THE RELATIONSHIP BETWEEN ADIPOKINES (CHEMERIN, VISFATIN AND OMENTIN) AND LIPID PROFILE IN SAUDI FEMALE PATIENTS WITH HYPERTHYROIDISM

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Abstract
Background: It is well known that thyroid dysfunction as well as adipokines have an important effect on lipid profile. However, the effect of adipokines on lipid profile in hyperthyroid patients is not well elucidated.
Objective: This study aimed to examine changes in serum lipid profile and to evaluate the correlation between these changes and the adipokines chemerin, visfatin and omentin in Saudi female patients with hyperthyroidism.
Materials and Methods: A total of 140 participants were recruited for this study. The participants were sub-grouped as a control group (n = 70) and hyperthyroid patient group (n = 70). Serum adipokines (chemerin, visfatin and omentin), lipid profile, thyroid profile (TSH, FT3, FT4, TT3, TT4 and Thyroxine) and thyroglobulin were measured for all participants.
Results: Serum concentrations of total cholesterol and low-density lipoprotein cholesterol (LDL-c) were significantly lower in the hyperthyroid patients than in the control group. Thyroid hormones TT3 and TT4 were positively correlated with triglycerides, while FT3 was negatively correlated with total cholesterol and LDL-c. Although visfatin and omentin showed no significant correlation with lipid profile, chemerin was positively correlated with triglycerides and negatively correlated with high-density lipoprotein cholesterol (HDL-c).
Conclusion: The changes in chemerin concentration that occur in hyperthyroid patients play a role in regulating lipid metabolism and may lead to dyslipidemia.

Keywords: Chemerin, lipid profile, omentin, thyroid hormones, visfatin.

INTRODUCTION

Thyroid hormones regulate a wide array of metabolic parameters. Hyperthyroidism, also called overactive thyroid, is a condition in which the thyroid gland makes excessive amounts of thyroid hormone. It is well known that thyroid dysfunction has an important effect on lipid
profile. A few studies have shown that hyperthyroidism decreases the level of plasma cholesterol, triglycerides, low-density lipoprotein cholesterol (LDL-c) and high-density lipoprotein cholesterol (HDL-c). Hyperthyroidism changes the composition of lipoproteins due to the role that thyroid hormones have in regulating the activity of key enzymes involved in lipoprotein transport. However, further investigation has been suggested to support these current findings.

Present evidence indicates that the severe alterations in lipid metabolism is correlated with the absence or excess of individual adipokine. Thus, one can conclude that thyroid hormones and adipokines together might affect the regulation of lipid metabolism. However, the effect of adipokines on lipid profile in hyperthyroid patients is not well elucidated.

Materials and Methods

Study participants
140 total participants were recruited between the ages of 20 and 45. They were divided into control group (n=70) and hyperthyroidism group (n=70) who were recruited from different hospitals in Jeddah, Saudi Arabia (King Abdulaziz University Hospital, King Fahd Hospital and King Fahd Armed Forces Hospital). Elevations in serum concentrations of T3 (Triiodothyronine) and T4 (Thyroxine) and a reduction in serum concentration of thyroid stimulating hormone (TSH) were used to distinguish hyperthyroid patients from controls. Exclusion criteria were the presence of pregnancy, treatment with radioactive iodine and any disease, including diabetes and hypertension. Women who had been on antithyroid medication for more than two years were also excluded from this study. This study was approved by the ethical committee of the Faculty of Medicine, King Abdulaziz University (reference number 418-6) and the health affairs office of the city of Jeddah (reference number 412), and all participants gave informed consent.

Biochemical measurements
Blood samples were collected from all study participants after overnight fasting (12–14 h). Serum was separated by centrifugation and frozen immediately at -80°C until assayed. An enzyme-linked immunosorbent assay kit (ab155430-Chemerin Human ELISA Kit, Abcam, USA) was used according to the manufacturer’s protocol to determine serum chemerin quantitatively. Serum omentin and visfatin levels were measured quantitatively by using a human omentin-1 ELISA kit (SG-10741, SinoGeneclon Biotech Co.,Ltd) and human visfatin ELISA kit (SG-10381, SinoGeneclon Biotech Co.,Ltd), respectively. Thyroid hormones (TT3, TT4, FT3 and FT4), TSH and thyroglobulin were all measured by an electrochemiluminescent immunoassay (ECLIA) method using COBAS e 411 automated machine analyzer (Roche Company, USA). Serum concentrations of total cholesterol, triglycerides, HDL-c and LDL-c were all measured automatically by enzymatic methods using Dimension Vista® system (Siemens, Germany).
Statistical analysis

Statistical analysis was performed using Graphpad Prism 7. Mean ± standard error of the mean (SEM) was used for the descriptive data analysis of the study sample. The evaluation of the differences in the general characteristics and serum lipid profile between the two groups was done using a Mann–Whitney U test. Spearman’s correlation coefficients were used to assess the relationship between serum thyroid hormone concentration and lipid profile and to examine the association between serum adipokines and lipid profile. A P-value of less than 0.05 was considered statistically significant.

