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Research Article

Association of Hypothyroidism with High Non-HDL Cholesterol and Ankle Brachial Pressure Index in Patients with Diabetes: 10-Year Results from a 5780 Patient Cohort. A Need for Intervention

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Abstract

Diabetes is commonly associated with thyroid gland disorders, especially hypothyroidism. Among diabetic subjects with hypothyroidism there is a need to study biochemical and other parameters for risk of cardiovascular and kidney diseases. In the past, no study was conducted which has demonstrated significant associations of non-HDL-cholesterol and Ankle Brachial Index (ABI) in such patients. This was accomplished in the current study which has recruited a cohort of 5780 diabetic patients with hypothyroidism, during more than 10-years of follow up, with a hypothesis that hypothyroidism could be associated with higher non-HDL-C and ABI measurements. Statistical analysis of this research has demonstrated that subjects with hypothyroidism have significantly higher levels of non-HDL-C as compared to those without hypothyroidism (153 ± 42.7; 95% CI 146.6 to 158.8 verses148 ± 40; 95% CI 142.5 to 151.6; $p < 0.001$). Right foot ABI was higher among diabetics with hypothyroidism (1.34 ± 0.387; 95% CI 1.19 to 1.56 versus 1.23 ± 0.314; 95% CI 1.12 to 1.26; $p < 0.001$), as well as for the left foot ABI (1.32 ± 0.375; 95% CI 1.23 to 1.54 versus 1.23 ± 0.371; 95% CI 1.12 to 1.28).

Higher levels of non-DHL-C and ABI are associated with cardiovascular and diabetic kidney disease risk and progression. These conditions when associated with hypothyroidism, carry a higher risk of mortality and morbidity. Hence early intervention and screening is required for diabetic subjects for hypothyroidism, dyslipidemia and ABI for lower limbs, to prevent further complications.

Keywords: Hypothyroidism; Dyslipidemia; Diabetic; CKD

Introduction

Thyroid gland disorders or dysfunctions are associated with changes in insulin sensitivity, insulin resistance and impaired glycemic control [1]. Regarding non diabetic and general population, subclinical hypothyroidism occurs in 5–15% among them and may be a risk factor for the development aortic atherosclerosis and myocardial infarction [2-4]. This has been attributed to several mechanisms, including diastolic blood pressure and dyslipidemia. Additionally, research trials have shown that they have a higher Intima-Media Thickness (IMT) of the carotid artery with left ventricular systolic dysfunction, which worsens during effort and a risk for myocardial infarction; these patho-physiological changes can be reversed with Thyroxine Replacement Therapy (TRT) [5-9].

Hypothyroidism is also significantly associated with altered lipoprotein metabolism and dyslipidemia, i.e., a higher total cholesterol, LDL-C (low density lipoprotein cholesterol) and triglycerides, which in turn is a risk factor for Coronary Heart Disease (CAD) and Chronic Kidney Disease (CKD) [10-15]. Additionally, HDL-Cholesterol (HDL-C) is considered as a good cholesterol (as compared to LDL cholesterol and triglycerides, which are considered as bad cholesterol and CAD risk factors). Conversely, non-HDL-C can be derived simply by abstracting HDL-C from total cholesterol, which will give a better index of overall bad cholesterol, a risk for CAD. Recently importance of non-HDL cholesterol as a potential secondary marker of dyslipidemia and CAD risk factor has emerged [16,17]. Previous research trials have not measured non-HDL in hypothyroid diabetic subjects, which calls to conduct such research trial.

Furthermore, extensive research has shown that not only a low ABI (≤ 0.9) is a predictor of Cardiovascular Diseases (CVD), but an abnormally elevated ABI is also associated with high CVD risk [18-24]. Furthermore, it has been demonstrated that subjects with high ABI have poor prognosis or survival, as compared to those with a normal ABI or low ABI [25]. Similarly, Patients with Type 2 Diabetes Mellitus (T2DM) are at higher risk of developing macrovascular disease, especially CAD, cerebrovascular disease, and PAD. A high ABI can be utilized as a simple screening diagnostic test for such patients and a prognostic indicator for CVD and PVD. However, its direct association with hypothyroidism needs to be studied in depth.

