clinic laboratory and echocardiographic data for all study cases.

Parameter	SH (Ort ±SD)	OH (Ort ±SD)	CG (Ort ±SD)	P value
Gender (F/M)	8/42	4/28	6/31	NS
Age (year)	35.3±9.5	37.4±9.6	35.6±13.9	NS
BMI (kg/m²)	25.2±3.8	26.2±3.9	31.4±44.9	NS
SBP (mm/Hg)	119.4±12.8	124.8±13.1	120.9±13.8	NS
DBP (mm/Hg)	74.0±8.9	7820±9.5	74.7±7.3	NS
TSH (mlU/mL)	**7.9±3.6**	**18.8±16.2**	**1.6±0.8**	**<0.001**
FT3 (pmol/L)	**4.8±0.8**	**4.3±1.3**	**5.2±0.6**	**0.001**
FT4 (pmol/L)	**14.7±1.8**	**9.7±2.4**	**16.4±2.1**	**<0.001**
Anti TPO (lU/mL)	**207.3±227.1**	**216.5±210.8**	**16.4±18.5**	**<0.001**
Anti-TG (lU/mL)	**617.3±1164.6**	**299.0±667.7**	**43.1±74.8**	**0.008**
APG (mg/dl)	95.3±7.3	95.9±7.6	92.7±7.7	NS
HOMA IR	**2.4±1.7**	**3.7±3.6**	**2.3±1.0**	**0.018**
LDL (mg/dl)	108.1±38.1	117.7±35.0	103.0±26.5	NS
HDL (mg/dl)	50.3±11.8	49.4±11.1	46.6±11.9	NS
VLDL (mg/dl)	**21.6±10.2**	**45.5±60.6**	**20.4±10.1**	**0.002**
T-Chol (mg/d)	181.7±37.4	178.5±75.9	169.0±34.8	NS
TG (mg/dl)	104.7±52.7	106.1±111.1	102.6±57.5	NS
LVEF (%)	58.3±2.1	59.5±1.96	60.2±1.75	NS
MPI	**0.51±0.05**	**0.53±0.06**	**0.44±0.05**	**<0.001**

NS – not significant; CG – control group; SH – subclinic hypothyroid group; OH – overt hypothyroid group; BMI – body mass index; SBP – systolic blood pressure; DBP – diastolic blood pressure.

respectively, for euthyroid. To determine the insulin resistance, fasting blood glucose and insulin values are used in calculation with the formula of [*HOMA IR=fasting plasma glucose (mmol/l) × fasting plasma insulin (μU/ml)/22.5*], and HOMA insulin resistance index was calculated. HOMA IR values over 2.7 were accepted as insulin resistance.

Statistical methods

Statistical assessment of our study was performed by using the SPSS (Statistical Package for Social Sciences) 18.0 computer program. P<0.05 value was accepted to be statistically significant. The results were indicated in average ±SD and in percentage (%). One-way ANOVA was used for comparing all 3 groups. The independent-samples *t* test was used for comparing the 2 groups, and the *t* test was used for variables. For correlation analysis between the parameters, Pearson correlation coefficients were used. Regression analyses were performed with MPI dependent variables such as age, VKI, SKB, DKB, TSH, ST4, ST3, LDL, HDL, TG, TKOL, and independent variables such as VLDL.

Results

A total of 50 subclinical hypothyroid (SH) patients, 32 overt hypothyroid (OH) patients, and 37 control group (CG) subjects were included into the study. None of the participating patients had any cardiovascular and metabolic disease history or diagnosis that could adversely affect the study and the results thereof. The mean ages of the patients were 35.3±9.5 and 37.4±9.6 years for the SH and OH groups, respectively. The male/female ratio was 8/42 (19%) in the SH group and 4/28 (14%) in the OH group. The mean age of the control group was 35.6±13.9, and the male/female ratio was 6/31 (19%). The mean age and male/female ratio of the control group were similar to those of the patients who participated in the study. The measurement data of SH and OH patients and the control group, as well as their comparisons, are summarized in Table 1. The comparison between SH and the control group is shown in Table 2, between OH and the control group in Table 3, and between SH and OH groups in Table 4

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Table 2. Clinic laboratory and echocardiographic data for SH and control groups.