RESULTS

This study included a total of 140 participants, and their general characteristics are shown in Table 1. For all subjects, the mean age was 32.2 ± 0.81 years, the mean body mass index (BMI) was 26.7 ± 0.59 kg/m² and the mean value of the waist to hip ratio (WHR) was 0.72 ± 0.01. The data also indicates that the values of the mean of the participants’ systolic blood pressure (SBP) and diastolic blood pressure (DBP) were 115 ± 0.80 and 73.1 ± 0.83, respectively. Of the 140 study participants, the statistical analysis found no significant differences in the mean of any of the characteristics between the two groups.

Table 1. General characteristics of the study participants

<table>
<thead>
<tr>
<th>Parameter</th>
<th>All (n=140)</th>
<th>Control (n = 70)</th>
<th>Hyperthyroid patients (n = 70)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>32.2 ± 0.81</td>
<td>32.2 ± 0.90</td>
<td>36.2 ± 1.34</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>26.7 ± 0.59</td>
<td>25.2 ± 0.67</td>
<td>26.6 ± 0.9776</td>
</tr>
<tr>
<td>WHR</td>
<td>0.72 ± 0.01</td>
<td>0.72 ± 0.68</td>
<td>0.72 ± 1.62</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>115 ± 0.80</td>
<td>116 ± 1.00</td>
<td>114 ± 1.42</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>73.1 ± 0.83</td>
<td>73.3 ± 0.99</td>
<td>72.9 ± 1.42</td>
</tr>
</tbody>
</table>

BMI: body mass index, WHR: waist to hip ratio, SBP: systolic blood pressure, DBP: diastolic blood pressure

Regarding lipid profile, mean total cholesterol for all subjects was 4.57 ± 0.08 mmol/l and mean triglycerides were 0.90 ± 0.04 mmol/l. The results for mean LDL-c and HDL-c were 2.93 mmol/l and 1.42 mmol/l, respectively. However, the patients with hyperthyroidism showed significantly lower serum concentrations of total cholesterol and LDL-c than the controls. In addition, triglyceride and HDL-c concentrations appeared to demonstrate a trend toward a non-significant decrease in the hyperthyroid patients (Table 2).

Table 2. Differences in lipid profile concentrations between the control and hyperthyroid groups

<table>
<thead>
<tr>
<th>Parameter</th>
<th>All (n=140)</th>
<th>Control (n = 70)</th>
<th>Hyperthyroid patients (n = 70)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total cholesterol (mmol/l)</td>
<td>4.57 ± 0.08</td>
<td>4.70 ± 0.09</td>
<td>4.30 ± 0.12**</td>
</tr>
<tr>
<td>LDL-c (mmol/l)</td>
<td>2.93 ± 0.08</td>
<td>3.03 ± 0.98</td>
<td>2.70 ± 0.11*</td>
</tr>
<tr>
<td>HDL-c (mmol/l)</td>
<td>± 0.03</td>
<td>1.44 ± 0.35</td>
<td>1.40 ± 0.41</td>
</tr>
<tr>
<td>Triglycerides (mmol/l)</td>
<td>0.90 ± 0.04</td>
<td>0.98 ± 0.05</td>
<td>0.89 ± 0.04</td>
</tr>
</tbody>
</table>

LDL-c: low density lipoprotein cholesterol, HDL-c: high density lipoprotein cholesterol.
* P < 0.05, ** P < 0.01
The correlation coefficients for lipid profile and TSH, thyroid hormones, thyroglobulin and adipokines are shown in Table 3. The data indicates that TSH was negatively correlated with HDL-c, and FT3 was negatively correlated with total cholesterol and LDL-c. In addition, TT3 and TT4 were both positively correlated with triglycerides. In regard to adipokines, chemerin was positively correlated with triglycerides and negatively correlated with HDL-c. In contrast, visfatin and omentin showed no significant correlation with lipid profile.

Table 3. The Spearman’s correlations between lipid profile and TSH, thyroid hormones, thyroglobulin and adipokines

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Total cholesterol</th>
<th>LDL-c</th>
<th>HDL-c</th>
<th>Triglycerides</th>
</tr>
</thead>
<tbody>
<tr>
<td>TSH</td>
<td>0.110</td>
<td>0.153</td>
<td>-0.199*</td>
<td>0.140</td>
</tr>
<tr>
<td>TT3</td>
<td>-0.087</td>
<td>-0.085</td>
<td>-0.048</td>
<td>0.221*</td>
</tr>
<tr>
<td>TT4</td>
<td>-0.043</td>
<td>-0.029</td>
<td>-0.017</td>
<td>0.182*</td>
</tr>
<tr>
<td>FT3</td>
<td>-0.231*</td>
<td>-0.188*</td>
<td>-0.139</td>
<td>0.083</td>
</tr>
<tr>
<td>FT4</td>
<td>-0.046</td>
<td>-0.059</td>
<td>-0.059</td>
<td>-0.108</td>
</tr>
<tr>
<td>Thyroglobulin</td>
<td>-0.094</td>
<td>-0.038</td>
<td>-0.145</td>
<td>0.062</td>
</tr>
<tr>
<td>Chemerin</td>
<td>-0.026</td>
<td>0.024</td>
<td>-0.182*</td>
<td>0.260***</td>
</tr>
<tr>
<td>Visfatin</td>
<td>0.071</td>
<td>0.367</td>
<td>0.091</td>
<td>-0.092</td>
</tr>
<tr>
<td>Omentin</td>
<td>-0.005</td>
<td>-0.032</td>
<td>0.148</td>
<td>-0.032</td>
</tr>
</tbody>
</table>