Under this research background, the aim of current study was to measure non-HDL cholesterol and ABI among diabetic hypothyroid subjects and to study their significant associations, which until date has not been studied.

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Materials and Methods

Laboratory samples collection, and data retrieval

Current study is a prospective, cross sectional and observational cohort study. Present study included the diabetic patients who were on routine follow up in diabetology clinic of Aseer Diabetes Center and referred from primary health care centers to tertiary care diabetic center for routine evaluations and follow up. Study included known type-1 and type-2 diabetic patients. Children (age <13 years), pregnant diabetic subjects, and patients on End Stage Renal Disease (ESRD) or on dialysis and with active hepatic disease were excluded from the study. Data were collected for more than 10 years (10 years and 6 month), from August 2005 to February 2016.

Detailed history was taken and physical examination was done to complete assessments. Diabetic patients, who were recently diagnosed (within 3-4 months) with subclinical or clinical hypothyroidism by endocrinology department, and following regularly with diabetologist for diabetes management, were also selected. These patients were labeled as "Hypothyroidism ". Blood pressure, weight and height were measured by standardized methodology. Body Mass Index (BMI) was measured by the formula, weight (kg)/height (m^2). BMI ≥ 30 kg/m^2 was labeled as obesity.

All laboratory measurements were done in fasting state, early in the morning of not less than 12 hours, and were sent to Aseer Central Hospital laboratory.

HDL-C (mg/dl) was measured in plasma by Automated High Density Lipoprotein (AHDL) method by the Dimension® clinical chemistry system and analyzer (Siemens healthcare diagnostics Inc. Newark, DE 19714, U.S.A), an in vitro diagnostic test intended for quantitative determination of High Density Lipoprotein Cholesterol (HDL-C). Total cholesterol was measured directly by CHOL method (based on enzymatic procedures), a quantitative determination by the Dimension® clinical chemistry system and analyzer. Then their difference were calculated for the measurement of non-HDL-Cholesterol (i.e., non-HDL-C = total cholesterol – HDL-C).

Ankle Brachial Index (ABI) was measured by a standardized doppler ultrasonic device or arterial doppler, atys Mèdical Doppler System Inc. USA (approved by FDA). Measurements were carried out on the patients after a 5-minute rest in the supine position. First, Doppler probe (8 MHz) was used to measure brachial pressure in right arm. Then same procedure was applied to right foot pressure (dorsalis pedis or posterior tibial artery, whichever was higher). Right ABI was calculated as the ratio of the two pressures (i.e., ABI = brachial pressure / foot pressure). Same procedure was repeated to measure for the right side of arm and foot (left ABI).

All sample requests were entered and retrieved by central computerized network, Natcom Hospital Information System (NATCOM HIS; National Computer System Co. Ltd) [26], a server based hospital management information system interconnecting all departments of Aseer Central Hospital and its diabetes center.

This study was reviewed and approved by the research committee of Aseer Diabetes Center; consent was taken from the participating patients and all methodologies on subjects reported in current study were in accordance with Helsinki Declaration of 1975 (revised in 2008).

Table 1: Demographic data of diabetic patients.

Parameters	Description with N (%) ; Totals = 5780	
Gender	Male	Female
	3699 (64 %)	2081 (36%)
Type of Diabetes	Type-1	Type-2
	815 (14%)	4965 (86%)
Obesity	Obese	Non-Obese
	2427 (42 %)	3353 (58%)
Hypothyroid (on TRT)	Yes	No
	1390 (24%)	4390 (76 %)

Table 2: Variables with Mean ± SD.

Variables	Mean ± SD
Age	57.3 ± 14.6
Duration of diabetes	15.7 ± 9.3
BMI	28.9 ± 5.5
Total cholesterol (mg/dl)	190 ± 48.8
HDL-cholesterol (mg/dl)	41.4 ± 13.2
Non HDL-cholesterol (mg/dl)	149.23 ± 46.5
ABI right foot	1.237 ± 0.318
ABI left foot	1.243 ± 0.374

Statistical methods

Variables of interest were entered, and all data were analyzed using IBM® SPSS® Statistics version 20 for Windows (SPSS®Inc, USA). All statistical tests were performed by standardized bio-statistical methodologies. Student's t test was utilized to measure significant difference for the variables among groups (with and without hypothyroidism).