Parameter	SKH (Ort ±SD)	AH (Ort ±SD)	KG (Ort ±SD)
Gender (F/M)	8/42	6/31	NS
Age (year)	35.3±9.5	35.6±13.9	NS
BMI (kg/m²)	25.2±3.8	31.4±44.9	NS
SBP (mm/Hg)	119.4±12.8	120.9±13.8	NS
DBP (mm/Hg)	74.0±8.9	74.7±7.3	NS
TSH (mlU/mL)	**7.9±3.6**	**1.6±0.8**	**<0.001**
ST3 (pmol/L)	4.8±0.8	5.2±0.6	NS
ST4 (pmol/L)	14.7±1.8	16.4±2.1	NS
Anti TPO (lU/mL)	**207.3±227.1**	**16.4±18.5**	**<0.001**
Anti-TG (lU/mL)	**617.3±1164.6**	**43.1±74.8**	**0.004**
APG (mg/dl)	95.3±7.3	92.7±7.7	NS
HOMA IR	2.4±1.7	2.3±1.0	NS
LDL (mg/dl)	108.1±38.1	103.0±26.5	NS
HDL (mg/dl)	50.3±11.8	46.6±11.9	NS
VLDL (mg/dl)	21.6±10.2	20.4±10.1	NS
T-ChoL (mg/d)	181.7±37.4	169.0±34.8	NS
TG (mg/dl)	104.7±52.7	102.6±57.5	NS
LVEF (%)	58.3±2.1	60.2±1.75	NS
MPI	**0.51±0.05**	**0.44±0.05**	**<0.001**

NS – not significant; CG – control group; SH – subclinic hypothyroid group.

When SH, OH, and CG are compared, no significant differences were found in age, sex, VKI, APG, SKB, DKB, LDL-kol, HDL-kol, T-kol, or TG (Table 1), but there were statistically significant differences in levels of TSH, ST4, anti-TPO, anti-TG, ST3, VLDL, and HOMA IR. When sub-groups were assessed individually, the values of TSH, anti-TPO, and anti-TG, in the SH group were significantly different (p<0.001). There was no significant difference between the 2 groups in age, ST3, ST4, and HOMA IR values. In the OH group, TSH and anti-TPO values were significantly higher in comparison to the control group (p<0.001). There were significant differences between the 2 groups in terms of anti-TG, HOMA IR, VLDL, FT3, and FT4 values. In the OH group, FT3 and FT4 values were lower in comparison to the control group, and anti-TG, HOMA IR, and VLDL values were lower in comparison to the control group (p=0.03for anti-TG, p=0.029 for HOMA IR, p=0.016 for VLDL, p=0.001 for ST3, and p<0.001 for ST4). There were no significant differences between SH and control groups in terms of HOMAR IR, ST3, or ST4 levels. There were no significant differences between SH and OH groups for age, body mass index (BMI), systolic blood pressure (SBP), diastolic blood pressure (DBP) anti-TPO, anti-TG, APG, LDL, HDL, T-Chol, or TG levels. In the OH group TSH, HOMA IR, and VLDL levels were significantly higher compared to the SH group (p<0.001 for TSH, p=0.030 for HOMA IR, and p<0.008 for VLDL). ST3 and ST4 were significantly lower (p=0.037 for ST3 and p<0.001 for ST4) (Table 4).

MPI values between patient groups and control group were statistically compared. MPI average of the control group was significantly lower in comparison to the SH and OH groups. (p<0.001) (Table 1).

OH and SH groups were compared with each other. When MPI average of the OH group was compared to that of the SH group, no statistically significant difference was determined (Table 4).

Discussion

Cardiovascular diseases still are the leading cause of mortality and morbidity all over the world [14]. There are many data in the literature suggesting that both overt and subclinical hyperthyroid is associated with increased cardiovascular diseases [15,16].

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Table 3. Clinic laboratory and echocardiographic data forAH and control groups.

Parameter	OH (Ort ±SD)	CG (Ort ±SD)	P value
Gender (F/M)	4/28	6/31	NS
Age (year)	37.4±9.6	35.6±13.9	NS
BMI (kg/m²)	26.2±3.9	31.4±44.9	NS
SBP (mm/Hg)	124.8±13.1	120.9±13.8	NS
DBP (mm/Hg)	7820±9.5	74.7±7.3	NS
TSH (mlU/mL)	**18.8±16.2**	**1.6±0.8**	**<0.001**
FT3 (pmol/L)	**4.3±1.3**	**5.2±0.6**	**0.001**
FT4 (pmol/L)	**9.7±2.4**	**16.4±2.1**	**<0.001**
Anti TPO (lU/mL)	**216.5±210.8**	**16.4±18.5**	**<0.001**
Anti-TG (lU/mL)	**299.0±667.7**	**43.1±74.8**	**0.03**
APG (mg/dl)	95.9±7.6	92.7±7.7	NS
HOMA IR	**3.7±3.6**	**2.3±1.0**	**0.029**
LDL (mg/dl)	117.7±35.0	103.0±26.5	NS
HDL (mg/dl)	49.4±11.1	46.6±11.9	NS
VLDL (mg/dl)	**45.5±60.6**	**20.4±10.1**	**0.016**
T-Chol (mg/d)	178.5±75.9	169.0±34.8	NS
TG (mg/dl)	106.1±111.1	102.6±57.5	NS
LVEF (%)	59.5±1.96	60.2±1.75	<0.001
MPI	**0.53±0.06**	**0.44±0.05**	**<0.001**