LDL-c: low density lipoprotein cholesterol, HDL-c: high density lipoprotein cholesterol, TSH (Thyroid stimulating hormone), FT3 (Free Triiodothyronine), FT4 (Free Thyroxine), TT3 (Total Triiodothyronine), TT4 (Total Thyroxine). * P < 0.05, *** P < 0.001.

**DISCUSSION**

Abnormal lipid profile levels have been reported in patients with thyroid dysfunction.[2,6-9] An excess of thyroid hormones is well known to participate in lipid metabolism and may lead to dyslipidemia.[10] The results from the present study demonstrate that patients with hyperthyroidism presented with significantly lower serum concentrations of total cholesterol and LDL-c, which is consistent with previous studies.[9,11-13] Although it has been reported that FT4 is the main determinant of the change in the serum HDL-c and LDL-c concentrations,[14] we found no significant correlation between FT4 and any lipid profile parameter. On the other hand, FT3 was inversely correlated with total cholesterol and LDL-c. These results confirm that thyroid hormones negatively regulate lipid metabolism and can decrease their concentration in plasma as has been reported in previous studies.[3,15] However, TT3 and TT4 were both positively correlated with triglycerides, which may suggest that TT3 and TT4 positively regulate serum triglyceride concentration.

Beyond the effect on lipid profile, thyroid hormones can influence adipocyte metabolism and the production of adipokines. Our previous study[5] reported a significant increase in serum concentration of chemerin and a significant decrease in serum concentration of visfatin and omentin in a hyperthyroid group. The current study focused on investigating the possible correlation between these adipokines and lipid profile. The data indicated that visfatin and omentin showed no significant correlation with any lipid profile parameter. In contrast, other studies have reported that visfatin was significantly correlated with lipid profile. A study by Wang et.al. showed that visfatin was correlated positively with HDL-c and negatively with triglycerides. Their results stated that circulating visfatin, in non-diabetic Caucasian subjects, is an indicator of a beneficial lipid metabolism.[16] Another study showed that visfatin had a positive correlation with HDL-c but a negative correlation with LDL-c in female subjects.
aged 40 or older. In addition, a study by Gligor et al. found a negative correlation between visfatin and triglycerides in diabetic patients. They also discovered that, while visfatin was negatively correlated with HDL-c in diabetic and obese patients, it was positively correlated with HDL-c in a control group. These studies all imply that visfatin may play a beneficial role in lipid metabolism. In regard to omentin, limited studies have been performed investigating its correlation with lipid profile; however, a couple of reports have shown that omentin was positively correlated with HDL-c in people with a higher BMI. Accordingly, we suggest that our insignificant correlation between lipid profile and visfatin and omentin might be due to differences in the patients’ characteristics, including BMI/obesity, age group, race and diabetes. Moreover, to the best of our knowledge, our study was the first to investigate this correlation in hyperthyroid patients. Therefore, further studies are needed to clarify the role of visfatin and omentin in lipid homeostasis in hyperthyroidism. Chemerin is highly expressed in liver and adipose tissue and is known to regulate lipid metabolism. In this study, the correlation between chemerin and lipid profile was also examined. Our results were compatible with previous studies that reported that chemerin in general is positively correlated with triglycerides and negatively correlated with HDL-c. In addition, a recent study on hyperthyroid patients reported the same correlations where chemerin had a significant positive correlation with triglycerides and a significant negative correlation with HDL-c. These results reinforce the concept that plasma chemerin levels may be influenced by thyroid hormone disorders, and this could be an adaptive mechanism for the alterations in basal energy spending in thyroid disorders.

In conclusion, hyperthyroidism might affect adipokine secretion patterns, which in turn influence lipid profile. However, the role of adipokines in hyperthyroidism and its associate effect on lipid metabolism is complex, and the metabolic effects of chemerin, visfatin and omentin are still being elucidated. Therefore, further studies are needed to clarify the interplay or any underlying linking mechanism between adipokines and lipid profile in hyperthyroidism.

There were some potential limitations to the current study, the hyperthyroid patients were not sub-grouped according to disease cause.

**Authorship**

U. O. contributed to concepts, study design, data acquisition, data analysis and statistical analysis.

H.M.A contributed to literature search, data analysis, manuscript preparation, manuscript editing, and manuscript review.

E.A. contributed to literature search, clinical studies, experimental studies and manuscript review.

R.M contributed to literature search, data analysis, manuscript preparation, manuscript editing, and manuscript review.

**Conflict of interest**

All authors declare no conflict of interest
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REFERENCES