This study was designed to have a statistical power of 90% to detect significant changes. All p-values were two-sided, and p-values less than 0.05 were considered statistically significant.

Results

Data for 5780 patients were analyzed for the significant results. There were 3699 (64%) males and 2081 (36%) females in the study with 815 (14%) type-1 and 4965 (86%) type-2 subjects. Obesity was found in 2427 (42%); 1390 (24%) were hypothyroid and were on TRT. These demographic data is presented in Table 1. Data for univariate descriptive statistics is shown in Table 2.

Results for the data of grouped variables with mean, ± SD and 95% CI are shown in Table 3, which demonstrates that non-HDL-C values were higher among hypothyroid diabetic subjects as compared to those without hypothyroidism (153 ± 42.7; 95% CI 146.6 to 158.8 verses148 ± 40; 95% CI 142.5 to 151.6). Similarly, right foot ABI was higher among diabetics with hypothyroidism (1.34 ± 0.387; 95% CI 1.19 to 1.56 versus 1.23 ± 0.314; 95% CI 1.12 to 1.26) and with similar results for the left foot ABI (1.32 ± 0.375; 95% CI 1.23 to 1.54 versus 1.23 ± 0.371; 95% CI 1.12 to 1.28).

Table 4 shows t-tests for the group of variables, i.e., Non-HDL-C,

Table 3: Grouped variables; comparison of non-HDL-C, and ABI (right and left foot) in diabetic patients with and without hypothyroidism.

Variables with Mean ± SD (95%CI)	
Non HDL-C for the subjects with hypothyroidism	**Non HDL-C for the subjects without hypothyroidism**
153 ± 42.7 (95% CI 146.6 to 158.8)	148 ± 40 (95% CI 142.5 to 151.6)
Right foot ABI for the subjects with hypothyroidism	**Right foot ABI for the subjects without hypothyroidism**
1.34 ± 0.387 (95% CI 1.19 to 1.56)	1.23 ± 0.314 (95% CI 1.12 to 1.26)
Left foot ABI for the subjects with hypothyroidism	**Left foot ABI for the subjects without hypothyroidism**
1.32 ± 0.375 (95% CI 1.23 to 1.54)	1.23 ± 0.371 (95% CI 1.12 to 1.28)

Table 4: T-test for group of variables (Non-HDL-, right and left ABI).

T-tests for group of variables	F-statistic	T-statistic	P-value
Non-HDL-C levels with and without Hypothyroidism	6.71	3.17	< 0.001
Right foot ABI values with and without hypothyroidism	3.73	2.1	< 0.001
Left foot ABI values with and without hypothyroidism	3.12	2.3	< 0.001

right and left ABI. It is evident from the data that Non-DHL, and ABI values for the right and left foot were significantly different among the patients with hypothyroidism and those without this disease state; all p-values were significant at the level <0.05.

Discussion

Hypothyroidism has adverse effects on lipoprotein or lipid metabolism, and has been well demonstrated in medical research; levels of Low Density Lipoprotein Cholesterol (LDL-C), total cholesterol, and triglycerides are found to be higher in hypothyroidism with association of carotid intima-media thickness [27-31]. These changes are also related with worse cardiovascular outcomes and changes in wide variety of clinical parameters [32-37]. Recently is has been also recommended to consider seriously non-HDL cholesterol for reducing cardiovascular morbidity and mortality as HDL-C is a strong inverse covariate of triglyceride [38,39].

Regarding guidelines for management in dyslipidemia, National Cholesterol Education Program (NCEP) has recommended a target for LDL-C to be <100 mg/dl in diabetic patients, followed by a target of non-HDL cholesterol <130 mg/dl as a secondary target if triglyceride level remains elevated (>200 mg/dl). American Diabetes Association (ADA) has provided the same recommendation for managing dyslipidemia among diabetic subjects [40,41]. There are several studies conducted in recent years which have shown the importance of HDL-C/non-HDL and its association with ischemic heart disease and nephropathy or microalbuminuria [42,43]. In fact, it is demonstrated that higher levels of HDL-C are associated with lower risk of diabetic kidney disease (microalbuminuria / macroalbuminuria) and cardiovascular risk [44,16].