NS – not significant; CG – control group; OH – overt hypothyroid group.

Many important studies were performed in prediction of cardiovascular diseases by means of MPI (Tei index), which was first defined by Tei Chuwa et al. in 1995 [12]. There are even results suggesting that MPI is an independent predictor of cardiovascular mortality [13–17].

In the present study, SH and OH patients were assessed. MPI values of SH and AH patients, who had no cardiovascular diagnosis, were compared with those of controls. The numerical increase in MPI reveals a disordered trend in cardiac functions (systolic and diastolic). As mentioned in the Findings section, these values are higher in OH and SH patients in comparison to the control group (MPI: CG=0.44±0.05; SH=0.51±0.05; OH=0.53±0.06 p<0.001). In comparison of the 2 patient groups (SH and OH), this value was a little bit higher in the OH group, but it was not statistically significant (MPI: SH=0.51±0.05; OH=0.53±0.06 NS).

Echocardiography is an easy, repeatable, and reliable method of diagnosis. Developing new parameters in echocardiographic examinations and using such parameters for predictions in future has always been an objective; MPI is one of them.

Clinic or subclinical hypothyroidism is common. The prevalence of subclinical hyperthyroid is around 4–10% [1–3].

Therefore, the many people have both cardiovascular diseases and thyroid diseases [18] and it is important to increase the data available in this field.

In the comparisons performed in our study between SH and OH groups and the control group consisting of normal healthy volunteers, we found a negative change of MPI values (increase in numerical values). These data are compatible with those reported in the literature [19].

Furthermore, small-scale studies have reported that improvement might occur in cardiac functions and MPI as a result of hypothyroidism treatment [20]. In particular, such prospective data should be increased, and there is a need for prospective data related to cardiac function, which is expected to be cured through hypothyroidism treatment, and cardiovascular outcomes of these patients.

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Table 4. Clinic laboratory and echocardiographic data for SKH and AH groups.

Parameter	SH (Ort ±SD)	OH (Ort ±SD)	P value
Gender (F/M)	8/42	4/28	NS
Age (year)	35.3±9.5	37.4±9.6	NS
BMI (kg/m^2)	25.2±3.8	26.2±3.9	NS
SBP (mm/Hg)	119.4±12.8	124.8±13.1	NS
DBP (mm/Hg)	74.0±8.9	7820±9.5	NS
TSH (mlU/mL)	**7.9±3.6**	**18.8±16.2**	**<0.001**
FT3 (pmol/L)	**4.8±0.8**	**4.3±1.3**	**0.037**
FT4 (pmol/L)	**14.7±1.8**	**9.7±2.4**	**<0.001**
Anti TPO (lU/mL)	207.3±227.1	216.5±210.8	NS
Anti TG (lU/mL)	617.3±1164.6	299.0±667.7	NS
APG (mg/dl)	95.3±7.3	95.9±7.6	NS
HOMA IR	**2.4±1.7**	**3.7±3.6**	**0.030**
LDL (mg/dl)	108.1±38.1	117.7±35.0	NS
HDL (mg/dl)	50.3±11.8	49.4±11.1	NS
VLDL (mg/dl)	**21.6±10.2**	**45.5±60.6**	**0.008**
T-Chol (mg/d)	181.7±37.4	178.5±75.9	NS
TG (mg/dl)	104.7±52.7	106.1±111.1	NS
LVEF (%)	58.3±2.1	59.5±1.96	NS
MPI	0.51±0.05	0.53±0.06	NS

NS – not significant; SH – subclinic hypothyroid group; OH – overt hypothyroid group.

Comcusions

We calculated MPI of healthy volunteers since it is an echocardiographic parameter for hypothyroid patients characterized with high TSH, and we compared the results with those of healthy volunteers. Our aim was to provide a resource for prospective studies to determine whether or not MPI could be a predictive parameter in research on cardiovascular disease development in hypothyroidism patients.

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