Non HDL cholesterol can provide a single index of all apolipoprotein-B containing lipoproteins. Furthermore, LDL-C alone is not sufficient to estimate atherogenic risk in patients with elevated triglycerides; LDL-C can be misleading if triglycerides > 400mg/dl. One cohort research trial had demonstrated that non-HDL cholesterol was a better predictor of CVD than LDL cholesterol [45]. In other words, if HDL-C is subtracted from given total cholesterol, the remaining non-HDL-C can provide overall cardiovascular risk index (non-HDL-C = total cholesterol – HDL-C). This technique is usually ignored in general busy clinical practice and should be considered among diabetic and hypothyroid patients.

However, significant association of non-HDL-C with hypothyroidism was not measured in the past research studies. This was achieved in the current research which has shown that non-HDL levels were significantly higher among the subjects with hypothyroidism (153 ± 42.7; 95% CI 146.6 to 158.8 verses148 ± 40; 95% CI 142.5 to 151.6); p < 0.001). This is an alarming fact that patients with hypothyroidism and with diabetes should have dyslipidemia screening at initial diagnosis. If non-HDL-C is higher, especially in the presence of hypothyroidism, treatment to lower lipids should be considered to prevent cardiovascular disease and nephropahty progression.

The ABI is the ratio of systolic blood pressure at the ankle to the systolic blood pressure at the arm and in a normal healthy person is >1.00. However, The ABI might be falsely elevated (>1.3) due to calcification of medial arteries in patients with diabetes, and in such cases, other vascular tests should be performed to rule out PAD / LEAD (peripheral arterial disease / lower extremity arterial disease, respectively) [46].

ABI has been shown to be a strong predictor of subsequent atherosclerosis, endothelial dysfunction, coronary or cardiovascular events, stroke in patients with peripheral arterial disease and also associated with high mortality and morbidity including diabetic patients [47-56].

It was also the aim of the current research to assess the ABI of the diabetic patients who has also the disease state of hypothyroidism. Although there are various studies to show the ABI levels among diabetics, however until date there are no studies which have demonstrated significant ABI difference among diabetic subjects who have hypothyroidism or free from this disease state. Our current research has demonstrated a significant ABI differences (in both lower limbs) among diabetic patients with hypothyroidism. Hence subjects with hypothyroidism have significantly higher ABI as compared to those without hypothyroidism. This was proved to be true with both lower limbs/feet; right foot ABI was higher among diabetics with hypothyroidism (1.34 ± 0.387; 95% CI 1.19 to 1.56 versus 1.23 ± 0.314; 95% CI 1.12 to 1.26; p < 0.001), as well as for the left foot ABI (1.32 ± 0.375; 95% CI 1.23 to 1.54 versus 1.23 ± 0.371; 95% CI 1.12 to 1.28).

These significant associations provide a first demonstration in medical research that diabetic patients with hypothyroidism have higher ABI. This again needs early intervention as higher ABI is a cardiovascular or macrovascular risk and hypothyroidism further aggravates the pathology and has been proved in recent years as well [57].

The screening for ABI and diabetic foot disorders id essential part of initial evaluations, and monitoring diabetes associated diseases. If ABI is found at higher levels, with associated hypothyroidism and dyslipidemia, this should warn the diabetologist or physicians involved in diabetes management that such type of patients are at risk. Hence tight glycemic control with management of associated complications is corner stone's of multidisciplinary diabetes management.

Conclusion

In the current research cohort, elevated non-HDL-C and high ABI were found to be associated with hypothyroidism. In turn, all of these abnormalities are associated with Cardiovascular and diabetic Kidney Diseases (or CKD). Efforts should be initiated to screen the cases of hypothyroidism, dyslipidemia among diabetic subjects and to initiate the treatment early. Furthermore, it is always required to follow the best available guidelines for diabetes management, and research studies which have followed evidence based methods in medical practice [58-60].

Recommendations

The diabetologists should consider measurement of lipids (especially non-HDL-C) and ABI among diabetic patients. In case of hypothyroidism with dyslipidemia, the management should be aggressive to lower the lipids and to prevent of CAD/CVD and diabetic kidney diseases and their progression.

There is a need to conduct studies at multicenter levels, internationally, to confirm the evidence provided by the current study and to develop guidelines for the management of diabetes with hypothyroidism and dyslipidemia.

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